GILEAD

FINAL STUDY REPORT

Study Title	Multicentre, Non-Interventional, Retrospective, Matched Cohort Study of Patients Monoinfected with Chronic Hepatitis B and with Moderate or Severe Renal Impairment Treated with Viread or Baraclude
Version identifier of the study report	1.0
Date of last version of the final study report	5 March 2018
EU PAS Register No	ENCEPP/SDPP/12897
Active substances	Tenofovir Disoproxil Fumarate ATC Code: J05AF Nucleoside and nucleotide reverse transcriptase inhibitors Entecavir (as monohydrate) ATC Code: J05AF Nucleoside and nucleotide reverse transcriptase inhibitors
Medicinal products	Tenofovir Disoproxil (as Fumarate) [Viread®] Entecavir (monohydrate) [Baraclude®]
Product references	For Viread • EU/1/01/200/001- 003 For Baraclude • EU/1/06/343/001- 007
Study Sponsor	Gilead Sciences Europe Ltd. 2 Roundwood Avenue Stockley Park, Uxbridge, Middlesex UB11 1AF United Kingdom
Joint PASS	No
Research question and objectives	The primary objective of this study was: • To retrospectively evaluate the safety of Viread among chronic hepatitis B patients with moderate or severe renal impairment, focusing on renal events of special interest. The secondary objective of this study was: • To describe the effectiveness of Viread in the treatment of chronic hepatitis B in patients with moderate or severe renal impairment. The tertiary objective of this study was: • To compare safety and effectiveness between Viread and Baraclude among the study arms.
Countries of study	55 centres in the United Kingdom, Germany, France, Italy and Spain
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1. GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
CHB	Chronic Hepatitis B
CrCl	Creatinine Clearance
DNA	Deoxyribose nucleic acid
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B s antibody
HBsAg	Hepatitis B s antigen
HBV	Hepatitis B Virus
HBV DNA	Hepatitis B Virus DNA
HIV	Human immunodeficiency virus
HR	Hazard Ratio
IEC	Independent ethics committee
IPTW	Inverse probability of treatment weighting
IRR	Incidence Rate Ratio
MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple Imputation
MICE	Multiple Imputation by chained equations
NSAID	Non-Steroidal Anti Inflammatory Drug
OR	Odds Ratio
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PRT	Proximal Renal Tubulopathy
PSM	Propensity score matching
PVE	Pharmacovigilance and Epidemiology
RTD	Renal Tubular Dysfunction
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SSR	Special situation report
Analytical dataset / Analysis set	The minimum set of data required to perform the statistical analyses leading to the results of the primary objective(s) of the study

Bias	Systemic error in the design, conduct or analysis of a study that results in a mistaken estimate
Cases	Group of individuals with the condition of interest
Cohort	Group of people characterized by a common experience (e.g., occurrence of a specified disease, exposure to a given medication)
Confounder	Extraneous factor that accounts for a difference in disease frequency between the exposure groups; associated factors serving as surrogates for these factors are also commonly called confounders
Date at which a study commences	Date of the start of data collection
Effect modifier	If an effect measure varies within categories or levels of a variable, that variable is described as an effect-measure modifier
End of data collection	The date on which sites completed data entry
Exposure	Treatment with study drug
External validity	Whether or not the results from the study can be generalized to other populations
Internal validity	Whether or not the study provides an unbiased estimate of what it claims to estimate
Odds ratio	The ratio of the probability that an event will happen to the probability that it will not happen
Outcome	An event (such as disease occurrence or death) that is studied in relation to exposure
Rate	A measure of event occurrence, calculated by dividing the total number of events by the total amount of person-time within an exposure category
Renal Impairment	For the purposes of this study moderate to severe renal impairment was defined as a patient having a creatinine clearance of 20-60 mL/min (inclusive) given by the Cockcroft-Gault formula.
Risk	The proportion of a fixed cohort in which an outcome occurs during a specified period of time
Start of data collection	Date from which information on the first study patient is first recorded in the study dataset

2. ABSTRACT

Title	Multicentre, Non-Interventional, Retrospective, Matched Cohort Study of Patients Monoinfected with Chronic Hepatitis B and with Moderate or Severe Renal Impairment Treated with Viread or Baraclude
Keywords	Hepatitis B, Viread, Baraclude, Renal Impairment, Entecavir, Tenofovir
Rationale and background:	This non-interventional study was designed to evaluate the safety and effectiveness of either Viread (tenofovir disoproxil fumarate, TDF) or Baraclude (entecavir, ETV) in chronic hepatitis B (CHB) patients with moderate or severe renal impairment.
Research question and objectives	The primary objective of this study was: • To retrospectively evaluate the safety of Viread among chronic hepatitis B patients with moderate or severe renal impairment, focusing on renal events of special interest. The secondary objective of this study was: • To describe the effectiveness of Viread in the treatment of chronic hepatitis B in patients with moderate or severe renal impairment. The tertiary objective of this study was: • To compare safety and effectiveness between Viread and Baraclude among the study arms.
Setting:	Data for this retrospective study was collected from the medical records of patients who had attended one of 54 centres in the United Kingdom, Germany, France, Italy and Spain. Each patient's data was de-identified and collected from the first recorded date on which their creatinine clearance (CrCL) was documented to be between 20-60 mL/min, while taking Viread or Baraclude. To be included in the study, patients had to meet all of the following eligibility criteria: **Inclusion Criteria** 1. Male or female patients older than 18 years (inclusive). 2. Chronic hepatitis B patients. 3. Patients who had been treated with Viread (monotherapy),

	administered either as oral granules once daily and/or as a tablet formulation once daily or in prolonged dosing intervals, or patients who had been treated with Baraclude (monotherapy) as a tablet formulation once daily and/or as oral solution. 4. Patients treated with Viread or Baraclude at any time between 23 April 2008 (centralised European marketing authorisation approval date for Viread tablets in hepatitis B virus (HBV) indication) and 31 December 2015. 5. Patients who had experienced at least one occurrence of moderate or severe renal impairment with CrCL between 20-60 mL/min inclusive (based on Cockcroft-Gault formula), while treated with Viread or Baraclude. **Exclusion Criteria** 1. Patients with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis D virus (HDV) co-infection. 2. Patients who had been prescribed treatment with Viread and Baraclude in combination with each other when the CrCL of 20-60 mL/min occurred. 3. Patients who had been prescribed treatment with either Viread or Baraclude in combination with other HBV therapies when the CrCL of 20-60 mL/min occurred. **Definition of sub-groups in this study:** 1. Patients who received once daily reduced-dose Viread using oral granule formulation and/or extended interval dosing using Viread tablets. Or patients who received once daily reduced-dose Baraclude using oral solution and/or extended interval dosing using the Baraclude 0.5 mg or 1 mg tablets. 2. Patients with renal impairment (CrCL of 20-60 mL/min by Cockcroft-Gault formula) prior to initiation of Viread or Baraclude treatment. 3. Patients with renal impairment (CrCL of 20-60 mL/min by Cockcroft-Gault formula) after initiation of Viread or Baraclude treatment. 4. Patients who experienced a renal adverse event (AE) during treatment with either Viread or Baraclude.

	5. Patients who were treatment experienced. 6. Patients who were treatment naïve. **7.** Patients with renal impairment prior to the start of the study with missing data at baseline. **Definition of Adverse Events of Special Interest (AESIs):** 1. Presence of an AE of proximal renal tubulopathy (PRT) and/or renal tubular dysfunction (RTD). 2. Renal AEs leading to withdrawal of either Viread or Baraclude treatment. 3. Renal AEs leading to initiation of hemodialysis or other forms of renal support (i.e. peritoneal dialysis). 4. Renal SAEs including those leading to death. 5. Decline in renal function if reported as an AE.
Study design	Multicentre, non-interventional, retrospective, cohort study.
Patients and study size	This study consisted of adult CHB monoinfected patients who had experienced at least one occurrence of moderate or severe renal impairment with CrCL 20-60 mL/min (by Cockcroft-Gault formula), while concomitantly treated with either Viread or Baraclude (monotherapy) at any time between 23 April 2008 and 31 December 2015. Each patient's data was to be collected from the first recorded date on which their CrCL was documented to be between 20-60 mL/min, while treated with Viread or Baraclude. Results from two interventional studies, GS-US-174-0102 and GS-US-174-0103, showed an incidence of specific renal adverse events (AEs) (renal AEs leading to dose reduction, treatment interruption, or discontinuation) of 3.4% in patients taking Viread. Taking this value as the assumed effect size and accounting for 80% power, the following table was produced using a one proportion test for differing sample sizes.

Sample Size for Viread patient group	100	200	300	400	500	600	700
Effect size (%)	6.0	4.1	3.1	2.8	2.5	2.2	2.1

The number of patients recruited exceeded those expected during the early development of this study with 345 patients recruited into the Viread arm and 170 patients into the Baraclude arm. The

<table>
<tr><td></td><td>Baraclude arm served as a referent group for the Viread arm for comparative analyses as part of the tertiary objective of this study.</td></tr>
<tr><td>Data sources</td><td>The primary sources of data for this study were the patient medical records.
All data was de-identified and collected for patients meeting all eligibility criteria by means of electronic Case Report Forms (eCRF), this included a unique patient identifier for each patient by participating centre.</td></tr>
<tr><td>Variables collected</td><td>Due to the non-interventional nature of this study, only data available from routine medical care was collected. The following parameters, regardless of study drug assignment were de-identified and collected from eligible patients medical records.

For the purposes of this study, baseline was defined as:
The date of first occurrence of renal impairment with CrCL between 20-60 mL/min inclusive, if the treatment was initiated first.
Or, the date of treatment initiation, if the patient had pre-existing renal impairment with CrCL between 20-60 mL/min at the time of treatment initiation.
The end of the observation period was defined as either:
The date on which the patient discontinued taking Viread or Baraclude plus a follow-up period depending on the reason for discontinuation.
Or the 31 December 2015, whichever came first.
The follow-up period added was:
up to up to 12 weeks after Viread/Baraclude therapy was replaced by other HBV therapies or
up to 6 months after Viread/Baraclude therapy was terminated in case of discontinuation for reasons of decreasing renal function.
Baseline Variables:<table><tr><th>Subject</th><th>Variables Collected</th></tr><tr><td>Patient characteristics</td><td>Age group
Gender
Height
Weight</td></tr><tr><td>Baseline HBV disease</td><td>Estimated date of CHB diagnosis.
Hepatitis B e antigen (HBeAg) status (negative or</td></tr></table></td></tr>
</table>

characteristics	positive). Clinical evidence of cirrhosis and decompensated liver disease (present or absent).
HBV treatment	Prior HBV treatment history (type and duration). Initiation date of either Viread or Baraclude treatment. Viread/Baraclude dosage form and dosing schedule (dose and frequency). Changes in Viread/Baraclude dosage form and dosing schedule (dose and frequency). Viread/Baraclude treatment interruptions or discontinuation dates including reason for discontinuation.
Renal impairment status at baseline	The information on whether the current renal impairment episode with CrCL between 20-60 mL/min was present before or after the initiation of Viread/Baraclude treatment.
Relevant medication use	Concomitant use of potentially nephrotoxic drugs, including non-steroidal anti-inflammatory drugs [NSAIDs].
Presence of relevant comorbidities	Presence of certain comorbidities (i.e. hypertension, diabetes and hyperlipidaemia) which, in the investigator's opinion, could have adversely impacted renal function or could have contributed to renal insufficiency.

Safety Variables:

Subject	Variables collected
Safety events	Renal AEs or renal serious adverse events (SAEs). Fatal AEs. Adverse drug reactions (ADRs) considered related to either Viread or Baraclude by the investigator. Special situation reports (SSRs).

Laboratory Variables:

Subject	Variables collected
Renal tests	CrCL as given according to the Cockcroft-Gault formula. Serum phosphate.
Liver tests (at baseline)	Alanine aminotransferase (ALT). Aspartate aminotransferase (AST). International normalized ratio (INR). Platelet count. Serum bilirubin. Serum albumin.

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<tr><td></td><td>
Effectiveness Variables:
<table>
<tr><th>Subject</th><th>Variables</th></tr>
<tr><td>HBV disease characteristics</td><td>HBV DNA levels at baseline and during treatment. Serological status at baseline and serologic response (i.e. loss of HBeAg and/or seroconversion to anti-HBe, loss of HBeAg and/or seroconversion to anti-HBs) during treatment.
Clinical evidence of cirrhosis and decompensated liver disease (present or absent).</td></tr>
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<tr><td>Results</td><td>
From 515 patients originally recruited, 487 patients were included in the study analyses, with more patients being enrolled into the Viread arm (319 Viread vs 168 Baraclude). Both study arms recruited similar proportions of males (≈70%) and females. At baseline 282 Viread patients had non missing CrCl values giving a mean baseline CrCl value of 52.4 mL/min (95% CI 51.5-53.4).

Describing safety in Viread patients

Rates of AESIs

Among 319 Viread patients, 41 experienced at least one AESI while on treatment giving an overall rate of 29.2 per 1,000 person years (95% CI 21.0-39.7). Twenty-four of those patients experienced a renal event leading to withdrawal of Viread resulting in a rate of 16.7 per 1,000 person years (95% CI 10.7-24.8). No renal SAEs leading to death were reported and there were no renal AEs leading to the initiation of haemodialysis or other forms of renal support.

Describing effectiveness in Viread patients
Overall few Viread patients (n=35) were viremic at baseline. The numbers of patients remaining viremic fell from 35 at the start of Week 48 to 3 at Week 192, with most patients becoming virological suppressed by the end of Week 48. Only 7 occurrences of patients not achieving viral suppression were observed throughout the study.

Comparison of safety and effectiveness between Viread and Baraclude study arms

Comparison of safety
In total, 60 AESIs were observed in the study overall; For Viread, 48 AESIs were observed in 41 patients. For Baraclude, 12 AESIs were observed in 11 patients. An Inverse Probability of Treatment Weighted (IPTW) Poisson regression model comparing the incidence of AESIs overall between the two study arms estimated a non-significant incidence rate ratio of 1.8 (95% CI 0.94-3.6).
</td></tr>
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	However, 11 AEs of PRT and/or RTD and 26 renal AEs leading to withdrawal of treatment were observed in the Viread arm, in contrast to none in the Baraclude arm. ***Comparison of effectiveness*** An IPTW Cox regression model to estimate the overall hazard ratio (HR) of a patient achieving virological suppression found no statistically significant difference between the two treatment arms; HR 1.0 (95% CI 0.61 1.8).
Discussion	The data collected in this study showed that patients on the Baraclude arm had a lower CrCl at baseline in comparison to patients within the Viread arm, 46.2 mL/min (95% CI 44.3-48.2) versus 52.4 mL/min (95% CI 51.5-53.3) respectively, which may suggest that clinicians prefer the use of Baraclude in patients with diminished renal function in comparison to Viread. A comparison of the overall safety between Viread and Baraclude showed no statistically significant difference between these two study arms. That said it is prudent to note that 11 events of PRT and/or RTD occurred in the Viread arm and 26 renal AEs leading to withdrawal of Viread whereas none occurred in patients taking Baraclude. The comparison of the Viread and Baraclude arms showed no significant difference in effectiveness, overall and in the sub-groups analysed.
Conclusion	Overall Viread showed high effectiveness as only few Viread patients were viremic at baseline and very few occurrences of patients not achieving virological suppression were observed during the study. The analysis of rates of patients experiencing AESIs showed that patients who were already renally impaired before starting Viread treatment had much higher rates of AESIs than patients who experienced renal impairment while on treatment, which is in line with current recommendations that Viread should only be used in patients with impaired renal function if the benefits outweigh the risks. In this non-interventional study no significant difference was found in the effectiveness between Viread and Baraclude. Also, no statistical difference was found in the overall safety between Viread and Baraclude. However, there were renal AEs exclusively found in the Viread arm (11 events of PRT and/or RTD and 26 renal AEs leading to discontinuation) versus none in the Baraclude arm. This finding is aligned with the current

	understanding of the effectiveness and safety of Viread.
Marketing Authorisation Holder	For Viread: Gilead Sciences International Ltd. Flowers Building, Granta Park Cambridge, CB21 6GT United Kingdom