NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY

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**

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**
Study code	GS-DE-174-0225
EUPAS Register No.	EUPAS4215 (Old: ENCEPP/SDPP/4215)

Objective	The primary objective of this study is to prospectively describe the virological response, defined as HBV-DNA concentration, during 6 years Viread® treatment for chronic hepatitis B (CHB) in real life setting. The secondary objectives are to evaluate the safety and tolerability of 6 years Viread® in CHB in real life setting including the report of adverse drug reactions, renal safety and the histological improvement of the liver.
Study description	Prospective, non-interventional and multicenter cohort post-authorization safety study in Germany
Study phase	Non-interventional post-authorization safety study

Sponsor	Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried Germany
Marketing authorization holder	Gilead Sciences International Ltd. Cambridge CB21 6GT United Kingdom

Study Director (Sponsor)	Dr. Nicole Forestier Gilead Sciences GmbH
Author	Dr. Karola Wittig INPADS GmbH
Responsible Company	INPADS GmbH Dr.-Hugo-Bischoff-Str. 1a D-67098 Bad Dürkheim

First documented date in a visit	28-Jan-2013
Last documented date in a visit	24-Mar-2016
End of data collection	30-Jun-2016
Date of report	16-Dec-2016

1 Signatures

Medical Project Manager Gilead Sciences GmbH	Dr. Kathrin Hüging	19 Dec 2016 Date
Clinical Manager Gilead Sciences GmbH	Corinna Seifritz	16-DEC-2016 Date
Statistics & Data Management INPADS GmbH (CRO)	Dipl.-Ing. Christian Mehl	11.1.2017 Date
Medical Writing INPADS GmbH (CRO)	Dr. Karola Wittig	11-JAN-2017 Date

2 Synopsis

Name of sponsor	Gilead Sciences GmbH Fraunhoferstr. 17 82152 Martinsried Germany	
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Study design	Prospective non-interventional multicenter cohort post-authorization safety study (single treatment case series)	
Clinical phase	Post-authorization safety study	
Number of centres	Planned	25
	Recruited	23
	Analyzed	16
Number of patients	Planned	250
	Recruited	218
	Analyzed	112
First documented date in a visit	28 Jan 2013	

Last documented date in a visit	24 Mar 2016
Patients	Roll-over study in adult, HBV-mono-infected CHB patients who started CHB treatment with Viread® in GEMINIS [GX-DE-174-0129].
Study treatment	Viread® 245mg film-coated tablets Active substance: Tenofovir disoproxil as fumarate (TDF) Additional ingredients: Lactose monohydrate, Croscarmellose-Sodium Magnesiumstearate (E572), Microcrystalline Cellulose (E460), Starch, Triacetin (E1518) Hypromellose (E464), Indigocarmine-Aluminium salt (E132), Titandioxide (E171) Timing of doses should be handled according to the summary of product characteristics (SmPC).
Statistical methods	The biometric analysis will provide a descriptive statistical evaluation of all collected criteria. Absolute and relative frequencies of nominal and ordinal values were displayed.
Criteria for evaluation	Documentation of routine visits at months 48, 60 and 72, covering the following parameters (if available): - Weight - Serum HBV-DNA concentration - HBeAg, anti-HBe, HBsAg, antiHBs - ALT-level - Serum creatinine, estimated creatinine clearance (eCrCl), serum phosphorus - Albumin, Bilirubin, Thrombocytes, Prothrombin time (e.g. Quick value) - Liver histology staging, transient elastography - HCC development - Co-morbidities - Incident of 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

Results	The present report describes the data of the study VIR-Life. 218 patients were recruited but 106 of these patients had to be excluded due to unknown status of patient, missing consent or because the date of visit was not within the intended time frame. Thus, the analysis was based on data of 112 patients followed up by 16 study sites. VIR-Life is the extended follow up of the study GEMINIS (year 1-3 documentation of Viread® therapy. Therefore, the baseline data of the VIR-Life patients were collected at GEMINIS baseline (i.e. three years prior to the beginning of VIR-Life study). 71.4% of the participating patients were male and 28.6% female. The mean age was 44.1 years and the mean height 170.5 cm. At GEMINIS baseline, the majority of patients were HBeAg-negative (63.4%) and more than half of patients were treatment-experienced before being treated with Viread® (56.3%). Two patients died before the beginning of the documentation in the VIR-Life study (1.8%). 95 patients (84.8%) were documented over the whole observation period of three years in the VIR-Life study (i.e. year 4-6 of their therapy with Viread®), 17 have a documented early termination. Three of these 17 patients died, six patients were lost to follow-up. During the VIR-Life study, weight and corresponding BMI remained relatively stable. The proportion of patients with detectable HBV-DNA decreased from 21.1% in visit year 4 to 10.1% in visit year 6. The same could be found for the mean HBV-DNA concentration for patients with detectable HBV-DNA in the serum which clearly decreased from 112,033.5 IU/ml in visit year 4 to 764.6 IU/ml at the end of documentation in year 6. 3 patients (30.0%) with detectable DNA levels had a serum HBV-DNA concentration of ≥ 69 IU/ml at the end of the study, which was defined as upper analysis level. Regarding the HBV serology, we found that 20.8% to 27.1% (dependent on the visit) of patients with known status were HBeAg-negative. 76.7% to 85.7% of HBeAg-negative patients were anti-HBe-positive. Conversely, 88.9% to 100% of HBeAg positive patients were anti-HBe negative. HBsAg status was in 72.9% to 80.2% positive; in only five cases a negative status was documented during the VIR-Life study. Viread® treatment was stopped in 3 of these 5 patients. Most HBsAg positive patients with known anti-HBs status were anti-HBs negative (16.9% to 75.0%). Liver and renal function laboratory tests: Mean ALT (GPT) slightly decreased in both male and female patients. The values for albumin, bilirubin, platelets, and prothrombin time (quick value) were very stable and within the normal range. The same was found for the parameters of renal func-

	tion serum creatinine and serum phosphorus. The estimated creatinine clearance differed depending on the used formula, but all mean values were within the normal range and stable during the VIR-Life study. Nevertheless, renal failure occurred in 3 cases. Liver biopsy was documented in two cases in visit year 4. In both cases, low to moderate fibrosis (F1/F2) was diagnosed. In addition, one patient was also affected by compensated cirrhosis. Transient elastography was performed in 11.1% to 12.8% of patients depending on the visit. Mean liver stiffness was relatively stable (visit year 4: 5.8 kPa, visit year 5: 5.7 kPa, visit year 6: 5.5 kPa) and corresponded to absent or mild fibrosis. One patient developed HCC during the study. Alcohol was consumed by 11.1% to 18.9% of patients. The mean amount of alcohol consumption was relatively stable (visit year 4: 6.7 glasses per week, visit year 5: 4.7 glasses per week, in visit year 6: 6.3 glasses per week). Viread® treatment was handled in accordance to the SmPC. In the vast majority, the dosage of Viread® was one tablet per day. In addition, Viread® was predominantly used as monotherapy; only two patients received an additional antiviral therapy with entecavir. Termination of Viread® treatment was documented in 4 cases in visit year 4, in five cases in visit year 5 and in 7 cases in visit year 6. Overall, reasons for termination of Viread® treatment were death of patient, adverse reaction, renal failure, patient's wish or change of treatment. In total, two co-infections were documented, one co-infection with HCV and one co-infection with HIV. 29 patients had concomitant diseases, most frequently hypertension (62.1%). Over the entire study period, 18 patients (8.3% = 18/218) reported a total of 38 adverse events, 8 of which were serious (21.1%). 3 of these events resulted in death. The most frequently documented events were pain (different locations) (38.9% = 7/18) and renal failure (16.7% = 3/18). A causal relationship of the event to Viread® was suspected in 6 cases (15.8% = 6/38). 2 of these patients were affected by serious adverse events (development of HCC, renal failure). In 3 cases, treatment with Viread® was permanently discontinued (7.9% = 3/38). Finally, there were five special situation reports during the study. 4 of these reports described medication errors. One patient became pregnant during the study while on Viread®, the pregnancy ended in a spontaneous abortion.
Conclusion	The primary objective of this roll-over study from

	GEMINIS was to prospectively describe the virological response, defined as HBV-DNA concentration, during six years of Viread® treatment. During the study VIR-life, the proportion of patients with detectable HBV-DNA decreased from 21.1% at start of the VIR-Life study (year 4 of treatment) to 10.1% in visit year 6. Moreover, the mean HBV-DNA concentration in patients with detectable HBV-DNA also clearly decreased from 112,033.5 IU/ml in year 4 of Viread® therapy to 764.6 IU/ml in year 6 of Viread® therapy. Based on these results we can conclude that the patients in the present NIS benefited from Viread® treatment. Secondary objectives were the investigation of safety and tolerability of Viread®, as well as renal safety and histological improvement of the liver. Fibroscan® was performed in 11.1% to 12.8% of patients and the results were consistent with absent or mild fibrosis. One patient developed HCC during the study. Over the entire study period, 18 patients reported a total of 38 adverse events, 8 of which were serious. The most frequently documented events were pain (38.9%) and renal failure (16.7%). A causal relationship of the event to Viread® was suspected in 6 cases. 2 of these patients were affected by serious adverse events. In 3 cases, treatment with Viread® was permanently discontinued (7.9%). Study results do not give rise to any new safety concerns regarding Viread.
Date of report	16-Dec-2016