Study Title	Viread Observational, Cross -Sectional Drug Utilisation Study in Children and Adolescents with Chronic Hepatitis B
Protocol ID	GS-EU-174-0224
Protocol Version/Date:	Amendment 1: 14 November 2014 FINAL: 16 July 2014 Original: 21 February 2013
EU PASS Register No	ENCEPP/SDPP/6987
Active substance / Medicinal Product	ATC Code: J05AF Nucleoside and nucleotide reverse transcriptase inhibitors Active substance: Tenofovir disoproxil fumarate Product: Viread®
Indication	Treatment of chronic hepatitis B in adults and paediatric patients 12 years of age and older
Product reference / Procedure number	Viread EU/1/01200/001 EU/1/01200/002
Joint PASS	No
Country (-ies) of study	European Union countries where the paediatric indication is authorized and Viread is marketed.
Marketing authorization holder / Sponsor:	Gilead Sciences International Ltd. Flowers Building, Granta Park Cambridge, CB21 6GT United Kingdom
Gilead Study Director:	Name: Tara MacCannell, PhD MSc Telephone: +1 650 235 3771 Fax: +1 650 522 5953 Pager: tara.maccannell@gilead.com
Gilead EU QPPV:	Name: Dr. Anne-Ruth van Troostenburg de Bruyn Telephone: +44 (0) 1223 897500

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1. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	Alanine Amino Transferase
BMD	Bone Mineral Density
CRF	case report form
CHB	Chronic Hepatitis B
CHMP	The Committee for Medicinal Products for Human Use
DSPH	Drug Safety & Public Health
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GSI	Gilead Sciences, Inc.
GVP	Good Pharmacovigilance Practices
HBeAg	Hepatitis B e-Antigen
HBIG	Hepatitis B Immunoglobulin
HCC	Hepato Cellular Carcinoma
ICH	International Conference on Harmonization
IRB	institutional review board
SmPC	Summary of Product Characteristics
TDF	tenofovir disoproxil fumarate
US, USA	United States, United States of America

2. RESPONSIBLE PARTIES

STUDY SPONSOR:	GILEAD SCIENCES INTERNATIONAL LTD., FLOWERS BUILDING, GRANTA PARK CAMBRIDGE, CB21 6GT, UNITED KINGDOM
STUDY DIRECTOR:	TARA MACCANNELL, PhD MSc

3. PROTOCOL SYNOPSIS/ABSTRACT

Gilead Sciences, Ltd.,
Flowers Building, Granta Park,
Cambridge, CB21 6GT, United Kingdom

Study Title:	Viread Observational, Cross -Sectional Drug Utilisation Study in Children and Adolescents with Chronic Hepatitis B
Rationale and Background:	Following the recent approval of the paediatric indication for Viread (tenofovir disoproxil fumarate; TDF) for the treatment of chronic hepatitis B (CHB), this Drug Utilisation Study is designed to assess whether physicians prescribing Viread to paediatric patients with CHB infection in the European Union (EU) are following the recommendations in the Viread Summary of Product Characteristics (SmPC) and educational brochures with respect to information relevant to paediatric patients. The study will examine whether physicians are utilising appropriate doses of Viread, and are complying with the recommendations with respect to monitoring of renal function and management of renal and bone abnormalities in these patient populations.
Research Question and Objectives:	The primary objective of this study is as follows: • To describe the characteristics of chronic hepatitis B patients less than 18 years old treated with Viread within the EU The secondary objectives of this study are as follows: • To describe pre-treatment and on treatment renal function and bone mineral density monitoring • To determine if a multidisciplinary approach is taken in paediatric patient management, including renal and bone toxicities
Study Design:	The surveyed physicians will complete questionnaires by undertaking retrospective reviews of their patient medical records. Data will not be collected on an individual patient level, but will be aggregated at the site level. Participating physicians will be sent 3 separate questionnaires over a 3-year period requesting information regarding their paediatric patients with CHB.

Population / Setting:	The questionnaires will collect aggregate data on paediatric (age <18 years) patients currently being treated with Viread. It is planned to approach as many physicians as possible caring for paediatric CHB patients throughout the EU and to gather data on all paediatric patients treated with Viread by these physicians.
Eligibility Criteria:	All chronic hepatitis B patients in the EU who initiate therapy with Viread at an age <18 years will be eligible.
Duration of Study:	Date of surveys: Q1 2015, Q2 2016, Q4 2017
Data Sources:	Data sources will be the patient medical records. Data from these sources will be aggregated by the physician on a site level to be recorded in the questionnaire.
Study Procedures:	Questionnaires will be provided to HBV treating physicians caring for paediatric patients. The participating physicians will complete the questionnaires using their patient charts in a retrospective fashion. Data will not be collected on the individual patient level, but will be aggregated at the site level. Physicians will be sent 3 separate questionnaires over a 3-year period requesting information regarding his/her paediatric patients with CHB. The questionnaires (Q1 2015, Q2 2016 and Q4 2017) will collect data on all CHB patients <18 years of age being currently treated with Viread.
Variables:	The study-specific questionnaire is designed to collect information on the following variables: number of children and adolescents with CHB receiving Viread therapy; age and weight range; prescribed Viread dose; frequency of renal function testing; bone mineral density (BMD) monitoring; criteria for and type of supplementation (e.g.vitamin D, phosphates); reasons for treatment withdrawal; proportion of patients with renal and bone adverse events; multidisciplinary approach regarding renal and bone toxicity management.
Sample Size:	Not specified
Matching / Statistical Methods:	Surveys are not subject to matching since there are no comparison groups. Data from the surveys of prescribers of Viread to children and adolescents with CHB will be summarized descriptively (numbers, proportions).

Milestones:	Date of surveys: Q1 2015, Q2 2016, Q4 2017
	Interim report 1: 29 May 2015
	Interim report 2: 31 December 2016
	Final report: 31 May 2018

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.

4. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	14 November 2014	Section 5 Milestones and throughout the protocol	Amendment	Adjustment of timelines and interim report dates due to delays in study start
		Title page and throughout the protocol		Corrections of EU QPPV contact details and sponsor address completion
		Section 9.1 And Section 11.1.2		Clarification of protocol text regarding physician responsibilities as participating physicians will not receive nor sign the protocol so it is Gilead's responsibility to ensure conduct the study according to protocol and applicable rules and regulations.

5. MILESTONES

Milestone	Planned date
Start of data collection	Q1 2015, Q2 2016, Q4 2017
End of data collection	Q1 2018
Interim report 1	29 May 2015
Interim report 2	31 December 2016
Final report of study results	31 May 2018
Registration in the EU PASS register	July 2014

6. BACKGROUND

6.1. Rationale for the Current Study

Chronic hepatitis B (CHB) is a serious global health care problem and a major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). Worldwide, approximately 350 to 400 million people have developed chronic hepatitis B and approximately 1 million people die annually of complications of chronic hepatitis B {23756}.

The highest risk of acquisition is associated with vertical transmission from HBeAg positive mothers: the risk of vertical transmission is approximately 90% when the infection is transmitted from HBeAg positive mothers and 10-20% when the mother is HBeAg negative {14155}. The rate of chronicization is approximately 90% if the infection is acquired in the perinatal period, regardless the maternal HBeAg status, 20-30% if the infection is acquired in the early infancy before 5 years of age, and 5-10% if the infection is acquired later {14155}. Since the rate of chronicization depends upon the age of acquisition, most adults with chronic HBV infection acquired the infection in infancy or early childhood: of the estimated 350 million individuals chronically infected with HBV worldwide, it is generally accepted that at least 50% acquired their infections either perinatally or in early childhood, especially in countries where HBV is endemic {23113}.

Despite the availability of HBV vaccine programs and although immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine are effective at reducing mother to child HBV transmission, new HBV infections are reported. Approximately 2% of infants born to mothers HBeAg negative and 10% of infants born to HBeAg positive mothers are still infected and suffer from chronic hepatitis B. Note that 1-2% of properly vaccinated infants do not develop long-lasting immunity against HBV {23113}.

Hence, paediatric infection is still a medical issue, not only in high endemic countries, but also in medium and low endemic countries, such as Eastern and Western Europe due to the immigration flows from high prevalence areas such as China, Southeast and Southwest Asia and Tropical Africa.

Tenofovir is principally eliminated via the kidney. Renal failure, renal impairment, elevated creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of Viread in clinical practice. Reductions in bone mineral density (BMD) Z-score have also been reported {23755}.

6.1.1. TDF in Adolescent CHB patients

The efficacy and safety of TDF in the treatment of adolescents 12-17 year old with CHB infection has been evaluated in a large (n=106 subjects) randomized, placebo-controlled, international Phase 3 study {23542}, through 72 weeks of treatment. After 72 weeks of treatment a significant higher viral response defined as HBV-DNA <400 copies/mL, (88.5% vs 0%, p<0.001) and ALT normalization rate (74% vs 31%, p<0.001) was observed in

patients randomized to TDF compared to patients on placebo. Over 72 weeks of treatment TDF was well tolerated and no patients met the primary safety endpoint of a 6% decrease in lumbar spine bone mineral density (BMD). Although both populations experienced an overall increase in mean lumbar spine and whole body BMD, the percent increase in spine and whole body BMD in TDF treated patients was less than the percent increase in whole body BMD observed in the placebo- treated patients (4.95% vs 8.14%, p= 0.053 [spine]; 2.8% vs 5.4%, p=0.013 [whole body]).

On 22 November 2012, the European Commission adopted a decision on an application to extend the indication for Viread to include adolescents with CHB infection aged 12 to <18 years.

The CHB adolescent indication for Viread is for the treatment of CHB in adolescents 12 to <18 years of age with compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis. The following formulations of Viread are commercially available and could be used in adolescents with CHB:

Viread 245 mg film-coated tablets for patients who weigh ≥ 35kg.

Viread 33 mg/g oral granules for patients who weight ≥ 35kg and for whom a solid dosage form is not appropriate.

The SmPCs updated in November 2012 for the different formulations of Viread will contain information relevant to paediatric patients, including the approved indications and appropriate doses of Viread, and recommendations on monitoring of renal function and management of renal and bone abnormalities. Moreover, an educational brochure, with specific information for the use of Viread in adolescents with CHB infection, has been developed. The brochure includes information on the approved paediatric indications, the appropriate dosing of TDF, monitoring of renal function, and management of renal and bone effects in paediatric patients in accordance with recommendations in the Viread SmPC.

6.1.2. Purpose of the Study

Drug utilisation research was pioneered in northern Europe and the UK {22375} in the mid 1960s.

The principal objective of drug utilisation research is to evaluate the use of a drug at an optimal dose with the correct information. Without the knowledge of how drugs are being prescribed and used, it is difficult to suggest measures to improve prescribing habits.

The purpose of this drug utilisation study is to better understand the characteristics of the paediatric population receiving Viread and also the characteristics and timing of patient monitoring and management, in order to determine the effectiveness of the SmPC and educational brochure.

7. OBJECTIVES / RESEARCH QUESTIONS

The primary objective of this study is:

- To describe the characteristics of chronic hepatitis B patients less than 18 years old treated within the EU with Viread.

The secondary objectives of this study are:

- To describe how the pre-treatment and on treatment renal function and bone mineral density are monitored

- To determine if a multidisciplinary approach is taken in paediatric patient management, including renal and bone toxicities.

8. RESEARCH METHODS

8.1. Study Design

For this observational cross-sectional drug utilisation study, a study-specific questionnaire will capture the respective aggregated data on Viread use, pre-treatment and on-treatment assessments and management of renal and bone toxicities. The participating physicians will complete questionnaires using their patient medical records retrospectively. Data will not be collected on the individual patient level, but will be aggregated at the site level. Physicians will be sent 3 separate questionnaires over a 3-year period on information regarding paediatric patients with CHB under care in their practices.

8.2. Setting / Study Population

Participating physicians will be asked to complete the questionnaires using their patient medical records retrospectively. Physicians will be sent 3 separate questionnaires over a 3-year period on information regarding his/her paediatric patients with CHB. The questionnaires (Q1 2015, Q2 2016 and Q4 2017) will collect data on all CHB patients <18 years of age being treated with Viread.

It is planned to identify and approach as many physicians caring for paediatric CHB patients as possible throughout Europe and to gather data on all paediatric patients treated with Viread by these physicians.

All CHB patients who initiate therapy with Viread before the age of 18 years will be eligible.

8.3. Exposure, Outcomes and other Variables

Exposure is determined by two factors: treatment duration of Viread and dosage prescribed. The study-specific questionnaire will collect information on the following variables: number of children and adolescents with CHB receiving Viread therapy; age and weight range; prescribed Viread dose; frequency of renal function tests; BMD monitoring; criteria for and type of supplementation (e.g. vitamin D, phosphates); reasons for treatment withdrawal; proportion of patients with renal and bone adverse events; multidisciplinary approach regarding renal and bone toxicity management.

8.4. Criteria for Discontinuation of Follow up

This is a cross-sectional study with no follow up.

8.5. Data Sources

Data sources will be the individual physician surveys. The questionnaires (Q1 2015, Q2 2016 and Q4 2017) will collect data for all CHB patients <18 years of age being treated with Viread at each participating site. Data from patient medical records and general treatment

procedures/decisions at the participating sites are to be aggregated by the physician on a site level to be recorded in the questionnaire.

8.6. Study size

As the number of patients initiating Viread therapy at an age <18 years is largely unknown and expected to be low, it is planned to include as many patients as possible. It is expected that approximately 200-400 physicians can be identified who potentially treat CHB patients with Viread at an age <18 years. These identified physicians will be asked if they are in fact treating CHB patients at an age <18 years with Viread and if they would be willing to participate in the survey. It is estimated that approximately 10 - 25% of the contacted physicians will be treating CHB patients at an age <18 years with Viread and are willing to participate.

8.7. Data Management

Surveys will use an electronic data entry system, physicians will receive specific access codes to enable them to enter their data. The data entry system will be made available for a specified time period for the duration of each survey to the participating physician. After that time, the system will be closed for data entry and the entered data will be extracted and analysed. For subsequent surveys, the same process will be followed.

8.8. Data Analysis

Data from the surveys of prescribers of Viread to adolescents and children with CHB will be summarized descriptively (numbers, ranges, proportions).

8.9. Quality Control

The electronic data entry system will contain automatic checks for data completeness and inconsistent data. No source data validation is planned in this study as the questionnaires will only collect aggregate data.

8.10. Limitations of the Study/Analysis

It is expected that the number of physicians who treat paediatric CHB patients, as well as the total number of paediatric CHB patients being treated with Viread will be small. Various approaches will be used to identify as many CHB treating physicians who care for paediatric patients. It is possible that physicians who only occasionally treat paediatric CHB patients or who treat only a very small number thereof might be less willing to participate in this study compared to physicians more specialized in CHB treatment or who treat a larger number of paediatric patients. This could potentially exclude physicians less interested or focused on treating paediatric patients with CHB and lead to a low survey response rate.

8.11. Statistical Power / Sample Size Considerations

It is expected that approximately 200-400 physicians can be identified who potentially treat patients with Viread at an age <18 years and that approximately 10 - 25% of the identified physicians are treating patients at an age <18 years with Viread and are willing to participate. This study is not investigating a pre-specified risk, and so statistical power and sample size considerations are not relevant.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Good Pharmacoepidemiology Practices

Gilead will ensure that this study is conducted in accordance with the principles of the guidelines of Good Pharmacoepidemiology Practices (GPPs), Good Pharmacovigilance Practices (GVP) and with the laws and regulations of the country in which the research is conducted.

9.2. Institutional Review Board (IRB) /Ethic Committee (EC) Review

This study will be conducted using aggregated data with no patient identifiable fields. As individual subjects can not be identified, no IRB or Ethic Committee review will be obtained in accordance with applicable legislation in all involved countries.

9.3. Informed Consent

No informed consent will be obtained.

9.4. Confidentiality

The collected data will contain no patient identifiable fields.

10. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

10.1. Adverse Events

This non-interventional study is observational in nature and does not evaluate safety in individual study subjects. Adverse events will not be solicited in this observational study.

11. RESPONSIBILITIES / PLANS FOR DISSEMINATING STUDY RESULTS

11.1. Physician Responsibilities

Participating physicians will be responsible for filling in each questionnaire accurately and completely.

11.1.1. Study Files and 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.

11.1.2. Protocol Compliance

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

11.2. Sponsor Responsibilities

11.2.1. Protocol Modifications

Protocol modifications may be made only by Gilead Sciences.

11.2.2. Study Report and Publications

Interim study reports will be prepared and provided to CHMP by 29 May 2015 and by 31 December 2016. A final report will be prepared and provided by 31 May 2018. Gilead Sciences will ensure that the report meets the standards set out in the STROBE Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) {22445}.

11.3. Joint Physician/Sponsor Responsibilities

11.3.1. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) in accordance with local legislation.

12. REFERENCES

14155 Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373 (9663):582-92.

22375 Lee D, Bergman U. Studies of Drug Utilization. In: Strom BL, ed. Pharmacoepidemiology. 3rd ed. England: John Wiley & Sons Ltd; 2000: 463-81.

22445 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61 (4):344-9.

23113 Jonas MM. Hepatitis B and pregnancy: an underestimated issue. Liver Int 2009;29 Suppl 1:133-9.

23542 Murray KF, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. Hepatology 2012;56 (6):2018-26.

23755 Duarte-Rojo A, Heathcote EJ. Efficacy and safety of tenofovir disoproxil fumarate in patients with chronic hepatitis B. Therapeutic advances in gastroenterology 2010;3 (2):107-19.

23756 World Health Organization (WHO). Weekly epidemiological record. Relevé épidémiologique hebdomadaire 2009:405-20.

13. APPENDICES

13.1. List of stand-alone documents

Number	Document Reference Number	Date	Title
1	NA	14 November 2014	ENCePP Checklist for Study Protocols
2	NA	14 November 2014	Study Acknowledgement
3	NA	16 July 2014	DUS Viread HBV Questionnaire (attached)

Appendix 1 Encepp Checklist For Study Protocols Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Viread Observational Cross-Sectional Drug Utilization Study in Children and Adolescents with Chronic Hepatitis B

Study reference number:
ENCEPP/SDPP/6987

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	10
1.1.2 End of data collection[2]	☒	☐	☐	10
1.1.3 Study progress report(s)	☐	☐	☒	10
1.1.4 Interim progress report(s)	☒	☐	☐	10
1.1.5 Registration in the EU PAS register	☒	☐	☐	10
1.1.6 Final report of study results.	☒	☐	☐	10

[1] 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.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	11
2.1.2 The objective(s) of the study?	☒	☐	☐	13
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	14
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	14
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	13
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

The study will use cross-sectional clinician questionnaires to identify the spectrum of clinical practice management and prescribing choices for Viread among children and adolescents with chronic hepatitis B

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	14
4.2 Is the planned study population defined in terms of:	☐	☒	☐	
4.2.1 Study time period?	☒	☐	☐	14/15
4.2.2 Age and sex?	☒	☐	☐	14/15

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.3 Country of origin?	☒	☐	☐	14
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	14

Comments:

The study population (i.e., pediatric specialists) will be identified among professional (e.g., ESPGHAN) and healthcare networks in the EU

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	14
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Within the questionnaire, clinicians will be instructed to respond to questions based on a subset of their patients receiving Viread (exposure)

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Within the questionnaire, clinicians will be instructed to respond to questions based on a subset of their patients receiving Viread (exposure) and the management / outcomes of those who develop select serious adverse events (endpoint)

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	16

Comments:

Sample size is based on estimated numbers of clinicians who treat children with chronic hepatitis B, and willingness to participate in completing the cross-sectional questionnaires

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	15
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	15
11.3 Are methods of quality assurance described?	☐	☐	☒	
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☒	
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	15
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	15
12.3 Does the protocol address other limitations?	☒	☐	☐	

Comments:

12.1.1 Using a questionnaire incurs the potential for a low response rate and may result in selection biases

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	17
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	17

Comments:

Questionnaire data are collected in aggregate or as proportions, and contain no personally identifiable information

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	9

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	19
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	19

Comments:

Name of the main author of the protocol: _Robertino Mera, MD PhD_____

Date: 11/14/2014

Signature: 

Appendix 2 Study acknowledgement

GILEAD SCIENCES, LTD.,
FLOWERS BUILDING, GRANTA PARK
CAMBRIDGE, CB21 6GT, UNITED KINGDOM

STUDY ACKNOWLEDGEMENT

Viread Observational, Cross -Sectional Drug Utilization Study in Children and Adolescents with Chronic Hepatitis B

Amendment 1: 14 November 2014

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

Tara MacCannell, PhD
Gilead Study Director

Signature

11/18/2014
Date

Dr. Anne-Ruth van Troostenburg de Bruyn
Gilead EU QPPV

Signature

Date

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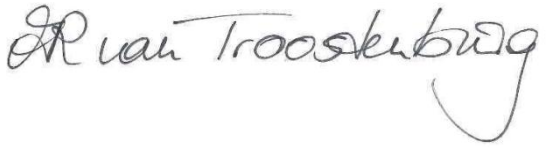
Amendment 1: 14 November 2014

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

Tara MacCannell, PhD Gilead Study Director	Signature
Date	
Dr. Anne-Ruth van Troostenburg de Bruyn Gilead EU QPPV	
	Signature
19 Nov 2014	
Date	

Appendix 3 Viread Dus Hbv Questionnaire

Refer to attached document