EU Risk Management Plan for HEPCLUDEX® (Bulevirtide)

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RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
7.0	30 July 2024	Refer to electronic signatures

Rationale for submitting an updated RMP:	To update the milestone (submission of final clinical study report) for Study MYR301.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant changes to RMP
Part II Safety Specification	Part II: Module SI: Epidemiology of the indication and target populations(s)	None
	Part II: Module SII: Nonclinical part of the safety specification	None
	Part II: Module SIII: Clinical study exposure	None
	Part II: Module SIV: Populations not studied in clinical studies	None
	Part II: Module SV: Postauthorization experience	Updated postauthorization exposure
	Part II: Module SVI: Additional EU requirements for the safety specification	None
	Part II: Module SVII: Identified and potential risks	None
	Part II: Module SVIII: Summary of the safety concerns	None
Part III Pharmacovigilance Plan		Update the milestone (submission of final clinical study report) for Study MYR301
Part IV Plan for postauthorization efficacy studies		None
Part V Risk Minimization Measures		None
Part VI Summary of RMP		None

Part	Module/Annex	Significant changes to RMP
Part VII Annexes		Update the milestone (submission of final clinical study report) for Study MYR301

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
6.0	EMEA/H/C/004854/II/0034 EMEA/H/C/004854/II/0031	31 October 2024 25 November 2024

QPPV name: Anne-Ruth van Troostenburg de Bruyn

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
ALT	alanine aminotransferase
ATC	anatomical therapeutic chemical (classification system)
BLV	bulevirtide
CHB	chronic hepatitis B
CHD	chronic hepatitis D
CHMP	Committee for Medicinal Products for Human Use
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DXA	dual energy X-ray absorptiometry
EASL	European Association for the Study of Liver
EC	European Commission
EEA	European Economic Area
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EPAR	European Public Assessment Report
EU	European Union
EU-RMP	EU Risk Management Plan
GVP	Good Pharmacovigilance Practice
HBeAg	hepatitis B e antigen
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
ICH	International Committee for Harmonisation
IFN-α	interferon-alfa
i.v.	intravenous
IVDU	intravenous drug use
NA	nucleos(t)ide analog
NOAEL	no-observed-adverse-effect level
NTCP	sodium taurocholate co-transporting polypeptide
PASS	post authorization safety study
PBRER	periodic benefit-risk evaluation report
PEF	peak expiratory flow
PEG-IFN-alfa	pegylated interferon alfa-2a
PenH	airway resistance index
PIF	peak inspiratory flow

PL	package leaflet
PSMF	Pharmacovigilance System Master File
PSUR	periodic safety update report
Q	quarter
QPPV	Qualified Person for Pharmacovigilance
QTc	corrected QT interval
RIA	radioimmunoassay
RMP	Risk Management Plan
RNA	ribonucleic acid
SAE	serious adverse event
s.c.	subcutaneous
SmPC	Summary of Product Characteristics
TDF	tenofovir disoproxil fumarate
Te	expiratory time
Ti	inspiratory time

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Bulevirtide
Pharmaco-therapeutic group(s) (ATC Code):	J05AX28
Marketing Authorization Holder	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Hepcludex®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: 47-amino acid peptide.
	Summary of mode of action: Bulevirtide (BLV) blocks the entry of hepatitis B virus (HBV) and hepatitis delta virus (HDV) into hepatocytes by binding to and inactivating an essential HBV and HDV entry receptor sodium taurocholate co-transporting polypeptide (NTCP).
	Important information about its composition: BLV is a synthetic peptide with a fatty acid, i.e. a myristoyl residue, at the N-terminus and an amidated C-terminus. It is available as acetate salt.
Hyperlink to the Product Information	HEPCLUDEX Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV ribonucleic acid (RNA) positive adult and pediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease.
	Proposed: Not applicable
Dosage in the EEA	Current: Adults: 2 mg s.c. once daily Pediatric patients: Once daily dose (based on weight) of: • 1 mg (body weight 10 kg to < 25 kg) • 1.5 mg (body weight 25 kg to < 35 kg) • 2 mg (body weight 35 kg and above) once daily
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Powder for solution for injection with the strength of 2 mg per vial (to be reconstituted with 1 mL sterile water for injection).
	Proposed: Not applicable
Is/Will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI—EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. Chronic Hepatitis Delta Virus Infection

The hepatitis delta virus (HDV) is a single-stranded, circular RNA virus that occurs only in individuals who are also infected with the hepatitis B virus (HBV) {Hercun 2020}, {Mentha 2019}, {Rizzetto 2009}, {Rizzetto 2015}, {Shah 2019}, {Wedemeyer 2010a}. Because the virus does not encode its own envelope protein and uses the hepatitis B surface antigen (HbsAg) for replication, HDV infection occurs either as a simultaneous acute HBV-HDV coinfection that is self-limiting in most cases or as a superinfection in patients with established HBV infection, which leads to chronic hepatitis in the majority of patients {Hercun 2020}, {Mentha 2019}, {Shah 2019}, {Wedemeyer 2010a}. Eight different HDV genotypes have been identified. Of these, genotype 1 is prevalent worldwide, genotype 2 is most common in Japan, Taiwan, and Russia, genotype 3 is prevalent in South America, genotype 4 is most common in Taiwan and Japan, and genotypes 5–8 are more prevalent in Africa {Coppola 2019}, {Mentha 2019}, {Rizzetto 2015}, {Shah 2019}.

Considered the most severe form of hepatitis infection, HDV is associated with an increased risk of cirrhosis, decompensated liver disease and hepatocellular carcinoma {Hughes 2011}, {Mentha 2019}, {Rizzetto 2009}, {Rizzetto 2015}, {Wedemeyer 2010b}.

SI.1.1. Incidence

Chronic hepatitis delta develops in 70–90% of patients with HDV superinfection. The liver disease associated with HDV runs a more progressive course than chronic hepatitis B (CHB) and may lead to cirrhosis within 2 years in 10–15% of patients {Yurdaydin 2010}. There have been no population-based studies estimating the incidence of HDV in children.

SI.1.2. Prevalence

The estimated prevalence of HDV in HBsAg-positive individuals is 4.5% (95% CI, 3.6-5.7) {Stockdale 2020a}. A recent systematic review and meta-analysis examined the current global prevalence, genotype, and risk factors for HDV. When the analysis was limited to European countries (Table SI.1), the prevalence of HDV in HbsAg-positive individuals with no history of intravenous drug use (IVDU) or high-risk sexual behaviors ranged from 1.26% (95% CI, 0.89-1.68%) in France to 18.98% (95% CI, 16.24-21.85%) in Romania {Chen 2019}.

Table SI.1. Summary of HDV Prevalence Estimates for the EU in HBsAg-positive Populations

Location	No. of studies	No. of events	Tested (n)	Prevalence (%)	95% CI
France	2	89	4522	1.26	0.89-1.68
Germany	2	206	3568	5.33	4.63-6.12
Greece	3	13	190	12.1	0.0-56.38
Italy	11	982	6367	17.28	12.74-22.32
Portugal	1	86	2071	4.15	3.37-5.10
Romania	3	862	3858	18.98	16.24-21.85
Spain	2	34	1114	1.97	0.0-6.40
United Kingdom	6	365	6057	9.11	4.55-14.98
Yugoslavia*	2	10	698	1.43	0.64-2.48

CI=confidence interval; N=number
*Studies published in 1993 just after the formal dissolution of the Socialist Federal Republic of Yugoslavia

Between-country variations in HDV prevalence are attributed, in part, to immigration from endemic regions where the prevalence of HBV is moderate or high as well as variations in policies regarding HBV vaccination {Gilman 2019}. When considering prevalence rates reported by older studies, it is important to consider that serologic assays may be less accurate in these studies, which may underestimate the burden of HDV. It is also important to distinguish between prevalence estimates for the general population, which will be substantially lower than those determined for HBsAg-positive groups {Chen 2019}, {Stroffolini 2009}, {Wedemeyer 2019a}.

There is very limited data on the prevalence of HDV in the pediatric population. It is generally thought to be rare in this age group given the lack of risk factors {Stockdale 2020b}. While there are no population-based studies reporting HDV prevalence in children, there are a few studies that provide case reports of children who acquired HDV in Taiwan, Romania, Albania, Turkey, and Italy. These studies reported between 2 and 26 children ranging from 4 months to 13 years old who were infected with HDV {Xue 2015}. Most of these case report studies are not recent and it is likely that infections in the pediatric age group are underreported given that testing in some regions may not be recommended or widely used. For example, current American Association for the Study of Liver Diseases (AASLD) testing guidelines recommend testing of individuals with HBV who are at risk for HDV, but the pediatric population may not typically fall into one of the risk categories {Terrault 2018b}. HDV testing in all individuals with HBV is recommended according to European and Asian guidelines. However, studies have indicated that in European countries, testing rates only range from 25% to 47%, and are even lower in the United States {European Association for the Study of the Liver 2023}, {Sarin 2016}, {Kushner 2023}, {Vaz 2015}, {Gonzalez 2005}. More adequate testing among both children and adults is therefore necessary to understand the true burden of HDV globally.

SI.1.3. Demographics of the Population in the Authorized Indication and Risk Factors for the Disease

Populations at increased risk for HDV infection include individuals from endemic areas, IVDU, men who have sex with men, individuals with human immunodeficiency virus (HIV) or hepatitis C virus (HCV), and patients who engage in high risk sexual behavior {Gilman 2019}. In children, the primary risk factor would be mother-to-child transmission, but transmission is unlikely given that individuals with HDV typically have low viral loads. Additionally, neonatal and early childhood HBV vaccination programs make HDV infection in children rare {Kushner 2023}, {Stockdale 2020b}. HDV is endemic worldwide, although the prevalence of infection varies across geographic regions {Rizzetto 2009}. Native populations with HDV infection in the EU are being replaced by immigrants from areas in which HDV remains endemic. Domestic patients are older, have long-standing infection, and advanced liver disease. Immigrants with HDV infections are younger, have more recent HDV infections, and often show a more aggressive hepatitis {Rizzetto 2015}. A recent narrative review summarized the prevalence of HDV infection in HBsAg-positive immigrants for various countries in Europe and North America. With 2 exceptions, prevalence rates were higher for immigrant populations and ranged from <1.0% in Italy in 1991 and Germany in 2015 to 42.5% from 2011-2016 in the US. The authors concluded that the impact of immigration on HDV endemicity in the host country was mediated by the different levels of endemicity between the country of origin and the host country. There was a strong impact when HDV endemicity was high in the native country and low in the host country. Lesser impact occurred when immigrants relocated to countries with a moderate or high endemic level of infection {Coppola 2019}.

The worldwide prevalence of HDV coinfection among HIV/HBV-coinfected patients is estimated to range from 1.2% to 25%, {Ferrante 2020} with similar rates reported for European countries. IVDU is one of the primary risk factors for HBV, HCV, and HDV as well as HIV {Hercun 2020}, {Mentha 2019}, {Rizzetto 2009}, {Rizzetto 2015}, {Shah 2019}, {Wedemeyer 2010a}. A recent meta-analysis found that the risk of HDV increased 15-fold in HBV-positive IVDUs compared to those who did not use drugs {Miao 2020}.

SI.1.4. Main Existing Treatment Options

Therapeutic options for patients with HDV infection are severely limited, with no currently approved treatment available for patients with CHD in the US and many other territories. Nucleoside/nucleotide analogues, while effective in patients with 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}. Based on clinical studies conducted over the past few decades, the current AASLD guidelines recommend the off-label use of pegylated interferon alpha (Peg-IFNα) for 12 months {Terrault 2018a}. Response rates with Peg-IFNα monotherapy have been variable, ranging from 17% to 35%, and treatment is associated with adverse effects such as flu-like symptoms, anemia, neutropenia, and thrombocytopenia that may result in poor tolerability {Alavian 2012, Wranke 2017}. Thus, there is an urgent need for new treatments for CHD that are safe and effective.

Bulevirtide 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 (NTCP) and acts as a potent, highly selective entry inhibitor of HDV into hepatocytes, and has the potential to offer patients with a much-needed treatment option for CHD. Bulevirtide 2 mg is fully approved under the brand name Hepcludex in the European Economic Area and other European countries, as well as in Russia under the brand name Myrcludex B® for the treatment of CHD in adults with compensated liver disease.

Based on data from clinical studies and real-world experience with BLV, European Association for the Study of Liver (EASL) Clinical Practice Guidelines on HDV were released in 2023 and recommend that all patients with CHD and compensated liver disease should be considered for treatment with BLV 2 mg {European Association for the Study of the Liver 2023}. Off-label use of Peg-IFNα for 12 months is also a treatment option for patients with CHD and compensated liver disease in the EASL guidelines, and a combination of BLV and Peg-IFNα can be considered in patients without Peg-IFNα intolerance or contraindications.

Real-world data on BLV 2 mg safety and effectiveness are described in the EASL HDV treatment guidelines and presented at international meetings or in full manuscripts are from over 500 BLV-treated patients in France, Germany, Austria, and Italy {Asselah 2021, de Ledinghen 2022, Degasperi 2022, Dietz-Fricke 2023, Herta 2022, Jachs 2022, Loglio 2022, Zollner 2022, Zoulim 2022}. Despite the limitation of heterogeneous treatment schedules and follow-up periods, the overall data support the efficacy and safety reported in clinical studies.

Additionally, recently presented data from a retrospective multicenter real-life European study that included 176 patients with liver cirrhosis, including esophageal varices at baseline in approximately 50% of patients, showed that treatment with BLV 2 mg for 96 weeks was associated with increasing virological and clinical responses over time with a low risk of progression to decompensation {Degasperi 2023}. These real-world data from Europe support the safe and effective use of BLV in the postmarketing setting and, along with clinical study data, have contributed to the updated HDV treatment guidelines released by EASL.

Other than bulevirtide, there are currently no marketed treatments for HDV infection.

SI.1.5. Natural History of the Indicated Condition in the Untreated Population, including Mortality and Morbidity

The clinical outcome of acute HDV varies depending on whether patients have coinfection or superinfection. In most patients with coinfection, HBV infection is self-limiting and HDV infection recovers, with only about 2% of cases progressing to chronic disease. Superinfection is a more serious form of liver disease and as many as 90% of patients experience a rapid progression to cirrhosis. HDV-positive cirrhotic patients are also at significantly increased risk of hepatocellular carcinoma (HCC) and liver decompensation {Castaneda 2021}, {Farci 2018}, {Romeo 2009}, {Wedemeyer 2010a}, {Yurdaydin 2010}.

SI.1.5.1. Liver Related Morbidity and Mortality

A retrospective analysis of medical data from an outpatient gastroenterology and hepatology clinic at a tertiary referral center serving southwestern Switzerland examined the liver-related and other outcomes of adult patients with chronic HBV infection with or without HDV coinfection over a 10-year period. Liver-related outcome was defined as the occurrence of cirrhosis, HCC, liver transplantation, or liver-related death. Among 672 patients, HDV coinfection was the strongest predictor for liver-related outcome (OR 6.06, 95% CI 2.93–12.54, *P*<.001), followed by hepatitis B e antigen positivity (OR 2.47, 95% CI 1.30–4.69, p = 0.006), age (OR per 10-year increase 2.03, 95% CI 1.63–2.52, p<0.001) and sex (OR for female 0.39, 95% CI 0.22-0.71, p = 0.002) {Vieira Barbosa 2021}. Similarly, a longitudinal study reported that 20% of patients with HDV infection developed a liver-related first event during median follow-up of 4.2 years compared to 8.5% of HBV mono-infected patients {Manesis 2013}. At baseline, 19.8% of adults with HDV had cirrhosis compared to 7.3% of CHB patients. HDV co-infection is associated with faster progression to fibrosis and cirrhosis, earlier onset of hepatic complications, and increased likelihood of liver transplantation {Buti 2011}, {Heidrich 2013}, {Niro 2010}. Among 299 patients with chronic HDV infection, the cumulative probability of cirrhosis at 20 years was 0.55 with an incidence rate of 4% per year and after a mean follow-up of 83 months after a diagnosis of cirrhosis, 15% of patients developed HCC, with an incidence rate of 2.8% per year {Romeo 2009}.

SI.1.5.2. Hepatocellular Carcinoma

Examination of the Swedish Hospital Discharge Register and Outpatient Registry identified 9160 patients in with chronic HBV infections between 1997 and 2002. Of these, 327 had chronic HDV infection and 323 had acute HDV infection. The standardized incidence ratios for HCC in acute HDV was 137.17 (95% CI, 62.19-261.51) and 99.26 (95% CI, 42.39-196.55) for chronic HDV compared to 26.90 (95% CI, 19.46-36.26) in patients with HBV monoinfection {Ji 2012}. A systematic literature review and meta-analysis of cohort and case-control studies examined the risk of HCC in patients with chronic hepatitis D. The overall analysis revealed that chronic hepatitis D was significantly associated with a higher risk of HCC (pooled OR, 1.28; 95% CI 1.05–1.57; P=.01; I^2= 67.0%), although there was substantial heterogeneity among the studies. Pre-planned subgroup analyses demonstrated that the association between HDV and HCC was significant only in cohort studies (pooled OR, 1.67; 95% CI, 1.28-2.18; *P*<.001; I^2=62.1%), prospective studies (pooled OR, 2.77; 95% CI, 1.79-2.48; *P*<.001; I^2=0%), studies with a low risk of bias (pooled OR, 1.55; 95% CI, 1.41-1.7; *P*<.001; I^2=0%), studies published after 2010 (pooled OR, 1.60; 95% CI, 1.31-1.95; *P*<.001; I^2=45.0%), and in studies of Asian populations (pooled OR, 1.44; 95% CI, 1.04-2.00; *P*=.03; I^2=68.5%). Of note, coinfection with HIV was associated with a significantly greater risk of HCC (pooled OR, 7.13; 95% CI, 2.83-17.92; P<.001; I^2=0%) {Alfaiate 2020}.

SI.1.6. Important Co-morbidities

The main co-morbidity is hepatitis B because the presence of HBV is required for the activation of HDV {Hughes 2011}, {Krause 2018}, {Mentha 2019}. Patients with HBV/HDV coinfection are also at increased risk of HCV infection, with 29% of HDV-infected adult patients from

Central Europe also anti-HCV positive {Heidrich 2009}. HIV infections are also frequently observed in HDV-infected patients, with a recent systematic review reporting that the prevalence of HDV among HIV/HBV-coinfected patients from Europe, Africa, South America, and Asia ranging from 1.2% to 25% {Ferrante 2020}. Patients who are IVDU are frequently infected by HCV and/or HIV {Buti 2011}. There is also a higher incidence of cirrhosis in co- or superinfected hepatitis delta patients in comparison to HBV monoinfected patients {Noureddin 2014}.

PART II: MODULE SII—NONCLINICAL PART OF THE SAFETY SPECIFICATION

Table SII.1. Table of Key Safety Findings from Nonclinical Studies

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
Toxicity For the evaluation of the single dose toxicity, a study in CD® rats was performed (single high dose was applied in limit test). The study included evaluation of safety pharmacology parameters (Irwin screen). Intravenous administration of 12.5 mg BLV/kg of body weight to rats did not reveal any signs of toxicity. No mortality did occur. The evaluation of some toxicology parameters (clinical signs, clinical chemistry/haematology evaluations) was included into a single dose chimpanzee secondary pharmacology and pharmacokinetic study. The repeat dose toxicity was evaluated after daily subcutaneous injection in rats (7 days, 4 weeks, 6 months) and in dogs (3 months). The studies incorporated cytokine evaluation (4 week rat) and safety pharmacology evaluations (3 months dog study). In all studies completed so far, no signs of test item related mortality, systemic or local intolerance, body weight and body weight gain, food and drinking consumption, hematology and clinical biochemistry parameters were observed. Macroscopic necropsy evaluation or histological evaluation did not reveal any signs of test item related changes. Genotoxicity studies are considered not applicable for this product because BLV is a peptide targeting a membrane-bound transporter protein and is not expected to enter the nucleus and interact directly with DNA or other chromosomal material. A mutagenic potential is not expected for the product (Guideline International Committee for Harmonisation [ICH] S6). Carcinogenicity studies are considered not applicable to this product because within non-target cells the peptide will undergo catabolic degradation.	No potential for functionally toxic primary or secondary pharmacological effects, or for off-target toxicity was identified. Overall, BLV has shown no toxicity potential, despite the treatment of rats and dogs with doses highly above pharmacologically active for a prolonged period of time, and significant exposure of animals. The peptide is derived from the L-protein of HBV and is binding to the HBV receptor, and the HBV virus itself is not cytopathic and is very specific in its potential for the target (NTCP) binding.

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
Safety pharmacology A separate study (LPT- 27084) was performed on the safety pharmacology of the respiratory system. Respiratory rate, tidal volume, minute volume, peak inspiratory flow (PIF), peak expiratory flow (PEF), inspiratory time (Ti), expiratory time (Te) and the airway resistance index (PenH) were monitored for a period of 4 hours following intravenous administration. No test item-related influence on pulmonary parameters were detected. Binding studies have shown highly specific exclusive targeting of fully differentiated hepatocytes and has not demonstrated any potential for pharmacologically driven off-target toxicity. Pharmacokinetic distribution and radioimaging studies show a very rapid accumulation of almost 100% of the total applied dose in the target organ (liver). Moreover, the evaluation of the immunological parameters during the preclinical toxicity studies and in vitro studies with human blood cells did not reveal any potential for unintended secondary pharmacological effects, mediated e.g. via cytokine release. Evaluation of the safety pharmacology parameters has been therefore included in toxicology studies and no separate studies were performed. In line with the restricted binding to the mature hepatocytes and strong accumulation in the liver, no effects on relevant organ systems could be detected. These results are consistent with the exclusive expression of NTCP on the basolateral membrane of only differentiated hepatocytes. In a quantitative pharmacophore, 94 drugs, including NTCP inhibitors and non-inhibitors were examined whether or not they caused drug induced liver injury. No relationship between NTCP inhibition and the risk of drug induced liver injury was found {Dong 2015}. A factor that can bias the interpretation of toxicology studies with potentially immunogenic substances is the appearance of neutralizing antibodies. However, in our case the antibody titers were low both in rats and dogs, the antibodies were not found to be neutralizing and the interpretation of the results of the studies was not compromised. Therefore, no specific significance was ascribed to the antibody response.	A single dose study in chimpanzees has shown that the exposure to the dose leading to more than 90% liver receptor occupancy was well tolerated and a quantitative pharmacophore showed that NTCP inhibition was not associated with drug induced liver injury.

PART II: MODULE SIII—CLINICAL STUDY EXPOSURE

SIII.1. Clinical Study Exposure

The tables in this section present exposure data to Hepcludex (2 mg monotherapy) (up to 30 January 2024) in participants with HDV from the following pivotal studies:

- Completed studies MYR202 and MYR203, and ongoing open-label study MYR301 (2 mg monotherapy)

Table SIII.1. Duration of Exposure

Duration of Exposure	Patients	Person-days
≥ 1 day	92	57,658
> 30 days	92	57,658
> 90 days	92	57,658
> 180 days	64	52,929
> 1 year	48	47,628
> 2 years	47	47,180

Table SIII.2. Exposure by Age Group and Gender

	Patients		Person-days	
Age Group	Male	Female	Male	Female
< 18 years	0	0	0	0
18 - 30 years	6	1	2868	1009
31 - 40 years	26	12	15,685	4614
41 - 50 years	15	14	9765	10,093
51 - 65 years	9	9	6893	6731
> 65 years	0	0	0	0

Table SIII.3. Exposure by Ethnic origin

Ethnic Origin	Patients	Person-days
White	77	48,395
Black or African American	0	0
Asian	15	9263
Native Hawaiian or Pacific Islander	0	0
Other	0	0

PART II: MODULE SIV—POPULATIONS NOT STUDIED IN CLINICAL STUDIES

As described in Part II: Module SIII, the majority of human drug exposure has occurred with adult Caucasian participants. These participants resided in Germany and Russia.

The following populations have not been studied:

- Pediatric populations
- Elderly populations greater than 65 years of age
- Pregnant/lactating women
- Patients with significant comorbidities (e.g., clinically significant renal impairment, decompensated liver disease, clinically significant cardiac impairment)
- Immunocompromised patients

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table SIV.1. Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Patients with clinically significant renal impairment	Exclusion criterion was chosen in order to select a clinically stable patient population for whom the exposure to a new medicinal product would be acceptable	Yes
Patients with decompensated liver disease	Exclusion criterion was chosen in order to select a clinically stable patient population for whom the exposure to a new medicinal product would be acceptable	Yes
Patients with clinically significant cardiac impairment	Exclusion criterion was chosen in order to select a clinically stable patient population for whom the exposure to a new medicinal product would be acceptable	No Rationale: Bulevirtide is a highly targeted peptide that binds exclusively to NTCP and is thus highly localized in its distribution toward the liver. NTCP is localized exclusively at the basolateral membrane of differentiated hepatocytes and its expression is hepatocyte-specific.

Criterion	Reason for Exclusion	Considered to be Missing Information
		In the nonclinical program, BLV was found to be exclusively distributed to the liver in all tested animals except for the cynomolgus monkey (which exhibits a mutated binding site for BLV). Pharmacokinetic studies performed with radiolabeled HBV pre-S1-derived peptides have shown a rapid accumulation 10 min after injection of radioactivity in the liver of all tested species including mice, rats and dogs. Radioactivity was not detected in the heart of mice, rats and dogs (DNM-001, DNM-002, DNM-101, DNM-404, and DNM-301). In line with ICH S6 (R1), safety pharmacology studies were incorporated into the toxicology program. Briefly, no BLV-related influence on pulmonary, neuropharmacological, cardiovascular, renal, hepatic, ophthalmologic, or auditory parameters were observed. The cardiovascular function was assessed in a 13-week repeated dose toxicity study in beagle dogs (Study 24196). This study did not show any drug-related abnormalities of the electrical complexes including the QT interval and corrected QT interval (QTc) nor any changes in the heart rate in dogs treated with 0.25, 1, and 2.5 mg BLV/day subcutaneously for 91 days. The no-observed-adverse-effect level (NOAEL) for the cardiovascular activity was therefore ≥2.5 mg/kg. Furthermore, BLV was administered to 3 female chimpanzees in a single dose 2 hourly i.v. infusion at 300 µg/kg (study report TBRI-101). In this study, no evidence of QT prolongation was confirmed, and electrocardiograms (ECGs) were considered normal for the sedation conditions. Six hundred and eighty-seven participants have been exposed to at least one dose of BLV in the BLV clinical trial program and no cardiovascular safety concerns have been identified. No cardiovascular signals have been observed in the postmarketing setting. Given the mode of action of BLV and the nonclinical and clinical data, no impact of BLV on the cardiac function is to be expected. The safety profile of BLV in patients with cardiac impairment is not expected to be different from its known safety profile in patients without cardiac impairment. Hence, this information was not considered missing in the RMP, in line with Good Pharmacovigilance Practice (GVP) Module V (Revision 2) guidance.

Criterion	Reason for Exclusion	Considered to be Missing Information
Immunocompromised patients	Exclusion criterion was chosen in order to select a clinically stable patient population for whom the exposure to a new medicinal product would be acceptable	No Rationale: Bulevirtide is a highly targeted peptide that binds exclusively to NTCP and is thus highly localized in its distribution toward the liver. NTCP is localized exclusively at the basolateral membrane of differentiated hepatocytes and its expression is hepatocyte-specific. Signs for immunotoxic potential were evaluated within the standard toxicity studies (e.g. haematological changes, alterations in immune system organ weights). The overall toxicology program of BLV did not raise any signs of immunosuppression or immunoenhancement in animals or in humans that warrant the conduct of additional immunotoxicity studies. Furthermore, no drug-drug interactions are expected with immunosuppressants that immunocompromised patients may be receiving, for example, post-liver transplantation. In in vitro studies, no cytochrome P450 (CYP) inhibition by BLV was observed at clinically relevant concentrations. However, the EU SmPC does recommend close monitoring of co-administered narrow therapeutic index drugs which are sensitive to CYP3A4 substrates, including immunosuppressants cyclosporine, sirolimus and tacrolimus, as a precautionary measure, given that increased levels of midazolam (a CYP3A4 substrate) were observed in a clinical study following coadministration with BLV (10 mg). In the clinical program, no risk of increased infections was identified as related to BLV. Given the mode of action of BLV, the nonclinical data, and lack of any anticipated drug-drug interaction with immunosuppressants (as BLV does not inhibit CYP), the safety profile of BLV in immunocompromised patients is expected to be similar to that in patients who are not immunocompromised. Hence, this information was not considered missing in the RMP, in line with GVP Module V (Revision 2) guidance.
Patients < 18 years of age	Exclusion criterion was chosen in order to select a clinically stable patient population for whom the exposure to a new medicinal product would be acceptable	No Rationale: The safety profile of BLV in pediatric patients is not anticipated to be significantly different compared to the adult population, based on expected BLV exposure in pediatric patients receiving BLV.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Study Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table SIV.2. Ability of the Clinical Study Development Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	Six hundred and eighty-seven (687) participants were exposed to BLV over the whole clinical trial program (including 2 mg, 5 mg and 10 mg doses, with or without Peg-IFNα).	Adverse drug reactions (ADRs) with a frequency greater than 1 in 229 could be detected if there were no background incidence.
Due to prolonged exposure	Three hundred and ninety-five (395) participants were exposed to BLV for >180 days in the clinical trial program. Two hundred and ninety (290) participants were exposed to BLV for > 365 days, and ninety-seven (97) participants were exposed to BLV for > 730 days in clinical trials.	No ADRs specifically associated with prolonged BLV exposure have been identified in the clinical trial program, nor have any symptoms or clinical sequelae of serum bile salt elevations been observed in up to 96 weeks treatment in Study MYR204 and 144 weeks treatment in Study MYR301. The potential for long-term consequences of total bile salts elevation is being monitored through routine pharmacovigilance in the postmarketing setting.
Due to cumulative effects	Three hundred and ninety-five (395) participants were exposed to BLV for >180 days in the clinical trial program. Two hundred and ninety (290) participants were exposed to BLV for > 365 days and ninety-seven (97) participants were exposed to BLV for > 730 days in clinical trials.	No cumulative effects have been identified in the clinical trial program. The potential for long-term consequences of total bile salts elevation is being monitored through routine pharmacovigilance in the postmarketing setting.
Which have a long latency	Three hundred and ninety-five (395) participants were exposed to BLV for >180 days in the clinical trial program. Two hundred and ninety (290) participants were exposed to BLV for > 365 days and ninety-seven (97) participants were exposed to BLV for > 730 days in clinical trials.	No ADRs with a long latency have been identified in the clinical trial program. The potential for long-term consequences of total bile salts elevation is being monitored through routine pharmacovigilance in the postmarketing setting.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Study Development Programs

Table SIV.3. Exposure of Special Populations Included or not in Clinical Study Development Programs

Type of special population	Exposure	Considered to be Missing Information
Patients < 18 years of age	Not included in the clinical development program.	No Rationale: The safety profile of BLV in pediatric patients is not anticipated to be significantly different compared to the adult population, based on expected BLV exposure in pediatric patients receiving BLV.
Pregnant women	Not included in the clinical development program.	No Rationale: Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is recommended to avoid the use of BLV during pregnancy and in women of child-bearing age who do not use contraception.
Breastfeeding women	Not included in the clinical development program.	No Rationale: It is unknown whether BLV is excreted in human breast milk. Therefore, it is recommended to either discontinue breastfeeding or to discontinue/abstain from treatment with BLV.
Patients with relevant comorbidities: • Patients with renal impairment • Patients with decompensated liver disease • Patients with cardiovascular impairment	Not included in the clinical development program.	Patients with renal impairment – Yes Patients with decompensated liver disease – Yes Patients with cardiovascular impairment – No Rationale: In animal studies, there were no BLV-related effects on the cardiovascular system. In clinical trials, no safety concerns have been raised regarding the safety of BLV in patients with cardiovascular impairment. Given the mode of action of BLV, it is highly unlikely that cardiovascular comorbidities could affect the safety profile of BLV.
Population with relevant different ethnic origin	The majority of study participants exposed to BLV were Caucasian; less than 20% were Asian participants.	No Rationale: No difference is expected for ethnicities not represented in the clinical program based on the mode of action as BLV binds to the NTCP and is derived from the most conservative part of the pre-S domain of the HBV large envelope.
Subpopulations carrying known and relevant genetic polymorphisms	NTCP polymorphism was studied among participants in MYR202 and MYR203 studies. As expected, no polymorphism was detected as this would lead to the abrogation of the susceptibility to HBV/HDV.	No Rationale: BLV is derived from the most conservative part of the pre-S domain of the HBV large envelope, binds specifically to the NTCP and acts as a potent, highly selective entry inhibitor of HDV into hepatocytes. Polymorphism in the binding regions of NTCP would lead to the abrogation of the susceptibility to HBV/HDV, as it would prevent the HBV envelope from binding to NTCP and the process of virus entry into hepatocytes would be disrupted.

PART II: MODULE SV—POSTAUTHORIZATION EXPERIENCE

SV.1. Postauthorization Exposure

SV.1.1. Method Used to Calculate Exposure

The exposure was calculated based on the number of units of cumulative doses sold up to 30 July 2024.

Patient exposure to marketed Hepcludex is estimated from sales data. The number of units sold was multiplied by 30 to provide the number of vials sold. As Hepcludex is taken as a once daily dose, the total number of vials sold were divided by 365.25 to provide patient-years of treatment.

SV.1.2. Exposure

Cumulative patient exposure to Hepcludex to 30 July 2024 is estimated to be 5668 patient-years. It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure due to the accumulation of drug stocks at pharmacies/distributors and wastage.

PART II: MODULE SVI—ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

The potential for misuse for illegal purposes is negated by BLV's mode of action. It is a highly specific receptor blocker, binding to and inactivating an essential HBV and HDV entry receptor, blocking the entry of these viruses into hepatocytes and probably misdirecting their entry route to an unproductive cellular pathway. Hence there is no potential for misuse.

Also, there has been no indication that BLV will cause dependence and therefore illegal use in that respect is not expected.

PART II: MODULE SVII—IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

SVII.1.1. Risk(s) not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII.1. Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Reason	List of Risks
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Hypersensitivity Hypersensitivity reactions have been observed with BLV, of which the majority were localized and resolved without countermeasures. However, some cases of hypersensitivity involving systemic symptoms have been reported in the postmarketing setting, including a case of anaphylactic reaction that required treatment discontinuation. In nonclinical studies, investigation of cytokine response incorporated into a 4-week rat toxicity study showed no effect of BLV treatment, compared to placebo, on serum levels of IL-6, IL-10, IL-12, TNF-α and IFN-γ on test day 29.
	Injection site reactions Evaluation of local tolerance was incorporated into the toxicology studies. No signs of local intolerance at sites of injection related to the test item could be detected in the studies completed so far. The histological evaluation of the injection sites in rat and dog studies did not reveal any test item related changes. In the clinical trials participants from all BLV treatment groups reported treatment related injection site reactions. The majority of injection site reactions were Grade 1 or 2 in severity, and none resulted in discontinuation of study drug. Treatment with corticosteroids and/or antihistamines for topical and systemic use were applied. All injection site reactions were considered resolved.
Known risks that do not impact the risk-benefit profile	Anti-drug antibodies As BLV is a synthetic 47-amino acid peptide of non-human origin, possible immunogenicity was considered from the start of the development. Appearance and role of antibodies to BLV were studied in nonclinical and clinical studies. To evaluate the possible appearance of antibodies during toxicity studies, a competitive radioimmunoassay (RIA) was developed and validated. In a human Phase 2a study, antibody determination was performed by a newly developed ELISA. Antibodies were detected in animals and humans following multiple drug administration, but no neutralizing activity against the drug occurred. No correlation was observed between the appearance of antibodies and pharmacodynamic parameters. Elevated levels of bile acids, which are a secondary pharmacodynamic parameter and are indicative for drug-target binding, were detected independent of antibody positivity. Virological and biochemical response was not different in participants who were antibody-positive versus those who were antibody-negative. No significant differences were observed in the AEs reported in participants with and without anti-drug antibodies in clinical trials. In summary, they do not appear to have any impact on drug efficacy, safety or pharmacokinetics.

SVII.1.2. Risk(s) Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1. Important Identified Risks

Table SVII.2. Important Identified Risks

Important Identified Risks	Risk-Benefit Impact
Hepatitis exacerbation after drug discontinuation	Hepatitis exacerbation after drug discontinuation is a well-described phenomenon following cessation of effective antiviral treatment for HBV and HDV, and is considered serious in a small number of participants. Therefore, hepatitis exacerbation after drug discontinuation is classified as an important identified risk.

SVII.1.2.2. Important Potential Risks

There are no important potential risks for Hepcludex.

SVII.1.2.3. Missing Information

Table SVII.3. Missing Information

Missing Information	Risk-Benefit Impact
Use in patients with moderate or severe renal impairment	Bile acid increase can be more pronounced in patients with renal impairment, as excess bile acids after NTCP block can be renally eliminated. Since patients with moderate or severe renal impairment have been excluded in clinical trials thus far and BLV is not contraindicated in this population, further data collection in these patients is considered warranted.
Use in patients with decompensated liver disease	In general, HDV is a highly pathogenic virus causing acute and chronic liver disease. Although benign course of the disease has been described, patients with chronic hepatitis delta usually have progressive liver disease leading to compensated or decompensated cirrhosis. Patients with decompensated liver disease were excluded from the clinical trials so far. Although patients with decompensated liver disease are not currently included in the indication, further data collection in these patients is ongoing through routine pharmacovigilance. In the postmarketing setting, off-label use of BLV in a small number of patients with decompensated liver disease has been described, but has not been associated with any safety concerns.
Long term safety of bile acid elevation	Through 96 weeks of treatment in Study MYR204 and through 144 weeks of treatment in Study MYR301, no symptoms or clinical sequelae of bile acid elevations have been identified. There are currently limited data available on the consequences of elevated bile acids beyond 144 weeks. Osteopenia/osteoporosis, vitamin D deficiency, deviations in sex hormones and blood lipids were described in overwise healthy carriers of p.Ser267Phe mutation leading to inhibition/abrogation of NTCP function and hypercholanemia.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No safety concerns have been identified or reclassified since submission of the last RMP.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

Table SVII.4. Important Identified Risk: Hepatitis Exacerbation After Drug Discontinuation

Important Identified Risk:	Hepatitis Exacerbation After Drug Discontinuation
Potential mechanisms	Hepatitis exacerbation after drug discontinuation is a well-described phenomenon following cessation of effective antiviral or Peg-IFNα treatment for HBV and HDV {Alexander 1987, Brook 1989, Honkoop 2000}. In patients with HDV, posttreatment hepatitis exacerbation (defined as increases of ALT of at least 2 times above end-of treatment values) has been reported to occur in 14% of participants after discontinuation of Peg-IFNα in the HIDIT-II study {Wedemeyer 2019b}. In patients with chronic HBV infection, acute hepatitis exacerbations seen in patients after therapy withdrawal are due to increased host immunity against virus infected hepatocytes. These flares may be beneficial as they could represent impending HBeAg seroconversion.
Evidence source and strength of evidence	Hepatitis exacerbation after drug discontinuation is a class effect of effective anti-HBV and anti-HDV treatment, and has been observed following discontinuation of BLV in all completed clinical trials (Studies MYR202 and MYR203, with 24 weeks of treatment-free follow-up, and Study MYR204, with 48 weeks of treatment-free follow-up). While the majority of occurrences are asymptomatic and resolved without treatment, the risk is considered important as some hepatitis exacerbations have been classified as serious adverse events (SAEs). There are also some cases that have been associated with clinical signs of decompensation (eg, jaundice) and/or have required corrective treatment (eg, restarting BLV, starting nucleoside or nucleotide analogue therapy for HBV, or other supportive treatment). To date, none of the posttreatment exacerbations of hepatitis have required liver transplant and none have resulted in fatal outcome.
Characterisation of the risk	In completed Study MYR204, post-treatment ALT > 5 × ULN was observed in 27% (40/150) of participants discontinuing BLV treatment (2 mg or 10 mg), with or without Peg-IFNα, in the 48-week post-treatment period, with the lowest frequency (18%) observed in the BLV 10 mg + Peg-IFNα treatment group. A total of 11% (17/150) of participants experienced ALT > 10 × ULN. Twenty-one of the 40 participants experiencing ALT > 5 × ULN had cirrhosis at baseline, and the ALT > 5 × ULN was most frequently observed at follow-up Week 8 or 16. The majority of the participants experiencing ALT > 5 × ULN were asymptomatic, most were associated with posttreatment HDV viremia rebound (with or without increases in HBV DNA) and most resolved without treatment. Median peak ALT posttreatment was 410 U/L (range 183 to 1430), and corrective treatment was required in 9/40 participants, including initiation of nucleoside/nucleotide analogue therapy and other supportive treatments. In 2 participants, posttreatment ALT > 5 × ULN was associated with jaundice (both participants had cirrhosis, one participant had Gilbert's syndrome; the event resolved without corrective

Important Identified Risk:	Hepatitis Exacerbation After Drug Discontinuation
	treatment in 1 participant, and resolved with supportive treatment in the other participant). One jaundice case (involving a patient with underlying Gilbert's syndrome) was reported as an SAE. One further SAE of HBV reactivation was reported on the last day of study treatment and was associated with ALT > 5 × ULN in the posttreatment period; the event resolved following initiation of TDF. In completed Study MYR202, 2 participants experienced SAEs of ALT increased in the 24-week posttreatment period following discontinuation of BLV, both of which resolved. One was associated with symptoms of weakness. No SAEs suggestive of post-treatment hepatitis have been reported from Study MYR203. In ongoing Study MYR301, SAEs suggestive of posttreatment hepatitis flare have been reported following completion of up to 144 weeks of BLV treatment, including cases that have required re-treatment with BLV 2 mg. Further posttreatment data from Study MYR301 are pending and will facilitate characterization of this important identified risk.
Risk groups or risk factors	All patients who discontinue effective HBV or HDV treatment are at risk of post-treatment hepatitis flares. So far, no dose relatedness or additive factors have been detected. In Study MYR204, the majority (36/40, 90%) of participants experiencing posttreatment ALT > 5 × ULN were non responders to finite treatment (ie, HDV RNA was detectable at both follow-up Week 24 and follow-up Week 48).
Preventability	While it cannot be foreseen whether a patient will experience this reaction, close monitoring of hepatic function with both clinical and laboratory follow-up for at least several months in patients who discontinue BLV will allow the identification of this reaction at an early stage. The reintroduction of BLV therapy may then be an adequate measure to minimise this risk. To prevent the risk associated with HBV DNA increase, a treatment with a nucleoside/nucleotide analogue approved for treatment of HBV infection (e.g. entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide) is recommended. In case of treatment discontinuation, careful monitoring of liver function including transaminase levels, as well as HBV DNA and HDV RNA viral load should be performed.
Impact on the benefit-risk balance of the product:	The benefit-risk balance of BLV for the treatment of CHD remains positive. Treatment with BLV should be continued as long as associated with clinical benefit. However, there is a risk of posttreatment exacerbation of hepatitis following discontinuation of treatment, which warrants close monitoring of hepatic function posttreatment, and, in certain circumstances, resumption of antiviral therapy.
Public health impact	The risk will impact individual patients who discontinue therapy with BLV. Therefore, the public health impact is expected to be low.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for Hepcludex.

SVII.3.2. Presentation of the Missing Information

Table SVII.5. Missing Information

Missing Information:	Evidence source
Use in patients with moderate or severe renal impairment.	Since the general health condition of patients with renal insufficiency is poorer than those with hepatitis delta alone, the impact of BLV therapy may be more pronounced. No renal excretion was detected for BLV, which is in line with the length of the peptide and a high degree of plasma binding. However, BLV leads to increase in bile acids, which can be subject to renal excretion. Based on an analysis of clinical trial data (completed Studies MYR202, MYR203 and MYR 204, and ongoing Study MYR301), no apparent difference in bile salt levels were observed between participants with normal renal function and participants with mild renal impairment (creatine clearance ≥60 to < 90 ml/min) treated with BLV for up to 96 weeks in Study MYR204 and 144 weeks in Study MYR301. Furthermore, no difference in the safety profile of BLV was observed in patients with mild renal impairment and those with normal renal function.
Use in patients with decompensated liver disease	In general, HDV is a highly pathogenic virus causing acute and chronic liver disease. Although benign course of the disease has been described, patients with chronic hepatitis delta usually have progressive liver disease leading to compensated or decompensated cirrhosis. Patients with decompensated liver disease were excluded from the clinical trials so far. In the postmarketing setting, off-label use of BLV in a small number of participants with decompensated liver disease has been described, but has not been associated with any safety concerns.
Long term safety of bile acid elevation	Asymptomatic increases in bile acids for up to 96 weeks have been observed. Patients with NTCP deficiency due to homozygous p.Ser267Phe mutation and also supposed asymptomatic hypercholanaemia have been recently identified {Liu 2017}. Liu and colleagues described a point mutation that manifests as an amino acid exchange in NTCP and results in a (partial) loss of function. The phenotype of this mutation appears to be asymptomatic, though abnormal increases in bile acids are observed. The authors describe 8 otherwise healthy individuals aged between 7 and 64 years who are homozygous for the point mutation. All patients exhibited vitamin D levels on the lower limit of normal or below, and 3 patients had signs of osteopenia/osteoporosis on dual energy X-ray absorptiometry (DXA) scans. Fluctuations in blood lipids and sex hormones were detected, without apparent clinical consequences. No other pathophysiological consequences like hepatotoxicity or vascular damage could be identified. The results seem to be transferable to NTCP targeting by BLV, which leads to an increase of bile acids without significant clinical consequences. No other signs of malabsorption of fat and fat-soluble vitamins were observed in clinical studies or in patients with homozygous p.Ser267Phe mutation. However, one must be cognizant of the limitations due to the limited number of patients exposed and the duration of treatment. Levels of bile acids were not associated with the presence or absence of pruritus in clinical studies of BLV in adults. Three articles described NTCP deficiency in pediatric patients {Deng 2021, Dong 2019, Vaz 2015}. Vaz et al {Vaz 2015} described a case report of a patient with NTCP deficiency with a relatively mild clinical phenotype. Dong et al {Dong 2019} described a retrospective, observational study of 13 NTCP deficient patients with an SLC10A1 gene mutation (NTCP receptor is encoded by the SLC10A1 gene). The authors reported that while some pediatric NTCP deficient patients can be asymptomatic, others showed some clinical expression, although the study was

Missing Information:	Evidence source
	limited to younger pediatric patients with the median age of 1.36 years. Deng et al {Deng 2021} described the genotypic and clinical phenotypic characteristics of 113 pediatric patients with NTCP deficiency. The authors concluded that all NTCP deficient patients reviewed in the study exhibited favorable clinical outcomes as a result of symptomatic and supportive treatment, suggesting NTCP deficiency is a generally benign condition. Anticipated risk/consequence of the missing information Increase in bile acids is inherent to the mode of action of BLV and occurs in the majority of patients receiving BLV, as observed in adult clinical studies. In these studies, bile acid levels rapidly returned to baseline levels after cessation of the drug in most participants. No clinical consequences were associated with the bile acid increase in the clinical studies so far, nor have any clinical consequences been noted in the postmarketing setting.

PART II: MODULE SVIII—SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	Hepatitis exacerbation after drug discontinuation
Important Potential Risks	None
Missing Information	Use in patients with moderate or severe renal impairment
	Use in patients with decompensated liver disease
	Long term safety of bile acid elevation

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires

There are no specific adverse reaction follow-up questionnaires for any of the safety concerns.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2. Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

GS-US-589-6206 – A Registry Study of Treatment with Bulevirtide in Participants with Chronic Hepatitis D Infection	
Rationale and Study Objectives	This current Registry study aims to collect postmarketing data from patients with chronic HDV infection who are treated with bulevirtide in countries where it is approved to create a unique clinical database to evaluate the safety and long-term effects of bulevirtide treatment on clinical progression of liver disease through the incidence of liver-related events. Primary objective: • To evaluate the long-term effects of bulevirtide treatment on clinical progression of liver disease through the incidence of liver-related events in participants treated with bulevirtide Secondary objectives: • To evaluate the development of cirrhosis in participants treated with bulevirtide who were previously noncirrhotic • To evaluate the safety of participants treated with bulevirtide
Study Design	This Registry study will seek to enroll participants who are receiving or scheduled to receive the medicinal product bulevirtide according to the approved label in countries where bulevirtide has been authorized for use by the local health authority.
Study Populations	Participants who participated in Study MYR-Reg-02 or are scheduled to receive bulevirtide according to the approved product label and not currently enrolled in a clinical treatment study.
Milestones	Estimated study completion date (submission of final clinical study report): August 2027
MYR301 – A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta	
Rationale and Study Objectives	This study is designed to assess the long-term efficacy and safety of bulevirtide in patients with CHD. Primary efficacy and safety data will be assessed at week 48, when bulevirtide at 2 and 10 mg daily doses will be compared with delayed treatment. After week 48, patients of the delayed treatment arm in this study will be switched to bulevirtide at 10 mg daily dose for additional 96 weeks. The total duration of treatment period in this phase 3 study will be 144 weeks.

	Primary objectives: • The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta in comparison to delayed treatment. Secondary objectives: • To evaluate optimal treatment duration • To assess the safety of bulevirtide Exploratory objectives: • To investigate the immunogenicity of bulevirtide • To investigate the influence of bulevirtide on quality of life • HBV/HDV genotyping • Resistance testing
Study Design	This is a randomized, open-label, parallel group multicenter Phase III study. Randomization is stratified by the presence of liver cirrhosis (no/yes).
Study Populations	Adult male and female participants with chronic HDV infection and elevated ALT at Screening.
Milestones	Estimated study completion date (submission of final clinical study report): Q4 2025.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
GS-US-589-6206 – A Registry Study of Treatment with Bulevirtide in Participants with Chronic Hepatitis D Infection Planned	Primary objective: • To evaluate the long-term effects of bulevirtide treatment on clinical progression of liver disease through the incidence of liver-related events in participants treated with bulevirtide Secondary objectives: • To evaluate the development of cirrhosis in participants treated with bulevirtide who were previously noncirrhotic • To evaluate the safety of participants treated with bulevirtide	Long term safety of bile acid elevation	Estimated study completion date (submission of final clinical study report)	August 2027

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
MYR301 – A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta Ongoing	Primary objectives: • The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta in comparison to delayed treatment. Secondary objectives: • To evaluate optimal treatment duration • To assess the safety of bulevirtide Exploratory objectives: • To investigate the immunogenicity of bulevirtide • To investigate the influence of bulevirtide on quality of life • HBV/HDV genotyping • Resistance testing	Long term safety of bile acid elevation Hepatitis exacerbation after drug discontinuation	Estimated study completion date (submission of final clinical study report)	Q4 2025

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing postauthorization efficacy studies.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1. Routine Risk Minimization Measures

The routine risk minimization measure for Hepcludex in the EU comprise of the SmPC, the package leaflet (PL), and the legal status of the product. Hepcludex is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of hepatitis D virus infection (SmPC section 4.2). The routine risk minimization recommendations provided by the SmPC and PL are described further by safety concern in Table Part V.1. The legal status can be considered a general measure applicable to all individual safety concerns.

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
Hepatitis exacerbation after drug discontinuation	Routine risk communication: SmPC sections 4.4 and 4.8 PL sections 2 and 3 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for routine monitoring of HBV DNA, HDV RNA, and transaminase levels after the cessation of bulevirtide is included in the SmPC section 4.4 Other routine risk minimization measures beyond the Product Information: None
Missing Information	
Use in patients with moderate or severe renal impairment	Routine risk communication: SmPC sections 4.2, 4.8 and 5.2 PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for routine monitoring of the renal function is included in the SmPC section 4.2 and PL section 2 Other routine risk minimization measures beyond the Product Information: None
Use in patients with decompensated liver disease	Routine risk communication: SmPC sections 4.2, 4.4 and 5.2 PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None

Safety concern	Routine risk minimization activities
Long term safety of bile acid elevation	Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V Section V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary Risk Minimization Measures

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
Hepatitis exacerbation after drug discontinuation	Routine risk minimization measures: SmPC section 4.4. where advice is given on monitoring of HBV DNA, HDV RNA, and transaminase levels after the cessation of bulevirtide. SmPC section 4.8 PL sections 2 and 3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta
Missing information		
Use in patients with moderate or severe renal impairment	Routine risk minimization measures: SmPC sections 4.8 and 5.2 SmPC section 4.2 and PL section 2, where advice is given on the monitoring of renal function. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with decompensated liver disease	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 5.2 PL section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long term safety of bile acid elevation	Routine risk minimization measures: SmPC section 4.8 PL section 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: GS-US-589-6206 - A Registry Study of Treatment with Bulevirtide in Participants with Chronic Hepatitis D Infection MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR HEPCLUDEX (BULEVIRTIDE)

This is a summary of the risk management plan (RMP) for Hepcludex. The RMP details important risks of Hepcludex, how these risks can be minimised, and how more information will be obtained about Hepcludex's risks and uncertainties (missing information).

Hepcludex's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Hepcludex should be used.

This summary of the RMP for Hepcludex should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Hepcludex's RMP.

I. The Medicine and What is it Used for

Hepcludex is authorised for chronic hepatitis delta (CHD) – (see SmPC for the full indication). It contains bulevirtide as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Hepcludex's benefits can be found in Hepcludex's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/Hepcludex

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterize the Risks

Important risks of Hepcludex, together with measures to minimise such risks and the proposed studies for learning more about Hepcludex's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Hepcludex is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Hepcludex are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Hepcludex. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	Hepatitis exacerbation after drug discontinuation
Important Potential Risks	None
Missing Information	Use in patients with moderate or severe renal impairment
	Use in patients with decompensated liver disease
	Long term safety of bile acid elevation

II.B. Summary of Important Risks

Hepcludex has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should be initiated by a doctor experienced in the management of hepatitis D virus infection (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**Hepatitis exacerbation after drug discontinuation**
Evidence for linking the risk to the medicine	Worsening of hepatitis following discontinuation of antiviral treatment is anticipated and is routinely noted in other chronic viral diseases, like hepatitis B virus (HBV) monoinfection. It has also been observed following discontinuation of bulevirtide in clinical trials.
Risk factors and risk groups	All patients who discontinue effective HBV or HDV treatment are at risk of hepatitis flare after discontinuation. So far, no dose relatedness or additive factors have been detected. In one study (MYR204), most of the patients who experienced posttreatment hepatic exacerbation had not responded to finite treatment of BLV with or without Peg-IFNα.
Risk Minimization Measure(s)	Routine risk minimization measures SmPC section 4.4. where advice is given on monitoring of HBV DNA, HDV RNA, and transaminase levels after the cessation of bulevirtide. SmPC section 4.8 PL sections 2 and 3 Additional risk minimization measures None
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta See Section II.C of this summary for an overview of the postauthorization development plan.
Missing information	**Use in patients with moderate or severe renal impairment**
Risk Minimization Measure(s)	Routine risk minimization measures SmPC sections 4.8 and 5.2 SmPC section 4.2 and PL section 2, where advice is given on the monitoring of renal function Additional risk minimization measures: None
Missing information	**Use in patients with decompensated liver disease**
Risk Minimization Measure(s)	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 5.2 PL section 2 Additional risk minimization measures: None

Missing information	Long term safety of bile acid elevation
Risk Minimization Measure(s)	Routine risk minimization measures: SmPC section 4.8 PL section 4 Additional risk minimization measures: None
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta: additional monitoring for vitamin D levels and blood lipids GS-US-589-6206 - A Registry Study of Treatment with Bulevirtide in Participants with Chronic Hepatitis D Infection See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Hepcludex.

II.C.2. Other Studies in Postauthorization Development Plan

Table Part VI.3. Other Studies in Postauthorization Development Plan

Short Study Name	Purpose of the Study
GS-US-589-6206 – A Registry Study of Treatment with Bulevirtide in Participants with Chronic Hepatitis D Infection	This current Registry study aims to collect postmarketing data from patients with chronic HDV infection who are treated with bulevirtide in countries where it is approved to create a unique clinical database to evaluate the safety and long-term effects of bulevirtide treatment on clinical progression of liver disease through the incidence of liver-related events. Primary objective: • To evaluate the long-term effects of bulevirtide treatment on clinical progression of liver disease through the incidence of liver-related events in participants treated with bulevirtide Secondary objectives: • To evaluate the development of cirrhosis in participants treated with bulevirtide who were previously noncirrhotic • To evaluate the safety of participants treated with bulevirtide
MYR301 – A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta	This study is designed to assess the long-term efficacy and safety of bulevirtide in patients with CHD. Primary efficacy and safety data will be assessed at Week 48, when bulevirtide at 2 and 10 mg daily doses will be compared with delayed treatment. After Week 48, patients of the delayed treatment arm in this study will be switched to bulevirtide at 10 mg daily dose for additional 96 weeks. The total duration of treatment period in this Phase 3 study will be 144 weeks.

Short Study Name	Purpose of the Study
	Primary objectives: • The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta in comparison to delayed treatment. Secondary objectives: • To evaluate optimal treatment duration • To assess the safety of bulevirtide Exploratory objectives: • To investigate the immunogenicity of bulevirtide • To investigate the influence of bulevirtide on quality of life • HBV/HDV genotyping • Resistance testing

PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

None

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

None

Annex 7. Other Supporting Data (Including Referenced Material)

Annex 8. Summary of Changes to the Risk Management Plan over Time

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