NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY

Study Title	**VIR-Life**: Prospective assessment of the real-life treatment outcomes of six years of Viread® in CHB following-up on the German Multicenter Non-Interventional Study **GEMINIS**
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Indication	Chronic hepatitis B
Product reference / **Procedure number**	EU/1/01/200/001 EU/1/01/200/002
Joint PASS	No
Country (-ies) of study	Germany
Marketing authorization holder / Sponsor:	Marketing authorization holder: Gilead Sciences International Limited Cambridge CB21 6GT, United Kingdom Sponsor: Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried, Germany
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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AASLD	American Association for the Study of Liver Diseases
AR	Adverse drug reaction
AE	Adverse event
AFP	Alfa fetal protein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
C-G	Cockcroft-Gault
CHB	Chronic Hepatitis B
CrCl	Creatinine clearance
eCRF	Electronic case record form
CRO	Contract research organization
DNA	Deoxyribonucleic acid
DSPH	Drug Safety & Public Health
EASL	European Association for the Study of the Liver
EMA	European Medicines Agency
EudraCT	European Clinical Trials database
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practices
GEP	Good Epidemiological Practices (guidelines for)
GSI	Gilead Sciences, Inc.
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HDV	Hepatitis Delta Virus
HIV	Human immunodeficiency virus
IQR	Inter quartile ranges
IV	Intravenous
IFN	Interferon
LLQ	Lower limit of quantification
MDRD	Modification of Diet in Renal Disease
NIS	Non-interventional study
PEG	Polyethylene glycol
SAE	Serious adverse event
SD	Standard Deviation
SmPC	Summary of product characteristics
TDF	tenofovir disoproxil (as fumarate)

Cohort	Group of people characterized by a common experience (e.g., occurrence of a specified disease, exposure to a given medication)
Cases	Group of individuals with the condition of interest
Controls	Group of individuals without the condition of interest but are otherwise similar to cases, or unexposed to or not treated with the agent of interest
Exposure	A variable whose effect is of interest and is being studied
Outcome	An event (such as disease occurrence or death) that is studied in relation to exposure
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
Confounding by indication	A patient characteristic that is related to the outcome of interest and which influences treatment choice (exposure)
Effect modifier	If an effect measure varies within categories or levels of a variable, that variable is described as an effect-measure modifier
Bias	Systemic error in the design, conduct or analysis of a study that results in a mistaken estimate
Prevalence	Proportion of persons with the exposure/outcome at a specific point in time
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
Risk	The proportion of a fixed cohort in which an outcome occurs during a specified period of time
Relative Risk (RR)	A general term that can refer to the ratio of 2 risks or the ratio of 2 rates
Odds	The ratio of the probability that an event will happen to the probability that it will not happen
Internal validity	Whether or not the study provides an unbiased estimate of what it claims to estimate
External validity (generalizability)	Whether or not the results from the study can be generalized to other populations

3. RESPONSIBLE PARTIES

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4. PROTOCOL SYNOPSIS/ABSTRACT

Gilead Sciences GmbH
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Study Title:

VIR-Life**: Prospective assessment of the real-life treatment outcomes of six years of Viread® in CHB following-up on the German Multicenter Non-Interventional Study **GEMINIS

Rationale and Background:

The efficacy and safety of TDF is well established by data from randomized controlled trials (RCTs) in various patient populations, such as the Gilead sponsored studies GS-US-174-102 and GS-US-174-103 in treatment naïve patients, or GS-US-174-106, GS-US-174-115 and GS-US-174-121 in patients previously treated with oral antivirals.

Clinical studies, such as RCT´s investigate the efficacy and safety of a drug in predefined populations, therefore providing high internal validity. Data generated in real-life settings allows for investigating the external validity of the effects seen in RCTs. Thus the real-life treatment outcomes of the drug can be investigated in observational studies such as non-interventional studies (NIS).

The real-life treatment outcomes of Viread® have been investigated in GEMINIS for a period of 3 years. VIR-Life is the roll-over non-interventional study from GEMINIS to allow the prospective evaluation of the real-life treatment outcomes for additional 3 years.

Research Question and Objectives:

The primary objective of this study is as follows:

- Prospectively describe the virological response, defined as HBV-DNA concentration, during 6 years Viread® treatment for CHB in a real life setting.

The secondary objectives of this study are to evaluate the:

- Safety and tolerability of 6 years of Viread® in CHB in a real life setting
  - Adverse drug reactions (AR) (unrelated Adverse Events (AEs) will also be listed in the report)
  - Renal safety
    - Estimated creatinine clearance (eCrCl)
    - Serum creatinine level

- Serum phosphorus level

- Histological improvement of the liver

Study Design: Prospective non-interventional multicenter cohort post-authorization safety study (single treatment case series)

Population / Setting: Roll-over study in adult, HBV-mono-infected CHB patients who started CHB treatment with Viread® in GEMINIS

Duration of Study: 3 years after rolling over from GEMINIS

Variables: Documentation of routine visits at month 48, 60 and 72, covering the following parameters (if available):

- Weight
- Serum HBV-DNA concentration
- HBeAg, anti-HBe; HBsAg, antiHBs
- ALT-level
- Serum creatinine, eCrCL, serum phosphorus
- Albumine, Bilirubine, Thrombocytes, Prothrombine time (i.e. Quick value)
- Liver histology staging, transient elastography
- HCC development
- Co-morbidities,
- Incident co-infections with HIV, HCV or HDV
- Amount of alcohol consumption
- Adverse events
- Special Situations; pregnancies, medication error, abuse, misuse, overdose, lack of effect, adverse events in infants following exposure from breastfeeding and adverse events associated with product complaints
- Dosing of Viread®
- Reason for discontinuation of Viread®, if applicable

Data Sources: Collection of routine visit data via eCRF

Study Size: 250 patients

Data Analysis:

- Descriptive analysis:

  Categorical and ordinal variables will be described by sample size and the frequency of each modality (over the total number of responses).

  Quantitative variables will be described by the number of responses, mean, standard deviation, minimum, maximum & median of all available data.

- Inferential analysis:

  When deemed necessary, sub-group comparisons and/or between time point comparisons may be implemented.

- Multivariate analysis:

  The potential dependence of treatment outcome frequency with other outcome variables or baseline characteristics will be investigated through methods of multivariate analysis.

Milestones:

Start of data collection : approx. May 2013

End of Data collection: December 2016

Interim analysis: planned for Sept. 2014 (year 4 data) and Sept. 2015 (year 5 data)

Final Study report: April 2017 (year 6 data)

Publication: submission in Q2-3 2017

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) and 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
none				

6. MILESTONES

Milestone	Planned date
Start of data collection	Approx. May 2013
End of data collection	December 2016
Year four interim analysis	September 2014
Year five interim analysis	September 2015
Registration in the EU PAS register	before start of data entry into the eCRF
Final report of study results	April 2017
Submission of study report to authority	Q2-3 2017

7. RATIONALE AND BACKGROUND

7.1. Background and medical relevance of chronic hepatitis B (CHB)

Chronic hepatitis B is a serious global health care problem and a major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). Worldwide, approximately 350–400 million people have developed chronic hepatitis B and approximately 1 million people die annually of complications of chronic hepatitis B [1].

Following acute hepatitis B infection, approximately 5% of adults and up to 90% of infected babies fail to produce an immune response adequate to clear the infection; these individuals become chronic carriers of the virus [2–4].

Chronic hepatitis B has a broad clinical spectrum, ranging from asymptomatic, slowly progressive illness to severe, and more rapidly progressive liver disease. Chronic hepatitis B may remain quiescent for many years. However, 15–40% of patients with chronic hepatitis B will eventually develop serious liver disease and complications, such as cirrhosis, hepatic decompensation, and HCC [1]. In patients with chronic hepatitis B, the annual probability of developing cirrhosis varies from 0.1% to 1.0%, depending on the duration of HBV replication, the severity of disease, and the presence of concomitant risk factors. Worldwide, chronic viral Hepatitis B contributes to 30 % of all cases of liver cirrhosis and 53% of the cases of HCC [5].

Asian studies suggest that the level of viral replication is strongly correlated with disease progression towards cirrhosis and HCC [6,7] and that effective suppression of viral replication can alter the course of the disease and decrease morbidity, even in advanced liver disease [8]. However, the clinical benefit is lost if viral replication resumes as a result of emerging resistance mutations [8,9].

Although the hepatitis B virus is distributed worldwide, there are hyper endemic areas (>50% of the population anti-HBc positive) in Asia, the South Pacific, in sub-Sahara Africa, in South America and the Middle East. Areas with intermediate prevalence (10-15%) are the Mediterranean Region and Eastern Europe [2].

Germany is among the countries with low prevalence of chronic HBV infection. [10,11]. In the 1998 national health survey, the sero-prevalence of hepatitis B surface antigen in Germany was 0.6% [12]. Population migration is changing the prevalence and incidence of the HBV disease in several low endemic countries in Europe [2,13,14]. In Germany, especially during the 1960s economic boom, foreign workers were recruited under government programmes to work in Germany [15]. The majority of these workers and their families who migrated to Germany originate from areas with intermediate HBV prevalence, e.g. Turkey and Italy. In the 1990s, people with German descent from the countries of the former Soviet Union and Warsaw Pact States were allowed to repatriate to Germany under a special programme [16]. The effect of migration on the CHB prevalence in Germany is also reflected in a cross sectional study with 1535 patients with replicative chronic HBV infection (HBV DNA $>10^4$ copies/ml) living in Germany[13]. It was demonstrated that only 31.7% of the patients were originally from Germany while 68.3% of the CHB patients were born in other countries, mainly Turkey (22.4%), countries of the former Soviet Union (11.2%) and South-East Asia (9.4%) [13].

A safe and effective vaccination against HBV can support the prevention of an infection. It offers, however, no option of cure for those 350-400 million people worldwide, who are estimated to be chronically infected [1].

A significant proportion of chronic HBV carriers are infected with a variant that produces little to no hepatitis B e antigen (HBeAg) (commonly refered to as HBeAg-negative disease). Community based studies from different parts of the world have shown that the prevalence of HBeAg-negative disease can exceed 70%. For example, in Italy over the past decades, 90% of the patients with CHB were reported as HBeAg-negative [17]. The prevalence of HBeAg-negative CHB appears to vary geographically, with the greatest prevalence in the Mediterranean region (33%), followed by 15% in the Asia Pacific region and 14% in the United States and Northern Europe. Overall, the prevalence of HBeAg-negative CHB is apparently increasing worldwide [18].

This HBeAg-negative form of CHB is distributed worldwide with an increasing incidence and is becoming the predominant type of CHB in several countries, particularly in Europe. In patients who are infected with genotypes B and D, development of HBeAg-negative CHB occurs much more frequently than in patients infected with the other HBV genotypes, particularly genotypes A and C [19].

HBeAg-negative CHB disease is typically seen in older patients and develops during the course of HBeAg-positive HBV infection either during or after HBeAg loss or seroconversion [20]. Patients may have persistent or intermittent increases in ALT levels with lower levels of replicating virus as measured by serum HBV DNA. Frequently patients who present with HBeAg-negative disease have more advanced disease. Development of cirrhosis is frequent, associated with increased morbidity and mortality; if left untreated, 15% to 20% of patients will develop liver decompensation within 5 years, 15% will die within 5 years of any cause, and 15% to 30% will die of liver disease. Therefore, the need for effective treatment of HBeAg-negative CHB patients is obvious [21].

The goal of therapy for hepatitis B is to improve quality of life, morbidity and mortality by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death [2–4]. This goal can be achieved if HBV replication can be suppressed in a sustained manner, the accompanying reduction in histological activity of chronic hepatitis lessening the risk of cirrhosis and decreasing the risk of HCC in non-cirrhotic patients and probably also, but to a lesser extent, in cirrhotic patients [2–4]. However, HBV infection cannot be completely eradicated due to persistence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes [22].

According to current European and German clinical practice guidelines for the management of CHB [2,4] the indications for treatment are generally the same for both HBeAg-positive and HBeAg-negative CHB. It is based mainly on the combination of three criteria:

- Serum HBV DNA levels
- Serum ALT levels
- Severity of liver disease

According to the EASL Clinical Practice Guidelines [2], Patients should be considered for treatment when they have “HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal (ULN) and severity of liver disease assessed by liver biopsy (or non-invasive markers once validated in HBV-infected patients) showing moderate to severe active necroinflammation and/or at least moderate fibrosis using a standardised scoring system”. In patients who fulfill the above criteria for HBV DNA and histological severity of liver disease, treatment may be initiated even if ALT levels are normal.
Indications for treatment may also take into account age, health status, family history of HCC or cirrhosis and extrahepatic manifestations.

In the following special groups of patients, treatment is highly recommended:

- Patients with compensated cirrhosis with detectable HBV-DNA should be considered for treatment even if ALT levels are normal and/or HBV-DNA levels are below 2000 IU/ml [4].

- Patients with decompensated cirrhosis and detectable HBV DNA require urgent antiviral treatment.

The following groups of patients usually do not require treatment, however, treatment indication may be considered under certain circumstances:

- Immunotolerant patients: most patients under 30 years of age with persistently normal ALT levels and a high HBV-DNA level, without any suspicion of liver disease and without a family history of HCC or cirrhosis do not require immediate liver biopsy or therapy. Follow-up is mandatory. Consider liver biopsy or even therapy in such patients over 30 years of age and/or with a family history of HCC or cirrhosis

- HBeAg-negative patients with persistently normal ALT levels and HBV DNA levels above 2000 but below 20,000 IU/ml, without any evidence of liver disease, do not require immediate liver biopsy or therapy.

Currently, there are two distinct therapeutic principles for the treatment of chronic hepatitis B: Firstly, (Peg)-Interferon alpha (IFN) for subcutaneous injection, and secondly, orally administered HBV-polymerase inhibitors with direct antiviral activity. These are, in order of marketing approval date, Lamivudine (LAM), Adefovir dipivoxil (ADV), Entecavir (ETV), Telbivudine (LdT) and Tenofovir disoproxil (as fumarate, TDF).

Interferon alpha offers only a moderate antiviral effect, however the theoretical advantages are the absence of resistance and the potential immune modulating effect. Frequent side effects and the generally poor tolerance limit the number of potential patients suitable for treatment with IFN. IFN is contra-indicated in patients with decompensated liver disease [2–4].

Entecavir and TDF, both potent HBV inhibitors with a high barrier to resistance, are recommended as fist-line treatment in national German as well as international treatment guidelines [2–4]. According to the EASL Guidelines, the other three nucleos(t)ide analogues (NAs) should only be used in the treatment of CHB if more potent drugs with high barrier to resistance are not available or appropriate [2]. As of Lamivudine, the EMA has restricted the indication for Zeffix® (LAM) in 2010. Initiation of lamivudine treatment should now "only be considered when the use of an alternative antiviral agent with a higher genetic barrier is not available or appropriate" [23]

When viral resistance against an administered medication emerges, the German national guidelines [4] published in 2011, as well as the European Guidelines (EASL) published in 2012 [2] recommend switching to a non-cross-resistant second drug or adding it on top. As the choice of drugs with complementary resistance profiles is limited, the therapeutic choice should be driven by an effort to effectively avoid any development of resistance by using the most potent agents with the highest barrier to resistance in the initial first-line therapy of CHB [2,4].

7.2. Tenofovir Disoproxil Fumarate (Tenofovir DF)

Tenofovir disoproxil (245 mg, as fumarate; TDF, Viread®) is an oral prodrug of Tenofovir, a acyclic nucleotide (nucleoside monophosphate) analogue.

Tenofovir diphosphate, the activated (phosporylated) compound, is a potent and selective inhibitor of both human immunodeficiency virus type 1 (HIV-1) reverse transcriptase and hepatitis B virus (HBV) polymerase, inhibiting viral polymerases by direct competitive binding with the natural deoxyribonucleotide substrate (i.e., deoxyadenosine triphosphate, dATP) and, after incorporation into DNA, by DNA chain termination.

Tenofovir DF is the active ingredient in Viread®, which is approved as a once-daily, film-coated tablet for the treatment of HIV-1 infection in more than 50 countries worldwide. Tenofovir DF was approved in 2008 for the treatment of chronic hepatitis B in the European Union, Turkey, New Zealand, Australia, Canada, and in the United States.

Efficacy and safety of TDF in currently being investigated in mono-infected HBV patients in the open label follow up of the two phase III pivotal RCTs (GS-US-174-102 and GS-US-174-103). The first 48 weeks compared in a double blind randomized controlled design the efficacy and safety of TDF vs. Adefovirdipivoxil 10 mg QD in CHB. TDF showed superior anti-HBV activity compared to Adefovir both in HBeAg negative and positive patients [24].

Experience in patients with compensated liver disease at 48 weeks (studies GS-US-174-0102 and GS-US-174-0103)

At week 48, viral suppression occurred in more HBeAg-negative patients receiving TDF than patients receiving Adefovir (93% vs. 63%, P<0.001) and in more HBeAg-positive patients receiving TDF than patients receiving Adefovir (76% vs. 13%, P<0.001). Significantly more HBeAg-positive patients treated with TDF than those treated with Adefovir had normalized alanine aminotransferase levels (68% vs. 54%, P=0.03) and loss of hepatitis B surface antigen (3% vs. 0%, P=0.02). At week 48, amino acid substitutions within HBV DNA polymerase associated with phenotypic resistance to TDF or other drugs to treat HBV infection had not developed in any of the patients. TDF produced a similar HBV DNA response in patients who had previously received Lamivudine and in those who had not. The safety profile was similar for the two treatments in both studies [24,25].

Experience beyond 48 weeks

In studies GS-US-174-0102 and GS-US-174-0103, after receiving double-blind treatment for 48 weeks (either TDF 245 mg or Adefovir 10 mg), patients rolled over with no interruption in treatment to open-label TDF. In studies GS-US-174-0102 and GS-US-174-0103, 81% and 70% of patients continued in the study through to 240 weeks, respectively. At weeks 96, 144, 192 and 240, viral suppression, biochemical and serological responses were maintained with continued TDF treatment [25,26].

Paired baseline and week 240 liver biopsy data were available for 331/489 patients who remained in studies GS-US-174-0102 and GS-US-174-0103 (see Table 5 below). Ninety-five percent (225/237) of patients without cirrhosis at baseline and 99% (93/94) of patients with cirrhosis at baseline had either no change or an improvement in fibrosis (Ishak fibrosis score). Of the 94 patients with cirrhosis at baseline (Ishak fibrosis score 5-6), 26% (24) experienced no change in Ishak fibrosis score and 72% (68) experienced regression of cirrhosis by week 240 with a reduction in Ishak fibrosis score of at least 2 points [25,27].

Clinical resistance

426 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 TDF arm (i.e. excluding patients who received double-blind Adefovir and then switched to open-label TDF) with HBV DNA > 400 copies/ml at week 48 (n = 39), week 96 (n = 24), week 144
(n = 6), week 192 (n = 5) and week 240 (n = 4) on TDF monotherapy, showed that no mutations associated with TDF resistance have developed [25].

7.3. GEMINIS

The GEMINIS Study
GEMINIS was the first prospective non-interventional observational study on the real-life treatment outcomes and the patterns of use of three years of Viread® in Germany. The study recruited adult patients with HBV mono-infection. At inclusion, patients were TDF-naïve, however, previous treatment for CHB was accepted. Documentation and treatment decisions were at the sole discretion of the participating physician.

Baseline Characteristics
35 centers (20% hospitals, 80% office-based) enrolled 400 CHB patients from May 2009 - May 2010. Most frequent countries of birth were: 31% Germany, 19% Turkey, 8.5% Russia, 6.5% Vietnam, 3% Poland. The main reason for using Viread® was persistent viremia (25%) or virologic relapse despite previous treatment (10%). 90% initiated TDF monotherapy. Additional baseline characteristic are summarized in table 1.

Table 1: Baseline patient characteristics

Age • mean (+/-SD) [years]	44.5 (+/- 13.8)
• 18-65; > 65 [years]	91%; 9%
Male	69%
Caucasian	76%
ALT > ULN*	55%
HBeAg-negative	69%
Serum HBV DNA[IU/ml] Median (IQR) • entire group (N=400) $3.6x10^3$ ($40-4.0x10^5$) • naïve patients (n=183) $6.9x10^4$ ($2.8x10^3$ - $6.8x10^6$) • experienced patients (n=217) $2.6x10^2$ ($20 - 2.0x10^4$)	
Treatment naïve	46%
Biopsy done (fibrosis score ≥ 2**)	14% (37%)
Elastography data (advanced fibrosis***)	17% (22%)
Cirrhosis***	11%
TDF monotherapy	92%
*ULN: Male ≤ 43 IU/L, female ≤ 34 IU/L; **by Desmet-Scheuer or Metavir; *** as defined by physician	

GEMINIS – Results after 24 month of follow up

Viread® was primarily used as monotherapy. After 24 month of follow up, HBV replication was suppressed through 24 months in the majority of treatment naïve and experienced patients, regardless of pre-treatment status. HBeAg-loss/-seroconversion was documented in 23 % and 19 % of HBeAg+ patients, respectively. A 5.1 % cumulative probability for HBsAg-loss in HBeAg+ patients was observed. This rate is comparable to the 96 week result of TDF registration study 103 [24]. Two patients HBeAg-negative at baseline lost HBsAg. The overall safety profile of Viread®, including renal safety, was very favorable in this real-life setting (Table 2) [28].

Table 2: 2 years virological, serological and biochemical results[28]

	Treatment-naïve (n=183)	**Treatment - experienced (n=217)**
HBV-DNA < 169 IU/ml • HBeAg-positive • HBeAg-negative • prior LAM+ADV • prior ETV	 88 % 94 % NA NA	 94 % 97 % 100 % 96 %
HBV-DNA < 69 IU/ml • HBeAg-positive • HBeAg-negative • prior LAM+ADV • prior ETV	 81 % 80 % NA NA	 84 % 90 % 89 % 92 %
ALT < ULN*	71%	77 %
HBeAg-loss	23%	
HBeAg-seroconversion	19 %	
HBsAg-loss**(HBeAg+ at baseline)	5.1 %	
HBsAg-loss (HBeAg- at baseline)	2/226 with documented HBsAg	
*ULN: Male ≤ 43 IU/L, female ≤ 34 IU/L; ** Kaplan Meier Estimate (Cumulative probability in patients with documented HBsAg)		

Table 3: Creatine-clearance during follow-up

Estimated CrCl (Cockcroft-Gault)	Baseline (n = 361)	Month 6 (n = 299)	Month 12 (n = 289)	Month 24 (n = 255)
Mean [ml/min] (SD)	106.9 (31.6)	105.9 (33.8)	104.7 (31.7)	102.2 (31.3)
Mean change [ml/min] (SD)		-1.4 (16.1)	-3.2 (16.2)	-3.4 (15.4)

8. RESEARCH QUESTION AND OBJECTIVES

Clinical studies, such as RCT´s investigate the efficacy and safety of a drug in predefined populations, therefore providing high internal validity. Data generated in real-life settings allows for investigating the external validity of the effects seen in RCTs. Thus the real-life treatment outcomes of the drug can be investigated in observational studies such as non-interventional studies (NIS).

The real-life treatment outcomes of Viread® have been investigated in GEMINIS for a period of 3 years. VIR-Life is the roll-over non-interventional study from GEMINIS to allow for the continued prospective evaluation of the real-life treatment outcomes for additional 3 years.

The primary objective of this study is as follows:

- Prospectively describe the virological response, defined as HBV-DNA concentration, during 6 years Viread® treatment for CHB in a real life setting.

The secondary objectives of this study are to evaluate the:

- To describe the safety and tolerability of 6 years of Viread® in CHB in a real life setting, and report the following:
  - Adverse drug reactions (ADR) (unrelated Adverse Events (AEs) will also be listed in the report)
  - Renal safety
    - Estimated creatinine clearance (eCrCl)
    - Serum creatinine level
    - Serum phosphorus level
- Histological improvement of the liver

9. RESEARCH METHODS

9.1. Study Design

VIR-Life is a prospective non-interventional multicenter cohort post-authorization safety study of an individual case series. The study will follow patients who have been prospectively observed through three years in the GEMINIS NIS for additional three years. The study is designed as a multicenter, non-interventional observational study, in accordance with the German Drug Act (§4 Abs 23 Satz 3 AMG, and §4 Abs 34 AMG, §63f AMG).

9.1.1. Rationale for the study design

Tenofovir disoproxil 245 mg (as Fumarate; TDF; Viread®), is licensed in the EU for the treatment of chronic Hepatitis B since 2008. The efficacy and safety of TDF have been reported in hepatitis B virus mono-infection in HBeAg-negative patients and HBeAg-positive patients [24,26]. In two phase III studies evaluating the efficacy and safety of TDF vs. Adefovir dipivoxil, control of viral load was significantly higher in the TDF arm compared to the Adefovir arm. At 48 weeks, the proportions of patients with a viral load < 400 copies/mL were 93% vs. 63% for study GS-US-174-0102 (HBeAg-negative) and 76% vs. 13% for study GS-US-174-0103 (HBeAg-positive), respectively ($p < 0.001$ for the 2 studies; ITT analysis). Furthermore, in study GS-US-174-0103, the rate of negativation of HBsAg was significantly higher in the TDF arm (3.2% vs 0%; $p = 0.018$)[24]. No HBV resistance mutation has been reported in patients treated with TDF and the safety profile of TDF is satisfactory [24–26,29].

However, patients included in phase III clinical trials are selected according to strict, inclusion and exclusion criteria. These RCTs are designed to investigate the efficacy and safety of a drug in predefined populations, therefore providing high internal validity. The characteristics of patients treated in routine clinical practice after marketing of the product can therefore differ considerably from those on which the product was evaluated. Special subpopulations excluded from therapeutic trials may be treated: elderly, comorbidities, patients previously treated for hepatitis B, etc.
Data generated in real-life settings allows for investigating the external validity of the effects observed in RCTs. The treatment outcomes in real-life of the drug can be investigated in observational studies such as a non-interventional cohort study.

VIR-Life is designed to evaluate the treatment outcomes and the patterns of use of Viread® in routine clinical practice in patients infected by the hepatitis B virus in Germany. VIR-Life is a 3-year roll-over non-interventional cohort study from GEMINIS, the first non-interventional cohort study on the use of Viread® in Germany. VIR-Life will complete these data, concerning safety, clinical, virological, biochemical, serological outcomes and patterns of use of Viread® in patients with chronic HBV infection in clinical practice for a total of 6 years.

9.2. Setting / Study Population

VIR-Life is a roll-over study in adult, HBV-mono-infected CHB patients who started CHB treatment with Viread® in GEMINIS. Patients in GEMINIS, and therefore now in VIR-Life, are collected nationwide in a real-life setting at approximately 25 of the initial 35 GEMINIS sites. The study sites are either office based physicians with hepatological focus or hospitals with dedicated hepatological outpatient care units.

If the physician decided to treat and document a patient monoinfected with HBV with Viread® in GEMINIS and later in VIR-Life, he/she can document the course of the therapy (at months 48, 60 and 72) within the scope of a non-interventional study (NIS).

Eligibility criteria:
Patients completing 3 years in GEMINIS and still receiving a Viread®-containing regimen may roll over into this study

9.2.1. Rationale for the selection of the study sites

In Germany approx. 80% of the CHB patients under treatment are followed up by specialized centers. To obtain a representative view on the medical practice of CHB patients in Germany, out of the 35 specialized hepatology sites from GEMINIS approximately 25 centers which enrolled at least 5 patients into GEMINIS will be invited to participate in VIR-Life. These sites are primarily gastroenterological offices with designated focus on hepatology, as well as some of the largest hospital liver outpatient care units. Disproportionate distribution of sites across the federal states of Germany can be explained by unequal prevalence of chronic hepatitis B (e.g. East/West, or rural/-urban disproportion of CHB).

9.2.2. Rationale for the patient number

The target number of 250 patients, followed up at approximately 25 well distributed study sites, supports representativeness of the drawn sample to the overall CHB-population currently treated with Viread® in Germany. It is expected that the patient number of 250 supports conclusions on the treatment results in major subpopulations (e.g., elderly patients). The 6 year long term follow up data from 250 patients is expected to contribute to the safety profile of Viread in CHB patients in a real life setting.

9.2.3. Prevention of bias

- In GEMINIS all centers with large (>100) CHB patient volume were invited to participate in the study, however, disproportionate distributions across the federal states of Germany were expected due to the unequal distribution of prevalence of chronic hepatitis B.
- GEMINIS was open for all patients chronically (mono-) infected with Hepatitis B Virus, potentially eligible for treatment under current guidelines as stated earlier in the introduction section. Enrollment was allowed for to up to 400 patients treated with Viread®.
- To combat selection bias the participating sites in GEMINIS were asked to enroll every single new patient qualifying for inclusion until the NIS is fully recruited.
- For VIR-Life, all eligible GEMINIS patients remaining in the 25 participating sites are asked to be rolled over into the VIR-Life study
- For all eligible patients not enrolling into VIR-Life the sites have to document respective reasons (lost to follow-up, no signed ICF, death).

9.3. Variables

In this non-interventional post-authorization safety study the time the subject has taken Viread® is the exposure of interest. Outcome variables are the collected clinical and laboratory parameters, i.e.:

Primary outcome variable:

- Virology
    - Serum HBV-DNA

Secondary outcome parameters are:

- Serology
    - HBeAg/anti-HBe (qualitative)
    - HBsAg/anti-HBs (qualitative)
- Biochemistry parameter
    - ALT
- Renal function parameters

  - Serum creatinine
  - Creatinine Clearance (estimated via Cockcroft-Gault, MDRD or CKD Epi formula)
  - Serum phosphorus
- Liver synthesis parameters
  - Albumin
  - Bilirubin
  - Thrombocytes
  - Prothrombin time [i.e. Quick-Value]
- Safety parameters
  - Adverse events
  - Special Situations; pregnancies, medication error, abuse, misuse, overdose, lack of effect, adverse events in infants following exposure from breastfeeding and adverse events associated with product complaints
- Incident cases of co-infections
  - HIV
  - HCV
  - HDV
- Co-morbidities (incident and prevalent cases)
  - Ascites
  - Jaundice
  - Diabetes mellitus
  - Lipometabolic disorders
  - Coronary heart disease
  - Hypertension

- Alcohol consumption per week

- Liver histology and HCC
  - Liver biopsy results
  - Fibroscan
  - HCC
- Dosing and dose alterations
- Combination therapy
- Treatment discontinuations
  - Patients discontinuing Viread should not be discontinued from study follow up. All study variables in these patients shall be documented in VIR-life until month 72

9.4. Data Sources

The conduct of a non-interventional study (NIS) requires, according to definition of a ”non-interventional study“ in terms of Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 1), that the protocol does not stipulate or dictate on the diagnosis, therapeutic decisions and follow-up of the individual patient. The study only observes and collects the use of a drug and the corresponding clinical outcome by the treating physician in the specific indication.

Clinical data is collected from the physician’s documentation of the patient’s visit in patient medical records that is closest to the documentation time point (month 48, 60 and 72), each +/- 3 months. Primary data sources are electronic medical records, where available or paper records at the participating sites. This data will then be manually transcribed by the investigator into electronic case record form (eCRF).

In this non-interventional follow up study, the following findings are of special interest and information will be collected accordingly:

9.4.1. Baseline

VIR-life is the extended follow up of GEMINIS. Therefore, VIR-life baseline data is the data that was collected at GEMINS baseline.

9.4.2. During VIR-Life follow up and at end of follow up (month 48, 60 and 72):

- HBV- virology and serology parameters
- Biochemical serum-parameters
  - ALT
- Renal safety parameters
  - Serum creatinine, eCrCl, serum phosphorus
- Liver synthesis parameters
  - Albumin, bilirubin, thrombocytes, prothrombin time (Quick-Value)
- Liver histology, elastography, incident HCC
- Co-morbidities, Co-infections, alcohol consumption
- Adverse events
- Special Situations; pregnancies, medication error, abuse, misuse, overdose, lack of effect, adverse events in infants following breastfeeding, and adverse events associated with product complaints
- Dosing of Viread®
- Combination therapy
- Reason for discontinuation of Viread®, if applicable

9.5. Study Size

The planned study size is 250 patients. This number is pre-specified by the number of eligible patients to be rolled over from GEMINIS in the participating 25 study sites.

To maximize the possible sample size, all eligible patients in the participating sites shall be rolled over into the study.

9.6. Data Management

The study will use an electronic data entry system (eCRF), all users will receive specific access codes to enable them to enter their data. The electronic data entry system will contain automatic checks for data completeness and inconsistent data.

9.7. Data Analysis

- Descriptive analysis:

Categorical and ordinal variables will be described by sample size and the frequency of each modality (over the total number of responses).

Quantitative variables will be described by the number of responses, mean, standard deviation, minimum, maximum, median of all available data.

- Inferential analysis:

When deemed necessary, sub-group comparisons and/or between time point comparisons may be implemented.
Patients who are lost to follow-up or discontinue therapy for any reason, including leaving the study for non-medical reasons will be censored at the discontinuation date. Person time will be computed from baseline to discontinuation and used as such for any time to event analysis.

- Multivariate analysis

The potential dependence of treatment outcome frequency with other variables or baseline characteristics will be investigated through multivariate analysis.

9.8. Quality Control

The electronic data entry system will contain automatic checks for data completeness and inconsistent data.

9.9. Limitations of the research methods

In a non-interventional study all decisions on the management of the patient are made solely by the treating physician. This also includes the frequency of the evaluation of lab values and other collected variables. Documentation of study variables must not be made obligatory. Missing data of unpredictable extent can occur.

9.10. Other aspects

VIR-Life is the roll-over non-interventional study following GEMINIS. The study is designed to enable the prospective evaluation of the real-life treatment outcomes of Viread for a total of 6 years. This implies that the sample size is predefined by the number of available patients rolling over from GEMINIS.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Good Pharmacoepidemiology Practices

The investigator will conduct this study in accordance with the laws and regulations of the country and the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

10.2. Institutional Ethics Committee (IEC) Review

The protocol and any accompanying material to be provided to the subject (e.g. subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted to an *IEC*. The investigator will not begin to document data until approval from the *IEC* has been received.

10.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods and objectives of the study. The investigator must utilize the most current IEC approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person conducting the consent discussion.

10.4. Confidentiality

Subjects' anonymity will be strictly maintained. Only a unique subject identification code and the year of birth will be recorded in the eCRF system

The investigator agrees that all information received from Gilead 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

11.1. 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 unfavorable and/or unintended sign, symptom, or disease temporarily 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, medication error, drug abuse/misuse reports or reports of AEs in infants following exposure from breastfeeding. Preexisting events that increase in severity or change in nature during this non-interventional 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 and should be reported.

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

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed. These are considered to be preexisting conditions and should be documented on the medical history CRF (if applicable).

11.1.1. Adverse Reactions

An **adverse reaction** (AR) 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 the prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

11.1.2. 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.

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself. Therefore, if death occurred, the event that led to death needs to be reported as an SAE.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, is life-threatening, or meets any of the other definitions of an SAE, then it is an SAE.
- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis (and not the individual signs/symptoms) should be documented as the AE and/or SAE.

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

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Section 10.1**.** If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

11.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality, and for final review and confirmation of accuracy of event information and assessments.

11.2.1. Assessment of Causality for Study Drugs and Procedures

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 (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: A temporal relationship exists between the AE onset and administration of the drug that cannot be readily explained by the subject's clinical state or concomitant therapies. Or, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the drug. In case of cessation or reduction of the dose, the AE may abate or resolve and it may reappear upon rechallenge.

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

11.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to the CRO

During the defined study period (month 36 to months 72), each investigator has to document all Adverse Events he becomes aware of including seriousness and causality in the eCRF system within 24 hours. These are automatically forwarded via the eCRF system to the CRO safety department.

11.4. Special Situations Reports

11.4.1. Definitions of Special Situations

Special situation reports include reports of pregnancy; medication error, abuse, misuse, overdose; lack of effect; adverse events in infants following exposure from breastfeeding; and adverse events associated with product complaints.

A pregnancy report is used to report any pregnancy that occurs during the study.

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 or 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 a dose taken accidentally or intentionally that exceeds the dose as prescribed by the protocol or the maximal recommended daily dose as stated in the product labeling (as it applies to the daily dose for the subject in question). 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 labeling.

Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging, or distribution of the product.

11.4.2. Instructions for Reporting Special Situations

All special situations that occur during the defined study period are to be entered into the eCRF (Special Situations Form) within 24 hours of becoming aware of the special situation. These are automatically forwarded to the CRO Safety Dept. . (See 11.4.2.1 for reporting pregnancies.)

11.4.2.1. Instructions for Reporting Pregnancies

All pregnancies that occur during the defined study period and the outcome of the pregnancy are to be entered into the eCRF (Pregnancy Report/Outcome Form) within 24 hours of becoming aware of the pregnancy. These are automatically forwarded to the CRO Safety Dept. .

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 11.3.

The outcome should be entered into the eCRF using the Pregnancy Outcome Report Form.

Adverse events in infants following exposure from breastfeeding should be entered into the eCRF within 24h using the Special Situations Report Form, these will be automatically forwarded to the CRO Safety Dept.

11.5. Gilead Reporting Requirements

Gilead is responsible for reporting and analyzing reports of (S)AEs, (serious) adverse drug reactions (SARs), or suspected unexpected serious adverse reactions (SUSARs) as determined by country-specific legislation or regulations where the study is conducted. Gilead may be required to report to other regulatory agencies.

Assessment of expectedness for AEs and SAEs will be determined by Gilead using reference safety information specified in the relevant local label.

12. RESPONSIBILITIES / PLANS FOR DISSEMINATING STUDY RESULTS

12.1. Investigator Responsibilities

12.1.1. Retention of Records

This study relies on existing patient's medical records. These medical records have to be kept, handled and archived according to local legal requirements and regulations.

12.1.2. Inspections

The investigator will make available source documents or electronic source records for this study to appropriately qualified personnel from Gilead or its representatives.

12.1.3. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

12.2. Sponsor Responsibilities

12.2.1. Protocol Modifications

Protocol modifications, may be made only by Gilead. All protocol modifications will be submitted to the *IEC* in accordance with local requirements

12.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the applicable regulatory agencies. Gilead will ensure that the report meets the standards set out in the Guideline on Good Pharmacovigilance Practices (GVP). Note that an abbreviated report may be prepared in certain cases.

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead's request to

delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

12.3. Joint Investigator/Sponsor Responsibilities

12.3.1. Access to Information for Monitoring

In case of a monitoring visit, the investigator will provide the study monitor with direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

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

12.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory agencies or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory agency, the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide access to records, facilities, and personnel for the effective conduct of any inspection or audit by a regulatory agency or Gilead.

12.3.3. 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, IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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14. SIGNATURE PAGE

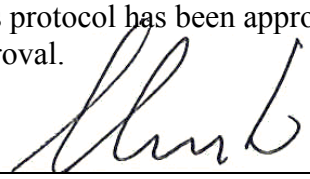
GILEAD SCIENCES GMBH

STUDY ACKNOWLEDGEMENT

VIR-Life**: Prospective assessment of the real-life treatment outcomes of six years of Viread® in CHB following-up on the German Multicenter Non-Interventional Study **GEMINIS

(Final version 14 May 2013)

This protocol has been approved by Gilead Sciences. The following signatures document this approval.



i.V. Dr. Armin Schuster
Director Medical Affairs

16. 05. 2013
Date

Signature

Gilead EU QPPV
Karen Pattenden

16 May 2013
Date

Signature