GILEAD

OBSERVATIONAL STUDY PROTOCOL

Study Title:	Clinical Benefit of Bulevirtide Therapy in Adult Patients With Chronic Hepatitis Delta Compared to a Historical Control Group Receiving Standard of Care
Short Title:	Liver-related Events in Patients Treated With Bulevirtide Versus a Historical Control Group Receiving Standard of Care
Marketing Authorization Holder:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
EU PAS Register No:	Registration planned
Clinical Trials.gov Identifier:	Not applicable
Indication:	Chronic Hepatitis Delta Infection
Medicinal Product:	Bulevirtide
Joint PASS:	Not applicable
Research Question and Objectives:	Compare the risk of liver-related events (ie, development of cirrhosis, hepatic decompensation, liver transplantation, hepatocellular carcinoma, and liver-related death) in patients treated with bulevirtide versus a historical control group receiving standard of care
Country (-ies) of study:	Countries in Europe and North America
Protocol ID:	GS-EU-589-6575
Protocol Version: **Date:**	Final 24 September 2024
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AASLD	American Association for the Study of Liver Diseases
ALT	alanine aminotransferase
APASL	Asian Pacific Association for the Study of the Liver
BLV	bulevirtide (GS-4438), Hepcludex®
CD	clusters of differentiation
CHB	chronic hepatitis B infection
CHD	chronic hepatitis delta infection
CI	confidence interval
CR	combined response
DNA	deoxyribonucleic acid
EAS	Effectiveness Analysis Set
EASL	European Association for the Study of the Liver
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FIB-4	Fibrosis-4 Index for Liver Fibrosis
GIB	gastrointestinal bleeding
Gilead	Gilead Sciences
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis delta virus
HEAC	hepatic events adjudication committee
HIV	human immunodeficiency virus
HR	hazard ratio
IEC	independent ethics committee
IRB	institutional review board
LSM	liver stiffness measurement
PCR	polymerase chain reaction
Peg-IFNα	pegylated interferon alpha
Peg-IFNλ	pegylated interferon lambda
RNA	ribonucleic acid
SMD	standardized mean difference
SMR	standardized mortality/morbidity ratio
ULN	upper limit of normal
US	United States

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

Study Title:	Clinical Benefit of Bulevirtide Therapy in Adult Patients With Chronic Hepatitis Delta Compared to a Historical Control Group Receiving Standard of Care
Short Title:	Liver-related Events in Patients Treated With Bulevirtide Versus a Historical Control Group Receiving Standard of Care
EU PAS Register No:	Registration planned
Study Sites Planned	Health centers in Europe and North America.
Rationale and Background:	The improvement in clinical outcomes, such as a decrease in the development of cirrhosis, decompensated liver disease, liver transplantation, hepatocellular carcinoma (HCC), and liver-related death, is the preferred clinical endpoint for the assessment of clinical benefit with medicines used to treat chronic hepatitis delta infection (CHD) {U.S Department of Health and Human Services (DHHS) 2019}. Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis. Week 48 results from Study MYR301 demonstrated that treatment with bulevirtide (BLV [GS-4438], Hepcludex®) monotherapy resulted in significant improvement in combined response (viral with biochemical response, a surrogate endpoint) compared to no treatment. Consequently, BLV has been granted full approval in the European Economic Area (EEA), Great Britain, Switzerland, and Australia (as Hepcludex®) and in Russia (as Myrcludex B®). Despite this progress, there remains a need to demonstrate the long-term clinical benefit of BLV. Since following untreated patients with HDV for longer than 48 weeks in the context of high unmet medical need and potential disease progression is considered to be unethical and infeasible, the use of a comparative external (historical) control group has been proposed as a way to demonstrate BLV's long-term clinical benefit. The overall intent of this study is to establish the clinical benefit of BLV by comparing the risk of liver-related events in adult patients with CHD who received BLV once daily in countries where BLV is available commercially or through an early access program to the risk of liver-related events in a historical control group of adult patients with CHD not treated with BLV and receiving standard of care.

Research Question and Objectives:	The primary objective of the study is to compare the risk of liver-related events (ie, development of cirrhosis, hepatic decompensation, HCC, liver transplantation, and liver-related death) in adult patients with CHD treated with BLV monotherapy (2 mg or 10 mg without concomitant pegylated interferon alpha [Peg-IFNα]) to the risk of liver-related events in a historical control group of adult patients with CHD not treated with BLV and receiving standard of care (ie, off-label treatment with Peg-IFNα or no CHD treatment) for up to 5 years following cohort entry (defined as BLV treatment initiation in the BLV group or first date in the study period when a historical control patient had a health care encounter and met all inclusion and exclusion criteria). The secondary objectives of the study are: • To compare the risk of each type of liver-related event (ie, development of cirrhosis, hepatic decompensation, liver transplantation, HCC, and liver-related death) in patients treated with BLV monotherapy with the historical control group. • To compare the risk of liver-related events in patients treated with BLV 2 mg or BLV 10 mg with or without concomitant Peg-IFNα (ie, patients initiating BLV monotherapy who may add concomitant Peg-IFNα during the course of BLV treatment) with the historical control group receiving standard of care (ie, off-label treatment with Peg-IFNα or no CHD treatment). CCI [redacted].
Study Design:	This is an observational, multicenter, multicountry study comparing the risk of liver-related events in patients treated with BLV (2 mg or 10 mg) to a historical control group of adult patients who received standard of care and were not treated with BLV during up to 5 years of follow-up time. Data on adult real-world patients with CHD who received BLV by daily subcutaneous injection will be collected through retrospective medical record abstraction based on routine care from the time of BLV initiation until 5 years of follow-up. The study period for the data collection on patients treated with BLV is from the time of BLV availability in a participating country (as early as 2019). Data will be collected through retrospective medical record abstraction at regular time points during the course of follow-up on patients treated with BLV. This study will also establish a contemporary historical control group by collecting data on adult patients with CHD who received standard of care

	and were not treated with BLV. Data will be collected on the historical control group through retrospective medical record abstraction from the time of cohort entry to up to 5 years of follow-up. The study period for the collection of data for the standard of care historical control group is from 01 January 2013 to the time of BLV availability in a given country. All patients with CHD meeting the inclusion and exclusion criteria during the study period will be eligible, and inclusion and exclusion criteria will be identical for data sources on the BLV-treated and historical control groups (except for BLV exposure).
Study Population and Main Eligibility Criteria:	The study population is adult patients with CHD without evidence of decompensated liver disease in the 2 years prior to cohort entry and without a history of HCC or solid organ transplantation. The BLV-treated group will be composed of patients who received BLV 2 mg or 10 mg as prescribed by a health care provider and meet the inclusion and exclusion criteria. The historical control group will be composed of patients who received standard of care for HDV infection at participating health centers within the study period who meet inclusion and exclusion criteria and have not received BLV before cohort entry. Propensity score methods will be used to ensure the comparability of demographic and clinical characteristics between the historical control and BLV-treated groups.
Follow-up:	Patients in the BLV-treated and historical control groups will be followed for up to 5 years.
Variables:	The primary outcome is the risk of liver-related events as a composite outcome of the development of cirrhosis (among patients without cirrhosis at baseline), hepatic decompensation (eg, ascites, hepatic encephalopathy, portal hypertension-related gastrointestinal bleeding [GIB], jaundice), HCC, liver transplantation, or liver-related death. The secondary outcome will evaluate the risk of each type of liver-related event separately. A Hepatic Events Adjudication Committee (HEAC) will review and independently adjudicate liver-related events to ensure that they are assessed in a consistent and transparent manner. Data will be extracted on clinical and laboratory variables related to liver disease assessment throughout the study periods. Demographic characteristics include age, sex, race, region of origin, and country of health center. Covariates of interest include variables related to liver disease severity, comorbidities, prior and ongoing treatment for viral hepatitis, and other medication use. For comparative analyses, the exposure of interest is BLV treatment for CHD.
Data Sources:	Data for both the BLV-treated and historical control groups will be retrospectively abstracted from medical records from participating sites and countries.

Study Size:	Gilead carried out power assessments for a range of analytical sample sizes from 200 to 400 per treatment group, with the assumption that approximately 45% of patients treated with BLV and historical controls will have < 5 years of follow-up. A total analytical sample size of 350 patients treated with BLV and 350 patients from a historical control group has approximately 90% power to detect a 70% reduction in the risk of liver-related events (hazard ratio [HR]: 0.3) by using the log-rank test at a 2-sided significance level of 0.05. The HR of 0.3 (ie, 70% reduction) corresponds to an assumed cumulative incidence of 6.6% at Week 240 in the BLV group and 20.3% in the historical control group. The assumed cumulative incidence in the historical control group is based on the reported rates in Romeo et al. {Romeo 2009} and Kamal et al. {Kamal 2020}. Data collection on 500 historical controls is expected to yield an effective sample size of approximately 350 historical control patients after applying standardized morbidity/mortality ratio (SMR) weighting.
Data Analysis:	Propensity score methods (SMR weighting) will be used to balance baseline characteristics between the patients treated with BLV and historical control patients. To assess the balance produced by a propensity score model, standardized mean differences between patients treated with BLV and historical control patients before and after SMR weighting will be provided. The primary endpoint is the time to liver-related events. Inverse probability of censoring weighting may be utilized to address informative censoring. Incidence rates of liver-related events will be calculated as the number of events per 100 person-years in patients treated with BLV and in patients from the historical control group not treated with BLV. A Cox proportional hazards model will be constructed with treatment included as the main effect to compare the risk of liver-related events in patients treated with BLV to the historical control group. The Cox model will be weighted with SMR weights, and the standard error of the estimated treatment effect will be estimated with a robust variance estimator to account for the use of weights. The estimated HR and 95% CI from the Cox model will be reported. The primary endpoint will be considered met if the estimated HR is < 1.00 and the *P* value corresponding to the treatment effect is < 0.05. Comparable analyses will be conducted for the secondary objective. CCI [redacted]

PLANNED MILESTONES

Table 1. Planned Milestones

Milestone	Planned Date
Start of data collection	Q1 2025
End of data collection	Q1 2033
Final report of study results	Q2 2033

Q = quarter

1. INTRODUCTION

1.1. Hepatitis Delta Virus Infection

Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis, estimated to affect between 10 million and 20 million persons worldwide {Stockdale 2020}. Delta hepatitis is caused by a defective RNA virus that requires the presence of the hepatitis B surface antigen (HBsAg) for its complete replication and transmission {Rizzetto 2009, Sureau 1993, Taylor 2015}, and, as such, this form of hepatitis only occurs in individuals also infected with the hepatitis B virus (HBV). Prevalence rates vary widely; however, HDV infections are mostly concentrated in low- and middle-income countries, with the highest rates reported in Brazil, Mongolia, and parts of Africa {Lempp 2016, Razavi-Shearer D. 2022}. In the United States (US) and European Union (EU), HDV infection is considered an orphan disease, with an estimated prevalence of 100,000 and 130,000 patients, respectively {Rizzetto 2009, Romeo 2018, Wedemeyer 2010}. Globally, a total of 8 HDV genotypes have been identified to date, with significant geographical variability. Genotype 1 is the most widely distributed, including in Europe and North America, while genotypes 2 and 4 are predominantly found in Asia, genotype 3 in South America, and genotypes 5 to 8 are seen in Africa {Manesis 2013, Romeo 2009}.

A high proportion of patients with HDV have advanced liver disease at the time of diagnosis or enrollment in clinical cohorts (eg, > 20% with cirrhosis) {Kamal 2020, Palom 2020, Romeo 2009, Scheller 2021}. Several studies have found that over 30% of noncirrhotic patients with HDV at baseline progress to cirrhosis within a mean follow-up period of 2 to 5 years {Miao 2020, Scheller 2021, Wranke 2017}. In a nationwide retrospective cohort study in Sweden, approximately half of patients with cirrhosis and detectable HDV RNA experienced liver-related events by 5 years, and approximately three-quarters experienced liver events by 15 years of follow-up{Kamal 2020}. The 5-year cumulative incidence of hepatocellular carcinoma (HCC) among cirrhotic patients with HDV RNA viremia has been estimated to be > 10% {Fattovich 2000, Kamal 2020}.

Patients with chronic hepatitis delta infection (CHD) usually have undetectable or very low levels of HBV DNA because coinfection with HDV has been shown to suppress HBV replication {Heidrich 2012, Palom 2020}. Achievement of undetectable or very low levels of HBV DNA among patients receiving nucleoside/nucleotide analogue therapy has been observed to have no meaningful impact on the clinical outcomes of patients with CHD infection {Palom 2020}. Demographic and clinical factors observed to influence the risk of liver-related events in patients with HDV infection include higher age at baseline {Bockmann 2020, Calle Serrano 2014}, country of origin {Calle Serrano 2014, Kamal 2020, Roulot 2020}, baseline liver disease severity {Calle Serrano 2014, Kamal 2020}, low platelet count {Bockmann 2020, Calle Serrano 2014}, detectable HDV RNA {Palom 2020}, HDV genotype {Roulot 2020}, and use of interferon alpha based therapies {Wranke 2017}.

1.2. Treatment for Hepatitis Delta Virus Infection

The therapeutic options for patients with HDV infection are severely limited. Nucleoside/nucleotide analogs, while effective in patients with chronic hepatitis B infection (CHB) wherein they are widely used, have not been shown to have a meaningful therapeutic effect on HDV RNA levels in patients with CHD {European Association for the Study of the Liver 2023}. Instead, these antivirals are prescribed for the underlying infection with HBV in accordance with established treatment guidelines. Currently in the US, there is no approved treatment available for CHD. Based on clinical studies conducted over the past few decades, the current guidelines of the American Association for the Study of Liver Diseases (AASLD), the Asian Pacific Association for the Study of the Liver (APASL), and the European Association for the Study of the Liver (EASL) recommend the off-label use of pegylated interferon alpha (Peg-IFNα) for 12 months {Cornberg 2020, European Association for the Study of the Liver 2023}. Response rates with Peg-IFNα have been variable, ranging from 17% to 35%, and treatment is frequently associated with adverse effects such as flu-like symptoms, anemia, neutropenia, and thrombocytopenia that result in poor tolerability and subsequent high rates of discontinuation {Alavian 2012, Wranke 2017}. Furthermore, among patients who achieve a response (undetectable HDV RNA posttreatment) when treated with Peg-IFNα, approximately 50% relapse in long-term follow-up {Heidrich 2014}. Overall, Peg-IFNα therapy is estimated to provide a lasting benefit (ie, loss of HBsAg) for approximately 10% of patients {Heidrich 2014}. Thus, there is an urgent need for new treatments for CHD that are safe and effective, particularly for long-term use.

Bulevirtide (BLV [GS-4438], Hepcludex®), is a novel 47–amino acid, N-terminally myristoylated, HBV large envelope protein–derived, synthesized lipopeptide that binds specifically to the sodium taurocholate cotransporting polypeptide and acts as a potent, highly selective entry inhibitor of HDV into hepatocytes {Elazar 2022}.

As of August 2024, BLV (2 mg) is fully approved under the brand name Hepcludex® in the EEA, Great Britain, Australia, and Switzerland, as well as in Russia under the brand name Myrcludex B® for the treatment of CHD in adults with compensated liver disease. The Clinical Practice Guidelines on HDV released by EASL in 2023 recommends that all patients with CHD and compensated liver disease be considered for treatment with BLV, and a combination of BLV and Peg-IFNα can be considered in patients without Peg-IFNα intolerance or contraindications {European Association for the Study of the Liver 2023}.

1.3. Key Clinical Studies of Bulevirtide

Study MYR301 is an ongoing Phase 3, randomized, open-label, multicenter, parallel-group study evaluating the efficacy and safety of BLV administered at a dose of 2 mg and 10 mg once daily for treatment of CHD in participants with compensated cirrhosis or without cirrhosis. Participants (n = 150) were randomized in a 1:1:1 ratio to receive BLV 2 mg or 10 mg once daily for 144 weeks or receive BLV 10 mg once daily for 96 weeks following an observation period of 48 weeks (delayed treatment group). After Week 144, all participants across the 3 treatment groups are followed off treatment for 96 weeks (ie, through Week 240).

In Study MYR301, participants randomized to receive BLV at either 2 mg or 10 mg given once daily by subcutaneous injection showed a superior treatment response compared with the delayed treatment group at Week 48, as measured by the surrogate endpoint of combined response ([CR], defined as undetectable HDV RNA or ≥ 2 $\log_{10}$ IU/mL decline from baseline and alanine aminotransferase [ALT] normalization), which was the primary efficacy endpoint (44.9% in the BLV 2 mg group [$P < 0.0001$] and 48.0% in the BLV 10 mg group [$P < 0.0001$] versus 2.0% in the delayed treatment group) {Wedemeyer 2023}. The proportion of participants who achieved a CR was numerically similar between the BLV 2 mg and BLV 10 mg groups. The treatment response was consistent across all subgroups, including those with and without cirrhosis, when assessed at each of the 2 dose levels of BLV. Final study results are expected in 2025.

Study MYR204 was a randomized, open-label, active-controlled, parallel-group, multicenter Phase 2b study evaluating the efficacy and safety of BLV at daily doses of 2 mg and 10 mg in combination with Peg-IFNα compared with BLV 10 mg monotherapy and monotherapy with Peg-IFNα in participants with CHD. The aim of this study was to investigate potential finite treatment regimens for CHD with BLV. The primary endpoint was the rate of sustained viral response (undetectable HDV RNA) 24 weeks after the end of treatment. The BLV 10-mg + Peg-IFNα treatment group met the primary endpoint of undetectable HDV RNA 24 weeks after end of treatment (follow-up Week 24) with the highest rate of response at 46% (vs 12% with BLV 10 mg monotherapy; 17% with Peg-IFNα monotherapy; 32% with BLV 2 mg + Peg-IFNα), which remained durable through 48 weeks posttreatment (follow-up Week 48) {Asselah 2024}.

1.4. Rationale for the Current Study

As indicated in the US Food and Drug Administration (FDA) Guidance on Chronic HDV Infection: Developing Drugs for Treatment Guidance for Industry, the preferred clinical endpoint for the assessment of medicines to treat HDV infection is improvement in clinical outcomes, such as a decrease in the development of cirrhosis, decompensated liver disease, liver transplantation, HCC, and liver-related death {U.S Department of Health and Human Services (DHHS) 2019}. Hepatitis delta virus infection is the most severe form of viral hepatitis; therefore, in light of Week 48 results from Study MYR301, following untreated participants with HDV for longer than 48 weeks in the context of high unmet medical need and potential disease progression can be considered unethical. As such, controlled comparisons for BLV treatment in Study MYR301 were limited to only 48 weeks in the delayed treatment group of the 144-week study treatment period. Multiple ethical and operational concerns preclude executing another controlled prospective study of sufficiently prolonged duration and sample size that would allow

adequate assessment of the impact of BLV on liver-related clinical outcomes, including the increasing commercial availability of BLV and a low reported prevalence of HDV infection.

This study will compare the risk of liver-related events in a real-world cohort of adults who received BLV (2 mg or 10 mg) in countries where BLV is available commercially or through an early access program to the risk of liver-related events in a contemporary historical standard of care cohort. The composite primary endpoint to examine the clinical benefit of BLV includes the development of cirrhosis, hepatic decompensation (ie, ascites, hepatic encephalopathy, portal hypertension-related gastrointestinal bleeding [GIB], jaundice), HCC, liver transplantation, and liver-related death.

2. RESEARCH QUESTIONS AND OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to compare the risk of liver-related events (ie, development of cirrhosis, hepatic decompensation [ie, ascites, hepatic encephalopathy, portal hypertension-related GIB, jaundice)], HCC, liver transplantation, and liver-related death) in adult patients with CHD treated with BLV monotherapy (2 mg or 10 mg without concomitant Peg-IFNα) to the risk of liver-related events in a historical control group of adult patients with CHD not treated with BLV and receiving standard of care (ie, off-label treatment with Peg-IFNα or no CHD treatment) for up to 5 years following cohort entry (defined as BLV treatment initiation in the BLV group or first date in the study period when a historical control patients had a health care encounter and met all inclusion and exclusion criteria).

2.2. Secondary Objective

The secondary objectives of the study are:

- To compare the risk of each type of liver-related event (ie, development of cirrhosis, hepatic decompensation, liver transplantation, HCC, and liver-related death) in patients treated with BLV monotherapy with the historical control group.

- To compare the risk of liver-related events in patients treated with BLV 2 mg or BLV 10 mg with or without concomitant Peg-IFNα (ie, patients initiating BLV monotherapy who may add concomitant Peg-IFNα during the course of BLV treatment) with the historical control group receiving standard of care (ie, off-label treatment with Peg-IFNα or no CHD treatment).

CCI [redacted]

[redacted]

3. RESEARCH METHODS

3.1. Study Design

This is an observational, multicenter, multicountry study to compare the risk of liver-related events in patients treated with BLV (2 mg or 10 mg) to a historical control group of adult patients who received standard of care and were not treated with BLV during up to 5 years of follow-up time.

Data on adult real-world patients with CHD who received BLV by daily subcutaneous injection will be collected through retrospective medical record abstraction based on routine care from the time of BLV initiation until 5 years of follow-up. The study period for the data collection on patients treated with BLV is from the time of BLV availability in a participating country (as early as 2019). Data will be collected through retrospective medical record abstraction at regular time points during the course of follow-up on patients treated with BLV.

This study will also establish a contemporary historical control group by collecting data on adult patients with CHD who received standard of care and were not treated with BLV. Data will be collected on the historical control group through retrospective medical record abstraction from the time of cohort entry to up to 5 years of follow-up. The study period for the collection of data for the standard of care historical control group is from 01 January 2013 to the time of BLV commercial availability in a given country. All patients with CHD meeting the inclusion and exclusion criteria during the study period will be eligible, and inclusion and exclusion criteria will be identical for the BLV-treated and historical control groups (except for BLV exposure). Gilead Sciences (Gilead) will seek to collect data on 500 patients in the historical control group and at least 350 patients treated with BLV.

The periods described below will be used to identify patients for inclusion, evaluate baseline characteristics, and define the follow-up period.

3.1.1. Historical Control Group of Patients With Chronic Hepatitis Delta Not Treated With BLV

- Study period: 01 January 2013 to date of commercial availability of BLV in a given country. Cohort entry date for historical control patients should occur between 01 January 2013 and a minimum of 5 years before commercial availability of BLV in the country (reimbursement approval or equivalent, including reimbursement limited to patients meeting certain criteria) or availability through early access programs equivalent to commercial availability (where access to BLV was available to a substantial number of patients [ie, not limited to specific sites within a country]).

- Study inclusion and exclusion criteria: refer to Sections 3.2.1 and 3.2.2.

- Cohort entry date: first date during the study period when the patient with HDV infection had a health care encounter and met all inclusion and exclusion criteria.

- Baseline period: all information about liver-related and nonliver-related diseases, conditions, and surgeries will be collected to the extent available in the medical records. All prior and ongoing treatment for viral hepatitis in the medical records will be recorded. Age will be determined at cohort entry.

  — Baseline value for an assessment is defined as the last assessment prior to or at cohort entry, unless specified otherwise. The most recent result for liver biopsy, imaging, or liver stiffness assessments within 6 months prior to cohort entry will be considered as the baseline assessment. For laboratory results, if no assessment is available within 90 days prior to the cohort entry date, the earliest assessment within 90 days after the cohort entry date will be considered the baseline value.

- Follow-up period (primary analysis): follow-up will begin at cohort entry date until the earliest occurrence of the following: outcome of interest, censoring event (ie, initiation of BLV [eg, through a clinical study or compassionate use] or another investigational agent for HDV infection [eg, lonafarnib, Peg-IFNλ; Peg-IFNα is not considered an investigational agent], nonliver-related death), lost to follow-up (ie, last health care encounter), or end of the study period (ie, up to 5 years after cohort entry date), whichever occurs first. Initiation of Peg-IFNα is not a censoring event for the historical control group in the primary or secondary analyses, but will be included as a censoring event in a sensitivity analysis. Information on deaths occurring after the last health care encounter will be accounted for if available.

  — In analyses for the secondary objective to examine individual types of liver-related events, liver transplantation and liver-related death will be included as additional censoring events when examining the development of cirrhosis, hepatic decompensation, and HCC.

  — For historical control patients, data will be collected to the extent available following cohort entry to allow for a sensitivity analysis to examine the possible impact of the index date of the historical control group on study results (Section 3.7.1.7).

3.1.2. Cohort of Patients With Chronic Hepatitis Delta Treated With BLV

- Study period: the study period for the collection of data on real-world patients treated with BLV is according to the period of BLV availability by country. Bulevirtide has been available through early access programs or commercially in certain countries since 2019.

- Cohort entry date: BLV treatment initiation.

- Baseline period: all information about liver-related and non-liver-related diseases, conditions, and surgeries will be collected to the extent available in the medical records. All prior and ongoing treatment for viral hepatitis in the medical records will be recorded. Age will be determined at BLV treatment initiation.

  — Baseline value for an assessment is defined as the last assessment prior to or at cohort entry, unless specified otherwise. The most recent result for liver biopsy, imaging, or liver stiffness assessments within 6 months prior to cohort entry will be considered as the baseline assessment. For laboratory results, if no assessment is available within 90 days prior to the cohort entry date, the earliest assessment within 90 days after the cohort entry date will be considered the baseline value.

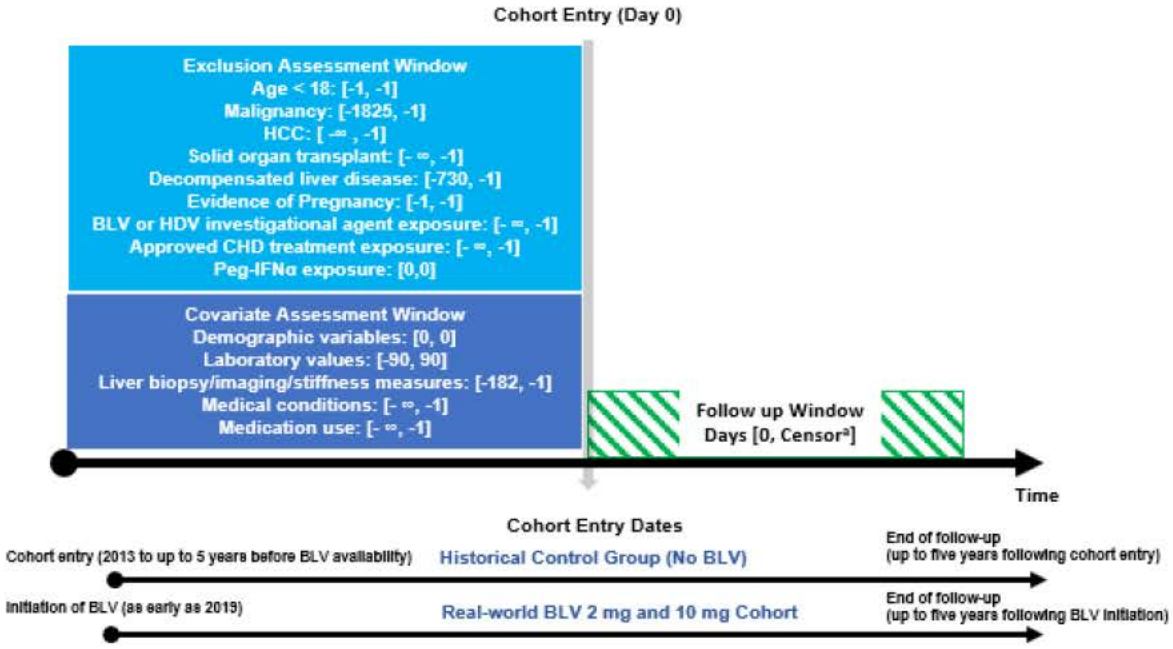
- Follow-up period (primary analysis): patients will be followed for the period of BLV treatment up to 5 years. The follow-up period starts at the date of the first dose of BLV until the earliest occurrence of the following: outcome of interest, censoring event (ie, non-liver-related death, discontinuation of BLV treatment greater than 1 month in continuum, initiation of another investigational agent for HDV infection [eg, lonafarnib, Peg-IFNλ], or initiation of Peg-IFNα), loss to follow-up (ie, last clinical encounter), or end of the study period (ie, 5 years following cohort entry date).

  — Patients who discontinue BLV treatment prior to 5 years will be censored at the health care encounter occurring nearest to and up to 1 month following the time of discontinuation of BLV in the primary analysis. Any liver-related events that occur up to 1 month following BLV discontinuation will be attributed to the BLV group.

  — In analyses for the secondary objective to examine BLV with or without concomitant Peg-IFNα, initiation of Peg-IFNα after cohort entry is not a censoring event in the BLV-treated group.

  — CCI [redacted] CCI [redacted]

Figure 1. Study Design Schematic



a. Censor at earliest of outcome of interest, loss-to-follow-up, censoring event, or end of the study period.

BLV = bulevirtide (GS-4438), Hepcludex®; CHD = chronic hepatitis delta infection; HCC = hepatocellular carcinoma; HDV = hepatitis delta virus

3.2. Setting

This study will include patients from health centers in Europe and North America. Efforts will be made to enroll the same sites for data collection on patients in both the historical control and BLV-treated groups. If the historical control group includes patients from sites not included in the BLV-treated group, these sites will be clinical centers in North American and European countries with comparable patient management and care.

Based on information collected on the expected number of eligible patients from feasibility assessments, sample size targets for each treatment group will be developed for each site; for sites with populations of potentially eligible patients larger than the established targets, random sampling will be undertaken to avoid selection bias. The sampling procedure will be carried out by an independent group and/or site personnel blinded to postbaseline data. CCI [redacted]

3.2.1. Inclusion Criteria for BLV and Historical Control Patients With Chronic Hepatitis Delta

The inclusion criteria for enrollment of real-world patients in the BLV-treated and historical control groups are provided in Table 2.

Table 2. Inclusion Criteria for Enrollment of Patients in the BLV and Historical Control Groups

Inclusion Criteria
≥ 18 years of age at cohort entry.
Diagnosed with chronic HDV infection for at least 6 months, confirmed by respective documentation in the patient's medical records (eg, at least 2 positive tests for HDV infection [serum anti-HDV antibody results and/or PCR results for serum/plasma HDV RNA] for at least a 6-month period, or other documentation of HDV infection [diagnosis codes, clinician notes, etc.] for at least 6 months in the medical records).
Patients must have a medical file with available biopsy, imaging, liver stiffness, or laboratory data on platelets to establish cirrhosis status at baseline (according to the operational definition) and at least 1 follow-up visit after cohort entry date.
Detectable HDV RNA within the 6 months prior to cohort entry.[a]
Patients in the BLV-treated group only: patients who have newly initiated BLV 2 mg or 10 mg monotherapy (ie, without concomitant Peg-IFNα) in countries where BLV is available commercially or through an early access program during the study period and receive at least 1 dose of BLV.

BLV = bulevirtide (GS-4438), Hepcludex®; HDV = hepatitis delta virus; PCR = polymerase chain reaction; Peg-IFNα = pegylated interferon alpha

a Cohort entry date is determined by meeting inclusion and exclusion criteria, including the presence of positive HDV RNA results (refer to Section 3.7.1.1).

For patients in the historical control group who may initiate BLV at a later time and contribute follow-up time to both the historical control group and BLV-treated group, inclusion and exclusion criteria will be assessed at the time of entry into each cohort (ie, cohort entry date for the historical control cohort and treatment initiation in the BLV cohort).

3.2.2. Exclusion Criteria for BLV and Historical Control Patients With Chronic Hepatitis Delta

The exclusion criteria for enrollment of real-world patients in the BLV-treated and historical control groups are provided in Table 3.

Table 3. Exclusion Criteria for Enrollment of Patients in the BLV and Historical Control Groups

Exclusion Criteria
Exposure to BLV (eg, in a clinical study) or other investigational agents for HDV infection (eg, lonafarnib, Peg-IFNλ; not including Peg-IFNα treatment) prior to cohort entry date.
Treatment with any other approved treatments for CHD on or prior to cohort entry date.[a]
Treatment with Peg-IFNα therapy on cohort entry date.[b]
Solid organ transplantation prior to cohort entry during the study period.
Diagnosis or laboratory or clinical evidence of hepatic decompensation within 2 years prior to cohort entry during the study period (ie, ascites, hepatic encephalopathy, portal hypertension-related GIB, jaundice).
Evidence of suspicious lesions consistent with HCC on imaging performed within 4 months prior to cohort entry for patients with cirrhosis and within 6 months prior to cohort entry for patients without cirrhosis.
Evidence of an active or suspected malignancy or a history of malignancy, or an untreated premalignancy disorder within the 5 years prior to cohort entry (with the exception of carcinoma of the cervix in situ and basal cell carcinoma or squamous cell carcinoma); history of HCC prior to cohort entry.
Evidence of pregnancy at cohort entry date.
BLV-treated group only: concurrently enrolled in the BLV Patient Registry (Study GS-US-589-6206).[c]

BLV = bulevirtide (GS-4438), Hepcludex®; CHD = chronic hepatitis delta; GIB = gastrointestinal bleeding; HCC = hepatocellular carcinoma; HDV = hepatitis delta virus; Peg-IFNα = pegylated interferon alpha; Peg-IFNλ = pegylated interferon lambda

a At the time of protocol development, there are no approved treatments for CHD other than BLV.

b Patients who are being treated with Peg-IFNα at a potential cohort entry date are not eligible for inclusion in the historical control group. However, at the time when Peg-IFNα is discontinued, a patient may be eligible for entry into the historical control group if all other eligibility criteria are met at that time.

c Participants in the BLV Patient Registry (Study GS-US-589-6206) will be eligible to enroll in Study GS-EU-589-6575 following completion of their enrollment in Study GS-US-589-6206. Data for these patients will be collected for up to 5 years of follow-up through medical record abstraction for Study GS-EU-589-6575.

Refer to Appendix 2 for operational definitions of inclusion and exclusion criteria.

3.3. Variables

3.3.1. Exposure

For the analyses comparing the historical control group of participants not treated with BLV to the cohort of participants who received BLV 2 mg or 10 mg, the exposure of interest is BLV treatment for CHD.

3.3.1.1. Participants Receiving Standard of Care During the Study Period in the Historical Control Group

Participants in the historical control group should not have received treatment with BLV but may have received off-label treatment with Peg-IFNα therapy prior to cohort entry or during follow-up time. Patients with ongoing treatment with Peg-IFNα at cohort entry are not eligible for inclusion in the historical control group; however, at the time when Peg-IFNα is discontinued, a patient may be eligible for entry into the historical control group if all other eligibility criteria are met at that time. Participants should not have received treatment with BLV

or investigational therapies for CHD prior to cohort entry and will be censored at initiation of BLV or another investigational CHD agent (eg, lonafarnib, Peg-IFNλ; Peg-IFNα is not considered an investigational agent).

3.3.1.2. Participants With CHD Treated With BLV

This study will examine patients treated with BLV 2 mg or 10 mg as indicated for the treatment of chronic HDV infection in adult patients with compensated liver disease. Patients with concomitant treatment with Peg-IFNα at cohort entry are not eligible for inclusion in the BLV-treated group. The primary analysis will examine patients treated with BLV 2 mg or 10 mg monotherapy (without concomitant Peg-IFNα during BLV treatment), and the secondary analysis will examine BLV 2 mg or 10 mg with or without concomitant Peg-IFNα during BLV treatment (ie, patients initiating BLV monotherapy who may add concomitant Peg-IFNα during the course of BLV treatment).

The recommended duration of treatment with BLV is undefined and the optimal treatment duration is unknown. According to the EU Summary of Product Characteristics for Hepcludex®, treatment should be continued as long as it is associated with clinical benefit. The expected average duration of BLV treatment in the real-world is currently unknown. In the primary analysis, the risk of liver-related events in the treated group will be examined during treatment with BLV 2 mg or 10 mg (for up to 5 years) and patients will be censored at BLV discontinuation (refer to Section 3.1.2 for censoring approach that includes a lag period of up to one month following BLV discontinuation). CCI [redacted] .CCI [redacted] .

3.3.2. Outcomes

3.3.2.1. Hepatic Events Adjudication Committee

This study will utilize an independent Hepatic Events Adjudication Committee (HEAC) to review and independently adjudicate liver-related events to ensure that liver-related events are assessed in a consistent and transparent manner. The same operational definitions of liver-related events, including for cirrhosis events, will be applied to all patients in the BLV-treated and historical control groups in order to ensure consistency.

The frequency of health care encounters and clinical observations is expected to be similar between the treated and control groups based on care and treatment guidelines for patients with CHB and CHD, which indicate patients with CHD would be expected to be seen by their providers at least every 6 months {European Association for the Study of the Liver 2023, European Association for the Study of the Liver (EASL) 2017}. All liver-related events identified at baseline and subsequent time points will require confirmation by the HEAC. Documentation of the occurrence of a liver-related event in the electronic case report form

(eCRF) will be the primary modality for initiation of the adjudication process by the HEAC. In addition, for the development of cirrhosis, an automated assessment process to identify potential cirrhosis events for adjudication by the HEAC will be implemented. The process for automated assessment of cirrhosis status at baseline and subsequent time points will be described in the HEAC Adjudication Charter. All deaths will be adjudicated to determine if they are due to liver disease. The HEAC's membership, conduct, and meeting schedule will be defined in the HEAC charter.

3.3.2.2. Outcome Definitions

The primary outcome is a composite outcome of the development of cirrhosis, hepatic decompensation, liver transplantation, HCC, and liver-related death. Secondary outcomes are the occurrence of each individual liver-related event.

The operational definitions of liver-related events are meant for the HEAC to use as reference when confirming the occurrence of a liver-related event in conjunction with the committee member's clinical judgement. These definitions are as follows:

1) Cirrhosis at baseline and the development of cirrhosis will be defined as meeting at least one of the following {Lutterkort 2017, Niro 2010, Romeo 2009, Sandmann 2023, Surana 2021}:

   a) Cirrhosis diagnosed on biopsy (Ishak 5 or 6 by Ishak fibrosis score or F4 by Metavir fibrosis score)

   b) Varices confirmed by endoscopy

   c) Imaging findings consistent with cirrhosis with portal hypertension (ie, portosystemic collaterals, and/or splenomegaly with a dysmorphic or nodular liver)

   d) Development of hepatic decompensation (eg, ascites, hepatic encephalopathy, portal hypertension-related GIB, jaundice)

   e) Fibrosis-4 Index for Liver Fibrosis (FIB-4) ≥ 3.25 at ≥ 2 time points within 1 year (date of cirrhosis confirmation will be at the first time point)

   f) Liver stiffness measurement (LSM) ≥ 15 kPa with a platelet count $< 150 \times 10^9$/L at ≥ 2 time points within 1 year with no other obvious etiologies

2) Hepatic decompensation {D'Amico 2022, Garcia-Tsao 2010} including any of the following:

   a) Ascites: clinically or radiographically apparent ascites. Clinically diagnosed ascites must be confirmed by radiography or paracentesis.

   b) Hepatic encephalopathy: mental status changes or disorientation, or evidence of asterixis on exam (Grade 2 or above).

c) Gastrointestinal/variceal bleeding due to liver disease: any portal hypertension-related gastrointestinal/variceal bleeding confirmed by endoscopy and presence of appropriate clinical signs such as hematemesis, melena, or hematochezia.

d) Jaundice: jaundice at clinical examination consistent with hepatic decompensation with no other obvious etiology for the hyperbilirubinemia (eg, hepatobiliary obstruction, hemolytic anemia) and total bilirubin > 3 mg/dL.

3) Liver transplantation: receipt of liver transplantation.

4) HCC: histologic confirmation or characteristic appearance on multiphasic contrast-enhanced ultrasound, computed tomography, or magnetic resonance imaging (Liver Imaging Reporting and Data System criteria).

5) Liver-related death: death attributed to complications of chronic HDV infection.

Determination of liver-related events will be based on clinical and laboratory variables related to liver disease assessments (including radiography, endoscopy, and autopsy reports) occurring throughout the study period, as documented in medical records.

In addition to outcomes captured in medical records, consideration will be given to ascertainment of outcomes for the BLV-treated and historical control group patients through mechanisms not dependent on encounters between patients and providers (eg, linkage to cancer, transplant, or hospitalization registries, or death registries/vital statistics systems) in complement to medical record abstraction, if possible, in a given health system. Accessibility and possible utilization of these data sources will be assessed in collaboration with participating sites.

3.3.3. Covariates and Other Variables

Demographic characteristics include age, sex, race, region of origin, and country of health center. Covariates of interest include variables related to liver disease severity, comorbidities, prior and ongoing treatment for viral hepatitis, and other medication use.

The variables to be collected are listed in Table 4, with all available data for each variable to be captured to the extent available from patient medical records.

Table 4. Data Items and Timing for Collection

Variables	Prior to or at Cohort Entry	Follow-up Period[a]
Demographics (ie, age, sex, race, region of birth/origin, and country of health center)	X	
Evidence of pregnancy at baseline[b]	X	
Anthropometric measures (ie, height and weight in order to determine body mass index)	X	X
Medical history, including but not limited to: • Diabetes • History of tobacco use • History of alcohol abuse • History of injection drug use • HCV infection • HIV infection • Cirrhosis • Hepatic decompensation	X	X
Medication use	X	X
Prior and concomitant treatment for HDV, HBV, HCV, and HIV	X	X
BLV treatment (treated group only)	X	X
Qualitative HDV RNA	X	X
Quantitative HDV RNA	X	X
Hepatitis B surface antigen	X	X
Hepatitis B(e) antigen	X	X
Qualitative HBV DNA	X	X
Quantitative HBV DNA	X	X
HDV genotyping	X	X
HBV genotyping	X	X
Hematology[c]	X	X
Biochemistry[d]	X	X
Coagulation (INR)	X	X
HIVAb/HDVAb/HBsAb/HCVAb	X	X
Qualitative HCV RNA	X	X
Quantitative HIV RNA (if HIV positive)	X	X
CD4+ cell counts (if HIV positive)	X	X
Liver disease assessment • Noninvasive serologic tests (APRI/FIB-4) • Liver biopsy • Elastography (such as transient elastography, shear wave elastography, or magnetic resonance elastography) • Ultrasound/CT/MRI • Endoscopic results (presence and grade of varices)	X	X

Variables	Prior to or at Cohort Entry	Follow-up Period[a]
Liver-related events • Cirrhosis • Hepatic decompensation (eg, ascites, hepatic encephalopathy, portal hypertension-related GIB, jaundice) • HCC • Liver transplantation • Liver-related death		X
Hospitalizations (number, admission diagnosis, and duration)		X
Death from any cause		X

Ab = antibody; APRI = aspartate aminotransferase to platelet ratio index; CT = computed tomography; FIB-4 = Fibrosis-4 Index for Liver Fibrosis; GIB = gastrointestinal bleeding; HBV = hepatitis B virus; HBsAb = hepatitis B surface antibodies; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; INR = international normalized ratio; MRI = magnetic resonance imaging

a All available data for each variable to be captured to the extent available in patient medical records over the follow-up period.

b Evidence of pregnancy at baseline will be collected to confirm that only patients without evidence of pregnancy at baseline are included in the study.

c Includes hematocrit, hemoglobin, platelets, and white blood cells count.

d Includes alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, direct bilirubin, total bilirubin, blood urea nitrogen, creatinine, sodium, creatinine kinase, gamma glutamyl transferase, lactate dehydrogenase, and haptoglobin.

3.4. Data Sources

As events would have already occurred at the time of data extraction, pseudonymized patient data will come from the retrospective abstraction of patient medical records (secondary use of data) and other relevant secondary sources of patient data (eg, laboratory results; administrative data; cancer, transplant, or hospitalization registries; and vital statistics systems or death registries) from participating sites and countries and will be entered into a structured eCRF system for both the BLV-treated and historical control groups.

3.5. Study Size

3.5.1. Initial Power Assessment

Gilead carried out power assessments for a range of analytical sample sizes from 200 to 400 per treatment group, with the assumption that approximately 45% of patients treated with BLV and historical controls will have < 5 years of follow-up.

In order to be conservative in power calculations, among the 45% of patients treated with BLV who are assumed to discontinue the study prior to 5 years, it was assumed that half of these patients (22.5%) would discontinue due to lack of virologic response and therefore have a less pronounced reduction in risk of liver-related events during BLV treatment.

A total analytical sample size of 350 patients treated with BLV and 350 patients from a historical control group has approximately 90% power to detect a 70% reduction in the risk of liver-related events (hazard ratio [HR]: 0.3) by using the log-rank test at a 2-sided significance level of 0.05. The HR of 0.3 (ie, 70% reduction) corresponds to an assumed cumulative incidence of 6.6% at

Week 240 in the BLV group and 20.3% in the historical control group. The assumed cumulative incidence in the historical control group is based on Romeo et al {Romeo 2009} and Kamal et al {Kamal 2020}. In the cohort in Romeo et al, 30% of patients had received Peg-IFNα treatment, which is expected to be approximately comparable to what will be observed in the historical control group.

It is expected that data collection on 500 historical controls will yield an effective sample size of approximately 350 patients after application of standardized mortality/morbidity ratio (SMR) weighting, which weights the historical control patients by the ratio of the estimated propensity score to 1 minus the estimated propensity score (odds of treatment) (Section 3.7.1.3) {Sato 2003}.

An interim power assessment examining the distribution of key confounders and propensity score overlap will be conducted at 2 time points, when data on approximately 100 patients and 200 patients are available in each of the historical control group and the BLV-treated group (N = 200 and N = 400 total), to investigate whether the target analytic sample size will be sufficient to achieve the desired power {Austin 2021}; no data on outcomes will be examined during these interim assessments. If the interim power assessments demonstrate a notable lack of comparability of the baseline data between the 2 study groups or that the desired power will not be achieved, the sample size may then be increased.

Table 5. Statistical Power by Sample Size and Expected Effect Sizes Estimates

Sample Size (N Per Treatment Group)	Hazard Ratio	Proportion of Patients With Incomplete Follow-up (%)	Statistical Power (%)
200	0.25	45	79.8
	0.30	45	67.1
	0.35	45	54.3
250	0.25	45	88.0
	0.30	45	77.4
	0.35	45	64.3
300	0.25	45	93.2
	0.30	45	84.5
	0.35	45	71.9
350	0.25	45	96.0
	0.30	45	89.8
	0.35	45	78.8
400	0.25	45	97.7
	0.30	45	93.1
	0.35	45	83.6

3.6. Data Management

After finalization of the protocol, an eCRF will be built in an electronic data capture (EDC) system to collect the data listed in the variables section (Section 3.3) for the BLV-treated and historical control groups. Personal identifying data such as names, health record, or social security identifiers will not be collected.

Each investigational site user will receive a unique username and password from the EDC system administrator following completion of the EDC system training. Completion of training and receipt of a username and password will allow the site to enter data into the eCRF EDC system. Investigators will electronically sign the eCRF to confirm responsibility for the data following the completion of data entry and data quality activities. The same EDC database will be used to collect data for the historical control and BLV treatment group patients. Database lock will be performed once all expected data have been collected and validated according to the applicable Data Management study documentation. Study datasets will be stored on secure Gilead network drives with access restricted to authorized personnel only.

3.7. Data Analysis

Table 6. Summary of Study Objectives

Primary Objective	Primary Endpoint	Cohort Entry Date	Follow-up Period
BLV-treated group: time on BLV monotherapy Historical control group: time not on BLV treatment (standard of care)	Time to any liver-related outcome (composite outcome)	BLV group: BLV treatment initiation Historical control group: first date of cohort eligibility	Until outcome of interest, censoring event,[a] lost to follow-up (ie, last health care encounter), or end of the study period (ie, up to 5 years after cohort entry date), whichever occurs first.
Secondary Objectives	**Secondary Endpoints**	**Cohort Entry Date**	**Follow-up Period**
BLV-treated group: time on BLV monotherapy Historical control group: time not on BLV treatment (standard of care)	Time to each type of liver-related event (cirrhosis, hepatic decompensation, liver transplantation, HCC, and liver-related death)	BLV group: BLV treatment initiation Historical control group: first date of cohort eligibility	Until outcome of interest, censoring event,[b] lost to follow-up (ie, last health care encounter), or end of the study period (ie, up to 5 years after cohort entry date), whichever occurs first.
BLV-treated group: time on BLV treatment with or without Peg-IFNα Historical control group: time not on BLV treatment (standard of care)	Time to any liver-related outcome (composite outcome)	BLV group: BLV treatment initiation Historical control group: first date of cohort eligibility	Until outcome of interest, censoring event,[c] lost to follow-up (ie, last health care encounter), or end of the study period (ie, up to 5 years after cohort entry date), whichever occurs first.

CCI	Cohort Entry Date	Follow-up Period
	BLV group: BLV treatment initiation	Until outcome of interest, censoring event,[d] lost to follow-up (ie, last health care encounter), or end of the study period (ie, up to 5 years after cohort entry date), whichever occurs first.

BLV = bulevirtide (GS-4438), Hepcludex®; CHD = chronic hepatitis delta infection; HCC = hepatocellular carcinoma; HDV = hepatitis delta virus; Peg-IFNα = pegylated interferon alpha

a Censoring events in the BLV-treated group: nonliver-related death, discontinuation of BLV treatment greater than 1 month in continuum, initiation of another investigational agent for HDV infection, initiation of Peg-IFNα; and in the historical control group: initiation of BLV or another investigational agent for HDV infection, nonliver-related death

b Censoring events are the same as for the primary analysis, except that liver transplantation and liver-related death will be included as censoring events in the examination of cirrhosis, hepatic decompensation, and HCC.

c Censoring events are the same as for the primary analysis, except that initiation of Peg-IFNα is not included as a censoring event in the BLV-treated group.

d Censoring events are initiation of another investigational agent for HDV infection and non-liver-related death in the BLV-treated group.

3.7.1. Primary Objective

The primary objective is to compare the risk of liver-related events in adult patients with CHD who receive treatment with BLV to the risk of liver-related events in adult patients with CHD receiving standard of care.

3.7.1.1. Effectiveness Analysis Set

The Effectiveness Analysis Set (EAS) for the primary objective will contain:

- All patients from the BLV real-world cohort who meet the inclusion and exclusion criteria of this study, complete enrollment, and receive treatment with BLV 2 mg or 10 mg at least once.

- All patients not treated with BLV in the historical control group who meet the inclusion and exclusion criteria of this study and are enrolled in this study (Section 3.2) as historical control patients.

Cohort entry date (ie, index date) determines the point at which follow-up observation for clinical endpoints begins. For patients receiving BLV, the index date is the date of BLV treatment initiation. For historical controls, a qualifying index date is defined by meeting all the inclusion/exclusion criteria detailed in Section 3.2 including a positive polymerase chain reaction (PCR) result for serum/plasma HDV RNA within 6 months prior to cohort entry.

A single HDV patient may contribute follow-up time to the historical control group and subsequently to the BLV-treated group but not simultaneously; robust standard errors will be utilized to account for within-patient correlation.

3.7.1.2. Descriptive Analyses

Following the creation of the EAS, descriptive statistics will be used to summarize demographic and baseline characteristics, overall and by treatment groups (BLV-treated group versus historical control group). Categorical variables will be summarized by the number and percentage of patients at each level of the categorical variable. Counts for missing values will also be tabulated and reported. Continuous variables will be summarized descriptively (mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum).

3.7.1.3. Confounding Control Through Propensity Score Methods

The application of the same inclusion and exclusion criteria for the BLV-treated and historical control groups is intended to create comparable patient populations. However, since the patients in the BLV-treated and historical control groups were not randomized, imbalance in baseline characteristics between the BLV-treated and historical control patient groups may lead to confounding and bias in the estimated effect of treatment with BLV even after the application of the same inclusion and exclusion criteria. Under certain assumptions, propensity score methods can remove the effect of measured confounding by comparing outcomes in treated and untreated patients who have a similar distribution of measured baseline covariates {Rosenbaum 1983}. To reduce this potential confounding effect, propensity score methods will be used to balance baseline characteristics between the BLV-treated and historical control patients. All patients in the EAS will be included in propensity score modeling using a logistic regression model with treatment as the dependent variable and the observed baseline characteristics as the independent variables.

A review of the literature and consultation with subject matter experts identified the following variables as potential confounders or of potential prognostic importance for the occurrence of liver-related events, which will be prioritized for inclusion as baseline factors in the propensity score model (Table 7). Because the propensity score model may need to be refined to achieve balance on key covariates, clinical experts will serve on the analytic decision-making team to prioritize variable importance and guide model-building and troubleshooting.

Table 7. Variables for Confounding Control: Evidence for Reported Associations With Outcomes of Interest (Liver-related Events)

Variable[a]	Type and Strength of Evidence for Relationship With Liver-related Events	Sources of Information	Prioritization for Confounding Control
Region of birth/origin	Associated with other determinants of liver-related outcomes, such as HBV and HDV genotype; place of birth and region of origin have been associated with risk of liver-related outcomes in patients with HDV infection.	Expert opinion and published studies: {Calle Serrano 2014, Kamal 2020, Roulot 2020, Stockdale 2020}	Not planned for confounding control; will be used for descriptive analyses to examine distribution of region of birth/origin in treated and control groups
Country of health center	Theoretical concern as a factor associated with health care system-related attributes that may influence care and be associated with risk of liver-related outcomes in patients with HDV infection.	Theoretical concern as factor involved in receipt of care and treatment that may be associated with liver-related outcomes.	High
Sex	Hypothesized causal effect on risk of liver-related events, based on clinical reports; some studies have observed an association of increased risk with male sex.	Expert opinion and published studies: {Calle Serrano 2014, Vieira Barbosa 2021}	High
Age	Older age is positively associated with any liver-related outcomes (composite event) in univariate and multivariate analyses in published literature.	Expert opinion and published studies:{Bockmann 2020, Buti 2011, Kamal 2020, Romeo 2009, Roulot 2020, Vieira Barbosa 2021}	High
Cirrhosis at baseline[b]	Positively associated with any liver-related event (composite) and each liver-related event individually in published literature.	Expert opinion and published studies: {Bockmann 2020, Brancaccio 2019, Buti 2011, Calle Serrano 2014, Palom 2020, Roulot 2020}	High
IFN treatment prior to cohort entry	IFN treatment has been associated with a lower risk of liver-related events in patients with CHD in some published literature.	Expert opinion and published studies: {Bockmann 2020, Romeo 2009}	High

Variable[a]	Type and Strength of Evidence for Relationship With Liver-related Events	Sources of Information	Prioritization for Confounding Control
Nucleoside/nucleotide analogue treatment prior to cohort entry	Associated with reduction in long-term clinical liver outcomes including decompensation, liver transplant, HCC, and liver-related death in univariate and multivariate analyses.	Expert opinion and published studies: {Bockmann 2020, Degasperi 2022, Scheller 2021}	High
Ongoing nucleoside/nucleotide analogue treatment at cohort entry	Associated with reduction in long-term clinical liver outcomes including decompensation, liver transplant, HCC, and liver-related death in univariate and multivariate analyses.	Expert opinion and published studies: {Bockmann 2020, Degasperi 2022, Scheller 2021}	High
Any evidence of advanced liver disease with impaired liver function based on laboratory results (platelets, albumin, INR, bilirubin)	Low platelet count, low albumin, elevated INR/prolonged prothrombin time, and elevated bilirubin have been associated with the development of liver-related events in multiple studies in both univariate and multivariate analyses.	Expert opinion and published studies: {Bockmann 2020, Brancaccio 2019, Calle Serrano 2014, Fattovich 2000, Palom 2020, Roulot 2020, Scheller 2021, Wranke 2017}	High
Diabetes	Positively associated with some liver-related clinical events in some published studies.	Expert opinion and published studies: {Campbell 2021, Kamal 2020}	High
Obesity/overweight	Positively associated with some liver-related clinical events in some published studies.	Expert opinion and published studies: {Kamal 2020, Patmore 2023, Roulot 2020}	High
History of alcohol abuse	Positively associated with some types of liver-related clinical events in some published studies.	Expert opinion and published studies: {Romeo 2009, Roulot 2020}	High
History of tobacco use	Positively associated with some types of liver-related clinical events in some published studies.	Expert opinion and published studies: {Roulot 2020}	High
History of injection drug use	Limited evidence regarding the role of injection drug use, with some published evidence indicating a positive univariate association with some types of liver-related clinical events (not a significant independent factor in multivariable analyses)	Expert opinion and published studies: {Roulot 2020}	Medium
Use of statins at cohort entry	Associated with a reduced risk of liver-related events among patients with CHB.	Expert opinion and published studies: {Li 2022, Liang 2020}	Medium

Variable[a]	Type and Strength of Evidence for Relationship With Liver-related Events	Sources of Information	Prioritization for Confounding Control
Years of nucleoside/nucleotide analogue treatment prior to cohort entry	Associated with reduction in long-term clinical liver outcomes including decompensation, liver transplant, HCC, and liver-related death in univariate and multivariate analyses.	Expert opinion and published studies: {Bockmann 2020, Degasperi 2022, Scheller 2021}	Medium
HBeAg positivity	Limited evidence regarding the role of HBeAg positivity, with some published evidence indicating that clinical outcomes are similar in HBeAg positive and HBeAg negative patients and some studies indicating that there is an association between HBeAg positivity and liver-related events.	Expert opinion and published studies:{Heidrich 2012, Rosina 1999, Vieira Barbosa 2021, Wranke 2017}	Medium
HIV or active HCV coinfection	Limited evidence regarding the role of HIV or HCV coinfection on risk of liver-related events in patients with CHD. HIV or HCV coinfection has not been consistently associated with increased risk of liver-related events in multivariable models.	Expert opinion and published studies: HIV {Beguelin 2023, Boyd 2013, Nicolini 2023, Ramos-Rincon 2021}; HCV: {Buti 2011, Roulot 2020}	Low

BLV = bulevirtide (GS-4438), Hepcludex®; CHB = chronic hepatitis B infection; CHD = chronic hepatitis delta infection; HBeAg = hepatitis B virus e antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis delta virus; IFN = interferon; INR = international normalized ratio
Table adapted from {Gatto 2019}.
a Refer to Appendix 2 for operational definitions of covariates.
b Cirrhosis status at baseline will be determined according to the definition in Section 3.3.2.

SMR weighting will be used as the primary propensity score method {Sato 2003}. SMR weighting in the context of an external control group creates an external control group with a distribution of covariates that resembles that of the treated patients. Using SMR weighting ensures that all patients treated with BLV will be included in the analysis; these patients are given a weight of 1. Weights for historical control group patients are defined as the ratio of the estimated propensity score to 1 minus the estimated propensity score (odds of treatment). Thus, SMR weighting yields a control population that is representative of the treated population with respect to the baseline characteristics included in the propensity score model.

To assess the balance that is produced by a propensity score model, standardized mean differences (SMDs) between patients treated with BLV and historical control patients before and after SMR weighting will be provided. An absolute SMD < 0.1 indicates a negligible difference in the mean or prevalence of a covariate between treatment groups {Stuart 2013}. Propensity score matching will be carried out as a sensitivity analysis to examine the consistency of the results as appropriate.

Segregation by analytic role and stage: To improve transparency and protect the validity of study results, the staged approach recommended for observational studies that use propensity score methods will be followed {McGrath 2021, Rubin 2007, Yue 2012}. The process is analogous to investigator blinding in randomized studies, which separates factors affecting treatment decisions from clinical outcomes. In this observational study, we will 1) separate the research team into analysts and decision makers and 2) not include outcome data in analytic datasets until decision makers verify covariate balance and that there is an adequate sample size after propensity score modeling. Decision makers will not be granted access to study data at any stage. In the first stage, analysts will construct propensity score models using datasets that do not contain outcome data. Analysts will provide summary results, including baseline characteristics before and after SMR weighting to check covariate balance, and will report any failure of model convergence. Model specifications are finalized by the decision-making team; after this, analysts will estimate incidence rates and effect measures for the primary, secondary, CCI [redacted] analyses. Throughout this process, all analytic decisions will be documented in a study log to be appended to the study report. The segregation of analytic stages will be implemented programmatically, with credentials required for access to project directories on the server, and implementation of analytic programs after relevant analytic decisions are made and quality checks are completed.

3.7.1.4. Intercurrent Events

Descriptive analyses will be carried out to characterize the reasons that patients in the treated and control groups have less than 5 full years of follow-up in this study, including due to the occurrence of liver-related events, lost to follow-up, or the occurrence of censoring events. In the primary analysis, the risk of liver-related events in the treated group will be examined during treatment with BLV (for up to 5 years) and patients will be censored at BLV discontinuation (refer to Section 3.1.2 for censoring approach that includes a lag period of one month following discontinuation). CCI [redacted] The reasons for BLV discontinuation in the BLV-treated group (eg, discontinuation due to an adverse event, death, pregnancy, investigator's decision, patient decision, etc.) will be reported.

According to data presented on the use of BLV in the real-world, health care providers are prescribing BLV with and without concomitant Peg-IFNα treatment and may introduce or discontinue concomitant Peg-IFNα therapy at various time points after initiation of BLV {Jachs 2022, Lampertico 2022}. For the primary analysis and secondary analyses, history of Peg-IFNα use will be included in the propensity score model. Patients in the BLV-treated group will be censored at the initiation of Peg-IFNα during follow-up in the primary analysis. Differences in the frequency of Peg-IFNα exposure during follow-up between the treated and control groups will be assessed, and additional analyses may be considered to explore the influence of Peg-IFNα use.

The relevance of intercurrent events across the BLV-treated and historical control group, including the frequency of Peg-IFNα use, will be assessed.

3.7.1.5. Interim Data Quality and Power Assessments

Following data collection from the medical charts of a prespecified number of BLV-treated and historical control group patients, data reliability and quality assessments will be performed. These checks will occur when data from approximately 50 and 100 patients are collected in each group (N = 100 and N = 200 total) in order to ensure the inclusion of data from different sites and countries. Interim data quality assessments of baseline data from the historical control group may proceed in advance of assessments of data collected on the treated group if those data are available sooner. Additional assessments of baseline data may be carried out; for example, when data on 200 and 300 patients are collected in the historical control group. Verification checks will be used to assess data conformance (ie, compliance with data definitions and standards), completeness (ie, frequencies of data attributes present in a dataset), and plausibility (ie, trustworthiness of data values). The available period of follow-up in the historical control group will be assessed by examining the time from index date to date of last recorded health care encounter (without examination of outcomes, censoring criteria, or postbaseline covariates). The number and frequency of health care encounters in the BLV-treated and historical control groups will be examined. Any issues with data reliability will be documented. No data on outcomes or postbaseline covariates will be assessed in the interim data quality assessments.

An interim power assessment examining the distribution of key confounders and propensity score overlap will be conducted at 2 time points, when data on approximately 100 patients and 200 patients are available in each of the historical control group and the BLV-treated group (N = 200 and N = 400 total), to investigate whether the target analytic sample size will be sufficient to achieve the desired power {Austin 2021}. A key factor that may influence the sample size is variance inflation due to propensity score weighting. The impact of the variance inflation factor on the effective sample size cannot be estimated before data are collected {Franklin 2021, Wang 2021}. All interim assessments will be carried out by a team of analysts without access to outcome data as described in Section 3.7.1.3. If the interim power assessments demonstrate a notable lack of comparability of the baseline data between the 2 study groups or that the desired power will not be achieved, the sample size may be increased.

3.7.1.6. Analysis for Primary Endpoints

The primary endpoint is the time to liver-related clinical events.

To compare the risk of liver-related events in the BLV-treated and historical control groups, a Cox proportional hazards model will be constructed with treatment included as the main effect in the model. Any predictor variables that were unable to achieve balance at the propensity score model-building stage will also be included in the model as predictors. The Cox model will be weighted with SMR weights, and the standard error of the estimated treatment effect will be estimated with a robust variance estimator to account for the use of weights and the possibility of patients contributing to both treatment groups. The estimated HR and 95% CI will be reported.

The primary endpoint will be considered met if the HR estimate is < 1.00 and the *P* value corresponding to the treatment effect is < 0.05.

Incidence rates of liver-related events will be calculated as the number of events per 100 person-year(s) in patients treated with BLV and in patients from the historical control group not treated with BLV. Person-time will be defined as all follow-up time from the first dose of BLV (for the BLV-treated group) or cohort entry (for the historical control group) through the first of the following: date of the outcome, censoring event, lost to follow-up, or end of planned follow-up specified in Sections 3.1.1 and 3.1.2.

The difference in the cumulative incidence functions between the historical control and BLV-treated groups will be examined for each year of follow-up time using SMR-weighted Kaplan-Meier methods; CIs will be constructed using the bootstrap resampling method.

3.7.1.7. Sensitivity Analyses

A sensitivity analysis for the primary endpoint will be carried out using propensity score matching instead of SMR weighting to examine the consistency of the results as appropriate (if an adequate number of patients can be included in the matched analysis). Propensity score matching will be carried out using the 1:1 greedy nearest neighbor matching algorithm, which matches each patient in the treated group with the first control patient exhibiting the nearest propensity score within a specified caliper width. Propensity score matching will be carried out as a sensitivity analysis rather than being used as the primary comparative analysis to maintain the totality of the data for analysis through SMR weighting.

In order to examine the possible impact of the index date of the historical control group on study results for the primary objective, a sensitivity analysis will be carried out that uses statistical modeling from data of patients from the BLV-treated group to generate eligibility durations for the control patients and establish index dates based on these eligibility windows. First, using only data from the BLV group, a model will be developed to examine the possible dependence of the eligibility duration (which is defined as the interval between when a BLV-treated patient meets the inclusion/exclusion criteria during the time period of BLV availability and first dosing of BLV) on country and individual characteristics. Depending on the actual distribution of the eligibility duration, the model may be specified as a censored (at 0) linear regression model or a log-scale linear regression model. A stepwise procedure will be used to select covariates into the model. This model-building step will be performed using the BLV data only, without access to the control data. Once the model is developed and estimated using the BLV data, the fitted model will be used to generate eligibility durations and index dates for the control patients based on their locations and individual characteristics. The health care encounter (ie, clinical assessment) for the control patients that occurs closest to the index date estimated from the fitted model will serve as the new index date. Inclusion and exclusion criteria, with the exception of a positive HDV RNA result and evidence of pregnancy, will be assessed at the new index date and historical control patients that no longer meet eligibility will be excluded. Baseline covariates will be based on the new index date for the historical control patients. For this sensitivity analysis, resulting data will be analyzed in the same manner as in the primary analysis.

Gilead will examine unweighted differences in baseline characteristics between the treated and control groups, including time since HBV and HDV diagnosis. Time since HDV diagnosis will be defined as time since first positive HDV antibody or RNA test result or first indication of positivity as documented in the medical chart (eg, "diagnosed with CHD in 2010"). If a patient's HDV diagnosis date is missing, the HBV diagnosis date will be used as a surrogate for the HDV diagnosis date. If notable differences in time since HBV and/or HDV diagnosis are observed between the treated and control groups, a sensitivity analysis will be carried out that adds time since diagnosis as a variable to the propensity score model.

In order to examine the influence of SMR weighting and the impact of patients with large weights on study results, a sensitivity analysis will be carried out to remove patients with large SMR weights from the primary analysis through percentile trimming {Cole 2008, Lee 2011}. Trimming will be performed using percentile cut points ranging from the 99th to the 90th percentiles, at 1% intervals. For example, when trimming at the 90th percentile, all weights with values above the 90th percentile will be set equal to the 90th percentile. The primary analysis will be implemented following the implementation of trimming and differences in the magnitude and statistical significance of the treatment effect will be assessed.

With respect to model misspecification, Gilead will add sensitivity analyses that investigate the impact of different statistical modeling strategies used to calculate the propensity score on the primary result. The current prespecified method for constructing the propensity scores is a main effects logistic regression model. Propensity scores will be estimated using other models (eg, random forests) and the primary analyses will be repeated.

Despite our methodological approaches to create similar populations for comparison, it is possible that misclassified or unmeasured confounders or selection bias may obscure the true effect measure. To assess the potential impact of uncontrolled confounding and selection bias, quantitative bias analysis will be employed to estimate the magnitude of possible biases in the observed association {Lash 2014}.

A sensitivity analysis will be carried out that censors follow-up time in patients in the historical control group at initiation of treatment with Peg-IFNα (ie, the same censoring criterion as in the BLV-treated group). In addition, if there are notable differences between patients who are censored and those who are not censored, inverse probability of censoring weighting will be applied to address informative censoring and examine consistency in the observed treatment effect.

Finally, sensitivity analyses will be carried out to examine nonliver-related mortality as a competing event instead of a censoring event using an SMR-weighted Fine-Gray model and cause-specific proportional hazards model.

3.7.2. Secondary Objectives

3.7.2.1. Risk of Each Liver-related Clinical Event

The secondary endpoints for this analysis are the time to each type of liver-related clinical event (ie, development of cirrhosis, hepatic decompensation [ie, ascites, hepatic encephalopathy, portal hypertension-related GIB, jaundice], HCC, liver transplantation, and liver-related death). The analytic approach described for the primary endpoint will be used for the secondary endpoint analysis.

3.7.2.2. Risk of Liver-related Clinical Events in BLV With or Without Peg-IFNα Compared to the Historical Control Group Receiving Standard of Care

In analyses for the secondary objective to examine BLV with or without concomitant Peg-IFNα, initiation of Peg-IFNα after cohort entry date is not a censoring event in the treated or control groups. The analytic approach described for the primary endpoint will be used for the secondary endpoint analysis.

CCI [redacted]

[redacted]

3.7.4. Supplementary Analyses

The number and proportion of patients treated with BLV in GS-EU-589-6575 that achieve ALT normalization and undetectable HDV RNA or a ≥ 2 $\log_{10}$ decrease in HDV RNA from baseline at postbaseline time points (eg, Week 48) will be reported for the BLV-treated group.

In addition, a supplementary analysis will be conducted to compare the risk of liver-related events in patients receiving BLV 2 mg and 10 mg monotherapy in Studies MYR301 and MYR204 to the historical control group during 144 weeks of follow-up (Appendix 3) in order to provide additional information regarding the clinical benefit of BLV.

3.8. Quality Assurance and Control

To ensure the quality and integrity of the study results, the EDC system will include automatic data validation checks. Gilead and/or contracted third party vendor will perform remote manual data quality review in accordance with the study data quality and monitoring documents. In addition, monitors will engage sites with regard to data quality and completeness via telephone calls and may perform onsite visits, as documented in the study monitoring plan. As part of their agreement to participate in the study, the investigators agree to respond to queries in a timely manner to enable the collation of data.

3.9. Potential Limitations of the Research Methods

Gilead recognizes the potential limitations of studies using a historical control group, and given this, the study will include a number of design elements and analytic methods to minimize potential biases. This study will identify historical control patients during the time period immediately preceding BLV availability, and all patients meeting the inclusion and exclusion criteria during the study period will be included in order to mitigate the possibility of selection bias. Propensity score methods will be used to ensure comparability of demographic and clinical characteristics between the 2 study populations, and approaches to minimize bias (eg, selecting into the historical control cohort consecutive patients meeting inclusion/exclusion criteria and carrying out propensity score estimation and SMR weighting without access to outcomes data) will be implemented.

Bulevirtide-treated patients and historical controls will come from the same countries with comparable HDV patient populations and clinical management. Although efforts will be made to control for all observed demographic and clinical differences in the clinical study and historical control populations, there may be unmeasured heterogeneity in patient and disease characteristics across geographic regions and countries.

This study relies on the abstraction of patient medical records, which contain information pertaining to managing patients in clinical practice rather than for research purposes. These data will be collected from countries with differences in their health care systems. Consequently, there may be limitations to the ability to standardize data across data sources. Likewise, some variables of interest may not be complete across the entire study population, and inadequate or inaccurate recording of data in patient records may introduce some degree of misclassification, which would be expected to be similar in both the BLV-treated and historical control groups.

HDV genotype 1 is the predominant genotype worldwide and it is expected that most patients in both the BLV-treated and historical control groups would be HDV genotype 1. Analyses accounting for HDV genotype in sensitivity analyses will be considered depending on the extent of genotype data available.

3.10. Other Aspects

This study will be conducted according to the Good Pharmacoepidemiology Practice and in line with the relevant Modules of the Heads of Medicines Agencies Good Pharmacovigilance Practices.

3.10.1. Joint Investigator/Gilead Responsibilities

3.10.1.1. Access to Information for Monitoring

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on the forms. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

3.10.1.2. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies and institutional review boards (IRBs)/independent ethics committees (IECs), where applicable.

4. PROTECTION OF HUMAN PATIENTS

4.1. Institutional Review Board or Independent Ethics Committee Review

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol and any accompanying material to an IRB or IEC. The investigator will not begin any study patient activities until approval from the IRB or IEC has been documented and provided as a letter to the investigator if required by local legislation.

Before implementation, the investigator will submit to and receive documented approval from the IRB or IEC for any modifications made to the protocol or any accompanying material to be provided to the patient after initial IRB or IEC approval, except for those necessary to reduce immediate risk to patients.

4.2. Confidentiality

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

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

4.3. Informed Consent

As this study is collecting data from medical records, no informed consent will be obtained unless specifically required by an appropriate ethics committee or required by country National Data Protection Laws for a participating site. All data used in this study will be pseudoanonymized and collected in an eCRF with a unique identifier for each patient by each participating site. No patient identifiers will be collected by Gilead in the eCRF.

Gilead Sciences, contracted CRO monitors and auditors, and Health Authorities may access patient medical records at sites, as needed, to complete relevant monitoring, auditing, and inspection activities, including source data verification. Gilead and contracted CRO monitors and auditors will restrict access to trained individuals who will only access the data necessary to complete the targeted reviews. Full confidentiality will be maintained during the relevant visit(s). No copies of medical records in any format (hard copies or electronic) will be taken from health centers participating in the study by Gilead or contracted CRO monitors and auditors.

5. RESPONSIBILITY AND STUDY CONDUCT

5.1. Protocol Modifications

The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

5.2. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

For studies based on use of secondary data, all analytical datasets will be maintained per records retention schedule and local regulations.

5.3. Access to Information for Audit and Inspections

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

5.4. Protocol Compliance

The study will be conducted according to this protocol.

6. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

This observational study is characterized by secondary use of data (medical chart reviews) previously collected from health care professionals for other purposes; therefore, expedited collection and submission of suspected adverse reactions in the form of individual case safety reports is not required. Should any adverse events/reactions be collected for the study, they will be recorded and summarized in the final study report. No interim safety analysis is planned for this study.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

7.1. Study Report and Publications

A study report will be prepared and provided to the applicable regulatory agencies.

The final study report will be submitted within 12 months of the final analysis. The results may be published as an abstract and/or manuscript.

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9. APPENDICES

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1. List of participating countries and cohort entry periods by country	Not applicable	Current document version can be provided upon request	List of participating countries and cohort entry periods by country

Appendix 2. Operational Definitions of Inclusion and Exclusion Criteria, Outcomes, and Key Covariates

Conceptual Definition	Operational Definition
Inclusion Criteria	
Age ≥ 18 years of age at cohort entry.	Age ≥ 18 years of age at cohort entry.
Chronic HDV infection for at least 6 months during the study period.	At least 2 positive tests for HDV infection (serum anti-HDV antibody results and/or PCR results for serum/plasma HDV RNA) for at least a 6-month period, or other documentation of HDV infection (diagnosis codes, clinician notes, etc.) for at least 6 months in the medical records during the study period.
Available medical file with clinical and laboratory data for establishing baseline cirrhosis status and at least 1 follow-up visit.	Available on medical file with biopsy, imaging, liver stiffness, or laboratory data on platelets to establish cirrhosis status at baseline (according to the operational definition) and at least 1 follow-up visit after cohort entry date.
Detectable HDV RNA within the 6 months prior to cohort entry.	Documentation of PCR positive result (quantitative or qualitative) for HCV RNA in medical record in the 6 months prior to cohort entry.
BLV-treated group only: newly initiated BLV 2 mg or 10 mg monotherapy (ie, without concomitant Peg-IFNα) in countries where BLV is available commercially or through an early access program during the study period and receive at least 1 dose of BLV.	Prescription or dispensing record for BLV documented in patient medical records during the study period (ie, time period of BLV availability commercially or through an early access program in a given country) and indication in the medical record that the patient received at least 1 dose.
Exclusion Criteria	
Exposure to BLV (eg, in a clinical study) or other investigational agents for HDV infection (eg, lonafarnib, Peg-IFNλ; not including Peg-IFNα treatment) prior to cohort entry date.	Indication in the medical records of exposure to BLV or other investigational agents for HDV treatment (eg, lonafarnib, Peg-IFNλ, REP-1239, VIR-3434, VIR-2218, BJT-778) prior to cohort entry date through a clinical study or other means (eg, compassionate use).
Treatment with any other approved treatments for CHD on or prior to cohort entry date.	Note: At the time of protocol development, there are no approved treatments for CHD other than BLV; this operational definition will be developed in the event that other therapies are approved over the course of the study.
Treatment with Peg-IFNα therapy on cohort entry date.	Prescription, dispensing records, infusion procedure claims, or any other documentation in medical record indicating any type of interferon/pegylated interferon exposure on cohort entry date.
Solid organ transplantation prior to cohort entry.	Any documentation in the medical record indicating a history of solid organ transplant including but not limited to test results, imaging, or physician notes.
Diagnosis or laboratory or clinical evidence of hepatic decompensation within 2 years prior to cohort entry, including ascites, hepatic encephalopathy, portal hypertension-related GIB, and jaundice.	Diagnosis or laboratory or clinical evidence of ascites, hepatic encephalopathy, portal hypertension-related GIB, and jaundice within 2 years prior to cohort entry, including the following: • Model for End-Stage Liver Disease score > 15 or Child-Turcotte-Pugh classification B or C • Ascites: documented presence of ascites in the medical chart • Hepatic encephalopathy: documentation of mental status changes or disorientation, or evidence of asterixis on examination (Grade 2 or above). • Gastrointestinal/variceal bleeding due to liver disease: documentation of any portal hypertension-related gastrointestinal bleeding confirmed by endoscopy and presence of appropriate clinical signs such as hematemesis, melena, or hematochezia • Jaundice: documentation of jaundice at clinical examination consistent with hepatic decompensation with no other obvious etiology for the hyperbilirubinemia (eg, hepatobiliary obstruction, hemolytic anemia) and total bilirubin > 3 mg/dL

Conceptual Definition	Operational Definition
Evidence of suspicious lesions consistent with HCC on imaging performed within 4 months prior to cohort entry for patients with cirrhosis and within 6 months prior to cohort entry for patients without cirrhosis.	Abdominal ultrasound or other imaging (performed within 4 months prior to cohort entry for patients with cirrhosis and within 6 months prior to cohort entry for patients without cirrhosis) that reveal evidence of a mass or lesions on the liver suspicious for HCC.
Evidence of an active or suspected malignancy or a history of malignancy, or an untreated premalignancy disorder within the 5 years prior to cohort entry; history of HCC prior to cohort entry.	Historical or current malignancies or an untreated premalignancy disorder as indicated by diagnoses or diagnostic codes, procedures indicating history or presence of malignancies (eg, surgeries, radiology procedures), medication dispensing indicating active or suspected malignancy or a history of malignancy within the 5 years prior to cohort entry (with the exception of carcinoma of the cervix in situ and basal cell carcinoma or squamous cell carcinoma). Any documentation in the medical record indicating a history of HCC including but not limited to diagnoses, test results, imaging, or physician notes.
Evidence of pregnancy at the time of cohort entry.	Evidence of pregnancy in the month prior to cohort entry as characterized by diagnoses, procedures, laboratory tests indictive of pregnancy (positive pregnancy tests, AFP tests, obstetric ultrasound, amniocentesis, rhesus factor test, chorionic villus sampling), basic pregnancy codes, pregnancy complication codes (for pregnancy-related anemia, pregnancy bleeding), multifetal pregnancy (twins or greater), predelivery codes (contractions, fetal position, induction), notation of obstetric hospital stays, and abortion referrals (termination of pregnancy requested, abortion counseling).
BLV-treated group only: concurrently enrolled in the BLV Patient Registry (Study GS-US-589-6206).	Simultaneous enrollment in the BLV Patient Registry (Study GS-US-589-6206); prior enrollment in Study GS-US-589-6206 is allowed if patients have completed participation in that study.
Outcomes (all liver-related events are adjudicated by the HEAC):	
Evidence of the development of cirrhosis as indicated in the medical records or from diagnostic testing	At least one of the following: • Cirrhosis diagnosed on biopsy (Ishak 5 or 6 by Ishak fibrosis score or F4 by Metavir fibrosis score) • Varices confirmed by endoscopy • Imaging findings consistent with cirrhosis with portal hypertension (ie, portosystemic collaterals, and/or splenomegaly with a dysmorphic or nodular liver) • Development of hepatic decompensation (eg, ascites, hepatic encephalopathy, portal hypertension-related GIB, or jaundice) • FIB-4 $\geq$ 3.25 at $\geq$ 2 time points within 1 year (date of cirrhosis confirmation will be at the first time point) • LSM $\geq$ 15 kPa with a platelet count $< 150 \times 10^9$/L at $\geq$ 2 time points within 1 year with no other obvious etiologies
Diagnosis, laboratory, or clinical evidence of hepatic decompensation, including ascites, hepatic encephalopathy, portal hypertension-related GIB, or jaundice.	Ascites: clinically or radiographically apparent ascites. Clinically diagnosed ascites must be confirmed by radiography or paracentesis. Hepatic encephalopathy: mental status changes or disorientation, or evidence of asterixis on exam (Grade 2 or above). Gastrointestinal/variceal bleeding due to liver disease: any portal hypertension-related gastrointestinal/variceal bleeding confirmed by endoscopy and presence of appropriate clinical signs such as hematemesis, melena, or hematochezia. Jaundice: jaundice at clinical examination consistent with hepatic decompensation with no other obvious etiology for the hyperbilirubinemia (eg, hepatobiliary obstruction, hemolytic anemia) and total bilirubin > 3 mg/dL.
Evidence of the development of HCC in medical records.	Histologic confirmation or characteristic appearance on multiphasic contrast-enhanced ultrasound, CT, or MRI (Liver Imaging Reporting and Data System criteria).

Conceptual Definition	Operational Definition
Evidence of receipt of liver transplantation.	Any documentation in the medical record indicating liver transplant including but not limited to test results, imaging, physician notes, ICD/CPT/HCPCS diagnosis or procedure codes.
Evidence in medical records indicating that death was attributed to chronic HDV infection.	Death attributed to complications of chronic HDV infection in medical records (or on death certificate if available).
Covariates (at baseline):	
Demographics:	
Region of birth/origin	Region or country of birth/origin as documented in medical records (country of birth will be classified by world region).
Country of health center	Country where the patient is receiving care from a participating site.
Sex of patient	Most recent sex recorded in medical records.
Age recorded on or before baseline	Age documented in medical records on or before baseline, including historical documentation of age that allows for calculation of age at cohort entry.
Evidence of cirrhosis at baseline (requires confirmation by HEAC)	Same definition as above.
Medical conditions that are risk factors for liver-related events:	
Evidence of diabetes	Evidence of diabetes as indicated by diagnosis of diabetes or diabetes-related condition (eg, diabetic retinopathy), laboratory results (HbA1c $\geq$ 6.5%) indicating diabetes, or prescription or dispensing records for antidiabetic medication (insulin or oral hypoglycemics in the absence of a diagnosis for prediabetes or polycystic ovarian disease).
Any history of alcohol abuse	Evidence of current or past alcohol abuse as indicated by diagnosis of alcohol abuse or results of questionnaires indicating alcohol abuse (eg, Alcohol Use Disorders Identification Test and AUDIT-Consumption [AUDIT-C] or clinician notes indicating history or current heavy drinking [eg, “alcohol intake above recommended drinking limits” and “hazardous alcohol use”]).
Any history of tobacco use	Evidence of current or past tobacco use as indicated by diagnosis codes related to tobacco use or tobacco cessation (eg, tobacco dependence syndrome, smoking).
Any history of injection drug use	Evidence of current or past injection drug use as indicated by diagnosis codes related to injection drug use, treatment for injection drug use, or clinician notes indicating history of injection drug use.
Evidence of obesity/overweight	Evidence of obesity/overweight as indicated by BMI $\geq$ 25 kg/m^2 as recorded in the medical records or calculated from height and weight within 1 year prior to cohort entry.
HIV or HCV coinfection:	
Diagnosis of HIV infection in medical records	Diagnosis of HIV infection, including but not limited to antibody, antigen, or nucleic acid testing indicating HIV infection or treatment for HIV infection prior to cohort entry.
Active HCV coinfection at baseline	Diagnosis of HCV infection without evidence of treatment or cure with direct-acting antivirals or laboratory results indicating active HCV infection at baseline (eg, HCV RNA test result indicating HCV infection status).

Conceptual Definition	Operational Definition
Medication use:	
Any exposure to interferon or pegylated interferon for any duration prior to cohort entry	Prescription, dispensing records, infusion procedure claims, or any other documentation in medical record indicating any type of interferon/pegylated interferon exposure for any duration prior to cohort entry. Interferon in medical records can include (but is not limited to): "interferon," "interferon alpha- 2a," "interferon alpha-2b," "peginterferon," "peginterferon alpha-2a," "peginterferon alpha-2b," and by brand names of IFN such as "Pegasys," "Pegintron," "PDferon B," and "Intron A."
Any exposure to nucleoside/nucleotide analogue treatment for HBV prior to cohort entry	Prescription, dispensing records, or any other documentation in medical record indicating exposure to nucleoside/nucleotide analogue treatment for HBV for any duration prior to cohort entry.
Ongoing treatment with nucleoside/nucleotide analogue treatment for HBV at cohort entry	Prescription, dispensing records, or any other documentation in the medical record indicating treatment with nucleoside/nucleotide analogue treatment for HBV in the month prior to cohort entry.
Years of nucleoside/nucleotide analogue treatment for HBV prior to baseline	Category of duration of treatment as identified through medical history, dispensing records, or clinician notes indicating duration of treatment in years of nucleoside/nucleotide analogue treatment for HBV infection (including fixed-dose combinations that include nucleoside/nucleotide analogue in HBV/HIV coinfected patients) prior to cohort entry.
Evidence of statin use at cohort entry	Prescription, dispensing records, or any other documentation in medical record (eg, GPI/NDC codes) indicating exposure to statins at cohort entry.
Viral measures and coinfections:	
Laboratory result from HBeAg testing	Most recent HBeAg laboratory result (positive or negative) within 90 days of prior to cohort entry (or 90 days after cohort entry if results prior to cohort entry are not available).
Laboratory results indicating potential advanced liver disease:	
Low platelet count indicating thrombocytopenia and potential advanced liver disease	Results of baseline laboratory test for platelet count up to 90 days prior to cohort entry date (or if no assessment is available within 90 days prior to the index day, the earliest assessment within 90 days after index date) indicating platelet count $< 150 \times 10^9$/L {Roulot 2020}.
Evidence of low albumin indicating potential advanced liver disease	Results of baseline laboratory test for albumin up to 90 days prior to cohort entry date (or if no assessment is available within 90 days prior to the index day, the earliest assessment within 90 days after index date) indicating albumin ≤ 35 g/L {Roulot 2020}.
Elevated INR indicating potential advanced liver disease	Results of baseline laboratory test for INR up to 90 days prior to cohort entry date (or if no assessment is available within 90 days prior to the index day, the earliest assessment within 90 days after index date) indicating INR > 1.5 {Wranke 2017}.
Evidence of elevated total serum bilirubin indicating potential advanced liver disease	Results of baseline laboratory test for serum total bilirubin up to 90 days prior to cohort entry date (or if no assessment is available within 90 days prior to the index day, the earliest assessment within 90 days after index date) indicating elevated serum total bilirubin > 17 µmol/L {Roulot 2020}.

AFP = alpha-fetoprotein test; BLV = bulevirtide (GS-4438), Hepcludex®; BMI = body mass index; CHD = chronic hepatitis delta infection; CPT = Current Procedural Terminology; CT = computed tomography; FIB-4 = Fibrosis-4 Index for Liver Fibrosis; GIB = gastrointestinal bleeding; GPI = Generic Product Identifier; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HBeAg = hepatitis B virus e antigen; HCC = hepatocellular carcinoma; HCPCS = Healthcare Common Procedure Coding System; HCV = hepatitis C virus; HDV = hepatitis delta virus; HEAC = Hepatic Events Adjudication Committee; ICD = International Classification of Diseases; IFN = interferon; INR = international normalized ratio; LSM = liver stiffness measurement; MRI = magnetic resonance imaging; NDC = National Drug Code; PCR = polymerase chain reaction; Peg-IFNα = pegylated interferon alpha; PT = prothrombin time.

Appendix 3. Supplementary Analysis Comparing Gilead-Sponsored Study Data to the Historical Control Group

A supplementary analysis will be conducted to compare the risk of liver-related events in patients receiving bulevirtide (BLV [GS-4438], Hepcludex®) 2 mg and 10 mg monotherapy in Studies MYR301 and MYR204 to the historical control group.

Patients Treated With BLV 2 mg and 10 mg Monotherapy in Studies MYR301 and MYR204:

In Study MYR301, exposure duration is for 96 weeks only in the delayed treatment group that rolled over to BLV 10 mg (n = 51 patients) and is for 144 weeks in the BLV 2 mg (n = 49 patients) and 10 mg (n = 50 patients) treated groups. In Study MYR204, exposure duration is for 96 weeks in the BLV 10 mg monotherapy treated group that will be included in this analysis (n = 50 patients) (Table A).

Table A. Duration of BLV Monotherapy at 2 mg and 10 mg Doses in Studies MYR301 and MYR204

Study	n	BLV Dose (mg)	Duration of Treatment
MYR301	51[a]	10	Up to 96 weeks
MYR301	49	2	Up to 144 weeks
MYR301	50	10	Up to 144 weeks
MYR204	50	10	Up to 96 weeks

BLV = bulevirtide (GS-4438), Hepcludex®
a Number of eligible patients in the delayed treatment arm may decrease after evaluation of inclusion/exclusion criteria at time of initiation of BLV.

Study Design Definitions for Clinical Study Patients Receiving BLV 2 mg and 10 mg Monotherapy in Studies MYR301 and MYR204:

- Study period: period of BLV treatment in Studies MYR301 and MYR204 (up to 96 or 144 weeks).
- Cohort entry date: BLV treatment initiation.
- Baseline period:
  - BLV-treated group: information about diseases, conditions, and surgeries related to the liver was collected for a lifelong period. Information about other diseases, conditions, and surgeries was collected if they occurred within 5 years before screening or regardless of the time if they are considered to be relevant by the investigator. All previous treatments for viral hepatitis were recorded. Prior therapy for other diseases was collected for therapies that a patient receives currently and therapies that were discontinued within 3 months before screening. Age will be determined at BLV treatment initiation.

— For any group, baseline value for an assessment is defined as the most recent assessment prior to/at first dose of BLV.

- Follow-up period: starting at date of first dose of BLV until the earliest occurrence of the following: outcome of interest, censoring event (ie, non-liver-related death, withdrawal of consent), lost to follow-up (ie, last clinical encounter), or end of the treatment period (Week 96 or Week 144 according to treatment arm).

  — Patients who discontinued BLV treatment prior to 96 weeks in MYR204 or 144 weeks in MYR301 will be followed until end of data collection in the study period if possible (up to a total of 96 weeks in MYR204 or 144 weeks in MYR301). Patients who discontinue due to withdrawal of consent or are otherwise lost to follow-up will be censored at the time of study discontinuation.

Effectiveness Analysis Set for the Supplementary Analysis Comparing MYR301 and MYR204 BLV 2 mg and 10 mg Groups to the Historical Control Group:

The Effectiveness Analysis Set (EAS) for the primary objective will contain:

- All participants from Studies MYR301 and MYR204 who completed enrollment and received treatment with BLV 2 mg or 10 mg monotherapy at least once after randomization, in addition to meeting inclusion and exclusion criteria for the comparative analysis to the historical control group at the time of BLV treatment start as participants treated with BLV.

- All patients not treated with BLV in the historical control group who meet the inclusion and exclusion criteria of this study and are enrolled in this study and meet additional inclusion/exclusion criteria of Studies MYR301 and MYR204 applied at the analytic stage as historical control participants.

Patients treated with BLV in Study MYR301 who had Child-Pugh hepatic insufficiency score of 7 at baseline will be excluded to align with inclusion/exclusion criteria for patients in the historical control group.

Patients not treated with BLV from the historical control group must meet the following additional inclusion criterion (aligned with Studies MYR301 and MYR204) to be included in the analysis:

- ALT level > 1 × upper limit of normal (ULN) but < 10 × ULN within 6 months prior to cohort entry date.

In addition, patients not treated with BLV from the historical control group who meet any of the following additional exclusion criteria (aligned with Studies MYR301 and MYR204) will be excluded from the EAS:

- > 65 years of age.

- Evidence of hepatitis C virus (HCV) or uncontrolled HIV coinfection. Participants with HCV antibodies can be enrolled, if an HCV RNA test is negative. Participants with HIV infection can be enrolled if CD4+ cell counts are > 500/mL and HIV RNA is below the limit of detection for at least 12 months.

- Evidence of New York Heart Association (NYHA) Class III-IV congestive heart failure.

- Evidence of systemic connective tissue disorders.

- Evidence of 1 or more additional known primary or secondary causes of liver disease, other than hepatitis B (eg, alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's Disease, other congenital or metabolic conditions affecting the liver, congestive heart failure, or other severe cardiopulmonary disease). Autoimmune hepatitis stigmata attributed to HDV infection are allowed.

- History of disease requiring regular use of systemic glucocorticosteroids (inhaled glucocorticosteroids are allowed) or other immunosuppressants.

- Use of interferons within 6 months before cohort entry date. Cohort entry date for patients with multiple courses of interferon treatment will commence after their final interferon treatment.

- Evidence of current alcohol abuse or alcohol abuse within 6 months prior to cohort entry date.

- Exposure to BLV or other investigational agents for HDV infection prior to cohort entry date.

- Evidence of uncontrolled arterial hypertension.

- Evidence of exclusionary laboratory values in the 6 months prior to cohort entry date:

  — Serum albumin < 28 g/L.

  — Creatinine clearance < 60 mL/min as estimated using Cockcroft-Gault formula.

  — Total bilirubin ≥ 34.2 μmol/L, unless Gilbert's syndrome is documented.

  — White blood cell (WBC) count < 3000 cells/mm^3 (< 1500 if African participants or participants of African descent).

  — Absolute neutrophil count < 1500 cells/mm^3 (< 1000 if African participants or participants of African descent).

  — Platelet count < 60,000 cells/mm^3.

For patients in the historical control group who have received prior Peg-IFNα treatment for HDV infection, follow-up start will occur 6 months following the end of Peg-IFNα use, to align with clinical study inclusion and exclusion criteria in Studies MYR301 and MYR204. Patients may not have received BLV or investigational therapies for HDV prior to cohort entry and will be censored at initiation of BLV or another investigational HDV agent (eg, lonafarnib, Peg-IFNλ; Peg-IFNα is not considered an investigational agent).

Following creation of the EAS, the analysis methods described in Section 3.7.1.6 for the primary endpoint will be utilized to compare the risk of liver-related events in patients receiving BLV 2 mg and 10 mg in Studies MYR301 and MYR204 to the historical control group. In this supplementary analysis, the end of the study period for the historical control group will be aligned with the maximum follow-up duration on BLV treatment in Studies MYR301 and MYR204. Approximately half of BLV-treated patients in MYR301 and MYR204 were followed for up to 96 weeks and the other half were followed for up to 144 weeks. In order to account for these differential exposures, bootstrapping will be used to randomly divide the historical control subjects into two equally sized groups with the follow-up period of up to 96 weeks in 1 group and up to 144 weeks in the other group. Further details of the analysis will be provided in the statistical analysis plan.

Appendix Table 1. Inclusion and Exclusion Criteria for Supplementary Analysis of Clinical Study Data and Historical Control Group

Inclusion criteria:

Study MYR301 Inclusion Criteria[a]	Study MYR204 Inclusion Criteria[a]	Historical Control Group Inclusion Criteria for Supplementary Analysis[b]
Male or female, aged 18 to 65 years (inclusive).	Male or female, aged 18-65 years (inclusive).	Male or female, aged 18 to 65 years (inclusive).
Chronic HDV infection: positive serum anti-HDV antibody results or PCR) results for serum/plasma HDV RNA for at least 6 months before screening.	Chronic HDV infection: positive serum anti-HDV antibody results or PCR results for serum/plasma HDV RNA for at least 6 months before screening.	Diagnosed with chronic HDV infection for at least 6 months prior to cohort entry, confirmed by respective documentation in the patients' medical records.
Positive PCR results for HDV RNA at screening.	Positive PCR results for HDV RNA at screening.	Positive PCR results for serum/plasma HDV RNA within 6 months prior to cohort entry date.
ALT level > 1 × ULN, but < 10 × ULN.	ALT level > 1 × ULN, but < 10 × ULN.	ALT level > 1 × ULN but < 10 × ULN within 6 months prior to cohort entry date.
Serum albumin > 28 g/L.	Serum albumin > 28 g/L.	Included as an exclusion criterion: evidence of serum albumin < 28 g/L within 6 months before cohort entry date.
Negative pregnancy test for females.	Negative pregnancy test for females.	Included as an exclusion criterion: evidence of pregnancy at cohort entry date.
Not included	Thyroid stimulating hormone within normal ranges (including on medication for control of thyroid function).	Not included

ALT = alanine aminotransferase; HDV = hepatitis delta virus; PCR = polymerase chain reaction; ULN = upper limit of normal
a Clinical study criteria regarding childbearing potential and use of contraceptives not included in table.
b Inclusion criteria applied at either the data collection or analytic stages of the study.

Exclusion criteria:

Study MYR301 Exclusion Criteria[a]	**Study MYR204 Exclusion Criteria[a]**	**Historical Control Group Exclusion Criteria for the Supplementary Analysis[a]**
Child-Pugh hepatic insufficiency score over 7 points. Uncomplicated esophageal varices allowed; Participants with current bleeding or ligation, or history of bleeding or ligation within the last 2 years are excluded.	Child-Pugh hepatic insufficiency score of B-C or over 6 points. NOTE: Child-Pugh hepatic insufficiency score of 6 points is allowed. Only participants with compensated cirrhosis are allowed. Uncomplicated esophageal varices allowed; Participants with current bleeding or ligation, or history of bleeding or ligation within the last 2 years are excluded.	Diagnosis or laboratory or clinical evidence of hepatic decompensation, including ascites, hepatic encephalopathy, portal hypertension-related GIB, or jaundice.
HCV or uncontrolled HIV coinfection. Participants with HCV antibodies can be enrolled if screening HCV RNA test is negative. Participants with HIV infection can be enrolled if CD4+ cell counts are > 500/mL and HIV RNA is below LOD for at least 12 months.	HCV or HIV coinfection. Participants with HCV antibodies can be enrolled, if screening HCV RNA test is negative.	Evidence of HCV or uncontrolled HIV coinfection. Patients with HCV antibodies can be enrolled if HCV RNA test is negative. Patients with HIV infection can be enrolled if CD4+ cell counts are > 500/mL and HIV RNA is below LOD for at least 12 months.
Creatinine clearance < 60 mL/min as estimated using Cockcroft-Gault formula.	Creatinine clearance < 60 mL/min as estimated using Cockcroft-Gault formula.	Evidence of creatinine clearance < 60 mL/min as estimated using Cockcroft-Gault formula in the 6 months prior to cohort entry date.
Total bilirubin ≥ 34.2 µmol/L. Patients with higher total bilirubin values may be included after the consultation with the study medical monitor, if such elevation can be clearly attributed to Gilbert's syndrome associated with low-grade hyperbilirubinemia.	Total bilirubin ≥ 34.2 µmol/L. (Participants with higher total bilirubin values may be included after the consultation with the study medical monitor, if such elevation can be clearly attributed to Gilbert's syndrome associated with low-grade hyperbilirubinemia).	Evidence of total bilirubin ≥ 34.2 µmol/L in the 6 months prior to cohort entry date unless Gilbert's syndrome is documented.

Study MYR301 Exclusion Criteria[a]	Study MYR204 Exclusion Criteria[a]	Historical Control Group Exclusion Criteria for the Supplementary Analysis[a]
Evidence of an active or suspected malignancy or a history of malignancy, or an untreated premalignancy disorder within the last 5 years (with the exception of successfully treated carcinoma of the cervix in situ and successfully treated basal cell carcinoma and squamous cell carcinoma not less than 1 year prior to screening [and no more than 3 excised skin cancer within the last 5 years prior to screening]) or history of hepatic carcinoma.	Evidence of an active or suspected malignancy, or an untreated premalignancy disorder, or a history of malignancy within the last 5 years (with the exception of successfully treated carcinoma of the cervix in situ and successfully treated basal cell carcinoma and squamous cell carcinoma not less than 1 year prior to screening [and no more than 3 excised skin cancer within the last 5 years prior to screening]) or history of hepatic carcinoma.	Evidence of an active or suspected malignancy or a history of malignancy, or an untreated premalignancy disorder within the last 5 years (with the exception of successfully treated carcinoma of the cervix in situ and successfully treated basal cell carcinoma and squamous cell carcinoma not less than 1 year prior to screening [and no more than 3 excised skin cancer within the last 5 years prior to screening]) or history of hepatic carcinoma.
Systemic connective tissue disorders.	Systemic connective tissue disorders.	Evidence of systemic connective tissue disorders.
New York Heart Association (NYHA) Class III-IV congestive heart failure.	NYHA Class III-IV congestive heart failure.	Evidence of NYHA class III-IV congestive heart failure.
Patients with uncontrolled arterial hypertension: systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg at screening.	Participants with uncontrolled arterial hypertension: systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg at screening.	Evidence of uncontrolled arterial hypertension.
Previous or unstable concurrent diseases or conditions that prevent participant's enrollment into the study.	Previous or unstable concurrent diseases or conditions that prevent participant's enrollment into the study.	Not included.
Patients with mental disorders or social circumstances that preclude them from following protocol requirements.	Participants with mental disorders or social circumstances that preclude them from following protocol requirements.	Not included.
Current or previous (within last 2 years) decompensated liver disease, including coagulopathy, hepatic encephalopathy, and esophageal varices hemorrhage.	Current or previous decompensated liver disease, including coagulopathy, hepatic encephalopathy, and esophageal varices hemorrhage.	Included above. (Laboratory or clinical evidence of hepatic decompensation in the 2 years prior to first health care encounter occurring during the study period.)
One or more additional known primary or secondary causes of liver disease, other than hepatitis B (eg, alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's Disease, other congenital or metabolic conditions affecting	One or more additional known primary or secondary causes of liver disease, other than hepatitis B (eg, alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's	Evidence of one or more additional known primary or secondary causes of liver disease, other than hepatitis B (eg, alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's Disease, other congenital or metabolic conditions affecting

Study MYR301 Exclusion Criteria[a]	Study MYR204 Exclusion Criteria[a]	Historical Control Group Exclusion Criteria for the Supplementary Analysis[a]
the liver, congestive heart failure or other severe cardiopulmonary disease, etc). Gilbert's syndrome, a benign disorder associated with low-grade hyperbilirubinemia, will not exclude patients from participation in this study. Autoimmune hepatitis stigmata attributed to HDV infection, in the opinion of the investigator, is allowed.	Disease, other congenital or metabolic conditions affecting the liver, congestive heart failure or other severe cardiopulmonary disease, etc.). Gilbert's syndrome, a benign disorder associated with low-grade hyperbilirubinemia, will not exclude participants from participation in this trial. Autoimmune hepatitis stigmata attributed to HDV infection in the opinion of the investigator are allowed.	the liver, congestive heart failure or other severe cardiopulmonary disease, etc). Autoimmune hepatitis stigmata attributed to HDV infection is allowed.
WBC count < 3000 cells/mm^3 (< 1500 if African patients).	WBC count < 3000 cells/mm^3 (< 1500 if African participants).	Evidence of WBC count < 3000 cells/mm^3 (< 1500 if African patients or patients of African descent) in the 6 months prior to cohort entry date.
Neutrophil count < 1500 cells/mm^3 (< 1000 if African patients).	Absolute neutrophil count < 1500 cells/mm^3 (< 1000 if African participants).	Evidence of absolute neutrophil count < 1500 cells/mm^3 (< 1000 if African patients or patients of African descent) in the 6 months prior to cohort entry date.
Platelet count < 60,000 cells/mm^3.	Platelet count < 90,000 cells/mm^3.	Evidence of platelet count < 60,000 cells/mm^3 in the 6 months prior to cohort entry date.
Not included	Hemoglobin < 12 g/dL.	Not included
Use of prohibited psychotropic agents at screening.	Use of prohibited psychotropic agents at screening.	Not included.
Use of interferons within 6 months before screening.	Use of interferons within 6 months before screening.	Use of interferons within 6 months before cohort entry date.
History of solid organ transplantation.	History of solid organ transplantation.	History of solid organ transplantation.
Current alcohol abuse or alcohol abuse within 6 months prior to enrollment in this study; past or current drug addict.	Current alcohol abuse or alcohol abuse within 6 months prior to enrollment in this study; current drug addict or history of drug use within 2 years prior to screening.	Evidence of current alcohol abuse or alcohol abuse within 6 months prior to cohort entry date.

Study MYR301 Exclusion Criteria[a]	Study MYR204 Exclusion Criteria[a]	Historical Control Group Exclusion Criteria for the Supplementary Analysis[a]
History of disease requiring regular use of systemic glucocorticosteroids (inhalative glucocorticosteroids are allowed) or other immunosuppressants.	History of disease requiring regular use of systemic glucocorticosteroids (inhalative glucocorticosteroids are allowed) or other immunosuppressants.	History of disease requiring regular use of systemic glucocorticosteroids (inhaled glucocorticosteroids are allowed) or other immunosuppressants.
Pregnant or breastfeeding females.	Pregnant or breastfeeding females.	Evidence of pregnancy at cohort entry date.
Participation in another clinical study with investigational drugs within 30 days prior to randomization.	Participation in another clinical study with investigational drugs within 30 days prior to randomization.	Exposure to BLV or other investigational agents for HDV infection prior to cohort entry date.
Receipt of BLV previously (eg, in clinical studies).	Receipt of bulevirtide previously (eg, in clinical trials).	Exposure to BLV or other investigational agents for HDV infection prior to cohort entry date.
Inability to follow protocol requirements and undergo all protocol procedures. NOTE: Patients with medical contraindication for liver biopsy are allowed to participate in this study. Such patients will exempt from liver biopsy requirements in this study. Patients receiving prohibited treatment at screening cannot be included into the study unless this treatment is withdrawn prior to randomization.	Inability to follow protocol requirements and undergo all protocol procedures. NOTE: Participants with medical contraindication for liver biopsy are allowed to participate in this study. Such participants will exempt from liver biopsy requirements in this study. Participants receiving prohibited treatment at screening cannot be included into the study unless this treatment is withdrawn prior to randomization.	Not included.
Not included	Contraindications, intolerance, or hypersensitivity to interferons alfa, genetically engineered E coli medications, polyethylene glycol or other components of peginterferon alfa-2a.	Not included
Not included	Presence or history of severe retinopathy, significant diabetic or hypertensive retinopathy.	Not included
Not included	Uncontrolled diabetes mellitus.	Not included
Not included	Uncontrolled cardiovascular disorders within 6 months before screening.	Not included

Study MYR301 Exclusion Criteria[a]	Study MYR204 Exclusion Criteria[a]	Historical Control Group Exclusion Criteria for the Supplementary Analysis[a]
Not included	History of autoimmune disorder (eg, myositis, hepatitis, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, severe psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus).	Not included
Not included	Presence or history of significant psychiatric disorder (eg, severe depression, suicide attempt, severe neurosis, or cognitive disorder).	Not included
Not included	Presence or history of chronic lung disease with respiratory malfunction.	Not included

BLV = bulevirtide (GS-4438), Hepcludex®; HCV = hepatitis C virus; HDV = hepatitis delta virus; LOD = limit of detection; WBC = white blood count

a Exclusion criteria applied at either the data collection or analytic stages of the study.

Appendix 4. Gilead Signature Page

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Clinical Benefit of Bulevirtide Therapy in Adult Patients With Chronic Hepatitis Delta Compared to a Historical Control Group Receiving Standard of Care

GS-EU-589-6575 FINAL, DATED 24 SEPTEMBER 2024

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

PPD

Name (Printed)
Author

Signature

Date

Appendix 5. Investigator Signature Page

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)	Signature
Date	Site Number

Protocol GS-EU-589-6575 Original

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Real-World Evidence eSigned	16-Oct-2024 17:44:48