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Human Medicines Development and Evaluation

CHMP variation assessment report

Type II variation EMEA/H/C/000419/II/0097

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

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

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1. Scientific discussion

1.1. Introduction

Viread was first approved in EU for the treatment of HIV-infected adults in February 2002. Viread was then approved in EU for the treatment of chronic hepatitis B (CHB) in adults in April 2008. Tenofovir is also a component of the fixed-dose combination tablets Truvada (emtricitabine 200 mg/tenofovir DF 300 mg tablet) and Atripla (efavirenz 600 mg/emtricitabine 200 mg/tenofovir DF 300 mg tablet), which are indicated for treatment of HIV-1 infection. The cumulative worldwide patient exposure to tenofovir DF since first marketing approval of Viread (for HIV-1 infection) in the US on 26 October 2001 to 31 March 2009 is estimated to be 2.4 million patient-years of treatment.

Approval of Viread for CHB was based primarily on data from 266 adult subjects with hepatitis B early antigen positive (HBeAg+) compensated CHB and 375 subjects with hepatitis B early antigen negative (HBeAg−) compensated CHB who enrolled in the similarly designed pivotal studies GS-US-174-0102 (HBeAg− subjects) and GS-US-174-0103 (HBeAg+ subjects).

The application for the CHB indication also included supportive safety data, blinded with regard to treatment assignment, from Study GS-US-174-0108, which is a double-blind, active-controlled study of tenofovir DF in subjects with CHB and decompensated liver disease. No efficacy data from this study have been presented previously.

A total of 112 subjects have been treated in this study, and the planned primary analyses of safety and efficacy, based on the first 48 weeks of treatment with tenofovir DF, the fixed-dose combination of emtricitabine/tenofovir DF, or entecavir, have been conducted and are presented in this submission. This study is ongoing with maximum planned treatment duration of 168 weeks.

On the basis of these study results, the MAH is seeking an extension of the current indication for Viread to include the treatment of patients with decompensated chronic hepatitis B.

The proposed wording for section 4.1 is as follows:

Hepatitis B infection:

"Viread is indicated for 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.*
- ***decompensated liver disease.***

This indication is based on histological, virological, biochemical and serological responses mainly in adult nucleoside naïve patients with HBeAg positive and HBeAg negative chronic hepatitis B with compensated liver function ***and in adults with chronic hepatitis B with decompensated liver function****".*

The principal clinical data provided to support the efficacy and safety of TDF in treatment of patients with decompensated liver disease were provided from the results of the MAH sponsored study GS-US-174-0108.

To allow assessment of the latest Viread safety information a CIOMS listing of all post marketing events from 01 October 2008 to 17 November 2009, and clinical trial data from ongoing hepatitis B studies was included in the application.

In accordance with Article 8 (ca) and (g) of Directive 2001/83EC, as amended, an update to the Viread Environmental Risk Assessment was provided. In addition, in accordance with Article 8 (ia) of Directive 2001/83 EC, as amended, and the CHMP's "Guideline On Risk Management Systems for Medicinal Products For Human Use (EMEA/CHMP/96268/2005)", in relation to significant changes to an indication, an update to the Gilead Pharmacovigilance System and an update to the Viread Risk Management Plan were submitted.

1.2. Environmental Risk Analysis

In the context of this variation, the MAH has provided an update of the environmental risk assessment (ERA). This ERA includes data already submitted in the context of the variation (EMEA/H/C/419/II/75) to extend the therapeutic indication of Viread to the treatment of chronic hepatitis B patients with compensated liver disease. These data included a Phase I estimation of exposure and results and reports from Phase II environmental fate and effect analysis studies.

Trier A: Fate and effect analysis

For the purposes of this application to extend the current chronic hepatitis B therapeutic indication for tenofovir DF to include treatment of chronic hepatitis B in patients with decompensated liver disease, amended calculations for Phase II Tier PEC Refinement and Outcome of Tier A fate and effect analysis have been provided.

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

Based on available data the statements already presented in Product information are considered appropriate:

SmPC: *'Any unused product or waste material should be disposed of in accordance with local requirements.'*

Package Leaflet: *'Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.'*

1.3. Design, Methods & Demographics of Study GS-US-174-0108

Study GS-US-174-0108 was a Phase 2, Double-Blind, Multi-centre, Randomised Study comparing Tenofovir Disoproxil Fumarate, Emtricitabine Plus Tenofovir Disoproxil Fumarate and Entecavir in the Treatment of Chronic Hepatitis B Subjects with Decompensated Liver Disease and in the Prevention of Hepatitis B Recurrence Post-Transplantation, conducted in 39 sites (including 17 sites in Europe, 13 in North America and 9 in Asia) from 4 April 2006 (1st subject screened) to 5 December 2008 (Last subject observation for 48 weeks report).

Methods

The primary objective was to evaluate and compare the safety and tolerability of tenofovir disoproxil fumarate (tenofovir DF), emtricitabine plus tenofovir DF, and entecavir in the treatment of chronic hepatitis B (CHB) subjects with decompensated liver disease.

The secondary objectives were:

- To provide a preliminary assessment of the relative efficacy of tenofovir DF, emtricitabine plus tenofovir DF, and entecavir in the treatment of CHB subjects with decompensated liver disease
- To determine the probability of remaining free from hepatitis B virus (HBV) recurrence post-transplantation in each treatment group
- To determine the incidence and patterns of drug resistance mutations in HBV deoxyribonucleic acid (DNA) polymerase in each treatment group

Treatments

Subjects were randomised in a 2:2:1 ratio to one of the following treatment groups:

- TDF 300 mg + FTC/TDF placebo + ETV placebo once daily (QD) (n=40)
- FTC 200 mg/TDF 300 mg + TDF placebo + ETV placebo QD (n=40)
- ETV 0.5 mg or 1 mg + TDF placebo + FTC/TDF placebo QD (n=20)

The ETV dose was 0.5 mg for subjects with < 6 months of prior lamivudine exposure and no history of lamivudine resistance mutations, and 1 mg for subjects with ≥ 6 months of prior lamivudine exposure and/or a history of lamivudine resistance mutations.

Study medication was administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal) at approximately the same time each day.

Randomization was stratified by Child-Pugh-Turcotte (CPT) score (≤ 9 or 10–12) and prior lamivudine exposure coupled with history of lamivudine resistance mutations (< 6 months of prior lamivudine exposure and no history of lamivudine resistance mutations or ≥ 6 months of prior lamivudine exposure and/or a history of lamivudine resistance mutations).

Subjects were switched from their existing anti-HBV regimen to their randomly assigned regimen at baseline (i.e., the last dose of the pre-study regimen was taken on the day before the baseline visit). A maximum randomised treatment duration of 168 weeks is planned. Since Study GS-174-0108 enrolled subjects with decompensated liver disease, it was necessary to provide early intervention strategies in the case that profound viral suppression was not expeditiously achieved. For this reason subjects with a decrease in plasma HBV DNA from baseline of less than 2 log10 copies/ml and plasma HBV DNA > 10,000 copies/ml (or plasma HBV DNA > 1,000 copies/ml for subjects who entered the study with HBV DNA < 10,000 copies/ml) at Week 8 had the option to start open-label emtricitabine 200 mg/tenofovir DF 300 mg fixed-dose combination and continue in the study. Subjects with a virologic breakthrough (≥ 1 log10 copies/ml increase from nadir in plasma HBV DNA on 2 consecutive determinations) or plasma HBV DNA that remains above 400 copies/ml (confirmed) at or after 24 weeks of treatment could be unblinded at the investigator's discretion for selection of alternative anti-HBV therapy that may include open-label FTC/TDF fixed-dose combination. Study drug discontinuation with treatment-free follow-up was contraindicated due to the potential risk of exacerbation of hepatitis in the setting of low hepatic reserve which could lead to further decompensation.

Study Participants

Adult subjects (18–69 years of age) with CHB (defined as positive serum HBsAg for at least 6 months, anti-HBV therapy for at least 6 months, or medical records indicating chronic HBV or negative HBc IgM) and :

- decompensated liver disease (CPT score of 7–12 or a past history of CPT score ≥ 7 and any CPT at screening ≤ 12),

- plasma HBV DNA ≥ 1000 copies/ml (determined by PCR Roche Cobas Taqman 48 assay, LLQ:169 copies/ml),
- ALT < 10 × ULN

Subjects must have had Clcr ≥ 50 ml/min, no HIV/HCV/HDV coinfection, no serologies evidence of hepatocellular carcinoma (based on α-fetoprotein and imaging results); no history of solid organ or bone marrow transplant; no prior use of TDF or ETV; < 24 months of prior adefovir dipivoxil exposure; no history of variceal bleeding, hepatorenal syndrome, Grade 3 or Grade 4 hepatic encephalopathy, or spontaneous bacterial peritonitis within 60 days of the screening visit; and < Grade 2 hepatic encephalopathy at screening.

Of note, among the reasons for removal of subjects from therapy were:

- Permanent study drug discontinuation was required for confirmed (within 72 hours) increases in serum creatinine of ≥ 0.5 mg/dL over baseline if no other reason for the increased creatinine existed or if the value did not return to within 0.3 mg/dL of baseline.
- Permanent discontinuation was required for any calculated creatinine clearance < 30 ml/min (dose adjustment was required for creatinine clearance < 50 ml/min).
- If ALT/AST values were > 2 × baseline and > 10 × ULN and bilirubin was confirmed at > 2.5 × ULN, prothrombin time at > 1.5 × ULN, or lactate was increased (symptomatic and > 2 × ULN or asymptomatic and > 4 × ULN), the investigator was to consider discontinuing study medication and initiating alternative approved therapy.

Planned: N=100 (40 each in the TDF and FTC/TDF groups, 20 in the ETV group)

Analysed: N=112 (45 each in the TDF and FTC/TDF groups, 22 in the ETV group)

Outcomes/endpoints

Primary Endpoint:

Coprimary study endpoints evaluated included the following:

- Tolerability failure, defined as permanent discontinuation of study drug due to a treatment-emergent AE; any subject who temporarily discontinued study due to an AE but did not restart study drug was considered a tolerability failure
- Confirmed increase in serum creatinine of ≥ 0.5 mg/dL from baseline or confirmed serum phosphorus of < 2.0 mg/dL

Secondary Efficacy Endpoints

The secondary efficacy endpoints included the following:

- Subjects with plasma HBV DNA < 400 and < 169 copies/ml by visit
- Change from baseline in HBV DNA by visit
- Absolute and change from baseline in MELD score by visit
- In the subset of subjects undergoing liver transplantation, time to recurrence of hepatitis B, defined as 2 consecutive plasma HBV DNA levels ≥ 400 copies/ml or 2 consecutive HBsAg+) results (listed only because of the small number of transplants)
- Subjects with normal ALT and normalised ALT (of subjects with elevated ALT at baseline) by visit
- ALT by visit

- Change from baseline in ALT by visit
- Subjects with increase or decrease in CPT score of ≥ 2 points by visit
- Absolute and change from baseline in CPT score by visit
- HBeAg loss and HBeAg seroconversion by visit (for subjects who were HBeAg+ at baseline)
- HBsAg loss and HBsAg seroconversion by visit
- Deaths and time to death through Week 48 (listed only because of the small number of deaths)
- Incidence and patterns of HBV DNA polymerase mutations potentially associated with drug resistance

Resistance surveillance

Resistance surveillance was conducted to identify changes within the HBV polymerase gene from subject viral isolates with detectable persistent viral replication in the presence of study drug treatment. Data available for this report included baseline viral genotypes (A–H), and presence of mutations associated with known drug resistance at baseline. Also included were changes within the HBV polymerase from baseline for viremic subjects at Week 48 (or early discontinuation at Week 24 or later), for subjects experiencing virologic breakthrough, and for subjects switching from blinded treatment with tenofovir DF to open-label treatment with emtricitabine/tenofovir DF.

In vitro phenotypic analysis of tenofovir and emtricitabine susceptibility was attempted on serum HBV samples obtained from subjects who developed an emerging amino acid substitution at conserved-sites of the HBV polymerase and for subjects with virologic breakthrough on tenofovir DF. Phenotypic analysis was also to be attempted for amino acid substitutions that developed at polymorphic sites if the change was observed in more than one subject.

Sample size

The planned enrolment was 100 subjects: 40 subjects treated with tenofovir DF 300 mg, 40 subjects treated with emtricitabine 200 mg/tenofovir DF 300 mg, and 20 subjects treated with entecavir 0.5 mg or 1 mg QD. The actual enrolment was 112 subjects. Calculations of 95% confidence intervals were repeated given the actual enrolment of 45, 45, and 22 subjects in the tenofovir DF, emtricitabine/tenofovir DF, and entecavir groups, respectively.

Statistical methods

Efficacy

All efficacy data were summarised descriptively with no statistical hypothesis testing.

Two analyses based on the RAT (randomised-and-treated) analysis set were provided. The first considered any subject who discontinued randomised study drug (including switch to open-label emtricitabine/tenofovir DF) as a failure (NC/S=F). The second analysis considered any subject who discontinued from the study (noncompleter) as a failure (NC=F).

Data collected on a subject who received a liver transplant were not included in the evaluation of secondary efficacy endpoints after transplant date, and the subject was considered censored (i.e., removed from the numerator and the denominator) for each visit at and after the time of transplant. Data from these subjects were included in the safety analyses.

In general, values for missing data were not imputed. For the analyses of categorical efficacy endpoints, the subject was considered a failure for these endpoints if the subject discontinued study drug for any reason and had missed the visit at the time point of interest.

Safety

Two analyses of the RAT analysis set were performed for the coprimary endpoints using 3 treatment groups (TDF, FTC/TDF, and ENT) and 2 treatment groups (TDF and FTC/TDF combined; and ENT). The first analysis was strictly by treatment group using all data collected through Week 48. The second analysis was also by treatment group, using all data collected during the double-blind portion of the trial and censoring all data collected after a subject switched to open-label emtricitabine/tenofovir DF.

Because of the small number of subjects meeting the coprimary endpoints, the originally proposed methods (Kaplan-Meier methods and stratified log-rank tests) were replaced by standard calculations of proportions, and the difference in proportions between the tenofovir DF-containing arms (combined) and the entecavir arm was evaluated using a Fisher exact test.

Subjects who received liver transplants were censored from the analyses of efficacy endpoints, but were included in all safety analyses.

Generating inferential statistics for comparisons among treatment groups was limited to the two coprimary safety endpoints. No adjustments for multiple comparisons were made.

Interim Analysis and Data Monitoring

An interim analysis of blinded safety data to support regulatory submissions was conducted, including data from the first 50 subjects through 03 July 2007 (1 to 337 days of treatment). This interim, blinded tabulation had no impact on the future conduct or continuation of the study.

This Week 48 analysis is the first analysis conducted with unblinded data. Results are presented by treatment group, but the subjects, investigators, and Gilead staff not directly involved with statistical analysis and report preparation (including all individuals with direct contact with the study sites) will remain blinded to individual treatment assignments through the end of the study. Of note, in the text of this report, individual subject numbers and their treatment assignments were not provided side-by-side (thus avoiding any unintentional unblinding) but were available in the data listings.

Interim analyses are planned every 48 weeks through the end of the study (Week 168). Since inferential statistics for comparisons among treatment groups are not planned, discussion of adjustment for multiple comparisons is not necessary.

An external independent multidisciplinary Data Monitoring Committee (DMC) reviewed the progress and safety for this study. The DMC examined the safety profile of the study in order to protect subject welfare and preserve study integrity, and provided recommendations as needed regarding study design and conduct. Given that the control treatment (i.e., entecavir) has regulatory approval for the treatment of compensated CHB, there is no intention of discontinuing the study prematurely if results favour another treatment arm. While the DMC is asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study. The DMC met five times in 2007–2008, and confirmed agreement with continuing the study.

Results

Patient disposition

The planned sample size was 100 subjects; 196 subjects were screened to enroll the planned sample size. A total of 112 subjects were successfully screened and randomised, and all were treated with at least one dose of study drug (45 subjects received TDF, 45 subjects received FTC/TDF, and 22 subjects received entecavir).

Table 1. Subject Disposition

Subject Disposition	TDF	FTC/TDF	ETV	Overall
Number Screened				196
Number Randomized	45	45	22	112
Number Randomized and Treated	45	45	22	112
Switched to Open-Label FTC/TDF?				
No	40 (89%)	43 (96%)	19 (86%)	102 (91%)
Yes	5 (11%)	2 (4%)	3 (14%)	10 (9%)
Study Completion Status				
Completed 48 Weeks on Randomized Treatment	32 (71%)	40 (89%)	16 (73%)	88 (79%)
Completed 48 Weeks After Switching to Open-Label FTC/TDF	5 (11%)	2 (4%)	3 (14%)	10 (9%)
Early Discontinuation While on Randomized Treatment	8 (18%)	3 (7%)	3 (14%)	14 (13%)
Early Discontinuation After Switching to Open-Label FTC/TDF	0	0	0	0
Reason for Early Discontinuation				
Lost to Follow-up	0	0	1 (5%)	1 (< 1%)
Investigator's Discretion	2 (4%)	0	0	2 (2%)
Protocol Violation	1 (2%)	1 (2%)	0	2 (2%)
Safety, Tolerability, or Efficacy Reasons	3 (7%)	2 (4%)	1 (5%)	6 (5%)
Withdrew Consent	2 (4%)	0	1 (5%)	3 (3%)

Source: Section 11.1, Table 10; Appendix 14, Listing 9

Demographic and Baseline characteristics (RAT population)

Overall, demographic and baseline characteristics were similar between the treatment groups. The majority of subjects (83.9%) were male and either Asian (53.6%) or white (42.0%), and the mean (SD) age was 51 (10.0) years.

Table 2. Demographic and Baseline characteristics (RAT population)

Characteristic	TDF (N=45)	FTC/TDF (N=45)	ETV (N=22)	Overall (N=112)	P-value[a]
Age (years)					
N	45	45	22	112	0.297
Mean (SD)	53 (8.8)	49 (10.1)	52 (12.0)	51 (10.0)	
Median	52	50	54	52	
Q1, Q3	48, 57	42, 58	47, 58	45, 58	
Min, Max	32, 70	27, 67	27, 70	27, 70	
Race					
Asian	23 (51.1%)	24 (53.3%)	13 (59.1%)	60 (53.6%)	0.830
Black	1 (2.2%)	1 (2.2%)	0	2 (1.8%)	
Other	2 (4.4%)	0	1 (4.5%)	3 (2.7%)	
White	19 (42.2%)	20 (44.4%)	8 (36.4%)	47 (42.0%)	
Ethnicity					
Hispanic/Latino	2 (4.4%)	1 (2.2%)	0	3 (2.7%)	0.862
Non-Hispanic/Latino	39 (86.7%)	39 (86.7%)	21 (95.5%)	99 (88.4%)	
Not Permitted	4 (8.9%)	5 (11.1%)	1 (4.5%)	10 (8.9%)	
Sex					
Female	8 (17.8%)	5 (11.1%)	5 (22.7%)	18 (16.1%)	0.444
Male	37 (82.2%)	40 (88.9%)	17 (77.3%)	94 (83.9%)	
Baseline Weight (kg)					
N	45	45	22	112	0.716
Mean (SD)	78.1 (17.02)	74.4 (15.41)	77.3 (16.64)	76.5 (16.26)	

The mean (SD) baseline HBV DNA level was 5.91 (1.686) log10 copies/ml. Subjects had been positive for HBV for a mean of 12.7 (14.07) years, 63.4% had an ALT value above the ULN at baseline, and the majority were HBeAg– (65.2%).

The median CPT score at baseline was 7 in all groups, and ranged from 5 to 12. Overall, 64.3% of subjects had CPT scores ≥ 7 at baseline, while the remaining 35.7% of subjects had a baseline CPT score < 7. The percentage of subjects with CPT scores ≥ 7 at baseline was highest in the emtricitabine/tenofovir DF group (71.1%) and was 62.2% and 54.5% in the tenofovir DF and entecavir groups, respectively. A total of 96 subjects (38, 40, and 18 in the tenofovir DF, emtricitabine/tenofovir

DF, and entecavir groups, respectively) had CPT scores ≤ 9 at screening, and 16 subjects (7, 5, and 4 subjects, respectively) had CPT scores > 9.

Table 3. Baseline Disease Characteristics

Baseline Disease Characteristics	TDF (N=45)	FTC/TDF (N=45)	ETV (N=22)	Overall (N=112)	P-value[a]
Baseline HBV DNA (log_{10} copies/mL)					
N	45	45	22	112	0.877
Mean (SD)	5.82 (1.542)	5.99 (1.753)	5.90 (1.888)	5.91 (1.686)	
Median	5.70	6.28	5.93	5.92	
Q1, Q3	4.88, 6.59	4.51, 7.31	4.22, 7.38	4.56, 7.31	
Min, Max	2.30, 8.74	2.71, 9.34	2.77, 8.40	2.30, 9.34	
Baseline ALT (U/L)					
N	45	45	22	112	0.596
Mean (SD)	60.53 (40.370)	86.78 (93.800)	63.73 (49.074)	71.71 (68.881)	
Median	48.00	54.00	52.00	52.00	
Q1, Q3	31.00, 73.00	34.00, 98.00	41.00, 66.00	33.00, 81.50	
Min, Max	18.00, 202.00	19.00, 521.00	16.00, 235.00	16.00, 521.00	
Baseline ALT as Multiple of ULN					
N	45	45	22	112	0.686
Mean (SD)	1.47 (0.970)	2.05 (2.171)	1.55 (1.126)	1.72 (1.599)	
Median	1.15	1.30	1.26	1.26	
Q1, Q3	0.81, 1.76	0.81, 2.28	1.05, 1.67	0.83, 1.91	
Min, Max	0.47, 4.70	0.44, 12.12	0.37, 5.47	0.37, 12.12	
Baseline ALT above ULN?					
No	18 (40.0%)	18 (40.0%)	5 (22.7%)	41 (36.6%)	0.330
Yes	27 (60.0%)	27 (60.0%)	17 (77.3%)	71 (63.4%)	
Years Positive for HBV					
N	42	40	22	104	0.227
Mean (SD)	13.0 (16.36)	11.4 (12.51)	14.6 (12.31)	12.7 (14.07)	
Median	4.6	7.0	11.6	6.8	
Q1, Q3	1.6, 20.5	3.1, 17.4	4.6, 23.9	2.6, 19.0	
Min, Max	0.1, 49.2	0.2, 65.5	1.1, 43.9	0.1, 65.5	
Baseline HBsAg[b]					
Positive, Confirmed	45 (100.0%)	45 (100.0%)	22 (100.0%)	112 (100.0%)	
Baseline HBeAg[b]					
Negative	31 (68.9%)	27 (60.0%)	15 (68.2%)	73 (65.2%)	0.661
Positive	14 (31.1%)	18 (40.0%)	7 (31.8%)	39 (34.8%)	
Previous Lamivudine Experience					
No	22 (48.9%)	21 (46.7%)	11 (50.0%)	54 (48.2%)	1.000
Yes	23 (51.1%)	24 (53.3%)	11 (50.0%)	58 (51.8%)	
Previous Lamivudine Experience ≥ 6 months					
No	26 (57.8%)	28 (62.2%)	14 (63.6%)	68 (60.7%)	0.906
Yes	19 (42.2%)	17 (37.8%)	8 (36.4%)	44 (39.3%)	
Previous Interferon Experience					
No	42 (93.3%)	45 (100.0%)	22 (100.0%)	109 (97.3%)	0.222
Yes	3 (6.7%)	0	0	3 (2.7%)	
Previous Adefovir Experience					
No	36 (80.0%)	35 (77.8%)	17 (77.3%)	88 (78.6%)	1.000
Yes	9 (20.0%)	10 (22.2%)	5 (22.7%)	24 (21.4%)	
Baseline CPT Score					
N	45	45	22	112	0.377
Mean (SD)	7.2 (1.94)	7.6 (1.87)	7.1 (1.85)	7.4 (1.89)	
Median	7.0	7.0	7.0	7.0	
Q1, Q3	6.0, 8.0	6.0, 9.0	6.0, 8.0	6.0, 9.0	
Min, Max	5.0, 12.0	5.0, 12.0	5.0, 11.0	5.0, 12.0	
Baseline CPT Category					
< 7	17 (37.8%)	13 (28.9%)	10 (45.5%)	40 (35.7%)	0.396
≥ 7	28 (62.2%)	32 (71.1%)	12 (54.5%)	72 (64.3%)	
Baseline MELD Score					
N	45	45	22	112	0.133
Mean (SD)	11.8 (4.42)	13.8 (5.49)	11.8 (4.01)	12.6 (4.87)	
Median	11.0	13.0	10.5	11.0	
Q1, Q3	9.0, 14.0	10.0, 17.0	9.0, 13.0	9.0, 15.0	
Min, Max	6.0, 27.0	6.0, 26.0	7.0, 20.0	6.0, 27.0	

Genotype at Baseline					
A	8 (17.8%)	8 (17.8%)	4 (18.2%)	20 (17.9%)	0.859
B	9 (20.0%)	13 (28.9%)	6 (27.3%)	28 (25.0%)	
C	10 (22.2%)	11 (24.4%)	5 (22.7%)	26 (23.2%)	
D	15 (33.3%)	10 (22.2%)	4 (18.2%)	29 (25.9%)	
E	1 (2.2%)	0	0	1 (0.9%)	
F	0	1 (2.2%)	1 (4.5%)	2 (1.8%)	
G	0	1 (2.2%)	0	1 (0.9%)	
Unable to Genotype	2 (4.4%)	1 (2.2%)	2 (9.1%)	5 (4.5%)	

a P-values for categorical data from an Exact test. P-values for continuous data from a Kruskal-Wallis test.
b Borderline values considered as positive for all serology markers.

Discussion on Design, Methods & Demographics

So far only two drugs have been granted an indication for the treatment of decompensated patients: lamivudine and adefovir. These are not parts of the comparator arms.

Due to their potent virologic activity and high genetic barrier, tenofovir and entecavir nowadays supersede existing therapeutic options. Despite not being granted any MA for the treatment of decompensated patients, they are already recommended in the therapeutic guidelines whereas lamivudine and adefovir are nowadays regarded as inadequate options due to their lower genetic barrier and the pejorative impact of resistance in this particularly vulnerable population.

By using the most potent drugs, the risk of suboptimal virological efficacy in this population was limited, specially taking into account that lamivudine and adefovir had already shown efficacy in this vulnerable population.

Therefore this study is mainly aimed at responding to the need for safety data as underlined in the therapeutic guidelines for safely using tenofovir in decompensated patients. The primary endpoint then relies on safety. This study is to be regarded as "confirmatory" for the efficacy.

The FTC/TDF arm is important to provide data on the use of FTC/TDF in the treatment of HBV infection, considering the wide off label use (supported by the therapeutic guidelines) of FTC/TDF in HIV-HBV co-infected patients whereas the current indication of FTC/TDF is so far confined to the treatment of the HIV infection.

Although a 2-arms study (comparing TDF and ETV) would have allowed larger sample size and drawing more robust conclusion, it is acknowledged that the use of bi-therapy in patients with decompensated CHB is of interest, since viral breakthrough and emergence of resistance can be potentially life threatening in this vulnerable population of patients with decompensated liver disease.

The primary endpoint of this study relies on safety. Efficacy is part of secondary endpoints. This approach can be regarded as reasonable. There is no predefined hypothesis on this safety endpoint. This is a descriptive analysis, the MAH only indicate what would be the precision of the estimation depending of the value of the point estimate. However, it is acknowledged that a much larger sample size would have been required whatever the tested hypothesis which would have seriously challenge the feasibility of the study given the targeted population.

The MAH could have predetermined the sample size to be targeted to achieve adequate precision of the estimation. The MAH has indeed taken the risk of being unable to interpret the efficacy results (by not taking into account variability in the treatment response and by not predefining adequate estimation for the response rate) whereas this study was to be regarded as confirmatory for efficacy.

A relatively high rate of screening failure was reported in this study. 71-73% of patients completed 48 weeks on randomised treatment in TDF and ETV arms whereas they were 89% in the FTC/TDF arm. A similar proportion of patients had switched to open-label FTC/TDF in the TDF and ETV arms (11-14%). The proportion of patients who prematurely discontinued study was also nearly comparable in the TDF

and ETV arms (18% and 14% respectively). It is worth noting that fewer patients prematurely withdrew from the study (7%) or switched to open-label FTC/TDF (4%) in the FTC/TDF arm.

A total of 6 subjects (TDF: 3, FTC/TDF: 2, ETV: 1) discontinued study prematurely due to safety reason, 4 of these subjects died. Two additional subjects had AEs leading to discontinuation and died but other primary reason for discontinuation was reported by the investigators. A total of 6 patients died in this study (2 in each arm). All deaths were considered to be the result of disease progression and/or sepsis and were considered as unrelated to study drugs. Overall, the mortality rate reported at week 48 in this small study (4-9%) appears lower than the rate reported in previous study in decompensated population, and might reflect to some extent the exclusion of patients with very advanced disease (variceal bleeding, grade 3-4 hepatic encephalopathy…).

The study population was a mix population of HBeAg+ and HBeAg- patients; 65% of those were HBeAg-. When compared to the baseline characteristics of patients with compensated CHB in pivotal Viread studies, patients were older (as expected for a population of patients with advanced disease). More patients were Asian and baseline HBV DNA was 1-3 log lower in this study (patients being under treatment at the time of inclusion).

About half of the population had previous lamivudine experience and 20% had previous adefovir experience in this study. Imbalance in the proportion of patients with CPT score ≥ 7 is observed, with more patients in the FTC/TDF arm having more advanced disease. The population enrolled in this study might be somewhat more representative of an EU population (where fewer patients are expected to be diagnosed at a very late stage of the disease).

1.4. Clinical Efficacy

Except for analyses of ALT normalization, CPT decrease ≥ 2 points, and HBeAg loss and sero-conversion, all analyses were based on the RAT analysis set, consisting of all subjects who were randomised and received at least one dose of study medication.

Table 4. Population Analysis Sets

	TDF	FTC/TDF	ETV
RAT Analysis Set	45	45	22
Biochemically Evaluable Analysis Set	27	27	17
CPT Evaluable Analysis Set	28	32	12
Serologically Evaluable Analysis Set	14	18	7

Secondary efficacy endpoints

Secondary efficacy analyses described in this report include subject data from the first 48 weeks of treatment.

Table 5. Key Efficacy Results at Week 48 (GS-US-174-0108)

	TDF (N = 45)	FTC/TDF (N = 45)	ETV (N = 22)
HBV DNA < 400 copies/mL[a], n/N (%)[b]	31/ 44 (70%)	36/ 41 (88%)	16/ 22 (73%)
95% CI	(57.0%, 83.9%)	(77.8%, 97.8%)	(54.1%, 91.3%)
Mean (SD) Change from Baseline in HBV DNA[a] (log_{10} copies/mL)	–3.30 (1.516)	–3.72 (1.769)	–3.24 (1.919)
Normal ALT[c], n/N (%)[b]	25/ 44 (57%)	31/ 41 (76%)	12/ 22 (55%)
95% CI	(42.2%, 71.5%)	(62.5%, 88.8%)	(33.7%, 75.4%)
Normalized ALT[c], n/N (%)[b]	12/ 26 (46%)	16/ 25 (64%)	7/ 17 (41%)
95% CI	(27.0%, 65.3%)	(45.2%, 82.8%)	(17.8%, 64.6%)
Mean (SD) Change from Baseline in Serum ALT (U/L)	–19 (37.0)	–54 (101.1)	–38 (53.8)
Mean (SD) Change from Baseline in CPT Score	–0.8 (1.54)	–0.9 (1.50)	–1.3 (1.18)
Mean (SD) Change from Baseline in MELD Score	–1.8 (2.48)	–2.3 (4.65)	–2.6 (2.85)
HBeAg Loss[d], n/N (%)[b]	3/ 14 (21%)	4/ 15 (27%)	0/ 7
95% CI	(0.0%, 42.9%)	(4.3%, 49.0%)	(0.0%, 0.0%)
HBeAg Seroconversion[d], n/N (%)[b]	3/ 14 (21%)	2/ 15 (13%)	0/ 7
95% CI	(0.0%, 42.9%)	(0.0%, 30.5%)	(0.0%, 0.0%)
Conserved-site Changes in HBV Polymerase	2	0	0

a Taqman assay LLQ =169 copies/mL (29 IU/mL); values below LLQ set to 168 copies/mL (28 IU/mL) for quantitative analyses.

b RAT analysis set, NC/S=F. Subjects who underwent liver transplantation are censored from the analysis of secondary efficacy endpoints.

c Normal ALT value defined as ALT value at or below ULN. Normalized ALT defined as ALT value at or below ULN for subjects with baseline ALT above ULN.

d Based on the percentage of RAT subjects with positive HBeAg at baseline

No subjects had HBsAg loss or seroconversion to anti-HBs (excluding subjects who underwent liver transplantation) through Week 48 of the study.

CPT Scores

There were no large differences overall among the treatment groups in the proportion of subjects with a 2-point decrease in CPT score during the first 48 weeks of the study, particularly considering the variability of the results (wide 95% CIs). At Week 48, the percentage of subjects with a 2-point decrease from baseline in CPT was 25.9%, 48.0%, and 41.7% in the tenofovir DF, emtricitabine/tenofovir DF, and entecavir groups, respectively.

Time to Death or HBV Recurrence Following Transplantation

Because of the small number of events, time-to-event analyses were not conducted.

Six subjects died through Week 48, including 2 subjects in each treatment group. All 6 deaths were considered unrelated to study medication. The immediate causes of death and time to death were the following:

• Tenofovir DF group: hepatic encephalopathy and hepatorenal syndrome (Day 12); end stage liver disease (Day 64)

• Emtricitabine/tenofovir DF group: liver failure secondary to cirrhosis and sepsis from bacterial peritonitis/bowel perforation (Day 12); hepatic liver failure (Day 119)

• Entecavir group: disease deterioration/exacerbation of hepatitis B (Day 29); septic shock (Day 122)

With the possible exception of an early flare precipitating decompensation in one subject in the entecavir group, no relationship to treatment or time to death is evident from these data.

Six subjects, all on tenofovir-containing regimens, received liver transplants during the first 48 weeks of the study. The transplant was pre-planned in 5 of the 6 subjects, and the study medication was interrupted. One subject (Subject 4002) received a liver transplant following hospitalization for ascites.

Resistance analysis

Patients with Resistance at baseline

Among the subjects randomised to the tenofovir DF group, 6 subjects (all with previous lamivudine experience only) had lamivudine-associated resistance mutations (rtM204V/I ± rtL180M), 1 subject (with previous lamivudine and adefovir dipivoxil experience) had a mutation associated with adefovir resistance (rtA181V), and 2 subjects (with previous lamivudine and adefovir dipivoxil experience) had mutations associated with resistance to both drugs. No resistance mutations were detected at baseline among the 4 subjects with only adefovir dipivoxil experience.

Table 6. Percentage of Treatment-Experienced Subjects with Resistance Mutations at Baseline (GS-US-174-0108)

Treatment-Experienced Subjects with Baseline Resistance Mutations[a], n/N (%)	TDF (N=45)	FTC/TDF[b] (N=45)	ETV (N=22)
Subjects with ADV Experience	0/4 (0%)	0/2 (0%)	0/0 (0%)
Subjects with LAM Experience	6/18 (33.3%)[c]	5/16 (31.3%)[c]	3/6 (50.0%)
Subjects with ADV and LAM Experience	3/5 (60.0%)	5/8 (62.5%)	0/5 (0.0%)[c]

a Resistance mutations included rtM204I/V ± rtL180M (LAM resistance) and rtA181V (ADV resistance).
b One treatment-naïve subject in the FTC/TDF group had an ADV resistance mutation at baseline.
c Genotyping at baseline was unsuccessful for 1 subject each in the TDF and FTC/TDF groups and 2 in the ETV group.

The majority of the subjects who entered the study with mutations associated with either lamivudine or adefovir were shown to have HBV DNA levels < 400 copies/ml at their last on-tenofovir DF monotherapy time point.

Year 1 Resistance surveillance

Serum samples for 13 viremic subjects out of the 112 subjects in the study (12% of the total RAT population) were evaluated as a component of the Year 1 resistance surveillance for this study.

Overall, 8 patients randomised to the TDF arm were included in Year 1 Resistance analysis. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/ml. Among them, 2 had conserved-site change (4.4%).

No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.

Discussion on Efficacy

An undetectable viral load (LOQ 400 copies/ml) was achieved for around 70% of patients receiving the monotherapy with either tenofovir or entecavir. A marked trend (>15%) for higher response rate was observed in the FTC/TDF arm (which might even be underestimated, given the trend for more severe patients at baseline in the combination arm). This virological difference is parallel with the proportion of patients with ALT normalization (around 20%).

However, this study was not designed (powered) to compare Viread and Truvada efficacy which precludes any conclusion in this field. Even though the data are suggestive of a superiority of Truvada over Viread the data derived from this study are too limited to enable reliable comparison between Viread and Truvada. The MAH was further requested to address this issue and commited to discuss the possibility of demonstrating the superiority of Truvada versus Viread in the therapeutic management of patients with decompensated liver disease. (see letter of undertaking).

Following CHMP request the MAH provided results according to the HBe Ag positive/negative status and viral genotype (A-D). These reanalysis further substantiate the efficacy of Viread and Truvada whatever the HBeAg status or viral genotype.

Of note, 6 subjects received liver transplants (1 in TDF arm, 4 in FTC/TDF arm and 1 in open-label FTC/TDF). None experienced recurrence (defined as HBV DNA > 400 copies/ml or confirmed HBsAg+ result), however, follow-up is limited at this stage.

Of note, no HBeAg seroconversion is observed in the entecavir arm. However, the sample size was very limited and only 7 patients were HBeAg positive.

In addition to the virological and biochemical endpoints, a difference in favour of FTC/TDF is also observed on the change in CPT score from baseline.

The change in CPT score from baseline was around 1 point at week 48 in each treatment arms and subjects with a 2-point decrease from baseline in CPT was 25.9%, 48.0%, and 41.7% in the tenofovir DF, emtricitabine/tenofovir DF, and entecavir groups, respectively. The difference across the groups was not statistically significant. It is not know why tenofovir performed less well than entecavir at this endpoint.

Regarding the Time to Death or HBV Recurrence Following Transplantation analysis, the trend in favour of the FTC/TDF arm, as previously discussed, is even more noticeable in patients with viral strains harbouring mutation of resistance to lamivudine.

Overall, 8 patients randomised to the TDF arm were included in Year 1 Resistance analysis. Among them, 2 had conserved-site change (4.4%). In comparison, 2% of patients treated with TDF had conserved site change at week 48 or 96 in Viread clinical studies (including 690 patients mostly naïve but also some LAM or ADV-experienced patients). Phenotypic evaluation of conserved site change showed that mutation that emerged under TDF (S85P, V27A) were not associated with phenotypic resistance *in vitro*: replication incompetent for S85P, EC50 almost unchanged (1.3 fold increase) for V27A. Furthermore, phenotypic assessment of the 3 subjects with breakthrough in the absence of conserved-site change (2 in TDF arm, 1 in FTC/TDF arm) showed that viral isolates remained sensitive to TDF or FTC *in vitro*.

Overall, similarly to patients with compensated CHB, no mutation associated with resistance to TDF was identified at week 48 in patients with decompensated disease in this study.

1.5. Clinical Safety

Patient exposure

The duration of exposure to randomised treatment through week 48 is presented in the table below:

Table 7. Duration of Exposure to Randomised Treatment through Week 48 (RAT Analysis Set, GS-US-174-0108)

Exposure[a] Data	DB TDF (N=45)	DB FTC/TDF (N=45)	DB ETV (N=22)	All TDF[b] (DB + OL) (N=93)
Days of Exposure				
N	45	45	22	93
Mean (SD)	302.4 (109.88)	336.9 (83.75)	303.2 (111.40)	326.9 (95.38)
Median	364.0	364.0	364.0	364.0
Q1, Q3	279.0, 364.0	364.0, 364.0	277.0, 364.0	364.0, 364.0
Min, Max	10.0, 364.0	2.0, 364.0	15.0, 364.0	2.0, 364.0
Number of Subjects by Weeks of Exposure:				
Baseline [1 Day]	45 (100.0%)	45 (100.0%)	22 (100.0%)	93 (100.0%)
24 Weeks [155–182 Days]	39 (86.7%)	42 (93.3%)	19 (86.4%)	83 (89.2%)
48 Weeks [323–364 Days]	32 (71.1%)	40 (88.9%)	16 (72.7%)	80 (86.0%)

Five patients in the TDF group, 2 patients in the FTC/TDF group and 3 patients in the ETV group switched to open-label FTC/TDF exposure prior to week 48. The mean open-label exposure by randomised treatment arm was 195.2, 99.5 and 206 days in the TDF, FTC/TDF and ETV arms respectively.

Co-primary safety endpoint:

The co-primary endpoints are the percentage of subjects with tolerability failure, defined as permanent discontinuation of the study drug due to a treatment-emergent AE (including temporary discontinuations if the study drug is not restarted), and the percentage of subjects with confirmed (two consecutive) ≥ 0.5 mg/dL increases from baseline in serum creatinine or confirmed serum phosphorus values < 2.0 mg/dL.

Table 8. The results for the co-primary safety endpoint are summarised in the table below:

% patient with	**TDF (N=45)**	**FTC/TDF (N=45)**	**TDF or FTC/TDF (N=90)**	**ETV (N=22)**	**P-value [c] TDF and FTC/TDF combined versus ETV**
Tolerability failure[a]	3 (6.7%)	2 (4.4%)	5 (5.6%)	2 (9.1%)	0.622
Confirmed[b] increase in creatinine of ≥ 0.5 mg/dL from baseline OR confirmed serum phosphorus values < 2.0 mg/dL.	4 (8.9%)	3 (6.7%)	7 (7.8%)	1 (4.5%)	1.000

a A tolerability failure is defined as permanent discontinuation of study drug due to a treatment-emergent AE. Any subject who temporarily discontinued study due to an AE but did not restart study drug was considered a tolerability failure.
b A confirmed value is defined as a value recorded on two consecutive visits, or the last value on drug, post-baseline
c P-values are from a two-sided Fisher exact test

Tolerability failure

The narratives for the seven patients who met the criteria for tolerability failure (including five cases with fatal outcome) are summarised thereafter.

TDF group

Subject 2007 (DEATH) concerned a 54-year-old Asian female with a CPT score of 11 at baseline. She had been treated with lamivudine for 3 years, which was discontinued due to virologic failure, liver cirrhosis, and gastrointestinal bleeding secondary to bleeding fundal varices. The patient's hepatic function had worsened before starting study medication. During the two first months after randomization in the TDF arm, liver function tests showed aggravation of hepatic decompensation (increased disorientation, elevated liver function tests, pulmonary congestion, signs of acute renal failure attributed to sepsis, along with decreases in hematologic parameters, electrolyte abnormalities, and metabolic acidosis. Study drug was discontinued, and the subject was taken off life support and died from end-stage liver disease on Day 64. AEs listed as resulting in study drug discontinuation were renal failure, ascites, coagulopathy, sepsis, urinary tract infection, contusion, metabolic acidosis, respiratory failure, and hypotension.

Subject 3003: a 48-year-old male patient developed acute renal failure as a complication 5 days following liver transplantation. According to the narrative, "the patient was discontinued from the study so that his HBV medications could be titrated relative to renal function". The events resolved one month later

Subject 3005 (DEATH) was a 63-year-old white female with a CPT score of 11 at baseline. Study drug (TDF) was interrupted because of AEs of hepatic encephalopathy and hepatorenal syndrome. Study drug was never resumed. The subject died 2 days after the last dose of study drug. The investigator noted that since screening for the study, the subject's encephalopathy had worsened and increased rapidly.

FTC/TDF group

Subject 1052 (DEATH) concerned a 48-year-old man with a medical history of alcoholic cirrhosis and a CPT score of 10 at baseline. On Day 5 of FTC/TDF study therapy, he developed ascites and fever. The subject's sister reported that the subject was started on another type of anti-hepatitis B medication. In the following days, the patient's medical conditions were aggravated and the subject died on Day 11 of liver failure secondary to alcoholic liver cirrhosis and sepsis from spontaneous bacterial peritonitis or bowel perforation.

Subject 2034: This subject in the FTC/TDF group discontinued on Day 2 because of a Grade 2 allergic reaction with severe skin itching, headache, runny rose and insomnia that occurred on the first day of dosing. These symptoms were responsive to corticoid and study drug discontinuation

ETV group

Subject 3002 (DEATH) was 55-year-old Asian male with a CPT score of 11 at baseline, and a history of cirrhosis, decompensated liver disease within the past 6 months and ascites. During the first two weeks after starting study medication, the patient was hospitalised twice since his medical condition aggravated. He had jaundice and deshydrated. Then, he developed hepatorenal syndrome and hepatic encephalopathy. Study medications were discontinued and the subject was put on open label entacavir due to his renal impairment. His condition continues to deteriorate and the patient died due to hepatic liver cirrhosis contributed by acute renal failure.

Subject 4005 (DEATH) described a 53-year-old female patient with a CPT score of 9 at baseline. The patient died due to septic shock secondary to a necrotizing fasciitis with infection by Vibrio vulnificus

after being bitten by a fish. AEs leading to discontinuation were wound infection, melena, necrotizing fasciitis and septic shock. All were considered unrelated to study drug.

No subjects who switched to open-label emtricitabine/tenofovir DF had tolerability failure through Week 48.

Confirmed changes in Serum Creatinine or Phosphorus:

The table below summarizes the percentage of patients with confirmed changes in renal parameters across treatment groups:

Table 9. Percentage of Subjects with Confirmed Changes in Renal Parameters (RAT Analysis Set, GS-US-174-0108)

Subjects with Confirmed[a] Changes in Renal Parameters[b], n (%)	TDF (N=45)	FTC/TDF (N=45)	TDF or FTC/TDF (N=90)	ETV (N=22)	P-value[c] TDF and FTC/ TDF Combined vs. ETV
Confirmed Increase in Creatinine of ≥ 0.5 mg/dL from Baseline OR Confirmed Phosphorus of < 2.0 mg/dL	4 (8.9%)	3 (6.7%)	7 (7.8%)	1 (4.5%)	1.000
Confirmed Increase in Creatinine of ≥ 0.5 mg/dL from Baseline	4 (8.9%)	1 (2.2%)	5 (5.6%)	1 (4.5%)	1.000
Confirmed Phosphorus of < 2.0 mg/dL	1 (2.2%)	2 (4.4%)	3 (3.3%)	0	1.000
Confirmed Increase in Creatinine of ≥ 0.5 mg/dL from Baseline AND Confirmed Phosphorus of < 2.0 mg/dL	1 (2.2%)	0	1 (1.1%)	0	1.000
Confirmed Creatinine Clearance of < 50 mL/min	4 (8.9%)	3 (6.7%)	7 (7.8%)	2 (9.1%)	1.000

Six subjects (4 in TDF arm, 1 in FTC/TDF arm and 1 in ETV arm) had confirmed increases in serum creatinine. All six also had confirmed creatinine clearance of < 50 ml/min.

Among those, one TDF-treated patient had confirmed changes in both creatinine and phosphorus, as well as confirmed calculated creatinine clearance < 50 ml/min, and was discontinued at the investigator's discretion due to overall poor health and noncompliance with ongoing SAEs of hepatic encephalopathy and bacterial peritonitis.

Two additional FTC/TDF-treated subjects had confirmed serum phosphorus values < 2mg/dl.

One subject who switched from double-blind TDF to open-label FTC/TDF at Week 8 had confirmed increases in serum creatinine (Week 24) and confirmed creatinine clearance < 50 ml/min at Weeks 16–24. None of the other subjects with confirmed changes in renal parameters had switched to open-label FTC/TDF.

The percentage of subjects with confirmed changes in renal parameters was also analysed by baseline CPT stratum (≤ 9 or > 9). Most of the confirmed increases in serum creatinine and the confirmed creatinine clearance values < 50 ml/min occurred in subjects with high baseline CPT scores (all but one subject in the tenofovir DF group and one subject in the entecavir group were in the CPT > 9 stratum). All events of confirmed serum phosphorus < 2.0 mg/dl occurred in subjects with low baseline CPT scores (≤ 9).

Adverse events

The table below summarizes adverse events through week 48 in each treatment arms and in the FTC/TDF open label phase.

Table 10. Overall Summary of Adverse Events through Week 48 (RAT Analysis Set, GS-US-174-0108)

Adverse Event Category, n (%)[a]	DB TDF (N=45)	DB FTC/TDF (N=45)	DB ETV (N=22)	Total OL FTC/TDF (N=10)
Any AE	37 (82.2%)	42 (93.3%)	17 (77.3%)	4 (40.0%)
Study Drug-Related AE	8 (17.8%)	7 (15.6%)	2 (9.1%)	2 (20.0%)
Grade 3 or 4 AE	14 (31.1%)	9 (20.0%)	5 (22.7%)	1 (10.0%)
Grade 3 or 4 Study Drug-Related AE	1 (2.2%)	0	0	1 (10.0%)
Grade 2, 3, or 4 AE	23 (51.1%)	23 (51.1%)	8 (36.4%)	4 (40.0%)
Grade 2, 3, or 4 Study Drug-Related AE	3 (6.7%)	5 (11.1%)	1 (4.5%)	2 (20.0%)
AE That Caused Permanent Discontinuation From Study Drug or Death	3 (6.7%)	3 (6.7%)	2 (9.1%)	0
AE That Caused Permanent Discontinuation From Study Drug but Who Did Not Die	1 (2.2%)	1 (2.2%)	0	0
Any SAE	11 (24.4%)	19 (42.2%)	5 (22.7%)	2 (20.0%)
Study Drug-Related SAE	1 (2.2%)	1 (2.2%)	0	0
Death	2 (4.4%)	2 (4.4%)	2 (9.1%)	0

DB = double blind; OL = open label
a Subjects are counted once only for each category at the maximum severity (based on the GSI-modified NIAID common severity grading scale).

The table below displays adverse events through week 48 according to CPT stratum

Table 11. Overall Summary of Adverse Events through Week 48 by CPT Stratum (RAT Analysis Set, GS-US-174-0108)

	Baseline CPT ≤ 9			Baseline CPT > 9		
Adverse Event Category, n (%)[a]	TDF (N=39)	FTC/TDF (N=36)	ETV (N=19)	TDF (N=6)	FTC/TDF (N=9)	ETV (N=3)
Any AE	31 (79.5%)	33 (91.7%)	15 (78.9%)	6 (100.0%)	9 (100.0%)	2 (66.7%)
Study Drug-Related AE	8 (20.5%)	6 (16.7%)	3 (15.8%)	0	1 (11.1%)	0
Grade 3 or 4 AE	10 (25.6%)	5 (13.9%)	5 (26.3%)	4 (66.7%)	4 (44.4%)	1 (33.3%)
Grade 3 or 4 Study Drug-Related AE	1 (2.6%)	0	1 (5.3%)	0	0	0
Grade 2, 3, or 4 Adverse Event	18 (46.2%)	15 (41.7%)	7 (36.8%)	6 (100.0%)	8 (88.9%)	1 (33.3%)
Grade 2, 3, or 4 Study Drug-Related AE	4 (10.3%)	4 (11.1%)	2 (10.5%)	0	1 (11.1%)	0
AE That Caused Permanent Discontinuation From Study Drug	0	1 (2.8%)	1 (5.3%)	2 (33.3%)	1 (11.1%)	1 (33.3%)
Any SAE	9 (23.1%)	11 (30.6%)	4 (21.1%)	4 (66.7%)	8 (88.9%)	1 (33.3%)
Study Drug-Related SAE	1 (2.6%)	1 (2.8%)	0	0	0	0
Death	0	0	1 (5.3%)	2 (33.3%)	2 (22.2%)	1 (33.3%)

Most frequent AEs

The most frequently reported AEs were:

In TDF group: nausea (20%), insomnia (17.8%), ascites (15,6%), oedema peripheral (15.6%), prurit (15.6%), abdominal pain, abdominal pain upper, dizziness, vomiting (all at 13.3%), pyrexia (11.1%)

In the FTC/TDF group: anaemia (13.3%), pruritus (13.3%), abdominal pain upper (13.3%) and pyrexia (11.1%)

In the ETV group: diarrhoea (22.7%), ascites (22.7%) oedema peripheral (18.2%), cough (18.4%), headache (18.4%)

In the open label FTC/TDF: no AE preferred term was reported in more than 1 subject.

Drug-related AEs:

In TDF group: 8 patients (17.8%) experienced 15 drug-related AES: nausea (n=4) and rash (n=2). Other drug-related AEs were reported in only subject each and included pruritus, abdominal distension,

abdominal pain, blood CPK increased, blood amylase increased, lipase increased, asthenia, myalgia and dizziness.

In the FTC/TDF group: 7 patients (15.6%) experienced 11 drug-related AEs: rash (n=2), blood CPK increased (n=2). Other drug-related AEs were reported in only subject each and included pruritus, nausea, vomiting, glucose urine present, hypersensitivity, hyperamylasemia and gynecomastia

In the ETV group: 2 patients (9.1%) experienced one drug-related AEs each: rash and asthenia

In the OL FTC/TDF: there were two patients (20.0%) who experienced 4 AEs : rash, rash pruritic and diarrhoea. Moreover, one patient in the ETV group had an AE of Grade 3 psoriasis during open-label treatment with FTC/TDF that was considered related to study drug with onset two months following switch and was unresolved at the time of the Week 48 visit.

Deaths

There were 6 deaths occurring through Week 48 of the study and within 30 days of the last dose of study drug, including 2 subjects in each treatment group. All had CPT>10 at baseline.

Five of them met the criteria of tolerability failure and are previously described in the corresponding section (see above for futher details). In the TDF arm, two patients (2007 and 3005) died from progression of liver disease. In the FTC/TDF arm, one patient (1052) died due to complications of underlying liver disease with sepsis and bacterial peritonitis. In the ETV arm, one patient (3002) died due to hepatic liver cirrhosis contributed by acute renal failure. The remaining ETV-treated subject died from complications of necrotizing fasciitis (4005).

The sixth fatal case (subject 3010) concerned a 36-year-old male patient who died from liver failure, hepatic encephalopathy and hepatorenal syndrome while receiving FTC/TDF therapy. This patient did not meet the criteria for tolerability failure, because study drug was not permanently discontinued (interruption for 4 days), and the subject was receiving study drug (FTC/TDF) at the time of death. The investigator assessed that AEs resulting in death were related to study disease.

One additional subject (Subject 1042) died 11 weeks after discontinuation of study drug treatment (TDF) at week 32. None of the AEs for this subject (worsening of ascites, hernia inguinalis incarcerated, decreased creatinine clearance) were considered by the investigator as resulting in permanent discontinuation. The primary reason for discontinuation on the study termination page is investigator's discretion due to patient's overall poor health and noncompliance (53.82% adherence overall).

Furthermore, seven additional deaths (3 in the TDF arms, 3 in the FTC/TDF arm and one in the ETV arm) have occurred in this study after the Week 48 visit.

TDF arm:

Subject 1010: the death certificate of this 49-year-old male patient receiving TDF therapy for 2.5 years listed the immediate cause of death as status epilepticus with liver failure as the underlying cause and hyperammonaemia as leading up to the cause of death. Gastrointestinal bleeding was also a significant condition contributing to the subject's death.

Subject 1029 this 49-year-old male patient developed hepatocellular carcinoma approximately 11 months after commencing TDF. Eight months later, he died due to spontaneous bacterial peritonitis with septic shock and hepatoma as a consequence of HCC.

Subject 2010 (67-year-old male patient) had a Child-Pugh score increase $\geq$ 2, gastrointestinal bleeding and HCC approximately two years after commencing study drug.

FTC/TDF arm:

Subject 1016 died from completed suicide (it was noted that the patient had lost his job and was worried about his health)

Subject 1034: this 39-year-old male patient with high medical history died du to septic shock with suspected esophageal variceal bleeding and suspected necrotizing fasciitis.

Subject 1036: this 54-year-old male patient died 13 months after commencing study drug due to cardiovascular collapse. No autopsy was performed. No additional information was provided.

ETV arm:

Subject 2020: this 68-year-old male patient experienced 15 months after commencing study drug right middle cerebral artery infarction and basal ganglion haemorrhage. He died in the following days.

Serious adverse events

SAEs were reported in 24.4% (n=11), 42.2% (n=19), and 22.7% (n=5) of subjects in the TDF, FTC/TDF, and ETV groups, respectively. Gastrointestinal disorders, infections and infestations, and hepatobiliary disorders were the most frequently reported SAEs, and included ascites in 6 subjects; abdominal pain in 5 subjects; sepsis and chronic hepatic failure in 4 subjects each; bacterial peritonitis and hepatorenal syndrome in 3 subjects each.

SAEs occurred more frequently among subjects with high baseline CPT scores, consistent with the greater severity of disease in these subjects.

Two SAEs (abdominal pain and allergic reaction in 1 subject each) were considered related to study drug (TDF and FTC/TDF).

Discontinuations and Dose Interruptions or Modifications Due To Adverse Events

Two subjects in each treatment groups were discontinued from the study because of AEs. All except the allergic reaction were considered unrelated to study drug. All were tolerability failures and are discussed in the corresponding section.

Adverse events resulting in dose modification or temporary interruption of study drug were reported in 11.1%, 20.0%, and 9.1% of subjects in the TDF, FTC/TDF, and ETV groups, respectively. AEs resulting in interruption or dose modification in more than 1 subject included hepatorenal syndrome and creatinine renal clearance decreased in 3 subjects each (2 in FTC/TDF group and one in TDF group), and abdominal pain, ascites, and esophageal varices hemorrhage in 2 subjects each.

Adverse events of interest

Renal events and renal laboratory parameters

Renal and urinary disorders were reported in 6 subjects randomised in the TDF arm (13.3%), 1 subject in the TDF/FTC arm (2.2%) and 4 subjects in the ETV arm (18.2%). Moreover, two subjects experienced renal and urinary disorders during the FTC/TDF open-label phase (20%). None of these AES were considered related to study drug by the investigator.

Other AEs related to renal function (displayed in other SOCs than renal and urinary disorders) included creatinine renal clearance decreased in 3 subjects (2 subjects in the TDF group and 1 in the FTC/TDF group), and blood creatinine increased in 2 subjects in the FTC/TDF group. None of these events were considered related to study drug by the investigator.

Among TDF-treated patients, one subject had three separate AEs of reduced creatinine clearance (including one which was also an SAE). All three resulted in temporary dose reduction to a once a day schedule (at Week 8 [42 ml/min], Week 16 [31 ml/min; Grade 3], and Week 28 (40 ml/min). This subject was discontinued at the investigator's discretion at Week 32, due to noncompliance.

The mean changes from baseline in serum creatinine and phosphorus at Week 48 were near zero in all three groups. Calculated creatinine clearance decreased slightly in all three groups (mean [SD] change from baseline at Week 48 of −0.7 [9.83], –3.1 [12.08], and −4.3 [14.38] ml/min in the TDF, FTC/TDF, and ETV groups, respectively).

Hepatic events

Hepatobiliary disorders were reported in 8 subjects (17.8%) in the TDF group, 8 (17.8%) in the FTC/TDF group, and 3 subjects (13.6%) in the ETV Group:

The most commonly reported hepatobiliary adverse reactions were chronic hepatic failure in 4 subjects, cholelithiasis, hepatorenal syndrome, and hyperbilirubinemia in 3 subjects each and hepatic function abnormal in 2 subjects.

Other AEs related to hepatic function (displayed in other SOCs than Hepatobiliary disorders) included hepatitis B in 1 subject in the ETV group, who died from disease deterioration/exacerbation of hepatitis, hepatic encephalopathy (4 subjects in the TDF group, 2 subjects in the FTC/TDF DF group, and 1 in the ETV group), hypoalbuminemia (2 subjects in the TDF group), and hepatocellular carcinoma (3 subjects in the TDF group and 1 subject each in the FTC/TDF and ETV groups, i.e 4.4% in TDF-containing regimens and 4.5% in the ETV arm).

None of these AEs were considered related to study drug by the investigator.

Liver transplants

Six subjects (4 in the FTC/TDF group and 2 in the TDF group) received liver transplants during the study. For 5 of the 6 subjects, the transplant was preplanned, and study drug was interrupted. For one subject in the TDF arm (Subject 4002), the transplant was not preplanned and the study drug was not interrupted. Except for one subject, the other subjects remained on study through Week 48.

On-treatment hepatic exacerbations:

Table 12. Incidence of On-Treatment Hepatic Exacerbations through Week 48 (GS-US-174-0108)

	DB TDF (N=45)	DB FTC/TDF (N=45)	DB ETV (N=22)	Total OL FTC/TDF (N=10)	All TDF[a] (DB + OL) (N=93)
Subjects With a Hepatic Exacerbation[b], n (%)	1 (2.2%)	2 (4.4%)	1 (4.5%)	0	3 (3.2%)

DB = double blind; OL = open label
a The All TDF (DB + OL) column refers to subjects receiving a treatment containing TDF (all double-blind TDF, FTC/TDF, or open-label FTC/TDF).
b On-treatment hepatic exacerbation/flare defined as (1) elevation of ALT > 2 × baseline and > 10 × ULN or (2) confirmed abnormal laboratory parameters suggestive of worsening hepatic function (abnormal bilirubin ≥ 2 mg/dL above baseline, abnormal PT ≥ 2 sec above baseline, INR ≥ 0.5 over baseline, abnormal albumin ≥ 1 g/dL decrease from baseline, or elevated serum lactate levels > 2 × ULN) along with any confirmed ALT elevation (i.e., 1-grade shift or 2 × previous value).

Bone events

Bone events (fracture, osteoporosis, osteopenia and osteoarthritis) were reported in 2 patients in the TDF arm (4.4%), 2 patients in the FTC/TDF arm (4.4%) and 1 patient in the ETV arm (4.5%). No bone events occurred during the FTC/TDF open-label phase.

Two patients experienced bone fractures during the course of the study:

One patient (subject 2027 in the TDF arm) experienced facial bones fracture, radius fracture, and wrist fractures (all SAEs) that were due to trauma (resulting from a fall).

Subject 1022 (in the TDF/FTC arm), who had a mild foot fracture at Week 21 had Grade 1 elevated alkaline phosphatase at screening.

According to the MAH, no other abnormalities in calcium, phosphorus, alkaline phosphatase, or renal laboratory parameters was reported in these patients.

Other AEs related to bone included osteoarthritis in 2 subjects, bone pain in 1 subject, osteopenia in 1 subject, and hyperphosphatemia in 1 subject. None of these AEs were considered related to study drug or resulted in dose modification, interruption, or discontinuation of treatment.

Laboratory findings

Table 13. Grade 3 and 4 Treatment-Emergent Laboratory Abnormalities Occurring through Week 48 (RAT Analysis Set, GS-US-174-0108)

Laboratory Parameter with a Grade 3 or 4 Abnormality[a] (n, %)[b]	DB TDF (N=45)	DB FTC/TDF (N=45)	DB ETV (N=22)	Total OL FTC/TDF (N=10)	All TDF[c] (DB + OL) (N=93)
Any Grade 3 or Grade 4 Laboratory Abnormality	21 (46.7%)	23 (51.1%)	10 (45.5%)	3 (30.0%)	46 (49.5%)
Chemistry					
Hyperglycemia	5 (11.1%)	2 (4.4%)	2 (9.1%)	0	7 (7.5%)
Serum Amylase	2 (4.4%)	3 (6.7%)	0	0	5 (5.4%)
Albumin	1 (2.2%)	2 (4.4%)	1 (4.5%)	0	3 (3.2%)
Creatinine (Rate Blanked)	1 (2.2%)	1 (2.2%)	1 (4.5%)	0	2 (2.2%)
Creatine Kinase	1 (2.2%)	1 (2.2%)	0	0	2 (2.2%)
Serum Lipase	1 (2.2%)	1 (2.2%)	0	0	2 (2.2%)
Hyperuricemia	1 (2.2%)	0	0	0	1 (1.1%)
Electrolytes					
Hyponatremia	1 (2.2%)	1 (2.2%)	1 (4.5%)	0	2 (2.2%)
Hyperkalemia	1 (2.2%)	0	0	0	1 (1.1%)
Hypernatremia	0	1 (2.2%)	0	0	1 (1.1%)
Hypokalemia	0	1 (2.2%)	0	0	1 (1.1%)
Serum Bicarbonate	1 (2.2%)	0	0	0	1 (1.1%)
Hematology					
Platelets	9 (20.0%)	8 (17.8%)	3 (13.6%)	1 (10.0%)	17 (18.3%)
WBC	5 (11.1%)	5 (11.1%)	1 (4.5%)	0	10 (10.8%)
Neutrophils	0	1 (2.2%)	1 (4.5%)	0	1 (1.1%)
Hemoglobin	0	1 (2.2%)	0	0	1 (1.1%)
Liver					
Total Bilirubin	9 (20.0%)	9 (20.0%)	2 (9.1%)	0	18 (19.4%)
AST (SGOT)	5 (11.1%)	4 (8.9%)	0	0	9 (9.7%)
ALT (SGPT)	5 (11.1%)	2 (4.4%)	0	0	7 (7.5%)
Prothrombin Time	4 (8.9%)	3 (6.7%)	0	0	7 (7.5%)
Alkaline Phosphatase	0	0	0	1 (10.0%)	1 (1.1%)
Urinalysis					
Urine Glucose	6 (13.3%)	3 (6.7%)	4 (18.2%)	1 (10.0%)	10 (10.8%)

DB = double blind; OL = open label

a GSI-modified NIAID common severity grading scale

b Subjects are counted only once for each laboratory test at the maximum severity.

c The All TDF (DB + OL) column refers to subjects receiving a treatment containing TDF (all double-blind TDF, FTC/TDF or open-label FTC/TDF).

Discussion on Safety

Final 48 week efficacy and safety from study GS-US-174-0108 were submitted to support the extension of indication of Viread (TDF) in the treatment of CHB patients with decompensated liver disease. A total of 112 subjects were included in this study including 45 each in the TDF and FTC/TDF

groups and 22 in the ETV group. The overall study duration is 168 weeks but only the results of the first 48 weeks of treatment were presented and discussed in this report.

Safety data represented the key elements of the evaluation of this study. Co-primary study endpoints included tolerability failure, defined as permanent discontinuation of study drug due to a treatment-emergent AE and renal laboratory abnormalities defined as confirmed increase in serum creatinine of > 0.5mg/dl from baseline or confirmed serum phosphorus of < 2.0mg/dl.

The 48 week results showed that the proportion of subjects experiencing the co-primary safety endpoints as defined above were similar across treatment groups. No meaningful difference was shown at this time regarding these specific criteria. The majority of reports of tolerability failure and confirmed renal laboratory abnormalities occurred in subjects who had a high CPT score at baseline, which is consistent with the greater severity of the disease in these subjects.

A total of seven cases with fatal outcome were reported in the 48 week CSR, including 3 subjects in the TDF group and 2 subjects of each of the FTC/TDF and ETV treatment groups. In all but one cases, patients had CPT>10 at baseline. All of them were related to the worsening of hepatic decompensation rather than to the study drug. Moreover, seven additional cases were reported after week 48 (3 in each of TDF and FTC/TDF arms and one in ETV arm), leading to a total of 14 deaths during the study. Overall, it seems that more deaths could be attributed to liver failure in the TDF group compared with the two other groups. This observation, probably related to chance is hardly interpretable due to the difference of samples in TDF-containing regimens and ETV regimen and the overall small sample sizes in this study. Specific attention should be paid to this issue in future reports. In the next submission, the MAH should continue to provide narratives of fatal cases and specify in each narrative the patients' baseline CPT score.

Patients with decompensated liver disease are expected to be at higher risk of experiencing renal disorders, which is the key safety profile of TDF. Therefore, special caution has been brought to renal toxicity and renal laboratory parameters reported in this dossier. Compared with safety data from the pivotal studies 0102 and 0103 in CHB patients with compensated liver disease, a slightly higher proportion of subjects with confirmed renal laboratory abnormalities were reported in patients with hepatic decompensation, which was not unexpected in this difficult-to-treat population of patients. Furthermore, no signal towards a higher risk of serious renal events including renal tubulopathy or related events was observed based on the final 48 week results. Globally, in all reported cases, renal impairment was related to the progression of the underlying liver disease rather than a direct toxicity of the drug. No marked difference was seen regarding this issue between the three treatment arms. However data is limited in HBV infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score >9.

Similar conclusions can be drawn for the proportion of subjects experiencing hepatobiliary disorders or other hepatic events. In most of cases, hepatic events were reported as a consequence of worsening of liver failure. A total of six subjects had liver transplant (4 in the FTC/TDF arm and 2 in the TDF group).

As a result of the above concerns a paragraph was included alerting prescribers that there are limited data on the safety and efficacy of tenofovir disoproxil fumarate in HBV infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Regarding bone events, which is also an issue under close scrutiny for Viread, no worrying data appear to be derived from the 48 week safety results of study 0108. However, the analysis of bone events was overall inconclusive due to the low number of subjects in each treatment arms and the short treatment

duration for the time being. Further data regarding this issue are expected in future clinical study reports.

Based on the final 48 week results from study 0108, the safety profile of TDF appears globally acceptable in subjects with liver decompensation and consistent with what expected in this population of patients characterised by a greater severity of the liver disease. No new safety concern has emerged. However, the degree of reassurance on the tenofovir safety that could be derived from this study is significantly hampered by the limited number of patients with CPT score >9, all the more that patients with tolerability failure and renal events are over-represented in this strata.

Further safety data on the final study report are expected to substantiate the safety profile of the drug in patients with decompensated liver disease with longer treatment duration.

1.6. Risk Management

The MAH provided an updated RMP: version 8.1, dated July 2010, which is summarised in table 14 (below).

Table 14. Summary Table of the EU Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risks		
Renal Toxicity	Routine pharmacovigilance activities Clinical studies (GS-99-903, ACTG 5202) Observational studies (EuroSIDA Cohort Study, GS-US-104-0353) Planned nonclinical studies on intestinal phosphate absorption	Routine Risk Minimisation Activities Statements in Section 4.2 of 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 modelling of single-dose pharmacokinetic data in non-HIV 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*

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		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 Viread SmPC: *Co-administration of other medicinal products: Viread should not be administered with any other medicinal products containing tenofovir disoproxil fumarate (Truvada or Atripla).* *Renal function: Renal safety with tenofovir has only been studied to a very limited degree in patients with impaired renal function (CrCl < 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) 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*

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		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 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.* Osteomalacia and myopathy listed in Section 4.8 of Viread SmPC: *Musculoskeletal and connective tissue disorders:* *Not known: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy* *The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not considered to be causally associated with tenofovir disoproxil fumarate therapy in the absence of proximal renal tubulopathy.* Update of labeling as appropriate <u>Additional Risk Minimisation Activities</u> Educational initiatives; Communications via published literature and conference presentations. Update of educational program as appropriate

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risks Continued		
Post-treatment hepatic flares in HBV monoinfected and HIV/HBV coinfected patients	Routine pharmacovigilance activities	Routine Risk Minimisation Activities Statement in Section 4.2 of 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 Viread SmPC: *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.* Statement in Section 4.8 of Viread SmPC: *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	Routine Risk Minimisation Activities Warning in Section 4.4 of 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 events. Rare cases of 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.* Update of labeling as appropriate.
Pancreatitis	Routine pharmacovigilance activities	Routine Risk Minimisation Activities Pancreatitis is listed in Section 4.8 of Viread SmPC: *Gastrointestinal disorders:* *Rare: pancreatitis* There is also a warning in Section 4.4 of the Viread SmPC regarding the risk of pancreatitis associated with the interaction with didanosine (see above). Update of labeling as appropriate.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Lactic acidosis and severe hepatomegaly with steatosis	Routine pharmacovigilance activities	Routine Risk Minimisation Activities Warning in Section 4.4 of Viread SmPC: *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 hyperlactatemia) 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 hyperlactatemia 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.* There is also a warning in Section 4.4 of the Viread SmPC regarding the risk of lactic acidosis associated with the interaction with didanosine (see above). Lactic acidosis is listed in Section 4.8 of Viread SmPC: *Metabolism and nutrition disorders:* *Rare: lactic acidosis* Update of labeling as appropriate.
Lipodystrophy	Routine pharmacovigilance activities	Routine Risk Minimisation Activities Precautionary statements in Section 4.4 of Viread SmPC: *Lipodystrophy (lipoatrophy/lipomatosis): In HIV infected patients, combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy). 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 Viread SmPC: *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).*

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		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-174-0106, GS-US-174-0108, GS-US-174-0121)	Routine Risk Minimisation Activities 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 (ie 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) on tenofovir disoproxil fumarate monotherapy, showed that no mutations associated with tenofovir disoproxil fumarate resistance have developed.* Update of labeling as appropriate.
Tenofovir DF monotherapy in HIV/HBV coinfected patients	Routine pharmacovigilance activities	Routine Risk Minimisation Activities Statement and warning in Section 4.4 of Viread SmPC: *HIV antibody testing should be offered to all HBV infected patients before initiating tenofovir disoproxil fumarate therapy.* *Co-infection with HIV-1 and hepatitis B: Due to the risk of development of HIV resistance, tenofovir disoproxil fumarate should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients.* Update of labeling as appropriate.
Important Missing Information		
Safety in children	Routine pharmacovigilance activities Clinical studies in HIV infected children (GS-US-104-0321, GS-US-104-0352) Clinical study in HBV infected adolescents	Routine Risk Minimisation Activities Statement in Section 4.2 of Viread SmPC: *Paediatric patients: Viread is not recommended for use in children below the age of 18 years due to insufficient data on safety and efficacy* Statement in Section 4.4 of Viread SmPC: *Tenofovir disoproxil fumarate has not been studied in patients under the age of 18.* Update of labeling as appropriate.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	(GS-US-174-0115)	
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 Minimisation Activities Statements in Section 4.6 of Viread SmPC: *Pregnancy* *Tenofovir disoproxil fumarate should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.* *Given that the potential risks to developing human foetuses are unknown, the use of tenofovir disoproxil fumarate in women of childbearing potential must be accompanied by the use of effective contraception.* Update of labeling as appropriate.
Safety of long-term exposure in HBV infected adults with compensated or decompensated liver disease	Routine pharmacovigilance activities Clinical studies (GS-US-174-0102, GS-US-174-0103, GS-US-174-0108)	Routine Risk Minimisation Activities Statements in Section 4.8 of updated Viread SmPC: *Treatment beyond 48 weeks: Continued treatment with tenofovir disoproxil fumarate for 144 weeks, in studies GS-US-174-0102 and GS-US-174-0103, did not reveal any new adverse reactions and no change in the tolerability profile (nature or severity of adverse events).* *Patients with decompensated liver disease: The safety profile of tenofovir disoproxil fumarate in patients with decompensated liver disease was assessed in a double-blind active controlled study (GS-US-174-0108) in which patients received treatment with tenofovir disoproxil fumarate (n = 45) or emtricitabine plus tenofovir disoproxil fumarate (n = 45) or entecavir (n = 22) for 48 weeks.* *In the tenofovir disoproxil fumarate treatment arm, 7% of patients discontinued treatment due to an adverse event; 9% of patients experienced a confirmed increase in serum creatinine of ≥ 0.5 mg/dl or confirmed decrease in serum phosphorus of < 2 mg/dl through week 48; there were no statistically significant differences between the combined tenofovir-containing arms and the entecavir arm. Subjects with a high baseline CPT score were at higher risk of developing serious adverse events.* *Hepatocellular carcinoma was diagnosed in 3 patients in the tenofovir disoproxil fumarate group and two patients in the tenofovir disoproxil fumarate group died while on study.*
Safety in HBV infected patients with decompensated liver disease and CPT score > 9	Routine pharmacovigilance activities Clinical study GS-US-174-0108	Routine Risk Minimisation Activities Statement in Section 4.4 of updated Viread SmPC: *Liver disease:* *There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in HBV infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.*
Safety in patients with renal impairment	Routine pharmacovigilance activities Clinical studies in HBV infected patients including patients with mild to moderate renal impairment (GS-US-174-0108, GS-US-174-0121,	Routine Risk Minimisation Activities See Renal Safety Concern regarding warnings in the Viread SmPC. Update of labeling as appropriate.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	GS-US-203-0107) Planned clinical study in HBV infected patients with moderate to severe renal impairment (GS-US-174-0127)	
Safety in liver transplant recipients infected with HBV	Routine pharmacovigilance activities Clinical study GS-US-203-0107 in HBV infected patients post liver transplantation	Routine Risk Minimisation Activities Statement in Section 4.4 of updated Viread SmPC: *Liver disease: Safety and efficacy data are very limited in liver transplant patients.* Update of labeling as appropriate.
Safety in elderly patients	Routine pharmacovigilance activities	Routine Risk Minimisation Activities Warning in Section 4.4 of Viread SmPC: *Tenofovir disoproxil fumarate has not been studied in patients under the age of 18 or 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 pharmacovigilance activities	Routine Risk Minimisation Activities Statements in Section 4.6 of Viread SmPC: *Lactation* *In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk. Therefore, it is recommended that mothers being treated with tenofovir disoproxil fumarate do not breast-feed their infants.* *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 pharmacovigilance activities	Routine Risk Minimisation Activities Update of labeling as appropriate.

Discussion on the EU RMP

Combined to available resistance data for compensated hepatic patients at week 144, the resistance data for decompensated hepatic patients at 48 weeks are reassuring.

Development of resistance in HBV infected patients remains a potential risk during long term exposure. The CHMP agrees with the proposed modification.

Following CHMP request the RMP was modified concerning missing information as follows: -safety in patients with decompensated liver disease should be kept in the RMP as missing information until long term data is generated and -to include limited safety data in HBV infected patients with decompensated liver disease and CPT score >9 and routine risk minimisation activities.

Considering available clinical data (Study GS-US-174-0108), the safety profile of Viread in HBV patients with decompensated liver disease does not appear markedly different from the safety profile in HBV patients with compensated liver disease.

Consequently the CHMP agrees that the proposed RMP is suitable for the new indication. Moreover current proposed pharmacovigilance plan and minimization activities are deemed sufficient.

At the time final data are available from this study the RMP will need to be further updated and the safety data on decompensated liver disease population needs to be further addressed.

1.7. Changes to the product information

Further to the assessment of the MAH proposals to amend the Product Information and in the light of the assessment of the submitted data, the Product Information was revised as follows:

Summary of Product Characteristics

Section 4.1 "Therapeutic indication"
The indication was revised to include the treatment of chronic hepatitis B in adults with decompensated liver disease. A reference in brackets was included to sections 4.4, 4.8 and 5.1.

The statement where the indication was based was deleted since it was considered misleading given that histological responses were not documented in study GS-US-174-0108 and most patients were treatment-experienced. In addition, the evidence submitted in support of the decompensated indication is quite limited when compared to data which supports compensated liver disease.

Section 4.4 "Special warnings and precautions for use"
A sentence was added to inform prescribers that safety and efficacy data are very limited in liver transplant patients.

This section was further updated following CHMP request to include a warning underlining the limited safety and efficacy data available in patients with decompensated liver disease and with CPT score > 9. These patients may be at higher risk of experimenting serious hepatic or renal adverse reactions and therefore hepatobiliary and renal parameters should be closely monitored in this patient population.

Section 4.8 "Undesirable effects"

This section was updated following CHMP request to include the result of co-primary safety endpoint (i.e the rate of study drug discontinuation in the TDF arm and the proportion of subjects with confirmed changes in renal parameters at week 48). Data concerning death and hepatocellular carcinoma in TDF-treated subjects at 48 weeks were also added to this section.

Section 5.1 "Pharmacodynamic properties"
This section was updated with clinical data in patients with decompensated liver disease at 48 weeks. The description of the outcomes of the decompensated study was tabulated following CHMP request.

Following CHMP request a sentence was included to highlight that the data derived from this study are too limited to draw definitive conclusion on the comparison of tenofovir/emtricitabine versus tenofovir.

This section was further updated with resistant data from this study.

Annex II
The annex II was revised to include the updated version 8.1 of the RMP

2. Overall Conclusion and preliminary benefit risk assessment

The MA of Viread was first granted for the treatment of HIV infection and more recently for the treatment of chronic HBV infection in patients with compensated liver disease. The MAH now applies for an extension of indication for the treatment of patients with chronic HBV infection and decompensated liver disease.

In support to this claim the MAH has submitted a Phase 2, Double-Blind, Multi-centre, randomised Study. This is a three arms study with two monotherapy arms: Tenofovir Disoproxil Fumarate, and Entecavir and a third arm with the fixed dose combination of Emtricitabine Plus Tenofovir Disoproxil Fumarate.

This study is ongoing with a 168 weeks follow-up. The 48 weeks data have been submitted.

Tenofovir and entecavir, due to their potent virologic activity and high genetic barrier, nowadays supersede existing therapeutic options. Despite not being granted any MA for the treatment of decompensated patients, they are already recommended in the therapeutic guidelines.

This study is mainly aimed at responding to the need for safety data for tenofovir in decompensated patients. The primary endpoint then relies on safety. Morever, this study is to be regarded as "confirmatory" for the efficacy as well.

The study comprises two coprimary safety endpoints (subject discontinuations due to tolerability failure and confirmed ≥ 0.5 mg/dL increase in serum creatinine or decrease in serum phosphorus to < 2.0 mg/dL).

As regards the efficacy results an undetectable viral load (LOQ 400 copies/ml) is achieved for around 70% of patients receiving the monotherapy with either tenofovir or entecavir.

A marked trend (>15%) for higher response rate was observed in the FTC/TDF arm (which might even be underestimated, given the trend for more severe patients at baseline in the combination arm). This virological difference is parallel with the proportion of patients with ALT normalization (around 20%). However, this study was not designed to compare Viread and Truvada efficacy. Even though the data are suggestive of a superiority of Truvada over Viread the data derived from this study are too limited to enable reliable comparison between these drugs. The MAH was further requested to address this

issue and committed to discuss the possibility of demonstrating the superiority of Truvada versus Viread in the therapeutic management of patients with decompensated liver disease (see letter of undertaking).

As regards safety results patients with decompensated liver disease are expected to be at higher risk of experiencing renal disorders, which is the key safety aspect profile of TDF. A slightly higher proportion of subjects with confirmed renal laboratory abnormalities were reported in patients with hepatic decompensation. In all reported cases, renal impairment was related to the progression of the underlying liver disease rather than a direct toxicity of the drug. No marked difference was seen regarding this issue between the three treatment arms.

Based on the final 48 week results from study 0108, the safety profile of TDF appears globally acceptable in subjects with liver decompensation and consistent with what expected in this population of patients characterised by a greater severity of the liver disease. The safety profile of Viread in HBV patients with decompensated liver disease does not appear markedly different from the safety profile in HBV patients with compensated liver disease. No new safety concern has emerged.

However, the degree of reassurance on the tenofovir safety that could be derived from this study is hampered by the limited number of patients with CPT score >9. Therefore, the CHMP considered appropriate the update of the SmPC with a warning alerting prescribers that there are limited data on the safety and efficacy of tenofovir disoproxil fumarate in HBV infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Combined to available resistance data for compensated hepatic patients at week 144, the resistance data for decompensated hepatic patients at 48 weeks are reassuring.

The MAH has submitted a RMP. The CHMP considered that development of resistance in HBV infected patients remains a potential risk during long term exposure. The CHMP considered that safety in patients with decompensated liver disease should be kept in the RMP as missing information until long term data is generated. Furthermore, following CHMP request the RMP was modified and limited safety data for in HBV infected patients with decompensated liver disease and CPT score >9 and routine risk minimisation activities was included as missing information in the RMP. The proposed RMP is suitable for the new indication.

Further safety data are expected from this study to substantiate the safety profile of the drug in patients with decompensated liver disease with longer treatment duration.

In conclusion based on the above data on safety and efficacy the CHMP endorsed the extension of indication to include the treatment of chronic hepatitis B in adults with decompensated liver disease.