# NON-INTERVENTIONAL SECONDARY DATA ANALYSIS STUDY PROTOCOL

| | |
|---|---|
| **Study Title** | Multicenter, 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® |
| **Protocol ID** | GS-EU-174-1846 |
| **Protocol Version/Date:** | Version 2.0: 14 December 2016 |
| **EU PAS Register No** | ENCEPP/SDPP/12897 |
| **Clinical Trials.gov Identifier** | Study not registered (non-interventional) |
| **Active substances** | Tenofovir disoproxil fumarate<br>ATC Code: J05AF Nucleoside and nucleotide reverse transcriptase inhibitors<br><br>Entecavir (as monohydrate)<br>ATC Code: J05AF Nucleoside and nucleotide reverse transcriptase inhibitors |
| **Medicinal Products** | Tenofovir Disoproxil (as Fumarate) [Viread®]<br>Entecavir (monohydrate) [Baraclude®] |
| **Product references** | For Viread®<br>EU/1/01/200/001<br>EU/1/01/200/002<br>EU/1/01/200/003<br><br>For Baraclude®<br>EU/1/06/343/001<br>EU/1/06/343/002<br>EU/1/06/343/003<br>EU/1/06/343/004<br>EU/1/06/343/005<br>EU/1/06/343/006<br>EU/1/06/343/007 |
| **Procedure number** | Not applicable |

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| **Joint PASS** | No |
| **Research question and objectives** | The primary objective of this study is to:<br>• Retrospectively evaluate the safety of Viread® among chronic hepatitis B patients with moderate or severe renal impairment, focusing on renal events of special interest.<br><br>The secondary objectives of this study are to:<br>• Describe the effectiveness of Viread® in the treatment of chronic hepatitis B in patients with moderate or severe renal impairment.<br>• Compare safety and effectiveness between Viread® and Baraclude® among the matched study cohort arms. |
| **Countries of study** | Up to 60 centers in the United Kingdom, Germany, France, Italy and Spain. |
| **Gilead Study Director / Author/ Contact Person:** | Name: Heribert Ramroth<br>Telephone: +44 (0) 208 587 2560 |
| **Marketing Authorization Holder** | For Viread®<br>Gilead Sciences International Ltd.<br>Flowers Building, Granta Park<br>Cambridge, CB21 6GT<br>United Kingdom |
| **MAH contact person** | Name: Jeanette Trent<br>Telephone: +44 (0) 1223 897342 |
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# 2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| BMS | Bristol-Myers Squibb Pharma EEIG |
| CHB | Chronic Hepatitis B |
| CHMP | Committee for Medicinal Products for Human Use |
| DNA | Deoxyribonucleic Acid |
| (e)CRF | (electronic) Case Report Form |
| CrCL | Creatinine Clearance |
| DSPH | Drug Safety and Public Health |
| EMA | European Medicines Agency |
| ETV | Entecavir |
| EU | European Union |
| FC | Foster City |
| FUM | Follow Up Measure |
| GPP | Good Pharmacoepidemiology Practices (guidelines for) |
| GVP | Good Pharmacovigilance Practices (guidelines for) |
| HBeAg | Hepatitis B e Antigen |
| HBsAg | Hepatitis B surface Antigen |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HDV | Hepatitis D Virus |
| HIV | Human Immunodeficiency Virus |
| HLGT | High-Level Group Term |
| HLT | High-Level Term |
| HMA | Heads of Medicines Agencies |
| IBW | Ideal Body Weight |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| INR | International Normalized Ratio |
| LLT | Lower-Level Term |
| MD | Medical Doctor |
| MAH | Marketing Authorization Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| PASS | Post-Authorization Safety Study |

| | |
|---|---|
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PRT | Proximal Renal Tubulopathy |
| PSM | Propensity Score Matching |
| PT | Preferred Term |
| QPPV | Qualified Person Responsible for Pharmacovigilance |
| SADR | Serious Adverse Drug Reaction |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| SSR | Special Situation Report |
| SUSAR | Serious Unexpected Suspected Adverse Reaction |
| TDF | Tenofovir Disoproxil Fumarate |
| TFV | Tenofovir |
| USA | United States of America |
| Cohort | Group of people characterized by a common experience (e.g., occurrence of a specified disease, exposure to a given medication) |
| End of data collection | The date from which the analytical dataset is completely available |
| Observation period | For each individual patient, defined from the first moderate or severe renal impairment occurrence while treated with either Viread® or Baraclude®,<br>- until 12 weeks after Viread®/Baraclude® therapy was terminated replaced by other HBV therapies<br>- for up to 6 months after Viread®/Baraclude® therapy was terminated in case of discontinuation of Viread®/Baraclude®, for reasons of decreasing renal function<br>- or until 31st December 2015, whichever occurred first. |
| Start of data collection | Date from which data extraction starts |

# 3. RESPONSIBLE PARTIES

**Table 1. Responsible Parties**

| Responsibility | Name, Title, Qualifications, Affiliation, Address, | Contact Information |
|---|---|---|
| Study Director | Heribert Ramroth<br>Associate Director,<br>Drug Safety and Public Health (DSPH) Epidemiology<br>Gilead Sciences Europe Ltd.<br>2 Roundwood Avenue<br>Stockley Park, Uxbridge,<br>Middlesex UB11 1AF<br>United Kingdom | Phone: +44 (0) 208 587 2560<br>Email: Heribert.Ramroth@gilead.com |
| Study Sponsor | Gilead Sciences Europe Ltd.<br>2 Roundwood Avenue<br>Stockley Park, Uxbridge,<br>Middlesex UB11 1AF<br>United Kingdom | |
| Clinical Operations | Chloe Phulpin<br>Clinical Operations Europe, Late Phase<br>Gilead Sciences Europe Ltd.<br>2 Roundwood Avenue<br>Stockley Park, Uxbridge,<br>Middlesex UB11 1AF<br>United Kingdom | Phone: +44 (0) 208 587 2681<br>Email: Chloe.Phulpin@gilead.com |
| Marketing Authorization Holder (MAH) | Gilead Sciences International Ltd.<br>Flowers Building, Granta Park<br>Cambridge, CB21 6GT<br>United Kingdom | Jeanette Trent<br>Director, Regulatory Affairs<br>Phone: +44 (0)1223 897342<br>Email: Jeanette.Trent@Gilead.com |
| Medical Monitor | Irina LaRose<br>Associate Director, DSPH<br>Gilead Sciences, Inc.<br>333 Lakeside Drive<br>Foster City, CA 27717-0530<br>United States of America (USA) | Phone: +1 650 522 5106<br>Email: Irina.LaRose@gilead.com |
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# 4. PROTOCOL SYNOPSIS/ABSTRACT

**Gilead Sciences Europe Ltd.**

**2 Roundwood Avenue**

**Stockley Park, Uxbridge,**

**Middlesex, UB11 1AF, United Kingdom**

| | |
|---|---|
| **Title:** | Multicenter, 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® |
| **Rationale and Background:** | This non-interventional study is designed to evaluate the safety and effectiveness of either Viread® or Baraclude® in chronic hepatitis B (CHB) patients with moderate or severe renal impairment. |
| **Research Question and Objectives:** | The primary objective of this study is:<br>• 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.<br>The secondary objectives of this study are:<br>• To describe the effectiveness of Viread® in the treatment of chronic hepatitis B in patients with moderate or severe renal impairment.<br>• To compare safety and effectiveness between Viread® and Baraclude® among the matched study cohort arms. |
| **Study Design:** | Multicenter, non-interventional, retrospective, matched cohort study. |
| **Population** | Cohort definition: Adult CHB monoinfected patients who had experienced at least one occurrence of moderate or severe renal impairment with creatinine clearance (CrCL) 20-60 mL/min (by Cockcroft-Gault formula), while concomitantly treated with either Viread® or Baraclude® (monotherapy) at any time between 23rd April 2008 (Centralized European marketing authorization approval date for Viread® tablets in HBV indication) and 31st December 2015.<br>Each patient's data will 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®. |

When either Viread® or Baraclude® therapy was terminated or replaced by another HBV therapy, documentation of available routine visit data will stop 12 weeks after Viread® or Baraclude® therapy termination or at the time of replacement therapy initiation or 31st December 2015, whichever occurred first. In case of discontinuation of Viread® or Baraclude® for reasons of decreasing renal function, the post-treatment observation period will capture renal laboratory parameters (i.e. creatinine clearance, phosphate, as per safety laboratory variables) and any new medications with the potential for renal toxicity for up to 6 months or until 31st December 2015, whichever occurred first.

Each participating center will also be asked to separately report the total number of adult CHB (monoinfected) patients who have been prescribed either Viread® or Baraclude® for HBV, at any time between 23rd April 2008 and 31st December 2015.

**Variables:**

This is a non-interventional study, only data available from routine medical care will be collected within the study.

Identical variables will be collected in both cohort arms, i.e. the Viread® cohort and the Baraclude® cohort.

When available, the following parameters will be de-identified and collected from patients' medical records:

- Patient characteristics:
  - Age group, gender, height, weight
- HBV disease characteristics:
  - Estimated date of CHB diagnosis
  - Hepatitis B e antigen (HBeAg) status (negative or positive)
  - Cirrhosis (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 reasons for discontinuation

- Renal impairment status: 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 will be collected at the start of the observation period.
- Relevant medication use (i.e. potentially nephrotoxic drugs and non-steroidal anti-inflammatory drugs [NSAIDs]) and presence of certain comorbidities (i.e. hypertension, diabetes and hyperlipidemia) which, in the investigator's opinion, could have adversely impacted renal function or could have contributed to renal insufficiency.

**Safety variables**

- Safety events:
  - Renal adverse events (AEs) or renal serious adverse events (SAEs)
  - Fatal adverse events
  - Adverse drug reactions (ADRs) related to either Viread® or Baraclude®
  - Special Situation Reports (SSRs)
- Laboratory evaluations:
  - Renal tests:
    - Creatinine clearance (CrCL), as given according to the Cockcroft-Gault formula[1]
    - Serum phosphate
  - Liver tests (to be collected at the start of the observation period only):
    - Alanine aminotransferase (ALT)
    - Aspartate aminotransferase (AST)
    - International Normalized Ratio (INR)
    - Platelet count
    - Serum bilirubin
    - Serum albumin

[1] Creatinine clearance will be calculated by the investigative centers based on Cockcroft-Gault formula.
CrCL (mL/min) = [(140 - age in years) * (weight in kg) * (0.85 if female)] / [(72 * (serum creatinine in mg/dL)]

| | |
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| | **Effectiveness variables**<br>• HBV disease characteristics:<br>— Serological response (i.e. loss of HBeAg and/or seroconversion to anti-HBe, loss of HBsAg and/or seroconversion to anti-HBs)<br>— HBV DNA levels<br>— Clinical evidence of disease progression (i.e. development of cirrhosis or decompensated liver disease) |
| **Data Sources:** | The primary data source will be the patient medical record. All data will be de-identified and collected for those patients meeting all eligibility criteria by means of electronic Case Report Forms (eCRF), including a unique subject identifier for each patient by each participating center. |
| **Study Size:** | Up to 60 centers in the United Kingdom, Germany, France, Italy and Spain, countries wherein Viread® oral granule and/or tablet formulations have been the most widely used in CHB patients.<br>Based on current estimates, it is assumed that data for up to 650 patients treated with Viread® and up to 350 Baraclude® patients may be available for this study. This would result in a total of approximately 1000 patients. |
| **Data Analysis** | Data will be summarized using univariate descriptive statistics. Continuous variables will be summarized by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum. Categorical variables will be summarized by number and percentage of patients in each categorical definition including according 95% confidence intervals.<br>Multivariate analyses will be used to estimate adjusted rates and proportions. In order to maximize homogeneity between the two cohorts and reduce the impact of treatment-selection bias a retrospective propensity score matching (PSM) approach will be applied. One Baraclude® patient will be matched to one or more Viread® patients using a variable-ratio matching technique. Conditional multivariate logistic or linear regression models will be used to assess differences between the two study cohorts. |

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| **Milestones:** | Start of data collection: Q2 2016 |
| | End of Data collection: Q1 2017 |
| | Progress report: Q4 2016 |
| | Final Study report: Q3 2017 |

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

# 5. AMENDMENTS AND UPDATES

| Amendment or Update Number | Date | Section of Study Protocol | Amendment or Update | Reason |
|---|---|---|---|---|
| Update #1 | 12 January 2016 | Sections 6, 7.1, 8, 9.2, 9.3, 9.5, 9.7, 10.3, 11.4, 11.5, 12.1 | Update | Changes to address comments received from the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency. |
| Update #2 | 18 March 2016 | Sections 6, 7.1, 8, 9.1, 9.2, 9.3, 9.5, 9.7, 9.9, 11 | Update | Changes to address comments received from the PRAC; addition of a control arm with entecavir. |
| Amendment #1 | 14 December 2016 | Sections 9.1, 9.2, 9.3, 9.5, 9.7, Appendix 1 | Amendment | This protocol amendment is needed in order to :<br>• Update MAH contact person<br>• Correct inconsistency in collected variables<br>• Update number of participating centers<br>• Update number of patients<br>• Add missing data imputation<br>• Change matching technique<br>• Use last available version of the ENCePP checklist. |

- **Protocol Modifications**

Protocol modifications may be made only by Gilead Sciences Europe Ltd. Approval must be obtained before changes can be implemented.

# 6. MILESTONES

| Milestone | Planned Date |
|---|---|
| Registration in the EU PASS register | Prior to start of data collection |
| Start of data collection | Q2 2016 |
| End of data collection | Q1 2017 |
| Progress report | Q4 2016 |
| Final report of study results | Q3 2017 |

# 7. RATIONALE AND BACKGROUND

## 7.1. Rationale for the Current Study

Tenofovir disoproxil fumarate (TDF; Viread®) is an antiviral prodrug of tenofovir (TFV). Following absorption, TDF is rapidly and completely converted to TFV, a nucleoside monophosphate (nucleotide) analogue. Within the cell, TFV is converted to its active form, tenofovir diphosphate, which inhibits the activity of hepatitis B virus (HBV) reverse transcriptase by competing with the natural substrate deoxyadenosine 5' triphosphate, leading to deoxyribonucleic acid (DNA) chain termination.

TDF has activity against HBV, and is indicated for treatment of chronic HBV infection in adults and adolescents 12 to <18 years of age.

TFV is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70 to 80% of the dose excreted unchanged in urine following intravenous administration. TDF is an oral prodrug that is never given intravenously. The proof of concept study (Study 701) for TFV in HIV used an intravenous form of TFV {Deeks 1998}.

TDF, as Viread® 245 mg tablets, was approved for the treatment of CHB in adults within the European Union (EU) on 23rd April 2008.

Viread® 33 mg/g oral granules were approved on 22nd November 2012 by the EU Committee for Medicinal Products for Human Use (CHMP).

This study uses a cohort of patients treated with entecavir as a comparator to the Viread®-treated cohort. Entecavir serves solely for the purposes of comparison in this study. Entecavir (ETV; Baraclude®), a guanosine nucleoside analogue with activity against HBV polymerase, is efficiently phosphorylated to the active triphosphate (TP) form. Entecavir-TP functionally inhibits HBV reverse transcriptase, by competing with the natural substrate deoxyguanosine TP {Bristol-Myers Squibb Pharmaceutical Limited 2014}.

ETV, as Baraclude® 0.5 mg and 1 mg tablets and oral solution (0.05mg/mL), was approved for the treatment of CHB in adults within the European Union (EU) on 26th June 2006.
The Marketing Authorisation Holder is Bristol-Myers Squibb Pharma EEIG (BMS).

The clearance of entecavir decreases with decreasing creatinine clearance. Dose adjustment is recommended for patients with creatinine clearance < 50 ml/min, including those with end-stage renal disease maintained on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A reduction of the daily dose using Baraclude® oral solution is recommended. As an alternative, in case the oral solution is not available, the dose can be adjusted by increasing the dosage interval. The proposed dose modifications are based on extrapolation of limited data, and their safety and effectiveness have not been clinically evaluated. Therefore, virological response should be closely monitored. {Pipili 2013}.

There are limited data on the safety and efficacy of TDF in adult patients with moderate and severe renal impairment. Therefore, in adult patients with renal impairment TDF should only be used if the potential benefits of treatment are considered to outweigh the potential risks {Pipili 2013}. Adjustments of the daily dose of TDF 33 mg/g granules are recommended in patients with moderate or severe renal impairment based on modelling of single-dose pharmacokinetic data in HIV negative and non-HBV infected subjects with varying degrees of renal impairment. These pharmacokinetic modelling data have not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Given that the recommended dose adjustments are not based on clinical responses, there is a need to evaluate the safety and efficacy of Viread® in HBV patients with moderate or severe renal impairment.

With regards to safety and efficacy data from ongoing or previously completed studies with TDF in chronic HBV patients with moderate to severe renal impairment, Gilead has identified only 37 patients in Gilead-sponsored HBV trials with a creatinine clearance between 20 to 60 mL/min by the Cockcroft-Gault method on at least one occasion (GX-DE-174-0129 and GX-FR-174-0130).

Given the limited nature of existing data, this non-interventional study is being undertaken to collect real-world data on the use of Viread® in patients with moderate or severe renal impairment in a retrospective fashion. These data are intended to gain a better understanding of the use, safety and effectiveness of Viread® in this special patient population.

# 8. RESEARCH QUESTIONS AND OBJECTIVES

The primary objective of this study is

- To retrospectively evaluate the safety of Viread® among adult chronic hepatitis B patients with moderate or severe renal impairment, focusing on renal events of special interest.

The secondary objectives of this study are:

- To describe the effectiveness of Viread® in the treatment of chronic hepatitis B patients with moderate or severe renal impairment.
- To compare safety and effectiveness between Viread® and Baraclude® among the matched study cohort arms.

# 9. RESEARCH METHODS

## 9.1. Study Design

This is a multicenter, non-interventional, retrospective, matched cohort study.

Safety and efficacy data will be de-identified and retrospectively collected from medical records for those patients meeting all eligibility criteria.

## 9.2. Setting

Data will be retrospectively collected from medical records of patients meeting 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,

4) or patients who had been treated with Baraclude® (monotherapy) as a tablet formulation once daily and/or as oral solution.

5) Patients treated with Viread® or Baraclude® at any time between 23rd April 2008 (Centralized European marketing authorization approval date for Viread® tablets in HBV indication) and 31st December 2015.

6) 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.

In case a given patient had been treated by both Viread® and Baraclude®, and experienced at least one occurrence of moderate to severe renal impairment while treated by both Baraclude® and Viread®, this patient will be included in the treatment cohort corresponding to the treatment they were on during the first occurrence of moderate to severe renal impairment.

Each patient's data will be de-identified and collected from the first recorded date on which their CrCL was documented to be between 20-60 mL/min, while on study treatment (either Viread® or Baraclude®).

When study treatment (Viread® or Baraclude®) was terminated or replaced by other HBV medications, documentation of available routine visit data will stop 12 weeks after therapy termination or at the time of replacement therapy initiation or 31st December 2015, whichever occurred first. In case of discontinuation of Viread® or Baraclude® therapy for reasons of decreasing renal function, the post-treatment observation period will capture renal laboratory parameters (i.e. creatinine clearance and phosphate, as per safety laboratory variables) and any new medications with the potential for renal toxicity for up to 6 months or until 31st December 2015, whichever occurred first.

For ease of analyses and to avoid patients being included in the study a second time with a different patient identifier, a patient who re-initiated study treatment (Viread® or Baraclude®) after the end of the follow-up period and again experienced moderate to severe renal impairment will not be included again in the study.

Each participating center will also be asked to separately report the total number of adult CHB (monoinfected) patients who have been prescribed either Viread® or Baraclude® for HBV, at any time between 23rd April 2008 and 31st December 2015.

## 9.3. Variables

This is a non-interventional evaluation, only data available from routine medical care will be collected within this study.

Identical variables will be collected in both cohort arms, i.e. the Viread® cohort and the Baraclude® cohort.

When available, the following parameters will be de-identified and collected from patients' medical records:

- Patient characteristics:
  - Age group, gender, height, weight
- HBV disease characteristics:
  - Estimated date of CHB diagnosis
  - Hepatitis B e antigen (HBeAg) status (negative or positive)

- Cirrhosis (present or absent)

- HBV treatment:
  - Prior HBV treatment history, if applicable (type and treatment 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 reasons for discontinuation

- Renal impairment status: 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 will be collected at the start of the observation period.

- Relevant medication use (i.e. potentially nephrotoxic drugs and non-steroidal anti-inflammatory drugs [NSAIDs]) and presence of certain comorbidities (i.e. hypertension, diabetes and hyperlipidemia) which, in the investigator's opinion, could have an adversely impacted renal function or could have contributed to renal insufficiency.

**Safety variables**

- Safety events:
  - Renal adverse events (AEs) or renal serious adverse events (SAEs)
  - Fatal adverse events
  - Adverse drug reactions (ADRs) related to either Viread® or Baraclude®
  - Special Situation Reports (SSRs)

- Laboratory evaluations:
  - Renal tests:
    - Creatinine clearance (CrCL), as given according to the Cockcroft-Gault formula[2]
    - Serum phosphate
  - Liver tests (to be collected at the start of the observation period only):
    - Alanine aminotransferase (ALT)

[2] Creatinine clearance will be calculated by investigator based on Cockcroft-Gault formula.
CrCL (mL/min) = [(140 - age in years) * (weight in kg) * (0.85 if female)] / [(72 * (serum creatinine in mg/dL)]

- Aspartate aminotransferase (AST)
- International Normalized Ratio (INR)
- Platelet count
- Serum bilirubin
- Serum albumin

**Effectiveness variables**

- HBV disease characteristics:
  - Serological response (i.e. loss of HBeAg and/or seroconversion to anti-HBe, loss of HBsAg and/or seroconversion to anti-HBs)
  - HBV DNA level
  - Clinical evidence of disease progression (i.e. development of cirrhosis or decompensated liver disease)

## 9.4. Data Sources

The primary data source will be the patient medical record. All data will be de-identified and retrospectively collected for those patients meeting all eligibility criteria by means of electronic Case Report Forms (eCRF) with a unique subject identifier for each patient, by each participating center.

## 9.5. Study Size

Data will be collected on all patients meeting eligibility criteria from up to 60 centers in the United Kingdom, Germany, France, Italy and Spain, namely countries wherein Viread® oral granule and/or tablet formulations have been the most widely used in CHB patients.

Previous Viread® studies in Germany and France identified only very few HBV patients with moderate or severe renal impairment. The German study (GX-DE-174-0129) including 400 patients across 33 centers identified 7 patients with moderate and 2 patients with severe renal impairment enrolled in a period of 12 months. The respective numbers for the French study (GX-FR-174-0130) were 27 patients (moderate) and 1 patient (severe) out of 440 patients over the same time period across 58 study centers.

Based on preliminary estimates from identified centers above, it is assumed that data for up to 650 patients treated with Viread® and up to 350 Baraclude® patients may be available for this study. This would result in a total of up to 1000 patients. The Baraclude® arm will serve as a reference point for the Viread® cohort and exploratory comparative analyses will be conducted to support the secondary objective of the study. One Baraclude® patient will be matched to one or more Viread® patients using a variable-ratio matching technique {Pimentel 2015}.

Cumulative open label data through year 8 in two prospective Viread® studies (GS-US-174-0102 and GS-US-174-0103) revealed an incidence of renal events leading to dose reduction, treatment interruption, or discontinuation during the open label period of 3.4% {Gilead Sciences Inc 2015, Marcellin 2014}. A study that compared Viread® and Baraclude® showed similar risks of renal events among patients treated with tenofovir or entecavir for chronic hepatitis B although higher risks in the Viread® arm were anticipated {Gish 2012}.

The following table shows a list of estimated differences in the incidence of renal events (effect sizes) for a range of potential sample sizes under the assumption of 80% power and an expected incidence rate of 3.4%. As shown in the table, the higher the number of Viread® patients evaluated, the smaller the difference in renal event incidence between the treatments can be detected.

| **Sample Size for Viread® patients** | 100 | 200 | 300 | 400 | 500 | 600 | 700 |
|---|---|---|---|---|---|---|---|
| **Effect size (%)** | 6.0 | 4.1 | 3.1 | 2.8 | 2.5 | 2.2 | 2.1 |

## 9.6. Data Management

The study will use an electronic case report form (eCRF) and all users will receive specific access codes to enable them to enter their data. The eCRF will contain automatic checks for data completeness and to identify inconsistent data. Participating centers will enter available data from patient's medical records into the eCRF.

## 9.7. Data Analysis

Data from this non-interventional study will be summarized using univariate descriptive statistical methods. Continuous variables will be summarized descriptively (mean, standard deviation, and median, lower quartile, upper quartile, minimum, maximum, 95% confidence intervals). All categorical variables will be summarized by number and percentage of patients in each categorical definition and including 95% confidence intervals. Counts for missing values will be also tabulated but missing values will not be considered in the percentages.

Multivariate analyses will be used to model the odds for a given event (logistic regression models) adjusted for potential confounders. Conditional multivariate regression models will be used to show differences between the two study cohorts. Post data collection Propensity Score Matching (PSM) will be used to adjust for potential confounding, using patient characteristics, HBV disease and treatment characteristics, renal impairment status, relevant medication use and presence of certain comorbidities to create the propensity score. One Baraclude® patient might be matched to one or more Viread® patients using a variable-ratio matching technique {Pimentel 2015}.

The PSM approach will be applied in order to maximize homogeneity between cohorts and reduce the impact of treatment-selection bias. The propensity score is defined as a patient's probability of receiving a specific treatment (Viread®) conditional on the observed covariates {Rosenbaum 1983}. When propensity scores are used in matching, treatment effects are

unbiased under the condition that treatment assignment is strongly ignorable {D'Agostino 1998}. On the other hand, treatment assignment is strongly ignorable if treatment cohorts and the outcome variable are conditionally independent given the covariates. This independence assumption will not hold in situations where there are variables not included as propensity score covariates that are correlated with outcome events and time dependent treatment selection {Johnson 2009}.

Details will be described in the Statistical Analysis Plan (SAP).

The PSM procedure will include the following steps:

1) Model choice: The propensity score will be computed using binary regression with a logit or a probit link function, depending on model fitting statistics. Statistical based criteria will be used to specify the covariates, such as the degree of association with Viread® odds.

2) Matching algorithm choice: The nearest neighbor algorithm or the nearest neighbor within a specified caliper distance algorithm will be used as a matching algorithm. The nearest neighbor matching selects for variable matching to a given Viread® patient the Baraclude® patient whose propensity score is closest to that of the Viread® patient. Nearest neighbor matching within a specified caliper distance is similar to nearest neighbor matching with the further restriction that the absolute difference in the propensity scores of matched patients must be below some pre-specified threshold (the caliper distance) {Austin 2011b}, {Austin 2011a}.

3) Matching: Assign the matching membership and retain the propensity score for the case where further adjustment is needed. A variable-ratio matching technique will be used to account for the different sizes of Viread® and Baraclude® patient groups. Differences in age and renal functions might be responsible for reducing patient numbers in both patient groups for matching purposes.

The following sub-groups will be considered within each study cohort for modeling:

- Patients receiving once daily reduced-dose Viread® using oral granule formulation or extended interval dosing using Viread® tablets
- Patients receiving once daily reduced-dose Baraclude® using oral solution or extended interval dosing using the Baraclude® 0.5 mg or 1 mg tablet
- Patients with renal impairment (20-60 mL/min by Cockcroft-Gault formula) before either Viread® or Baraclude® treatment initiation
- Patients with renal AE during either treatment (Viread®/Baraclude®)

Safety will be estimated determining rates of AEs and summarising laboratory test results. The proportion of patients with tolerability failure (defined as an AE leading to permanent discontinuation of study drug), renal AEs, renal AEs of special interest and clinical laboratory tests will be collected and summarized through the first year and annually thereafter.

Effectiveness will be estimated determining the proportion of subjects with HBV DNA below 400 copies/mL (69 IU/mL) in week 48, 96, 144, etc.

Renal events of special interest are defined as:

- Presence of proximal tubulopathy (PRT)
- Renal AEs leading to withdrawal of either Viread® or Baraclude® treatment
- Renal AEs leading to dialysis
- Renal SAEs including deaths
- Decline in renal function if reported as an AE

The primary parameter for assessing effectiveness will be virologic response through serial monitoring of HBV DNA levels, which is a standard of care for patient with CHB.
For purposes of this retrospective study, response to therapy will be defined as achievement and/or maintenance of HBV DNA <2000 IU/mL. While the goal of therapy for HBV patients is to achieve complete undetectability of HBV DNA, the study will involve HBV DNA assessments obtained retrospectively from multiple local clinical laboratories; therefore, a more conservative definition will be applied. Achievement of an HBV DNA level below 2000 IU/mL is considered the viral level of suppression that is indicative of a therapeutic response (EASL Guidelines) {European Association for the Study of the Liver (EASL) 2012}, {Terrault 2015}. A signal for loss of effectiveness would therefore be any subject who initiates treatment with TDF and fails to achieve HBV DNA <2000 IU/mL after 48 weeks (primary nonresponse), or any subject who achieves virologic breakthrough, defined as achieving HBV DNA < 2000 IU/mL with subsequent development of viremia above 2000 IU/mL while on TDF/ETV treatment, or any subject who experiences a ≥ 1.0 log10 IU/mL increase from nadir who has not yet achieved HBV DNA <2000 IU/mL. Due to the observational nature of this study, a window of ±2 months around 12 months is acceptable. Virologic breakthroughs must be confirmed by two consecutive HBV DNA measurements.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the database.

Imputation methods will be used to account for missing values in the dataset adhering to current ENCePP guidelines {European Medicines Agency 2010}.

Details will be described in the SAP.

All statistical analyses will be conducted using SAS® software (SAS Institute, Cary, North Carolina, USA) or other standard software tools including Stata® (StataCorp LP, College Station, Texas, USA).

## 9.8. Quality Control

The electronic data entry system will contain automatic checks for data completeness and to identify inconsistent data and respective queries will be generated when necessary. Data and queries will be remotely monitored for consistency and completeness. Study monitors will not have access to patients' source data, in order to preserve the patients' anonymisation.

## 9.9. Limitations of the Research Methods

As documentation of study variables in a retrospective study is not obligatory missing data of unpredictable extent can occur.

Sites will be selected if in a given site's database there is at least one adult CHB monoinfected patient who 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). The time period during which a site must have treated at least one such patient is between 23rd April 2008 and 31st December 2015. A potential selection bias resulting from this procedure cannot be excluded.

Given the retrospective nature of this non-interventional study design, the fact that patients were managed by multiple physicians, and the likelihood that there is a preferred treatment option for patients with renal impairment (entecavir), it will be difficult to interpret the results of a comparator arm. Moreover, baseline demographics and disease characteristics may differ between groups (tenofovir treated patients may be expected to be older, with a longer treatment duration for hepatitis B, including prior failure to lamivudine therapy). Matching the groups might therefore result in a loss of patients, due to the exclusion of the non-matching patients.

## 9.10. Other Aspects

### 9.10.1. Joint Investigator/Sponsor Responsibilities

#### 9.10.1.1. Access to Information for Monitoring

The study monitor is responsible for routine remote review of the CRFs at regular intervals throughout the study to verify the completeness and consistency of the data being entered on the forms. The study monitor will not have access to patients' source data.

The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring activities are resolved.

#### 9.10.1.2. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies and independent ethics committees (IECs).

# 10. PROTECTION OF HUMAN SUBJECTS

## 10.1. Good Pharmacoepidemiology Practices and Pharmacovigilance Practices

The study will be conducted in accordance with the principles of the International Conference on Harmonization (ICH) Pharmacovigilance Planning E2E guidelines, and with the laws and regulations of the country in which the research is conducted.

The study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

## 10.2. Independent Ethics Committee (IEC) Review

Each participating center will be responsible to adhere to their appropriate local ethics approval procedures for this retrospective, non-interventional cohort study (i.e. to contact their local ethics committee to determine whether additional protocol approval is required). Data collected from patients' medical records will be de-identified: patient identifiers will be removed to ensure patient confidentiality.

## 10.3. Informed Consent

No informed consent will be obtained unless specifically required by an appropriate ethics committee or required by country National Data Protection Laws, for a participating center. All data used in this study will be de-identified and retrospectively collected in an eCRF with a unique subject identifier for each patient by each participating center.

## 10.4. Confidentiality

The investigator and Gilead must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only a unique identifier (as allowed by local law) and a unique study identification code should be recorded on any study-related document.

The investigator agrees that all information received from Gilead, including but not limited to this protocol, CRFs, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

# 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

## 11.1. Investigator Instructions for Collecting and Reporting Selected Safety Information to Gilead

The following retrospective safety information is required to be collected and reported for this study

- All fatal events (regardless of causality)
- All serious and non-serious renal adverse events
- All renal events of special interest (i.e. renal SAEs, AEs of proximal renal tubulopathy [PRT], decline in renal function if reported as an AE and renal AEs leading to related to Viread® or Baraclude® discontinuation or dialysis)
- All serious adverse drug reactions (SADRs) (related to Viread® or Baraclude®)
- All adverse drug reactions (ADRs) (related to Viread® or Baraclude®)
- All special situation reports (SSRs) occurring during the observation period

Timelines for reporting to Gilead are as follows:

- Within 3 calendar days of knowledge of all fatal events (regardless of causality) and SADRs/SAEs
- Within 30 calendar days of knowledge of the AE/ADRs
- Within 30 calendar days of knowledge for SSRs

Details of the methods for reporting AEs, SAEs, and SSRs to Gilead DSPH will be described in the CRF completion guidelines. If reporting of events is by electronic submission via eCRF, this method must always be used unless the eCRF system is not functioning. If for any reason it is not possible to record events electronically, the details should be recorded on the appropriate paper reporting forms (the Non-Interventional Study AE/SAE Report Form) and submitted by fax or e-mail, within the timelines given above to:

Gilead DSPH contact information is as follows:

E-mail: Safety_FC@gilead.com

Fax:+1 (650) 522-5477

As soon as it is possible to do so, any death, ADR, SADR, and SSR reported via paper must be transcribed into the eCRF database according to the instructions in the eCRF completion guidelines.

### 11.1.1. Instructions for Reporting Pregnancies

All pregnancies that occurred during the observation period while exposed to drug and the outcome of the pregnancy are to be reported to Gilead DSPH using the pregnancy report form within 30 calendar days of becoming aware of the pregnancy

The following information is required to be collected and reported for this study. All pregnancies that occurred during the observation period while exposed to drug Viread® or Baraclude®:

- Information on all pregnancies
- The outcome of the pregnancy, including any premature termination (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons)

Timelines for reporting to Gilead are as follows:

- Within 30 calendar days of knowledge of the pregnancy
- Within 3 calendar days of knowledge of all pregnancy related serious events (regardless of causality, e.g., a spontaneous abortion, hospitalization, etc.)

Pregnancy information should only be reported on the paper pregnancy report form, and the outcome should be reported on pregnancy outcome report form. However, if the event qualifies as an SAE then an SAE form should be reported as described in Section 11.1.

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) or SAE occurring as an adverse pregnancy outcome post-study must be reported with the 3-calendar-days timelines.

## 11.2. Gilead Reporting Requirements to Regulatory Authorities

Gilead is responsible for analyzing reports of all safety information and reporting to regulatory agencies as determined by country-specific legislation or regulations.

Assessment of expectedness for all safety reports will be determined by Gilead using reference safety information specified in the European summary of product characteristics (SmPC) {Bristol-Myers Squibb Pharmaceutical Limited 2014} {Gilead Sciences Inc 2015}.

The section hereafter lists standard definitions for management and reporting of adverse events/adverse reactions, and provides timelines and modus of reporting for the selected safety information required to be collected and reported in this study.

## 11.3. Definitions

### 11.3.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE.

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

- Any medical condition or clinically significant laboratory abnormality with an onset date before the first recorded date on which their creatinine clearance fell between 20-60 mL/min are considered to be preexisting conditions and should be documented on the medical history eCRF (if applicable).

### 11.3.2. Adverse Drug Reactions

An adverse drug reaction (ADR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

### 11.3.3. Serious Adverse Events

A serious adverse event (SAE) is defined as an event that, at any dose, results in the following:

- Death

- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

### 11.3.4. Serious Adverse Drug Reaction

A SADR is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

### 11.3.5. Special Situations Reports

Special situation reports include reports of pregnancy; medication error, abuse, misuse, overdose, lack of effect; off-label use, product complaints and occupational exposure.

A pregnancy report is used to report any pregnancy that occurs during the study, whether or not maternal or paternal exposure to the product occurred.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Lack of effect is defined as the failure of the expected or intended pharmacologic action or therapeutic effect as described in the pharmacology and/or indications section of the current product label.

Off-label use is defined as the intentional use of licensed medicinal product by a Health Care Professional for a medical purpose not in accordance with the authorized product information with respect to indication, dose, route of administration, or patient population (e.g., the elderly).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

### 11.3.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not assessed as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation must be assessed as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be assessed as an AE or SAE if they meet the definition of an AE or SAE as described in Section 11.3. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

## 11.4. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing all fatal adverse events, renal AEs, renal SAEs, renal events of special interest, and ADRs and SADRs related to either Viread® or Baraclude® for causality and for final review and confirmation of accuracy of event information and assessments.

### 11.4.1. Assessment of Causality

The investigator or qualified subinvestigator is responsible for assessing the relationship to drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is a reasonable possibility that the event may have been caused by the medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

In the context of this retrospective, non-interventional cohort study, relationship to Viread® or Baraclude® therapy should be clearly documented on the patient's eCRF and AE/SAE form.

# 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

## 12.1. Study Report and Publications

A study publication will be prepared and provided to the European Medicines Agency (EMA). Gilead Sciences will follow the standards set out in the STROBE Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) {von Elm 2008}. Gilead will submit publications to regulatory authorities within two weeks after first acceptance.

The final study report will be submitted to applicable authorities and review bodies within 6 months of study completion.

# 13. REFERENCES

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# 14. APPENDICES

| Number | Document Reference Number | Date | Title |
|---|---|---|---|
| 1 | Appendix 1 | 14 December 2016 | ENCePP Checklist for Study Protocols |
| 2 | Appendix 2 | 14 December 2016 | Study Acknowledgement |

## Appendix 1. ENCePP Checklist for Study Protocols

*ENCePP Checklist for Study Protocols (Revision 3)*
*Adopted by the ENCePP Steering Group on 01/07/2016*

**Study title:**
Multicenter, 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®

**Study reference number:**
GS-EU-174-1846

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[3] | ☒ | ☐ | ☐ | 6 |
| 1.1.2 End of data collection[4] | ☒ | ☐ | ☐ | 6 |
| 1.1.3 Study progress report(s) | ☒ | ☐ | ☐ | 6 |
| 1.1.4 Interim progress report(s) | ☐ | ☒ | ☐ | |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 6 |

Comments:

| |
|---|
| |

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | | | | |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 7 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 8 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 9 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☒ | ☐ | - |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | - |

Comments:

| |
|---|
| Main aim to describe rates and proportions, without a priori hypotheses formulation. |

[3] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[4] Date from which the analytical dataset is completely available.

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design) | ☒ | ☐ | ☐ | 9.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 9.2 |
| 3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk) | ☒ | ☐ | ☐ | 9.5 |
| 3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☒ | ☐ | ☐ | 9.7 |
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 9.3 |

Comments:

| |
|---|
| |

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9.2 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period? | ☒ | ☐ | ☐ | 9.2 |
| 4.2.2 Age and sex? | ☒ | ☐ | ☐ | 9.2 |
| 4.2.3 Country of origin? | ☒ | ☐ | ☐ | 9.2 |
| 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | 9.2 |
| 4.2.5 Duration of follow-up? | ☒ | ☐ | ☐ | 9.2 |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.5 |

Comments:

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|---|
| |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 9.2 |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 9.2 |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☒ | ☐ | ☐ | 9.2 |
| 5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☒ | ☐ | ☐ | 9.2 |

Comments:

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| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | 8 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 9 |
| 6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management) | ☐ | ☒ | ☐ | |

Comments:

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| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol describe how confounding will be addressed in the study? | ☒ | ☐ | ☐ | 9.7 |
| 7.1.1. Does the protocol address confounding by indication if applicable? | ☒ | ☐ | ☐ | 9.9 |
| 7.2 Does the protocol address: | | | | |
| 7.2.1. Selection biases (e.g. healthy user bias) | ☒ | ☐ | ☐ | 9.9 |
| 7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias) | ☒ | ☐ | ☐ | 9.9 |
| 7.3 Does the protocol address the validity of the study covariates? | ☒ | ☐ | ☐ | 9.3 |

Comments:

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| **Section 8: Effect modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☒ | ☐ | ☐ | 9.7 |

Comments:

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| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 9.2 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.2 |
| 9.1.3 Covariates? | ☒ | ☐ | ☐ | 9.2 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 9.3 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.3 |
| 9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 9.3 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 9.7 |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 9.7 |
| 9.3.3 Covariates? | ☐ | ☒ | ☐ | |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 9.6 |

Comments:

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| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 9.7 |
| 10.2 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7 |
| 10.3 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.7 |
| 10.4 Does the plan describe methods for adjusting for confounding? | ☒ | ☐ | ☐ | 9.7 |
| 10.5 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.7 |
| 10.6 Is sample size and/or statistical power estimated? | ☒ | ☐ | ☐ | 9.5 |

Comments:

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| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 9.6 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.8 |
| 11.3 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 9.10/ 12 |

Comments:

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| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☒ | ☐ | ☐ | 9.9 |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 9.5 |

Comments:

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| Section 13: Ethical issues | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | 10 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☒ | ☐ | ☐ | 10 |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 10 |

Comments:

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| Section 14: Amendments and deviations | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 5 |

Comments:

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| Section 15: Plans for communication of study results | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 12 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12 |

Comments:

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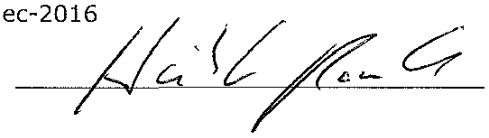
Name of the main author of the protocol: Heribert Ramroth

Date: 14-Dec-2016

Signature: 

**Appendix 2. Study Acknowledgement**

**GILEAD SCIENCES EUROPE LTD.**
***UNITED KINGDOM***

**STUDY ACKNOWLEDGEMENT**

***MULTICENTER, 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®.***
***(PROTOCOL VERSION 2.0: 14 DECEMBER 2016)***

This protocol has been approved by Gilead Sciences Europe Ltd The following signature documents this approval.

Heribert Ramroth
Author

Signature

14-Dec 2016

Date

Anne-Ruth van Troostenburg de Bruyn
Gilead EU QPPV

Signature

14 Dec 2016

Date

## INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences Europe Ltd. I will discuss this material with them to ensure that they are fully informed about the study.

| | |
|---|---|
| Principal Investigator Name (Printed) | Signature |
| Date | Site Number |