# PRODUCT REGISTRY PROTOCOL

## MYR-Reg-02

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

**Version: 1.2**

**Date: 3 March 2021**

**Study type:** Observational non-interventional registry with no experimental treatment

**Study Sponsor:** MYR GmbH

**Sponsor's Address:** Hessenring 89, 61348 Bad Homburg, Germany

Replaces all previous versions of this protocol

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# Synopsis

**Protocol Title**:

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

**Type of Study**:

Observational non-interventional registry with no experimental treatment.

**Participating Countries and Sites**:

This Registry will involve sites in countries across various regions, such as France, Austria, Germany. It is open for all countries and sites that have possibilities to participate in this Registry and collect data appropriately and where it is feasible from an organizational perspective.

**Registry Duration:**

This is an open-ended registry. Patients will be asked at the time of enrollment and after giving their consent to attend as many repeated visits as possible, as per routine practice, up to four visits per year. The Steering Committee will determine the Registry duration based on the rate of enrolment, interim results, feasibility of sites and other factors reviewed during the study.

**Registry Objectives**:

The overall goal of this Registry is to collect data on the rate of liver-related clinical events in patients with chronic hepatitis D virus infection and compensated liver disease receiving bulevirtide (BLV) treatment according to the current version of the Summary of Product Characteristics (SmPC); and to bridge these clinical events with the virological (HDV RNA) and biochemical (ALT) response, and to collect data on the safety profile of BLV in a real-world setting.

<u>Primary objective:</u>

Rate of liver-related clinical events in patients receiving BLV treatment:

- Cirrhosis development;
- Hepatic decompensation: ascites, bleeding from esophageal varices, encephalopathy, laboratory abnormalities associated with reduced liver function;
- Jaundice
- HCC development;
- Liver transplantation;
- Liver-related death;

<u>Secondary objectives:</u>

- For cirrhotic patients: change in CTP score;

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

**Registry Design**:

The Registry is a non-interventional observational study, the purpose is therefore not to test a formal hypothesis. No investigational medicinal product or study-specific drug will be administered in this Registry. Only data available during the routinely indicated medical follow up of the Registry participants will be collected and analyzed, no specific study-related evaluations are planned.

The Registry will be approved according to local regulatory requirements in each participating country/ site. Informed consent or non-opposition obtaining processes will be performed in each participating site according to the specific local regulatory and legal requirements.

In order to minimize bias, participating Investigators will make an attempt to obtain consent or non-opposition from all potentially eligible patients seen at the Registry site and sequentially enroll them.

All Registry data will be obtained from the patients' medical records. If a patient is receiving BLV treatment before participating in Registry, strong efforts should be made to collect baseline data prior to the start date of the BLV treatment. Preferably, baseline data should be not older than 3 months prior to start of BLV treatment. Patients will continue to be followed up in the Registry also when the BLV treatment has ended. There are no obligatory visits in this Registry. The timeframes and frequency of patients' visits are routinely established by the Investigator based on his/her opinion, not based on requirements of this protocol. Up to four visits per year can be included into the Registry.

The data will be collected from the patients' visits performed in routine practice. After obtaining written consent or non-opposition (depending on national regulations) the patient is enrolled into the Registry, and the baseline data described in the section "Study Visits and Variables" will be collected, as far as available, including patient demographics, liver-related medical history, liver disease parameters and previous/ongoing treatment for HBV and HDV infection. At the subsequent routine visits, further liver disease parameters and variables on ongoing treatment for HBV and HDV infection will be collected, as far as available. Further parameters will be collected if available, including vitamin D levels and results of bone density measurements. For all patients treated with BLV, adverse reactions will be collected as well. Any adverse reactions related to BLV treatment should be reported into the BLV pharmacovigilance (PV) system according to the respective requirements. Within the PV system, a separate evaluation of the reactions reported for patients participating in the Registry will be performed and reported within this protocol.

The data (except adverse reactions) will be entered to electronic Case Report Forms (eCRFs) by the trained personnel. During data collection, all personal data of the patient will be kept strictly confidential. The patients will be identified by their unique identification numbers assigned in this Registry and not by their names or other personal information.

Interim analysis for the Registry will be conducted annually and at least upon gathering data from 200 patient years of patients receiving BLV. Subsequent analyses will be planned by the Steering Committee.

**Patient Population**:

This Registry will enroll adult patients diagnosed with chronic HDV infection and compensated liver disease, receiving BLV treatment according to the current version of the SmPC, who are currently not participating in any clinical trial with experimental treatment.

Inclusion criteria:

To be included in this Registry, patients must meet all of the following inclusion criteria:

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

Exclusion criteria:

Patients cannot be enrolled into the Registry if they meet any of the following criteria:

- The patient is currently participating in a clinical trial with experimental treatment.

Discontinuation criteria:

The patient may discontinue the participation in the Registry due to one or more of the following reasons:

- Withdrawal of patient consent or non-opposition
- BLV treatment not according to the current version of the SmPC (e.g. use in chronic HDV patients with decompensated liver disease)
- Death
- Loss to follow up by the site

- Enrollment in any clinical trial with experimental treatment.

For the withdrawn patient, no special follow-up is required.

**Number of Subjects**:

Due to the observational and explorative nature of the Registry, the sample size is not based on statistical considerations; the sample size depends on the possibility of the Registry sites to enroll the described patient population.

This Registry will include as many eligible patients as possible and feasible from an organizational perspective. There is no upper limit of the sample size overall and by country/ site. There is no limit on the patient enrollment rate of each country/ site.

**Study Visits and Variables**:

Only the data available in the patient records will be collected and evaluated. No specific investigations or samplings will be performed in connection with the Registry. The following variables will be evaluated in this Registry:

**Baseline Visit:**

Baseline data can only be collected and reported into the eCRF once an informed consent has been obtained from the patient and an informed consent form (ICF) has been signed. If available, baseline data is data generated prior to initiation of treatment with BLV, preferably not more than 3 months in advance of treatment start. Baseline data can be collected retrospectively and/ or prospectively.

- Date of visit
- Demography
  - year of birth;
  - gender;
  - race.
- Physical data to calculate body mass index (BMI)
  - height;
  - body weight.
- HDV hepatitis history
  - Date of first diagnosis.
- Clinical status
  - Disease stage: Chronic hepatitis or Cirrhosis status; if cirrhosis, Child-Turcotte-Pugh (CTP) score calculator;
  - Upper gastrointestinal (GI) endoscopy: esophageal and/ or gastric varices;

  - Ascites (with grade);
  - Hepatic encephalopathy (with grade);
  - Upper GI bleeding;
  - Development and worsening of jaundice;
  - Hepatocellular carcinoma (HCC) development; active (details) or previously diagnosed and treated;
  - Drug-induced liver injury;
  - Liver transplantation.

- Laboratory data
  - Date and laboratory results: Bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT) or international normalized ratio (INR), serum albumin, bile salts, vitamin D levels, alpha-fetoprotein (AFP), creatinine, hemoglobin, platelets, white blood cells (WBC).
- Virological data
  - Date and laboratory results: qHBsAg, HBeAg, qHBV DNA, anti-HDV, qHDV RNA, HBV genotype, HDV genotype; anti-HIV, anti-HCV.
- Imaging or others
  - Fibroscan: date and results in kPa;
  - Bone density scan: date and results as classes (normal, osteopenia, osteoporosis);
  - Liver biopsy: date and stage of fibrosis (ISHAK score, METAVIR score).
- Current antiviral treatment
  - Bulevirtide: dose, start date;
  - Interferon: dose, start date;
  - Nucleotide/Nucleoside analogues: dose, start date;
  - Other HBV or HDV treatment: dose, start date.
- Previous antiviral treatment
  - BLV, Interferon; Nucleotide/Nucleoside analogues; other HBV or HDV treatment.
- Liver related hospitalization: amount of hospitalizations and duration of each period of hospitalization
- Other significant medical conditions and medication

**Routine Visits:**

- Date of visit

- Physical data to calculate BMI
  - body weight.
- Clinical status
  - Disease stage: Chronic hepatitis or Cirrhosis status; if cirrhosis, CPT score calculator;
  - Upper gastrointestinal (GI) endoscopy: esophageal and/ or gastric varices;
  - Ascites (with grade);
  - Hepatic encephalopathy (with grade);
  - Upper GI bleeding;
  - Development and worsening of jaundice;
  - Hepatocellular carcinoma (HCC) development; active (details) or previously diagnosed and treated;
  - Drug-induced liver injury;
  - Liver transplantation;
  - Liver-related death.
- Laboratory data
  - Date and results: Bilirubin, AST, ALT, PT or INR, serum albumin, bile salts, vitamin D levels, AFP, creatinine, hemoglobin, platelets, WBC.
- Virological data
  - Date and results: qHBsAg, HBeAg, qHBV DNA, qHDV RNA; anti-HIV, anti-HCV.
- Imaging or others
  - Fibroscan: date and results in kPa;
  - Bone density scan: date and results as classes (normal, osteopenia, osteoporosis);
  - Liver biopsy: date and stage of fibrosis (ISHAK score, METAVIR score).
- Current antiviral treatment
  - Bulevirtide: dose, start date;
  - Interferon: dose, start date;
  - Nucleotide/Nucleoside analogues: dose, start date;
  - Other HBV or HDV treatment: dose, start date.
- Previous antiviral treatment

  - BLV, Interferon; Nucleotide/Nucleoside analogues; other HBV or HDV treatment.

- Liver related hospitalization: amount of hospitalizations and duration of each period of hospitalization

- Other significant medical conditions and medication

**Safety**:

For patients treated with BLV the following safety data will be collected and reported:

- Adverse reactions (serious or non-serious) **related to BLV treatment**;
- The following lists special situations during BLV treatment:
  - Use of a medicinal product during pregnancy or breastfeeding.
  - Overdose;
  - Off-label use;
  - Misuse;
  - Abuse;
  - Medication error;
  - Falsified medicinal product;
  - Lack of therapeutic efficacy;
  - Suspected transmission of an infectious agent via a medicinal product.

All safety information should be reported immediately (within 24 hours of the Investigator's knowledge of the event) to the following contact:

PPD or by fax to: PPD

**Statistics**

Continuous variables will be summarized in terms of descriptive statistics including number of observations, mean, standard deviation, minimum, maximum and quartiles. Categorical variables will be summarized in terms of frequencies and percentages. To account for the different durations of observation, the incidences of events will be normalised to subject exposure to evaluate the incidence according to time of exposure (patient-years).

An appropriate time window pattern relative to baseline (enrolment) will be defined for the Registry data (e.g. months or quarters). Longitudinal data will be summarized by time window. If more than one measurement for a patient falls into the same time window the last measurement will be used.

Summaries will be provided by country and relevant concomitant treatment cohort.

**Patient disposition**

The number and relative frequency of patients who prematurely discontinued the participation in the Registry and reasons for discontinuation will be tabulated. The duration of observation will be summarized.

**Demographic and baseline data**

All demographic and disease characteristic variables will be summarized according to type of variable.

**Liver-related clinical events**

Liver-related events will be described by crude incidence rate (by patients) and observation time adjusted incidence rates (by patient-years) in each treatment cohort. Corresponding exact 95%-confidence interval will be presented. The time from BLV treatment start until the first occurrence of an event will be analysed using Kaplan-Meyer methods.

The influence of treatment and other covariables on the occurrence of events will be analysed by means of logistic and Cox regression models.

**Adverse reactions**

Adverse reactions (ARs) will be coded according to MedDRA. All ARs should be recorded on the Safety Case Report Form provided in the Investigator Site File and the reported immediately (within 24h of the Investigator's knowledge of the event) to PPD or by fax to: PPD. The subject identification number has to be added on the Safety Case Report Form to be able to assign the AR to the respective patient data from this Registry.

Frequency, percentages and observation time standardized rates of all ARs will be summarized according to primary system organ class (SOC) and preferred term and tabulated by treatment cohort including exact 95%-confidence intervals. Serious ARs, ARs leading to death, and ARs resulting in discontinuation of the participation in the Registry, will be tabulated separately.

Logistic models will be used to explore risk factors for the occurrence of the most frequent SOCs.

**Laboratory data**

Laboratory variables will be described as continuous, longitudinal data. Sample statistics for the observed values and for changes from baseline by time window will be presented. Wilcoxon sign rank test will be performed for changes from baseline at each time window.

**Exposure**

Exposure to documented HDV/ HBV infection treatment will be summarized according to type of drug administered.

**Interim analyses**

Periodical (annual) interim analyses with preparation of interim reports will be conducted. Additional analyses may be performed by decision of the Steering Committee.

# 1 List of Abbreviations

| | |
|---|---|
| AASLD | American Association for the Study of the Liver |
| AFP | Alpha-fetoprotein |
| AIDS | Acquired Immunodeficiency Syndrome |
| ALT | Alanine Aminotransferase |
| AR | Adverse Reaction |
| AST | Aspartate Aminotransferase |
| BLV | Bulevirtide |
| BMI | Body Mass Index |
| CHB | Chronic HBV Infection |
| CRF | Case Report Form |
| CRO | Clinical Research Organization |
| CTP | Child-Turcotte-Pugh score |
| DNA | Deoxyribonucleic Acid |
| EASL | European Association for the Study of the Liver |
| EC | Ethics Committee |
| eCRF | electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| EU | European Union |
| EUROHEP | European Concerted Action on Viral Hepatitis |
| EU-PAS | European Union electronic Register of Post-Authorisation Studies |
| FNRC | French National Reference Centre |
| FSI | First Subject In |
| GI | Gastrointestinal |
| HBeAg | Hepatitis B Virus e-antigen |
| HBsAg | Hepatitis B Virus s-antigen |
| HBV | Hepatitis B Virus |
| HCC | Hepatocellular Carcinoma |
| HCV | Hepatitis C Virus |
| HDIN | Hepatitis Delta International Network |

| | |
|---|---|
| HDV | Hepatitis Delta (D) Virus |
| HIV | Human Immunodeficiency Virus |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| INR | International Normalized Ratio |
| LSI | Last Subject In |
| LSO | Last Subject Out |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NTCP | $Na^+$ Taurocholate Cotransporter Polypeptide |
| Peg-IFNα | Pegylated Interferon Alpha |
| PT | Prothrombin Time |
| PV | Pharmacovigilance |
| RAP | Registry Analysis Population |
| RNA | Ribonucleic Acid |
| SAP | Statistical Analysis Plan |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| WBC | White Blood Cells |

# 2 General Information

## 2.1 Protocol identification

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

**Protocol number**: MYR-Reg-02

**Protocol version and date**: version 1.2 Date: 3 March 2021

**Type of study**: Observational non-interventional registry with no experimental treatment.

**EU-PAS ID:** EUPAS38678

## 2.2 Study organization

This Registry is organized, financed and sponsored by MYR GmbH, Germany. The Registry will be managed by the Medical Department of MYR GmbH.

The Sponsor may involve global CRO and/or local CROs in any participating country to delegate some of the study activities.

## 2.3 Steering Committee

The Sponsor will organize the Steering Committee of the Registry. The Steering Committee includes Sponsor team members, clinical experts and biostatisticians. The meetings of the Steering Committee will be held not less than annually. The Steering Committee is responsible for (including, but not limited):

- Review of the significant amendments of the protocol (after initiation of the Registry) of the Registry and SAP;
- Initiation of protocol amendment(s);
- Initiation of statistical analysis;
- Overseeing the monitoring and data quality control procedures;
- Promoting inclusion into the Registry
- Review of interim and final datasets and results;
- Approval, evaluation and coordination of proposed inquiries for projects/publications
- Support for Investigators concerning questions on the Registry conducted
- Determination of Registry duration based on rate of enrolment, interim results, feasibility of sites and other factors reviewed during the study.

## 2.4 Responsible parties

**Investigators:**

This Registry is open for all sites and countries that can enrol study population. The list of Investigators responsible for the conduct of the Registry at each site will be provided in the study report.

**Registry Sponsor:**

MYR GmbH

Hessenring 89, 61348 Bad Homburg, Germany

## 2.5 Sponsor's signature

| **MYR-Reg-01** | |
|---|---|
| **Sponsor:** MYR GmbH, Hessenring 89, 61348 Bad Homburg, Germany<br><br>Name: PPD<br>Position: PPD | 05-Mar-2021 PPD<br>Date, S PPD |
| Name: PPD<br>Position: PPD | 04.03.2021 PPD<br>Date, Signature |

## 2.6 Investigator's signature

I have read the protocol. I understand the content and intend to fully comply with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal authorization by the Sponsor in the form of a protocol amendment.

**Investigator**:

Signature: _____

Full Name: _____

Institution: _____

_____

Date: _____(DD/MMM/YYYY)

# 3 Background Information and Rationale

## 3.1 Background information

Hepatitis delta virus (HDV) was first discovered in 1977 by Mario Rizzetto in Turin, Italy, when the delta antigen and respective antibodies in chronic hepatitis B virus (HBV) surface antigen (HBsAg) positive carriers were described (1). HDV is a defective small RNA virus that requires the presence of the HBsAg for its complete replication and transmission (2) (3) (4). The envelopment process of HDV occurs through interactions between the HDV ribonucleoprotein complex and HBsAg (3) (4) (5). However, beyond interacting with HBV envelope proteins, controlling mechanisms exist by which HDV inhibits HBV DNA replication while allowing a selective transcription of HBV proteins (2) (5).

HDV can be transmitted as simultaneous HBV/HDV infection (coinfection) or HDV infection of an individual already chronically infected with HBV (superinfection) (2) (6) (7), and the latter occurs more frequently (2). HBV/HDV coinfection usually leads to acute hepatitis which can range from mild to fulminant hepatitis and death (6) (7). Chronic infection after acute HBV/HDV hepatitis is infrequent and leads to chronicity in only 2% of the cases (8). In contrast, 70-90% of patients with superinfection acquire chronic hepatitis delta. The liver disease associated with chronic HDV infection runs a more progressive course than chronic HBV monoinfection and may lead to cirrhosis within 2 years in 10–15% of patients (7) (8).

Evidence was reported in the literature, that unlike HBV infection, HDV infection can be associated with direct cytotoxicity which may hasten the fibrosis process (9) (10). However, the immune system plays the major role in the clearance of the infected hepatocytes; levels of HDV viremia are not directly associated with histological changes (11). As with any immune-mediated diseases, different patterns of progression, ranging from mild to severe progressive disease, are observed (7).

The HDV genotype is one of the factors that may influence the course of disease. At least eight HDV genotypes have been identified (4) (6) (12) (13). HDV genotype 1 is the most common genotype and is distributed throughout the world, especially in Europe, the Middle East, North America and North Africa. By contrast, HDV genotype 2 is observed in the Far East, and HDV genotype 3 is seen exclusively in the northern part of South America (4) (6). Genotypes 4–8 have primarily been identified in African patients, for example, in pregnant women in Gabon (14). HDV genotype 1 is associated with both severe and mild disease, whereas genotype 2 is associated with a mild disease course (15).

Epidemiology of hepatitis delta has been extensively studied since 1980s, where indirect antibody assays for the diagnosis of HDV became generally available (2). At the end of the 1980s it was estimated globally that approximately 5% of HBsAg carriers have HDV infection, and the approximate number of HDV carriers is 12 million; the prevalence and patterns of HDV infection vary in different areas (16). Since then, the epidemiologic scenario of hepatitis delta has changed in industrialized countries. In the past 20 years, the implementation of HBV vaccination, measures to reduce sexual transmission (prompted by the risk of AIDS) and the improvement of sanitation

and living conditions have led to the containment of HBV with a significant reduction of domestic networks of HBsAg carriers (6) (17). At the end of the last century, the decline of hepatitis delta in Southern Europe led to the assumption that hepatitis delta was no longer a relevant medical problem (18). However, hepatitis delta has not vanished from Europe, but is on the rise because of immigration. Most of those co-infected individuals are immigrants, mainly from sub-Saharan Africa and Eastern Europe (2) (17). A study conducted in France with 1112 patients from the French National Reference Centre (FNRC) database, showed that 86% of the included population were migrants (43). In regions of the developing world in which HBV remains endemic, the hepatitis delta epidemiology has not substantially changed (17).

In general, hepatitis delta virus is a highly pathogenic virus causing acute and chronic liver disease. Although benign course of the disease has been described (19), hepatitis delta is considered the most severe form of viral hepatitis in humans, and is associated with high risk of progression of liver disease, development of cirrhosis, decompensation and hepatocellular carcinoma (HCC) development (2) (6) (20). The study by the European Concerted Action on Viral Hepatitis (EUROHEP) demonstrated that HBV/HDV positive cirrhotic patients followed for a median of 6.6 years had a twofold mortality risk than chronic HBV patients (CHB) with cirrhosis. Moreover, the estimated risk for HCC was 13% for HBV/HDV cirrhotic patients as compared to 2–4% for HBV cirrhotic patients, thus increasing the risk to threefold (21). A study from Italy has shown existence of anti-HDV antibodies in as many as 40% of patients with liver cirrhosis in 1987. Although this number has declined to 11% in 2000 (18), the HDV-caused disease is still a significant burden. A longitudinal study has shown that 20% of hepatitis delta patients develop a liver-related first-time event during the median follow up time of 4 years, vs only 8.5% of HBV monoinfected patients (22). At baseline, 19.8% of the patients of this cohort had cirrhosis, compared to 7.3% of CHB patients. HDV infection was a cause of death for 60% of patients in a 28-year study from Italy (23). HDV co-infection is associated with faster progression to fibrosis and cirrhosis, earlier onset of hepatic complications and likelihood of liver transplantation (24) (25) (26). Liver cirrhosis and cancer occur 10-15 years earlier in HBV/HDV co-infection and the 5-year mortality of co-infected individuals is twice that of HBV monoinfection (27). Chronic HDV infection causes cirrhosis and HCC with annual rates of 4% and 2.8%, respectively (23). In a study conducted in Sweden, 337 anti-HDV positive patients (233 of them with HDV RNA viremia and 91 without HDV RNA viremia at baseline) were retrospectively studied, with a mean follow-up of 6.5 years. The study showed that patients with viremia, had a 2.6 fold higher risk of HCC and a 3.8 fold higher risk of liver-related events (HCC, hepatic decompensation, or liver-related death/transplantation), when compared to patients without viremia (44). In the USA a recent study utilizing data of a tertiary centre database revealed HDV prevalence of 8% among HBsAg carriers (28). 11% of injection drug users were tested positive for HDV in Baltimore; in those with chronic HBV infection, 50% were HDV positive (29).

Hepatitis delta is a major health problem, not only because of the severity of the disease. The first treatment for chronic HDV infection, the entry inhibitor bulevirtide, is approved by EMA since July 2020. Interferons, previously used as a de-factor treatment standard, show some degree of efficacy in a small proportion of patients with approximately 25% of virological and biochemical

response. Antiviral agents active against HBV do not work against HDV (25). Several clinical trials were recently performed investigating the use of pegylated interferon alpha in hepatitis delta. Two large trials in this indication, HIDIT-1 and HIDIT-2, did show only very modest long-term virological results. In the HIDIT-1 clinical trial, pegylated interferon was tested in combination with nucleotide analogue adefovir dipivoxil versus either drug alone in 91 chronically HDV infected patients (30). At test week 48, 23% of patients on combination therapy, 24% on pegylated interferon monotherapy, and no patients on adefovir reached HDV RNA negativation. The effect was sustained through follow up week 24. However, the follow up study revealed that from 16 individuals who have reached HDV RNA negativity at the end of treatment, 9 tested positive within the median follow up of 4.5 years (0.5-5.5 years) (31). In the HIDIT-2 clinical trial, 120 patients received pegylated interferon alpha with or without tenofovir disoproxil fumarate for 96 weeks. The prolongation of the interferon treatment to 96 weeks and addition of nucleotide analogue tenofovir did not improve sustained virological response rates: 30% of patients in the combination arm and 23% of patients in the monotherapy arm were HDV RNA negative 24 weeks after the end of treatment. Of note, 20 patients (16%) did not complete at least week 80 of treatment. A trial involving 49 patients treated with pegylated interferon alpha 2b has shown 33% of HDV RNA negativation at the end of treatment (48 weeks) and 25% at the end of follow up (32).

## 3.2 Rationale of the study

BLV is the first specific treatment for chronic HDV infection approved in the EU and Russian Federation. To collect data on the influence of BLV treatment on the rate of liver-related clinical events, an observational post-marketing Registry is planned.

In 2011, the Hepatitis Delta International Network (HDIN) Registry was established with centers in Europe, Asia, North- and South America (41). The authors reported on clinical and virological characteristics of the first 1576 patients with ongoing or past HDV infection included in the database until October 2016 and performed a retrospective outcome analysis. The majority of patients was male (n = 979, 62%) and the mean age was 36.7 years (range 1-79, with 9% of patients younger than 20 years). Most patients were HBeAg-negative (77%) and HDV-RNA positive (85%). Cirrhosis was reported in 48.7% of cases which included 13% of patients with previous or ongoing liver decompensation. HCC developed in 30 patients (2.5%) and 44 (3.6%) underwent liver transplantation. Regions of origin were independently associated with clinical endpoints and detectability of HDV RNA. Antiviral therapy was administered to 356 patients with different treatment uptakes in different regions. Of these, 264 patients were treated with interferon-alpha and 92 were treated with nucleoside and nucleotide analogues only. The HDIN Registry confirms the severity of hepatitis delta but also highlights the heterogeneity of patient characteristics and clinical outcomes in different regions (41). However, data on the HDV epidemiology and clinical course in large populations from other regions of the world are still absent.

As a supplement to clinical trials, registries can help to better understand the clinical course of diseases and variations in treatment and outcomes; to examine factors that influence prognosis and

quality of life; to describe care patterns, including appropriateness of care and disparities in the delivery of care; to assess effectiveness; to monitor safety and harm; and to measure quality of care (42). Another advantage of registries is the ability to provide data on populations not typically studied in clinical trials (e.g. elderly, minorities, those with multiple co-morbidities).

The current Registry aims to collect data from a significant population of patients with chronic HDV infection and compensated liver disease who are treated with BLV according to the current version of the SmPC from various countries and further create the unique clinical database. The data obtained in this Registry may be useful for determining healthcare policies, and may help to contribute to the development of treatment guidelines or emphasis actual scientific and clinical topics to facilitate future research.

# 4 Registry objectives

The overall goal of this Registry is to collect data on the rate of liver-related clinical events in patients with chronic hepatitis D virus infection and compensated liver disease receiving bulevirtide (BLV) treatment according to the current version of the SmPC, to bridge these clinical events with the virological (HDV RNA) and biochemical (ALT) response, and to collect data on the safety profile of BLV in a real-world setting.

Primary objective:

Rate of liver-related clinical events in patients receiving BLV treatment:

- Cirrhosis development;
- Hepatic decompensation: ascites, bleeding from esophageal varices, encephalopathy, laboratory abnormalities associated with reduced liver function;
- Jaundice
- HCC development;
- Liver transplantation;
- Liver-related death;

Secondary objectives:

- For cirrhotic patients: change in CTP score;
- Changes in HDV RNA to baseline;
- Changes in ALT to baseline;
- To collect data on the safety profile of BLV in patients receiving bulevirtide treatment:
    - Adverse reactions;
    - Vitamin D levels, bone density scans.

# 5 Registry methods

## 5.1 Overall Registry design

The Registry is a non-interventional observational study, the purpose is therefore not to test a formal hypothesis. No investigational medicinal product or study-specific drug will be administered in this Registry. Only data available during the routinely indicated medical follow up of the Registry participants will be collected and analyzed, no specific study-related evaluations are planned.

The Registry will be approved according to local regulatory requirements in each participating country/ site. Informed consent or non-opposition obtaining processes will be performed in each participating site according to the specific local regulatory and legal requirements.

In order to minimize bias, participating Investigators will make an attempt to obtain consent or non-opposition from all potentially eligible patients seen at the Registry site and sequentially enroll them.

All Registry data will be obtained from the patients' medical records. If a patient is receiving BLV treatment before participating in Registry, strong efforts should be made to collect baseline data prior to the start date of the BLV treatment. Preferably, baseline data should be not older than 3 months prior to start of BLV treatment. Patients will continue to be followed up in the Registry also when the BLV treatment has ended. There are no obligatory visits in this Registry. The timeframes and frequency of patients' visits are routinely established by the Investigator based on his/her opinion, not based on requirements of this protocol. Up to four visits per year can be included into the Registry.

The data will be collected from the patients' visits performed in routine practice. After obtaining written consent or non-opposition (depending on national regulations) the patient is enrolled into the Registry, and the baseline data described in the section "Study Visits and Variables" will be collected, as far as available, including patient demographics, liver-related medical history, liver disease parameters and previous/ongoing treatment for HBV and HDV infection. At the subsequent routine visits, further liver disease parameters and variables on ongoing treatment for HBV and HDV infection will be collected, as far as available. Further parameters will be collected if available, including vitamin D levels and results of bone density measurements. For all patients treated with BLV, adverse reactions will be collected as well. Any adverse reactions related to BLV treatment should be reported into the BLV pharmacovigilance (PV) system according to the respective requirements. Within the PV system, a separate evaluation of the reactions reported for patients participating in the Registry will be performed and reported within this protocol.

The data (except adverse reactions) will be entered to electronic Case Report Forms (eCRFs) by the trained personnel. During data collection, all personal data of the patient will be kept strictly confidential. The patients will be identified by their unique identification numbers assigned in this Registry and not by their names or other personal information.

Interim analysis for the Registry will be conducted annually and at least upon gathering data from 200 patient years of patients receiving BLV. Subsequent analyses will be planned by the Steering Committee.

## 5.2 Settings

### 5.2.1 Participating countries and sites

This Registry will involve sites in countries across various regions, such as France, Austria, Germany. It is open for all countries and sites that have possibilities to participate in this Registry and collect data appropriately and where it is feasible from an organizational perspective.

The sites will be selected based on their ability and resources to collect data and complete the eCRF, participate in all essential trainings and comply with local and national regulations for non-interventional and observational studies.

Physicians experienced in the treatment of patients with hepatitis delta will be considered as potential Investigators.

The Sponsor will provide study-related documents to the Investigators who were selected for participation, including the study agreement/ fees agreement and the confidentiality agreement. Each site who agrees to participate in the Registry will receive a unique site number assigned by the Sponsor. Before the beginning of the study the Investigators will be trained on the study protocol, the data collection and eCRF completion by phone/ using tele- or web-conference or during on-site visits.

### 5.2.2 Study population

#### 5.2.2.1 Patient enrollment

This Registry will include as many eligible patients as possible and feasible from an organizational perspective. There is no upper limit of the sample size overall and by country/ site. There is no limit on the patient enrollment rate of each country/ site.

The Investigator will contact the patient either via phone or e-mail to inform the patient about the nature and purpose of the Registry and data collection policy. If the patient freely gives consent or non-opposition to participate in the Registry after discussing the study with the Investigator, a participant informed consent form will be signed by the patient and the attending Investigator at the patient's next routine visit. If an eligible patient is attending the site for a routine visit, the Investigator should discuss the Registry and propose participation in the Registry at the visit. Patients will be enrolled only once a written informed consent or non-opposition have been obtained. The Investigator should also attempt to accommodate the patient by offering the patient to discuss the Registry and consent procedures at another time, which may be more convenient for the patient.

#### 5.2.2.2 Inclusion criteria

To be included in this Registry, patients must meet all of the following inclusion criteria:

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

#### 5.2.2.3 Exclusion criteria

Patients cannot be enrolled into the Registry if they meet any of the following criteria:

- The patient is currently participating in a clinical trial with experimental treatment.

### 5.2.3 Patient withdrawal from the Registry

The patient may discontinue the participation in the Registry due to one or more of the following reasons:

- Withdrawal of patient consent or non-opposition
- BLV treatment not according to the current version of the SmPC (e.g. use in chronic HDV patients with decompensated liver disease)
- Death
- Loss to follow up by the site
- Enrollment in any clinical trial with experimental treatment.

For the withdrawn patient, no special follow-up is required.

### 5.2.4 Termination of the study

This is an open-ended Registry. The Registry will be performed at least until 200 patient years from patients treated with BLV are collected. The Registry is considered as completed, when the Steering Committee defined that the Registry may be completed, all data is entered into eCRF, cleaned and ready for analysis.

Early termination of the Registry and/or participation of the Registry site can happen under the initiative of the Sponsor, the Steering Committee or the Investigator, as well as under the demand of Ethics Committees.

## 5.3 Study Visits and Variables

Only the data available in the patient records will be collected and evaluated. No specific investigations or samplings will be performed in connection with the Registry. The following variables will be evaluated in this Registry:

**Baseline Visit:**

Baseline data can only be collected and reported into the eCRF once an informed consent or non-opposition has been obtained from the patient and an informed consent form (ICF) or non-opposition form has been signed. If available, baseline data is data generated prior to initiation of treatment with BLV, preferably not more than 3 months in advance of treatment start. Baseline data can be collected retrospectively and/ or prospectively.

- Date of visit
- Demography
  - year of birth;
  - gender;
  - race.
- Physical data to calculate BMI
  - height;
  - body weight.
- HDV hepatitis history
  - Date of first diagnosis.
- Clinical status
  - Disease stage: Chronic hepatitis or Cirrhosis status; if cirrhosis, CPT score calculator;
  - Upper GI endoscopy: esophageal and/ or gastric varices;
  - Ascites (with grade);
  - Hepatic encephalopathy (with grade);
  - Upper GI bleeding;
  - Development and worsening of jaundice;
  - Hepatocellular carcinoma (HCC) development; active (details) or previously diagnosed and treated;
  - Drug-induced liver injury;
  - Liver transplantation.

- Laboratory data
  - Date and laboratory results: Bilirubin, AST, ALT, PT or INR, serum albumin, bile salts, vitamin D levels, AFP, creatinine, hemoglobin, platelets, WBC.
- Virological data
  - Date and laboratory results: qHBsAg, HBeAg, qHBV DNA, anti-HDV, qHDV RNA, HBV genotype, HDV genotype; anti-HIV, anti-HCV.
- Imaging or others
  - Fibroscan: date and results in kPa;
  - Bone density scan: date and results as classes (normal, osteopenia, osteoporosis);
  - Liver biopsy: date and stage of fibrosis (ISHAK score, METAVIR score).
- Current antiviral treatment
  - Bulevirtide: dose, start date;
  - Interferon: dose, start date;
  - Nucleotide/Nucleoside analogues: dose, start date;
  - Other HBV or HDV treatment: dose, start date.
- Previous antiviral treatment
  - BLV, Interferon; Nucleotide/Nucleoside analogues; other HBV or HDV treatment.
- Liver related hospitalization: amount of hospitalizations and duration of each period of hospitalization

  Other significant medical conditions and medication

**Routine visits:**

- Date of visit
- Physical data to calculate BMI
  - body weight.
- Clinical status
  - Disease stage: Chronic hepatitis or Cirrhosis status; if cirrhosis, CPT score calculator;
  - Upper gastrointestinal (GI) endoscopy: esophageal and/ or gastric varices;
  - Ascites (with grade);
  - Hepatic encephalopathy (with grade);
  - Upper GI bleeding;

  - Development and worsening of jaundice;
  - Hepatocellular carcinoma (HCC) development; active (details) or previously diagnosed and treated;
  - Drug-induced liver injury;
  - Liver transplantation;
  - Liver-related death.

- Laboratory data
  - Date and laboratory results: Bilirubin, AST, ALT, PT or INR, serum albumin, bile salts, vitamin D levels, AFP, creatinine, hemoglobin, platelets, WBC.
- Virological data
  - Date and laboratory results: qHBsAg, HBeAg, qHBV DNA, qHDV RNA; anti-HIV, anti-HCV.
- Imaging or others
  - Fibroscan: date and results in kPa;
  - Bone density scan: date and results as classes (normal, osteopenia, osteoporosis);
  - Liver biopsy: date and stage of fibrosis (ISHAK score, METAVIR score).
- Current antiviral treatment
  - Bulevirtide: dose, start date;
  - Interferon: dose, start date;
  - Nucleotide/Nucleoside analogues: dose, start date;
  - Other HBV or HDV treatment: dose, start date.
- Previous antiviral treatment
  - BLV, Interferon; Nucleotide/Nucleoside analogues; other HBV or HDV treatment.
- Liver related hospitalization: amount of hospitalizations and duration of each period of hospitalization
- Other significant medical conditions and medication

## 5.4 Data sources

All Registry data will be obtained from the patients' medical records. They might include, for example, questionnaires, hospital discharge files, abstracts of primary clinical records, clinical databases, electronic medical records, administrative records, prescription drug files, biological measurements.

When appropriate, retrospective data will be collected (e.g. liver-related disease parameters and HDV treatment) prior to BLV treatment start.

## 5.5 Selection bias

This study is an observational non-interventional Registry. No randomization or group comparison or testing statistical hypotheses are planned. The inclusion criteria allow collecting the data from the maximal possible number of patients with chronic HDV infection receiving BLV treatment. The Registry will enroll patients with chronic HDV infection receiving BLV treatment maximally close to general population of such patients, who are seen in a routine practice at the Registry sites.

To minimize selection bias, patients will be enrolled systematically, using similar procedures at all participating sites, and will be followed in a consistent way.

## 5.6 Registry size

This study is an observational non-interventional Registry. The sample size is not based on statistical considerations, but depends on the possibility of the Registry sites to enroll the described patient population.

The Registry will include as many eligible patients as possible and feasible from organizational perspective. There is no upper limit of the sample size overall and by country/ site.

## 5.7 Data management and archiving

All data obtained during the Registry will be captured via Electronic Data Capture (EDC) using web-based eCRF. A uniquely structured eCRF in English will be used in all participating countries. A highly secured eCRF system is used, and all data obtained from countries in the European Union will be handled according to EU data protection requirements. Only authorized and trained persons will be able to enter the data to eCRF, using their unique login and password.

The data management procedures (data entry, validation, cleaning and preparation of the analysis dataset) will be conducted in accordance with the Data Management Plan.

The Investigator is responsible for ensuring that all sections of the eCRF are completed accurately and correctly and that the entries can be verified against source data whenever applicable. The correctness of entries in eCRF will be confirmed by dated electronic signature of the responsible Investigator and might be reviewed by the responsible monitor of the Sponsor or CRO.

All data available in patients' medical records and required by the protocol must be transferred into the eCRF by the Investigator or a designated representative.

Data management specialist or EDC (automatically) may send queries to the site in case of missing data or inconsistencies that require clarifications from the responsible Investigator. When no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

The Investigator at each Registry site is responsible for appropriate archiving and storage of all essential Registry documents (paper documents and electronic copies of eCRFs) in accordance with all applicable local law and regulations.

## 5.8 Statistical procedures

### 5.8.1 General considerations

This section presents a summary of the planned statistical analyses. The Statistical Analysis Plan (SAP) to be finalized before the first Registry analysis, will describe the planned analyses in full detail.

### 5.8.2 Analysis populations

**Enrolled Population:** All patients who provided informed consent or non-opposition, depending on national regulations.

**Registry Analysis Population (RAP):** All enrolled patients with available data on any of the post-baseline assessment variables.

All analyses will be based on the RAP.

### 5.8.3 Statistical methods

Continuous variables will be summarized in terms of descriptive statistics including number of observations, mean, standard deviation, minimum, maximum and quartiles. Categorical variables will be summarized in terms of frequencies and percentages. To account for the different durations of observation, the incidences of events will be normalised to subject exposure to evaluate the incidence according to time of exposure (patient-years).

An appropriate time window pattern relative to baseline (enrolment) will be defined for the Registry data (e.g. months or quarters). Longitudinal data will be summarized by time window. If more than one measurement for a patient falls into the same time window the last measurement will be used.

Summaries will be provided by country and relevant concomitant treatment cohort.

#### 5.8.3.1 Patient disposition

The number and relative frequency of patients who prematurely discontinued the participation in the Registry and reasons for discontinuation will be tabulated. The duration of observation will be summarized.

#### 5.8.3.2 Demographic and baseline data

All demographic and disease characteristic variables will be summarized according to type of variable.

#### 5.8.3.3 Liver-related clinical events

Liver-related events will be described by crude incidence rate (by patients) and observation time adjusted incidence rates (by patient-years) in each treatment cohort. Corresponding exact 95%-confidence interval will be presented. The time from BLV treatment start until the first occurrence of an event will be analysed using Kaplan-Meyer methods.

The influence of treatment and other covariables on the occurrence of events will be analysed by means of logistic and Cox regression models.

#### 5.8.3.4 Adverse reactions

Adverse reactions (ARs) will be coded according to MedDRA. All ARs should be recorded on the Safety Case Report Form provided in the Investigator Site File and reported immediately (within 24h of the Investigator's knowledge of the event) to PPD or by fax to: PPD. The subject identification number has to be added on the Safety Case Report Form to be able to assign the AR to the respective patient data from this Registry.

Frequency, percentages and observation time standardized rates of all ARs will be summarized according to primary system organ class (SOC) and preferred term and tabulated by treatment cohort including exact 95%-confidence intervals. Serious ARs, ARs leading to death, and ARs resulting in discontinuation of the participation in the Registry, will be tabulated separately.

Logistic models will be used to explore risk factors for the occurrence of the most frequent SOCs.

#### 5.8.3.5 Laboratory data

Laboratory variables will be described as continuous, longitudinal data. Sample statistics for the observed values and for changes from baseline by time window will be presented. Wilcoxon sign rank test will be performed for changes from baseline at each time window.

#### 5.8.3.6 Exposure

Exposure to documented HDV/ HBV infection treatment will be summarized according to type of drug administered.

### 5.8.4 Handling of missing and non-evaluable data

As a general approach missing data will not be imputed.

### 5.8.5 Interim analyses

Periodical (annual) interim analyses with preparation of interim reports will be conducted. Additional analyses may be performed by decision of the Steering Committee.

## 5.9 Quality control and assurance

Study monitoring will be done by a clinical monitor according to SOPs of the Sponsor or designated CRO. The responsible monitor might review the entries into the CRFs on the basis of applicable source documents. The Investigators must allow the monitor to verify all essential documents and must provide support to the monitor at any time. Frequency of monitoring will be defined in the

Project Plan. By remote communications (letters, E-mail, telephone, fax) or onsite visits, the site monitor will ensure that the Registry is conducted according to the protocol and regulatory requirements.

Due to the observational nature of the Registry and large volume of data, the study monitoring will not provide 100 % data verification (e.g. all fields for all patients from all sites). The monitor will perform periodic review of the Registry data and use range and consistency checks that can help to ensure that inaccurate data are not entered into the eCRF. Such review will be made for the whole Registry and by site. The Sponsor will define the percentage of random patients that will be reviewed and verified regarding the correspondence to the source data on a regular basis based on the results of periodic review of the data quality.

### 5.10 Limitations of Registry design

As in any non-interventional study, the study data are obtained from the routine clinical practice and therefore may vary between sites/countries, depending on the local standards and management of patient population. Some data may be absent in patient's medical documentation, and therefore will be missing in the Registry database. Laboratory and instrumental measures may be obtained using different methods across the sites that may not be totally comparable.

# 6 Protection of Human Subjects

## 6.1 Ethical principles

The participation in the Registry is absolutely voluntary for a patient. The refusal/ denial to participate must not affect the quality of a patient's medical care, their rights and benefits.

The risk for patients related to the participation in the Registry is not greater than that associated with routine clinical practice.

The Registry will be conducted in accordance with all applicable personal data protection laws, principles of International Ethical Guidelines for Epidemiological Studies, and the ethical principles that are outlined in the Declaration of Helsinki (Fortaleza, 2013). Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at https://www.wma.net/policy/current-policies/.

## 6.2 Registry approval

Before the start of the Registry, the protocol, written informed consent form or non-opposition form, and any other written information that will be provided to potential subjects, will be approved in each participating country according to the specific local requirements. The type of approvals required and the estimated time to receive approvals depends on the country.

Before the first patient is enrolled in the Registry, all ethical and legal requirements must be met. All planned substantial changes will be approved as protocol amendments in accordance with specific local requirements in each participating country.

The Investigator agrees to allow the direct access for the corresponding authority representative to all relevant documents if required. The responsible Sponsor or CRO will keep a record of all significant communication regarding the approval.

## 6.3 Informed consent

The requirements for informed consent procedure and patient consent to access to medical records depend on local regulations in each country. Personal data will be collected based on local regulations.

Depending on the national regulations, the patient or legal representative should provide written informed consent to the nature of the study and data collection procedures which must previously be explained to the patient, before entering the Registry. The informed consent form describes the purpose, nature and procedures of this Registry and data collection, as well as procedures concerning personal data collection, handling and transferring. The patient will be informed that only pseudonymized data will be collected and transferred to the Sponsor, and that he/she has a right to withdraw his/her consent for providing personal data at any time (however, all data provided prior to that moment may be used by the Sponsor as described in the informed consent form). The informed consent form contains the statement that the study monitors, including personnel of CRO and the auditors will be granted direct access to the patient's original medical records for verification of study procedures and/or data.

The informed consent form must be written in understandable language. The informed consent form will indicate the data of the Investigator conducting the informed consent discussion and the contacts for further information regarding the Registry and the rights of the patients.

The informed consent form will be signed autonomously by the patient, or the patient´s legally acceptable representative, and by the assigned Investigator who conducted the informed consent discussion. If a patient or a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form is provided to patients, is read and explained to the patient or legal representative, and after the patient or legal representative has orally consented to the patient's participation in the Registry and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form was accurately explained to, and apparently understood by, the patient or legal representative, and that informed consent was freely given by the patient or legal representative.

Depending on national regulations, a non-opposition form can be used. The non-opposition form describes the purpose, nature and procedures of this Registry and data collection, as well as procedures concerning personal data collection, handling and transferring. The patient will be informed that only pseudonymized data will be collected and transferred to the Sponsor, and that he/she has a right to withdraw his/her consent for providing personal data at any time (however, all data provided prior to that moment may be used by the Sponsor as described in the non-opposition form). The non-opposition form contains the statement that the study monitors,

including personnel of CRO and the auditors will be granted direct access to the patient's original medical records for verification of study procedures and/or data.

The non-opposition form must be written in understandable language. The non-opposition form will indicate the data of the Investigator conducting the non-opposition discussion and the contacts for further information regarding the Registry and the rights of the patients.

The non-opposition form will be signed by the Investigator who conducted the non-opposition discussion. After the written non-opposition form is provided to patients, is explained to the patient, and after the patient has orally agreed to his/her participation in the Registry, the Investigator should sign and date the non-opposition form. By signing the non-opposition form, the Investigator attests that the information in the non-opposition form was accurately explained to, and apparently understood by, the patient, and that no opposition was given by the patient.

Two copies of the signed informed consent or non-opposition form will be stored at the site in the Registry Site File; one copy will be given to the patient or legal representative.

The patient or legal representative will be informed as soon as possible if any amendments come into force and if new information may influence his/her decision to participate in the Registry. The communication of this information will be documented.

## 6.4 Responsibilities of Investigator

An Investigator will be appointed at each Registry site.

An Investigator should ensure that all persons assisting in the Registry are adequately informed about the protocol, any amendments to the protocol, and data collection procedures. He/she should maintain a list of sub-investigators at his/her Registry site and other appropriately qualified persons to whom he/she has delegated significant study-related duties. A standard log (unified between sites) will be provided by the Sponsor in order to maintain the list of the study team at the site. On extraordinary occasions, the log sample routinely used at the site may be applicable.

## 6.5 Confidentiality

The data obtained in the course of the Registry will be treated pursuant to the applicable national and EU regulations.

During the Registry, patients will be identified solely by means of their year of birth and an individual identification code (subject identification number). The Registry findings will be stored in accordance with the local data protection law and be handled with strict confidentiality. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in their entirety.

For the Registry, a large number of centres will collaborate and collect their patients' data in the database. In order to be able to evaluate the data with regard to the aim of the register, the pseudonymised data can be passed on and exchanged within the network of participating centres for analysis purposes. The evaluations and analyses are in all cases approved and reviewed by a

steering committee. In all cases, the interests of medical confidentiality and data protection remain guaranteed, so that no connection can be established between the evaluated/published data and the patient.

The patient consents in writing or giving non-opposition to release the Investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by study monitors, including personnel of CRO and the auditors. Authorized persons (clinical monitors, auditors, inspectors) may inspect the patient-related data collected during the trial ensuring the data protection law.

The Investigator will maintain a hard-copy patient identification list (subject identification numbers with the corresponding patient names) to keep records identifiable and store it with other essential study documents. A standard log (unified between sites) will be provided by the Sponsor in order to maintain a patient identification list at the site. On extraordinary occasions, the log sample routinely used at the site may be applicable.

Patients who did not consent to distribution of their pseudonymized data will not be included into the Registry.

# 7 Reporting of Adverse Reactions

For patients treated with BLV the following safety data will be collected and reported:

- Adverse reactions (serious or non-serious) **related to BLV treatment**
- The following lists special situations during BLV treatment
    - Use of a medicinal product during pregnancy or breastfeeding.
    - Overdose;
    - Off-label use;
    - Misuse;
    - Abuse;
    - Medication error;
    - Falsified medicinal product;
    - Lack of therapeutic efficacy;
    - Suspected transmission of an infectious agent via a medicinal product.

All safety information should be reported immediately (within 24 hours of the Investigator's knowledge of the event) to the following contact:

PPD or by fax to: PPD

# 8 Plans for Disseminating and Communicating Registry Results

The Sponsor encourages the presentation and/or publication of the results of their studies, using only clean, checked and validated data in order to ensure the accuracy of the results.

All potential publications should be agreed with MYR GmbH and the Steering Committee. At least sixty (60) days in advance of proposed submission, the Investigator should forward a copy of the manuscript or abstract for review by MYR GmbH and the Steering Committee, and, if necessary, delay publication or communication for a limited time or modify it (in a reasonable and justifiable manner) in order to protect the confidentiality or proprietary nature of any information contained therein.

# 9 Confidentiality

Information in this document is proprietary to the Sponsor and may be disclosed to the third parties only with the written consent from the Sponsor. The right to review this information will be granted only to the Investigator(s) and members of the Registry site(s) staff, members of the independent ethics committee(s) and healthcare officials entitled to control the study conduct. Information sufficient to make a decision regarding consent to participate in the Registry will be provided to the patients whom the Investigator plans to enroll.

# 10 References

1. **Rizzetto M, Canese MG, Aricò S, Crivelli O, Trepo C, Bonino F, et al.** *Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. Gut. 1977 Dec;18(12):997-1003. doi: 10.1136/gut.18.12.997.*

2. **Rizzetto M.** *Hepatitis D: thirty years after. J Hepatol. 2009 May;50(5):1043-50. doi: 10.1016/j.jhep.2009.01.004.*

3. **Sureau C, Guerra B, Lanford RE.** *Role of the large hepatitis B virus envelope protein in infectivity of the hepatitis delta virion. J Virol. 1993 Jan;67(1):366-72. doi: 10.1128/JVI.67.1.366-372.1993.*

4. **Taylor JM.** *Hepatitis D Virus Replication. Cold Spring Harb Perspect Med. 2015 Nov 2;5(11). pii: a021568. doi: 10.1101/cshperspect.a021568.*

5. **Shirvani-Dastgerdi E, Tacke F.** *Molecular interactions between hepatitis B virus and delta virus. World J Virol. 2015 May 12;4(2):36-41. doi: 10.5501/wjv.v4.i2.36.*

6. **Wedemeyer H, Manns MP.** *Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. Nat Rev Gastroenterol Hepatol. 2010 Jan;7(1):31-40. doi: 10.1038/nrgastro.2009.205.*

7. **Yurdaydın C, Idilman R, Bozkaya H, Bozdayi AM.** *Natural history and treatment of chronic delta hepatitis. J Viral Hepat. 2010 Nov;17(11):749-56. doi: 10.1111/j.1365-2893.2010.01353.x.*

8. **Farci P, Niro GA.** *Clinical features of hepatitis D. Semin Liver Dis. 2012 Aug;32(3):228-36. doi: 10.1055/s-0032-1323628.*

9. **Cole SM, Gowans EJ, Macnaughton TB, Hall PD, Burrell CJ.** *Direct evidence for cytotoxicity associated with expression of hepatitis delta virus antigen. Hepatology. 1991 May;13(5):845-51.*

10. **Lacombe K, Boyd A, Desvarieux M, Serfaty L, Bonnord P, Gozlan J, et al.** *Impact of chronic hepatitis C and/or D on liver fibrosis severity in patients co-infected with HIV and hepatitis B virus. AIDS. 2007 Nov 30;21(18):2546-9. doi: 10.1097/QAD.0b013e3282f2a94f.*

11. **Zachou K, Yurdaydin C, Drebber U, Dalekos GN, Erhardt A, Cakaloglu Y, et al; HIDT-1 Study Group.** *Quantitative HBsAg and HDV-RNA levels in chronic delta hepatitis. Liver Int. 2010 Mar;30(3):430-7. doi: 10.1111/j.1478-3231.2009.02140.x.*

12. **Radjef N, Gordien E, Ivaniushina V, Gault E, Anaïs P, Drugan T, et al.** *Molecular phylogenetic analyses indicate a wide and ancient radiation of African hepatitis delta virus, suggesting a deltavirus genus of at least seven major clades. J Virol. 2004 Mar;78(5):2537-44. doi: 10.1128/jvi.78.5.2537-2544.2004.*

13. **Le Gal F, Gault E, Ripault MP, Serpaggi J, Trinchet JC, Gordien E, et al.** *Eighth major clade for hepatitis delta virus. Emerg Infect Dis. 2006 Sep;12(9):1447-50. doi: 10.3201/eid1209.060112.*

14. **Makuwa M, Mintsa-Ndong A, Souquière S, Nkoghé D, Leroy EM, Kazanji M.** *Prevalence and molecular diversity of hepatitis B virus and hepatitis delta virus in urban and*

*rural populations in northern Gabon in central Africa. J Clin Microbiol. 2009 Jul;47(7):22. doi: 10.1128/JCM.02012-08.*

15. **Su CW, Huang YH, Huo TI, Shih HH, Sheen IJ, Chen SW, et al.** *Genotypes and Genotypes and viremia of hepatitis B and D viruses are associated with outcomes of chronic hepatitis D patients. Gastroenterology. 2006 May;130(6):1625-35. doi: 10.1053/j.gastro.2006.01.035.*

16. **Stockdale, A.J., Kreuels, B., Henrion, M.Y.R., Giorgi E., Kyomuhangi, I., de Martel, C., Hutin, Y., & Geretti, A.M..** *The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. Journal of Hepatology, 2020 Apr; 7d3(3), 523-532.https://doi.org/10.1016/j.jhep.2020.04.008.*

17. **Rizzetto M.** *Hepatitis D Virus: Introduction and Epidemiology. Cold Spring Harb Perspect Med. 2015 Jul 1;5(7):a021576. doi: 10.1101/cshperspect.a021576.*

18. **Gaeta GB, Stroffolini T, Chiaramonte M, Ascione T, Stornaiuolo G, Lobello S, et al.** *Chronic hepatitis D: a vanishing Disease? An Italian multicenter study. Hepatology. 2000 Oct;32(4 Pt 1):824-7. doi: 10.1053/jhep.2000.17711.*

19. **Niro GA, Gravinese E, Martini E, Garrubba M, Facciorusso D, Conoscitore P, et al.** *Clearance of hepatitis B surface antigen in chronic carriers of hepatitis delta antibodies. Liver. 2001 Aug;21(4):254-9. doi: 10.1034/j.1600-0676.2001.021004254.x.*

20. **Romeo R, Petruzziello A, Pecheur EI, Facchetti F, Perbellini R, Galmozzi E, K et al.** *Hepatitis delta virus and hepatocellular carcinoma: an update. Epidemiol Infect. 2018 Jul 11:1-7. doi: 10.1017/S0950268818001942.*

21. **Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, et al.** *Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). Gut. 2000 Mar;46(3):420-6. doi: 10.1136/gut.46.3.420.*

22. **Manesis EK, Vourli G, Dalekos G, Vasiliadis T, Manolaki N, Hounta A, et al.** *Prevalence and clinical course of hepatitis delta infection in Greece: a 13-year prospective study. J Hepatol. 2013 Nov;59(5):949-56. doi: 10.1016/j.jhep.2013.07.005.*

23. **Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, et al.** *A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. Gastroenterology. 2009 May;136(5):1629-38. doi: 10.1053/j.gas.*

24. **Buti M, Homs M, Rodriguez-Frias F, Funalleras G, Jardí R, Sauleda S, et al.** *Clinical outcome of acute and chronic hepatitis delta over time: a long-term follow-up study. J Viral Hepat. 2011 Jun;18(6):434-42. doi: 10.1111/j.1365-2893.2010.01324.x.*

25. **Heidrich B, Manns MP, Wedemeyer H.** *Treatment options for hepatitis delta virus infection. Curr Infect Dis Rep. 2013 Feb;15(1):31-8. doi: 10.1007/s11908-012-0307-z.*

26. **Niro GA, Smedile A, Ippolito AM, Ciancio A, Fontana R, Olivero A, et al.** *Outcome of chronic delta hepatitis in Italy: a long-term cohort study. J Hepatol. 2010 Nov;53(5):834-40. doi: 10.1016/j.jhep.2010.06.008.*

27. **Cornberg M, Protzer U, Petersen J, Wedemeyer H, Berg T, Jilg W, et al; AWMF.** *[Prophylaxis, diagnosis and therapy of hepatitis B virus infection - the German guideline]. Z Gastroenterol. 2011 Jul;49(7):871-930. doi: 10.1055/s-0031-1273462.*

28. **Gish RG, Yi DH, Kane S, Clark M, Mangahas M, Baqai S, et al.** *Coinfection with hepatitis B and D: epidemiology, prevalence and disease in patients in Northern California. J Gastroenterol Hepatol. 2013 Sep;28(9):1521-5. doi: 10.1111/jgh.12217.*

29. **Kucirka LM, Farzadegan H, Feld JJ, Mehta SH, Winters M, Glenn JS, et al.** *Prevalence, correlates, and viral dynamics of hepatitis delta among injection drug users. J Infect Dis. 2010 Sep 15;202(6):845-52. doi: 10.1086/655808.*

30. **Wedemeyer H, Yurdaydìn C, Dalekos GN, Erhardt A, Çakaloğlu Y, Değertekin H, et al; HIDIT Study Group.** *Peginterferon plus adefovir versus either drug alone for hepatitis delta. N Engl J Med. 2011 Jan 27;364(4):322-31. doi: 10.1056/NEJMoa0912696.*

31. **Heidrich B, Yurdaydin C, Kabaçam G, Ratsch BA, Zachou K, Bremer B, et al; HIDIT-1 Study Group.** *Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. Hepatology. 2014 Jul;60(1):87-97. doi: 10.1002/hep.27102.*

32. **Gheorghe L, Iacob S, Simionov I, Vadan R, Constantinescu I, Caruntu F, et al.** *Weight-based dosing regimen of peg-interferon α-2b for chronic hepatitis delta: a multicenter Romanian trial. J Gastrointestin Liver Dis. 2011 Dec;20(4):377-82.*

33. **Rizzetto M, Niro GA.** *Myrcludex B, a novel therapy for chronic hepatitis D? J Hepatol. 2016 Sep;65(3):465-6. doi: 10.1016/j.jhep.2016.06.014.*

34. **Ni Y, Lempp FA, Mehrle S, Nkongolo S, Kaufman C, Fälth M, et al.** *Hepatitis B and D viruses exploit sodium taurocholate co-transporting polypeptide for species-specific entry into hepatocytes. Gastroenterology. 2014 Apr;146(4):1070-83. doi: 10.1053/j.gastr.*

35. **Slijepcevic D, van de Graaf SF.** *Bile Acid Uptake Transporters as Targets for Therapy. Dig Dis. 2017;35(3):251-258. doi: 10.1159/000450983.*

36. **Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, et al.** *Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife. 2012 Nov 13;1:e00049. doi: 10.7554/eLife.00049. Erratum in: Elife. 2014;3:e05570. doi: 10.7554/eLife.05570.*

37. **Blank A, Markert C, Hohmann N, Carls A, Mikus G, Lehr T, et al.** *First-in-human application of the novel hepatitis B and hepatitis D virus entry inhibitor myrcludex B. J Hepatol. 2016 Sep;65(3):483-9. doi: 10.1016/j.jhep.2016.04.013.*

38. **Bogomolov P, Alexandrov A, Voronkova N, Macievich M, Kokina K, Petrachenkova M, et al.** *Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study. J Hepatol. 2016 Sep;65(3):490-8. doi: 10.1016/j.jhep.2016.*

39. **Schulze A, Schieck A, Ni Y, Mier W, Urban S.** *Fine mapping of pre-S sequence requirements for hepatitis B virus large envelope protein-mediated receptor interaction. J Virol. 2010 Feb;84(4):1989-2000. doi: 10.1128/JVI.01902-09.*

40. **Volz T, Allweiss L, Ben MBarek M, Warlich M, Lohse AW, Pollok JM, et al.** *The entry inhibitor Myrcludex-B efficiently blocks intrahepatic virus spreading in humanized mice previously infected with hepatitis B virus. J Hepatol. 2013 May;58(5):861-7. doi: 10.1016/j.jhep.2012.12.008.*

41. **Wranke A, Pinheiro Borzacov LM, Parana R, Lobato C, Hamid S, et al; Hepatitis Delta International Network.** *Clinical and virological heterogeneity of hepatitis delta in different*

*regions world-wide: The Hepatitis Delta International Network (HDIN). Liver Int. 2018 May;38(5):842-850. doi: 10.1111/liv.13604. Epub 2017 Oct 26. PMID: 28963781.*

42. **Gliklich RE, Dreyer NA.** *Registries for Evaluating Patient Outcomes: A User's Guide. 3rd ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. Report No.: 13(14)-EHC111.*

43. **Roulot, D. & Brichler, Ségolène & Layese, Richard & Samuel, D. & Marcellin, Patrick & Chazouilleres, Olivier & Poynard, Thierry & Zoulim, F. & Ganne, Nathalie & Fontaine, H. & Benabdesselam, Z. & Gordien, Emmanuel & Roudot-Thoraval, F.** *P0600: Predictive factors of cirrhosis, hepatic decompensation and hepatocellular carcinoma in patients with chronic hepatitis delta. Journal of Hepatology. 62., Supplement 2, 2015, S541-S542. doi: 10.1016/S0168-8278(15)30806-0.*

44. **Kamal, H., Falcomer, K., Westman, G., Duberg, A.-S., Weiland, O., Wejstal, R., Carissson, T., Kampmann, C., Björkman, P., Nystedt, A., Cardell, K., Svensson, S., Stenmark, S., Wedemeyer, H., & Aleman, S.**. *Long-Term Liver-Related Outcomes in Hepatitis B and D Co-Infected Patients in Sweden. Hepatology, 68 (Suppl.1), 2018, 1190A–1191A.*

# 11 Amendments to the Protocol

This is version 1.2 of the protocol MYR-Reg-02, dated 3 March 2021.

Previous versions of the protocol:

Version 1.1 dated 18 January 2021.

The previous version of the protocol was amended in the following sections:

- Synopsis
- 1. Abbreviations
- 2. General Information
- 3. Background Information and Rationale
- 4. Registry Objectives
- 5. Registry Methods
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