FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Multinational Observational Registry Collecting Data on the Clinical Profile of Patients with Chronic Hepatitis D Virus Infection Receiving Treatment with Bulevirtide
Name of Test Drug:	Not applicable
Dose and Formulation:	Not applicable
Indication:	Chronic Hepatitis D
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 944404 USA
Study No.:	MYR-Reg-02
Phase of Development:	Non-interventional registry
IND No.: **EU CT No.:**	Non-IND study Not applicable
ClinicalTrials.gov Identifier:	Not applicable
Study Start Date:	03 December 2020 (first site initiated)
Study End Date:	27 April 2023 (last patient last visit for the primary objective and for this report)
Report Date:	01 May 2024
Previous Report Date:	02 February 2022 (Interim Progress Report)

The registry was conducted in accordance with all applicable personal data protection laws, principles of International Ethical Guidelines for Epidemiological Studies, and the ethical principles that are outlined in the Declaration of Helsinki.

STUDY SYNOPSIS

Study MYR-Reg-02
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Multinational Observational Registry Collecting Data on the Clinical Profile of Patients with Chronic Hepatitis D Virus Infection Receiving Treatment with Bulevirtide

Study Centers: patients were enrolled across 6 sites located in Austria, France, and Germany.

Publications: there were no publications at the time of this clinical study report.

Study Period:

04 December 2020 (first patient screened)
27 April 2023 (last patient last visit for this report)

Phase of Development: non-interventional registry

Study Objectives:

The overall goal of this registry was to collect data on the rate of liver-related clinical events in patients with chronic hepatitis delta virus (HDV) infection and compensated liver disease receiving bulevirtide (BLV [GS-4438], Hepcludex®) treatment according to the current version of the bulevirtide European Union (EU) summary of product characteristics (SmPC), to bridge these clinical events with the virological (HDV RNA) and biochemical (alanine aminotransferase [ALT]) response, and to collect data on the safety profile of BLV in a real-world setting.

The primary objective of this registry was as follows:

- Rate of liver-related clinical events in patients receiving BLV treatment:
  - Cirrhosis development
  - Hepatic decompensation: ascites, bleeding from esophageal varices, encephalopathy, laboratory abnormalities associated with reduced liver function
  - Jaundice
  - Hepatocellular carcinoma development
  - Liver transplantation
  - Liver-related death

The secondary objectives of this registry were as follows:

- For cirrhotic patients: change in Child-Turcotte-Pugh (CTP) score

- Change in HDV RNA to baseline
- Change in ALT to baseline
- To collect data on the safety profile of BLV in patients receiving BLV treatment:
  - Adverse reactions
  - Vitamin D levels, bone density scans

Methodology: the registry was a non-interventional observational study, and therefore, the purpose was not to test a formal hypothesis. No investigational medicinal product or study-specific drug was administered in this registry. Data available during routinely indicated medical follow up of the registry patients were collected and analyzed; no specific study-related evaluations were planned. The registry was approved according to local regulatory requirements in each participating country/site. Informed consent or nonopposition obtaining process was performed at each participating site according to the specific local regulatory and legal requirements. In order to minimize bias, participating investigators made an attempt to obtain consent or nonopposition from all potentially eligible patients seen at the registry site and sequentially enrolled them. All registry data were obtained from the patients' medical records. If a patient was receiving BLV treatment before participating in the registry, efforts were made to collect baseline data prior to the start date of the BLV treatment. Preferably, baseline data were not older than 3 months prior to the start of BLV treatment. Additionally, patients continued to be followed up in the registry after BLV treatment had ended. There were no obligatory visits in this registry. The timeframes and frequency of patients' visits were routinely established by the investigator based on his/her opinion, not based on requirements of the study protocol. Up to 4 visits per year were to be included in the registry. The data were to be collected from the patients' visits performed in routine practice.

After obtaining written consent or nonopposition, patients were enrolled in the registry, and the baseline data described in the clinical study protocol, Section 5.3 "Study Visits and Variables" (Section 16.1.1) were collected, if available, including patient demographics, liver-related medical history, liver disease parameters, and treatment for hepatitis B virus (HBV) and HDV infection prior to or during the study.

At the subsequent routine visits, further liver disease parameters and variables on ongoing treatment for HBV and HDV infection were collected, if available; as well as vitamin D levels and the results of bone density measurements, if available.

For all patients treated with BLV, suspected adverse reactions were collected as well. Any adverse reactions considered by the investigator to be related to BLV treatment were reported into the BLV pharmacovigilance (PV) system according to the respective requirements. Within the PV system, a separate evaluation of the reactions reported for a patient was performed per the protocol. The data (except adverse reactions) were entered into electronic case report forms by the trained personnel. During data collection, all personal patient data were kept strictly confidential. The patients were identified by their unique identification numbers assigned in this registry and not by their names or other personal information. Interim analysis for the registry was planned to be conducted annually and at least upon gathering data

from 200 patient years of patients receiving BLV. Subsequent analyses were to be planned by the Steering Committee.

Number of Patients (Planned and Analyzed): due to the observational nature of this study, no formal power or sample size calculations were used.

Planned: not applicable
Analyzed:

- Enrolled Population: 31 patients
- Registry Analysis Population (RAP): 30 patients

Diagnosis and Main Criteria for Inclusion:

To be eligible, patients must have met all of the following inclusion criteria:

- Adult (≥ 18 years) patients who had been diagnosed with chronic HDV infection by HDV RNA positive plasma (or serum) and compensated liver disease, confirmed by respective documentation in medical records.
- Patients who were receiving treatment with BLV according to the current version of the SmPC; or for whom the decision to start treatment with BLV according to the current version of the SmPC had been taken and treatment initiation was planned; or patients who previously received treatment with BLV according to the previously valid version of the SmPC (not in the framework of a clinical study).
- Patients who had provided written informed consent or nonopposition according to local requirements.

Patients were excluded if they met the following exclusion criterion:

- The patient was currently participating in a clinical study with an experimental treatment.

Duration of Treatment: there was no administration of study drug in this registry study. Patients received commercial BLV according to the current version of the SmPC.

The registry study was to be performed until at least 200 patient years from patients treated with BLV were collected.

Test Product, Dose, Mode of Administration, and Batch No.: there was no administration of study drug during this registry study. Patients received commercial BLV according to the current version of the SmPC.

Reference Therapy, Dose, Mode of Administration, and Batch No.: there was no administration of reference drug during this registry study.

Efficacy: the study was terminated prematurely following Gilead's decision to replace the registry study with a global registry Study GS-US-589-6206, and no efficacy analyses were performed.

Pharmacokinetics (PK)/Pharmacodynamics (PD): No PK/PD analyses were planned for this study.

Safety: Safety assessments included:

- Adverse events (AEs)
- Severe adverse events (SAEs)
- Hospitalizations
- Laboratory evaluations, if available:
  - Hematology (hemoglobin [g/dL], platelet count [$\times 10^9$/L], and white blood cells [$\times 10^9$/L])
  - Biochemistry (total bilirubin [µmol/L], direct bilirubin [µmol/L], aspartate aminotransferase [U/L], ALT [U/L], prothrombin time [%], international normalized ratio, albumin [g/L], total bile salts [µmol/L], vitamin D [ng/mL], creatinine [µmol/L], serum alpha-fetoprotein [µg/L], CTP score, and CTP grade)
  - Virology (HBV DNA [IU/mL], HBV DNA [$\log_{10}$ IU/mL], HDV RNA [IU/mL], and HDV RNA [$\log_{10}$ IU/mL])
  - Serology (hepatitis B e antigen [positive/negative], hepatitis B surface antigen [HBsAg] [IU/mL], HBsAg [$\log_{10}$ IU/mL], hepatitis C virus antibody [positive/negative], HDV antibody [positive/negative], and HIV antibody [positive/negative])
- Treatment for HBV/HDV and concomitant medications

Other (If Available): Bone density scan: date and results as classes (normal, osteopenia, osteoporosis); liver biopsy (ISHAK fibrosis stage and METAVIR fibrosis stage); and fibroscan (kPa).

Statistical Methods:

The final analysis was performed at the end of the study, after outstanding data queries were resolved or adjudicated as unresolvable, and the data were cleaned and finalized. The final analysis only included patients who consented to transfer data outside of the EU. Continuous variables were summarized in terms of descriptive statistics including number of observations, mean, SD, minimum, maximum, and quartiles. Categorical variables were summarized in terms of frequencies and percentages. To account for the different durations of observation, the incidences of events were normalized to patient exposure to evaluate the incidence according to time of exposure (patient-years).

This study was an noninterventional observational registry study; therefore, the purpose was not to test a formal hypothesis. Due to the observational and explorative nature of the study, the sample size was not based on statistical considerations. The sample size depended on the feasibility of the study sites to enroll the described patient population. Therefore, this study included as many eligible patients as possible. There was no limit on the overall sample size by country or site.

Efficacy: the study was terminated prematurely following Gilead's decision to replace the study with a global registry Study GS-US-589-6206, and no efficacy analyses were performed for this study.

Pharmacokinetics/Pharmacodynamics: no PK/PD analyses were planned for this study.

Safety: the safety analyses were performed based on the RAP. Adverse events were coded using the MedDRA Version 26.0 and were summarized using descriptive statistics.

SUMMARY OF RESULTS:

Patient Disposition and Demographics:

A summary of patient disposition in the Enrolled Population is provided in Table 1. Overall, the Enrolled Population included 31 patients who provided informed consent or nonopposition depending on national regulation. A total of 30 patients (96.8%) were included in the RAP that included all enrolled patients with available data on any of the postbaseline assessment variables. All patients (100%) prematurely discontinued the study. The majority of patients (64.5%) discontinued the study to enroll in another study. All patients were offered the opportunity to enroll in the replacement global registry study upon conclusion of registry MYR-Reg-02. A by-patient listing of disposition is provided in Listing 16.2.1.3. Key dates, including date enrolled, last visit, last laboratory, and last study day, are provided in Listing 16.2.1.1 for the Enrolled Population.

Table 1. MYR-Reg-02: Patient Disposition (Enrolled Population)

	Total
Enrolled Population	31
Registry Analysis Population	30 (96.8%)
Prematurely discontinued study	31 (100.0%)
Reason for premature discontinuation of study	
Enrollment in any clinical study	20 (64.5%)
Other	11 (35.5%)

Only data of patients who consented to transfer data outside of the European Union were included.
Enrolled Population includes all patients who provided informed consent or nonopposition depending on national regulation.
Registry Analysis Population (RAP) includes all enrolled patients with available data on any of the postbaseline assessment variables.
One patient did not have available data on any of the postbaseline assessment variables and was excluded from the RAP.
Percentages for completion status were calculated based on the number of patients in the Enrolled Population.
Source: Table 15.8.1.3.1

A by-participant listing of important protocol deviations is provided in Listing 16.2.2.2. None of the protocol deviations were related to COVID-19.

A summary of patient demographics and baseline characteristics for the RAP is presented in Table 2. The majority of patients (70.0%) were male. The race of patients included White (46.7%), Asian (16.7%), Black or African American (10.0%), and other race (26.7%). The mean age of patients was 50 years (range: 19-70), and the mean body weight was 75.7 kg (range: 46.0-95.0). The mean body mass index was 25.5 kg/m^2 (range: 18.9-32.1) (Table 2). A by-patient listing of demographics is provided in Listing 16.2.4.1.

The patients' genotype included HDV genotype 1 (5 patients [16.7%]) and genotype 5 and 7 (1 patient each [3.3%]). The HDV genotype was unknown in 19 patients (63.3%) and missing in 4 patients (13.3%) (Table 2).

The HBV genotype was unknown in 25 patients (83.3%) and missing in 4 patients (13.3%). One patient (3.3%) had HBV genotype D (Table 2).

Table 2. MYR-Reg-02: Demographics and Baseline Characteristics (Registry Analysis Population)

	Total (N = 30)
Age (years)	
N	30
Mean (SD)	50 (11.9)
Median	49
Q1, Q3	46, 58
Min, max	19, 70
Sex at birth	
Male	21 (70.0%)
Female	9 (30.0%)
Race	
Asian	5 (16.7%)
Black or African American	3 (10.0%)
White	14 (46.7%)
Other	8 (26.7%)
Weight (kg)	
N	29
Mean (SD)	75.7 (11.69)
Median	78.0
Q1, Q3	70.0, 81.0
Min, max	46.0, 95.0
Height (cm)	
N	29
Mean (SD)	172.0 (8.78)
Median	173.0
Q1, Q3	165.0, 180.0
Min, max	154.0, 186.0
Body mass index (kg/m^2)	
N	29
Mean (SD)	25.5 (3.44)
Median	24.9
Q1, Q3	23.3, 28.4
Min, max	18.9, 32.1
HDV Genotype	
Genotype HDV-1	5 (16.7%)
Genotype HDV-5	1 (3.3%)

Genotype HDV-7	1 (3.3%)
Unknown	19 (63.3%)
Missing	4 (13.3%)
HBV Genotype	
Genotype D	1 (3.3%)
Unknown	25 (83.3%)
Missing	4 (13.3%)

HBV = hepatitis B virus; HDV = hepatitis delta virus; Q1 = first quartile; Q3 = third quartile
Only data of patients who consented to transfer data outside of the European Union were included.
Denominator for percentages was the Registry Analysis Population.
Age (in years) was derived using the date of first informed consent was signed.
Body Mass Index (BMI) (kg/m^2) = [Weight (kg)/Height $(m)^2$]
Source: Table 15.8.3.1

Efficacy Results: no efficacy analyses were performed for this study. A by-patient listing of liver biopsy results indicating fibrosis staging is provided in Listing 16.2.6.1.

Pharmacokinetics/Pharmacodynamics Results: no PK/PD collections or analyses were planned for this study.

Safety Results: Overall, 15 AEs were reported in 8 patients (26.7%). The most common AEs were bile acids increased (4 patients) and drug ineffective (3 patients). A summary of AEs occurring during the study for the RAP is presented by preferred term in Table 3. A by-patient listing of AEs for the Enrolled Population is provided in Listing 16.2.7.1.

Table 3. MYR-Reg-02: Adverse Events by Preferred Term, Registry Analysis Population

	Total (N = 30)
Number (%) of patients with any adverse events	8 (26.7%)
Bile acids increased	4 (13.3%)
Drug ineffective	3 (10.0%)
Injection site erythema	2 (6.7%)
Injection site pruritus	2 (6.7%)
Hepatocellular carcinoma	1 (3.3%)
Off label use[a]	1 (3.3%)
Rash maculo-papular	1 (3.3%)
Viral load increased	1 (3.3%)

AE = adverse event; PT = preferred term
a Off label use due to reported use in an unapproved route of administration (oral rather than subcutaneous).
Only data of patients who consented to transfer data outside of the European Union were included.
Adverse events were coded according to MedDRA Version 26.0.
Multiple AEs were counted only once per patient for the highest severity grade for each PT.
PTs were presented by descending order of the total frequencies.
Source: Table 15.11.3.1

A by-patient listing of hospitalizations for the Enrolled Population is provided in Listing 16.2.7.2.

Serious adverse events were reported in 2 patients (6.7%) during the study. These included 1 patient (3.3%) who developed a hepatocellular carcinoma that was considered unrelated to BLV and 1 patient (3.3%) who developed a rash maculo-papular that was considered related to BLV (Listing 16.2.7.1). Serious adverse events in the RAP are presented by preferred term in Table 4. Narratives for SAEs are provided in Section 15.2.

Table 4. MYR-Reg-02: Serious Adverse Event by Preferred Term, Registry Analysis Population

	Total (N = 30)
Number (%) of patients with any serious adverse events	2 (6.7%)
Hepatocellular carcinoma	1 (3.3%)
Rash maculo-papular	1 (3.3%)

AE = adverse event; PT = preferred term
Only data of patients who consented to transfer data outside of the European Union were included.
Adverse events were coded according to MedDRA Version 26.0.
Multiple AEs were counted only once per patient for the highest severity grade for each PT.
PTs were presented by descending order of the total frequencies.
Source: Table 15.11.3.2

Table 5. MYR-Reg-02: Listings of Laboratory Results, Enrolled Population

Laboratory Results	Listings
Hematology (hemoglobin [g/dL], platelet count [$\times 10^9$/L], and white blood cells [$\times 10^9$/L])	16.2.8.1
Biochemistry (total bilirubin [µmol/L], direct bilirubin [µmol/L], aspartate aminotransferase [U/L], alanine aminotransferase [U/L], prothrombin time [%], and international normalized ratio)	16.2.8.2.1
Biochemistry (albumin [g/L], total bile salts [µmol/L], vitamin D [ng/mL], creatinine [µmol/L], alpha-fetoprotein [µg/L], Child-Turcotte-Pugh score, and Child-Turcotte-Pugh grade)	16.2.8.2.2
Virology (HBV DNA [IU/mL], HBV DNA [$\log_{10}$ IU/mL], HDV RNA [IU/mL], and HDV RNA [$\log_{10}$ IU/mL])	16.2.8.3
Serology (HBeAg [positive/negative], HBsAg [IU/mL], HBsAg [$\log_{10}$ IU/mL], HCV antibody [positive/negative], HDV antibody [positive/negative], and HIV antibody [positive/negative])	16.2.8.4

HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis delta virus

CONCLUSIONS: the conclusions from Registry Study MYR-Reg-02 are as follows:

- The study was terminated prematurely following Gilead's decision to replace the registry study with a global registry, GS-US-589-6206. Of the 31 patients who prematurely discontinued this study, 20 (64.5%) enrolled in replacement global registry GS-US-589-6206 (all patients were offered the opportunity to enroll in the replacement global registry upon conclusion of registry MYR-Reg-02).
- Overall, 15 AEs were reported in 8 patients (26.7%). The most frequently reported AE was bile acids increased (13.3%).
- Serious adverse events were reported in 2 patients (6.7%). These included 1 patient (3.3%) who developed a hepatocellular carcinoma that was considered unrelated to BLV and 1 patient (3.3%) who developed a rash maculo-papular that was considered related to BLV.

14. REFERENCES

None

15. TABLES, FIGURES, AND NARRATIVES REFERRED TO BUT NOT INCLUDED IN THE TEXT

15.1. Statistical Tables and Figures

15.2. Narratives of Deaths, Serious Adverse Events, and Certain Other Significant Adverse Events

Narratives are provided for patients in the Enrolled Population (patients informed consent or nonopposition, depending on national regulation, and consented to transfer data outside of the European Union) who had events in the following category:

- SAEs

APPENDICES

16. APPENDICES

For countries in which these appendices are not required by regulation or agency guidance, they are available upon request.

16.1. Study Information

16.1.1. Protocol and Protocol Amendments

The protocol was amended 2 times during the course of Study MYR-Reg-02, as indicated in the following table:

Protocol/Amendment	Date
Original Version 1.0	06 November 2020
Amendment 1 Version 1.1	18 January 2021
Amendment 2 Version 1.2	03 March 2021

16.1.5. Signatures of Sponsor's Responsible Medical Monitor and Principal or Coordinating Investigator

Signatures of the sponsor's medical monitor and the principal or coordinating investigator are available as follows:

- Signature of Sponsor's Responsible Medical Monitor
- Signature of Principal or Coordinating Investigator

16.1.9. Documentation of Statistical Methods

Documentation of statistical methods used to analyze data from the study is provided below:

- Statistical analysis plan (Version 1.0)

16.2. Patient Data Listings

By-patient data listings for Study MYR-Reg-02 are provided below.

16.2.1. Discontinued Patients

Listing 16.2.1.1 Participant Profiles, Enrolled Population

Listing 16.2.1.3 Participant Disposition, Enrolled Population

16.2.2. Protocol Deviations

Listing 16.2.2.2 Protocol Deviations, Enrolled Population

16.2.3. Patients Excluded From the Efficacy Analysis

Not applicable

16.2.4. Demographic Data

Listing 16.2.4.1 Demographics and Baseline Characteristics, Enrolled Population

Listing 16.2.4.2.1.1 Medical History of Hepatitis D, Enrolled Population

Listing 16.2.4.2.1.2 Other Medical History, Enrolled Population

Listing 16.2.4.2.2 Concomitant Disease, Enrolled Population

Listing 16.2.4.4.1 Concomitant Medications, Enrolled Population

Listing 16.2.4.4.2 Treatment for HBV or HDV, Enrolled Population

16.2.5. Compliance and/or Drug Concentration Data

Not applicable

16.2.6. Individual Efficacy Response Data

Listing 16.2.6.1 Biopsy Results, Enrolled Population

16.2.7. Adverse Events

Listing 16.2.7.1 All Adverse Events, Enrolled Population

Listing 16.2.7.2 Hospitalizations, Enrolled Population

16.2.8. Individual Laboratory Measurements

CSR-Final-Synoptic-MYR-REG-02

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Patient Safety eSigned	PPD