swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Hepcludex

International non-proprietary name: bulevirtide as bulevirtide acetate
Pharmaceutical form: powder for solution for injection
Dosage strength(s): 2 mg
Route(s) of administration: subcutaneous
Marketing authorisation holder: Gilead Sciences Switzerland Sàrl
Marketing authorisation no.: 68338
Decision and decision date: approved on 5 February 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for bulevirtide as bulevirtide acetate in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 para 1 a^{decies} no. 2 TPA.
Orphan drug status was granted on 18 March 2021.

2.2 Indication and dosage

2.2.1 Requested indication

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in adult patients with compensated liver disease.

2.2.2 Approved indication

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in adults with compensated liver disease.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Hepcludex should be administered at 2 mg once daily by subcutaneous injection.
Duration of treatment
The optimal treatment duration is unknown and should be continued as long as associated with clinical benefit.
Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment (Child-Pugh class A). The safety and efficacy of Hepcludex in patients of Child-Pugh class B or C or in patients with decompensated liver disease have not been established (see "Pharmacokinetics").
Renal impairment
No dose adjustment is required for patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 and < 90 mL/min). The safety and efficacy of Hepcludex in patients with [CrCl] < 60 mL/min have not been established (see "Pharmacokinetics").
Elderly
No data are available for a dosage recommendation for patients > 65 years (see "Pharmacokinetics).
Paediatric population
The safety and efficacy of Hepcludex in patients younger than 18 years of age have not been established.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	27 April 2023
Formal control completed	2 May 2023
List of Questions (LoQ)	5 July 2023
Response to LoQ	29 September 2023
Preliminary decision	17 November 2023
Response to preliminary decision	16 January 2024
Final decision	05 February 2024
Decision	approval

3 Medical context

Hepatitis D virus (HDV) is a circular RNA enveloped virus dependent on hepatitis B virus (HBV) for replication and was discovered in 1977. It encodes a single structural protein, the delta antigen (L-HDAg), forming a ribonucleoprotein with the RNA genome. HDV affects 15-20 million people globally, and is most prevalent in the Middle East, Asia, and Africa. In the United States and Europe, seroprevalence is 5-10%. Limited data are available for Switzerland, where a survey estimated the seroprevalence of hepatitis D to be 5.9% among HBsAg-positive patients (Genné D, Rossi I. Hepatitis delta in Switzerland: a silent epidemic. Swiss Med Wkly. 2011 Mar 18;141). Of note, prevalence data are usually based on anti-HDV antibodies and not RT-PCR assays, which might therefore overestimate the true active HDV disease rate, as up to 40% of anti-HDV seropositive patients clear HDV.

HDV infection occurs via coinfection with acute HBV or superinfection in chronic carriers. Transmission is mainly through parenteral exposure and more rarely by perinatal transmission.

Acute coinfection usually presents as a self-limited hepatitis with complete recovery, and only around 5% of patients will progress to the chronic HBV-HDV coinfection stage. Superinfection generally results in acute severe hepatitis, often progressing to chronic HDV infection with a higher mortality than the initial HBV infection. The clinical course is influenced by HDV and HBV genotypes and is accelerated, with a relative risk of cirrhosis and hepatocellular carcinoma about threefold higher than in HBV monoinfection.

Since HDV cannot infect subjects without the presence of an HBV infection, HBV vaccination is the best prevention measure against HDV acquisition. Treatment options are limited; pegylated interferon-alpha 2a (PEG IFN-α-2a) is used with partial efficacy (20 to 40% sustained virologic response), late relapses and significant side effects. Nucleoside/nucleotide analogues targeting the HBV polymerase are not efficient alone in HDV eradication, as studies showed that, in co-infected patients, HBV viraemia suppression by itself did not change liver-related outcomes (development of cirrhosis and hepatocarcinoma).
Bulevirtide (BLV) is a novel, HBV large envelope protein–derived, synthesised lipopeptide that binds specifically to the sodium taurocholate cotransporting polypeptide (NTCP) and acts as a selective entry inhibitor of HDV into hepatocytes. The de novo infection of liver cells is decreased, viral spread is inhibited, and the life cycle of HDV is disrupted. This event is expected to lead to both reduced necroinflammation and viral load decline.

4 Quality aspects

4.1 Drug substance

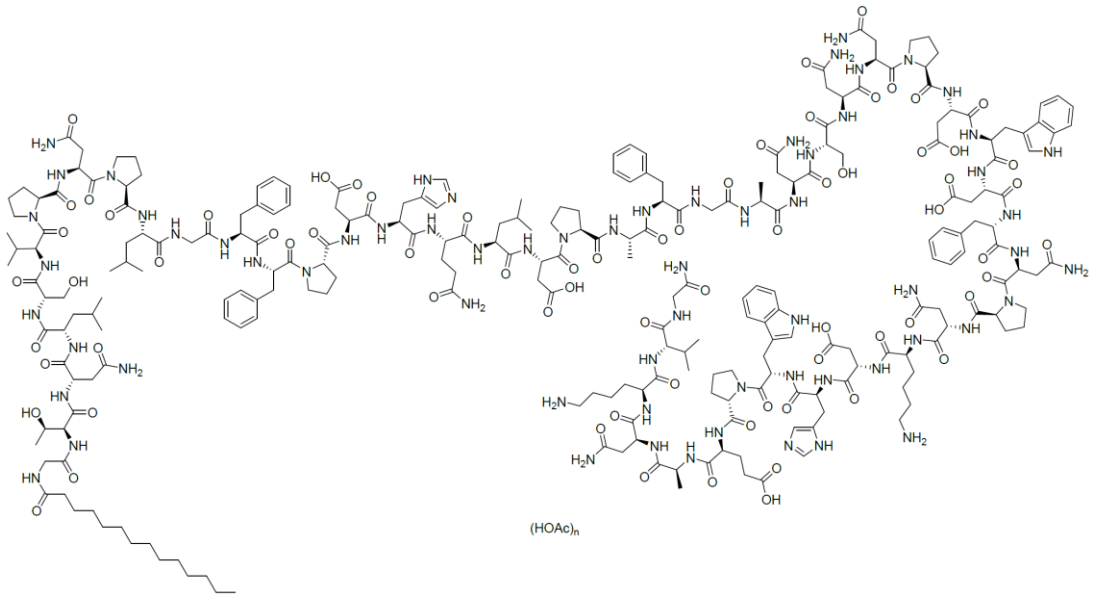
INN: Bulevirtide acetate

Chemical name: Myristoyl-Gly-Thr-Asn-Leu-Ser-Val-Pro-Asn-Pro-Leu-Gly-Phe-Phe-Pro-Asp-His-Gln-Leu-Asp-Pro-Ala-Phe-Gly-Ala-Asn-Ser-Asn-Asn-Pro-Asp-Trp-Asp-Phe-Asn-Pro-Asn-Lys-Asp-His-Trp-Pro-Glu-Ala-Asn-Lys-Val-Gly-NH_2, acetate salt

Molecular formula: $C_{248}H_{355}N_{65}O_{72}$ (net, acetate excluded)

Molecular mass: 5398.9 g/mol (average mass, net peptide, acetate excluded)

Molecular structure:



Physico-chemical properties: white to off-white powder, amorphous, hygroscopic. Slightly soluble in 50 % v/v AcOH in water; practically insoluble in acetonitrile, diethyl ether, and 2-propanol.

Synthesis: The drug substance is obtained by adopting solid phase peptide synthesis starting from Rink amide MBHA resin. After the amino acid derivatives and, finally, myristic acid are coupled to the resin, the crude peptide is cleaved from the solid support and deprotected, followed by filtration and purification by preparative HPLC. Next, salt exchange is performed, and bulevirtide acetate is finally isolated by lyophilisation.

Specification: In order to ensure a consistent quality of the drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described, and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability: Appropriate stability data have been presented. Based on the results, a satisfactory re-test period has been established when stored at –20 °C in amber, type III soda-lime glass bottles closed by a polypropylene screw cap with PTFE liner.

4.2 Drug product

Description and composition:
The finished product is a white to off white lyophilised powder for solution for injection supplied in single-use vials. Each vial contains bulevirtide acetate equivalent to 2 mg bulevirtide. The composition of the finished product was presented. The powder is intended to be dissolved in 1 ml of water for injection per vial. After reconstitution, the concentration of bulevirtide net peptide solution in the vial is 2 mg/ml.

Pharmaceutical development:
The formulation for Hepcludex was initially developed by an academic laboratory and was later transferred to commercial manufacturers, but the composition of the formulation remained unchanged throughout the clinical development. The active substance and product batches used during development were presented in the dossier.
The manufacturing process development history and the process changes have been presented. The proposed manufacturing process for future commercial finished product batches is clearly presented and was applied to produce registration batches of the 2 mg strength. The commercial manufacturing process is identical to the manufacturing process used by the manufacturer of the Phase 2 and Phase 3 clinical batches. Starting from the developmental composition, an industrial scale manufacturing process following GMP regulation and guidelines, using sterile filtration, aseptic processing and lyophilisation, was developed. Considering that the preparation of bulevirtide solution is a non-standard process, the manufacturing process development focused on the adequacy of the filter for sterilisation and the process parameters for the lyophilisation step. The assessment of the impact of the manufacturing site and batch size change has been evaluated through comparison of the manufacturing processes and has been satisfactorily discussed. In conclusion, no difference is discernible between the two manufacturing processes employed by the manufacturer of the Phase 2 and Phase 3 clinical batches and the manufacturers of the commercial batches. Both processes are considered as equivalent.
The container closure system for Hepcludex consists of a 2R clear glass vial, Ph. Eur. type I, and a grey rubber stopper, Ph. Eur. type I, with a flip-off aluminium cap with blue plastic disc. The glass vials are washed and depyrogenated, rubber stoppers are autoclaved prior to filling, and the flip-off caps are supplied ready-to-use. The integrity of the container closure system to prevent microbial contamination was also confirmed during process validation.

Manufacture:
The manufacturing process of Hepcludex consists of the following main steps: mixing of excipients and addition of active substance and pH adjustment, 1st sterile filtration and 2nd sterile filtration, vial filling, lyophilisation, sealing and packaging. Due to the aseptic processing step, the manufacturing process is considered to be a non-standard process. A flowchart of the process together with the proposed in-process controls was presented.
All materials and equipment that come into contact with product are sterilised according to a standard operating procedure. Equipment for compounding and filling, as well as filters, are autoclaved. Stoppers are autoclaved and dried directly after sterilisation inside the autoclave in a fractionated vacuum. Vials are washed, sterilised and depyrogenated according to a validated procedure in the hot air sterilisation tunnel.
Filter validation has been performed, and the key elements of the studies were summarised. Based on all available data and information, it can be confirmed that the selected filter type is validated for the full-scale production of Hepcludex 2 mg powder for solution for injection.
The critical steps of the process were identified, and suitable in-process controls were presented for each identified step. Holding times have been presented and justified. Overall, the proposed control strategy is deemed to be satisfactory.
Process validation has been performed on full production scale batches at both manufacturing sites, and the results have been presented.
The process is considered to be successfully validated and adequately under control in order to consistently obtain a product that complies with the specifications.

Specification:
The finished product release and shelf-life specifications include appropriate tests and limits for appearance (visual), primary packaging material (visual), identification (HPLC and UV), water content (Ph. Eur.), assay (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), colour and clarity of solution (Ph. Eur.), reconstitution time, visible and subvisible particles (Ph. Eur.) and pH of solution (Ph. Eur.).
The assay limits range and limits for impurities are based on available release and stability data.
The limits for the pH have been justified based on development data, as well as available release and stability data. The limits for the other specification parameters are acceptable and are based on available release and stability data.
A risk assessment of potential sources of contamination due to elemental impurities during manufacturing process was performed according to the ICH Q3D guideline. All obtained results were in compliance with the specifications for parenteral products and below the 30% threshold of the respective PDE value. Therefore, it is acceptable not to control elemental impurities in the finished product specification.
Risk assessments have been presented for both the finished product manufacturing process and the active substance with respect to potential formation of nitrosamine impurities. The outcome of the risk assessment confirms that there is no risk of nitrosamine impurity formation and no risk of cross-contamination with other products. The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.
Batch analysis data was provided for eleven commercial scale batches. The data demonstrate that all parameters are well within their specifications and therefore indicate consistent manufacture of the finished product.

Container closure system:
The container closure system for Hepcludex consists of a 2R clear glass vial, Ph. Eur. hydrolytic class I, and a grey rubber stopper for 2R vials, Ph. Eur. type I (13 mm diameter), with a flip-off aluminium cap with blue plastic disc (13 mm diameter).
Compliance with Ph. Eur. requirements and European legislation is stated for the primary packaging materials.

Stability:
The stability studies were carried out on seven commercial scale batches manufactured at the proposed manufacturing sites stored under long-term conditions (5°C) for up to 36 months and under accelerated conditions (25°C / 60% RH) for 6 months according to the ICH guidelines. The tested batches were packaged in the container closure systems intended for marketing.
Samples were tested for appearance, appearance after reconstitution, water content, reconstitution time, pH of solution, assay, related substances, visible particles and sterility.
No significant changes were observed, and the results are found to be well within the specification limits.

An in-use stability study was performed on bulevirtide lyophilised powder for solution for injection after reconstitution. The solution was tested for appearance, pH of solution, assay and related substances. All tested parameters met the specification and confirm the stability of the reconstituted product over a period of up to 24 hours when stored at room temperature.

A photostability study in compliance with ICH Q1B has been completed, and the results were provided. As it is already known that the active substance bulevirtide is photosensitive, preventive measures to limit any degradation due to exposure to light have been put in place, i.e. the finished product vials are kept in closed cartons protected from light and stored in a refrigerator.

Based on the overall stability data, the proposed shelf-life of 24 months when stored between 2°C and 8°C and stored in the original packaging in order to protect from light can be accepted. The storage conditions concerning the reconstituted product (2 hours at 25°C) are also accepted.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Bulevirtide binds to the plasma membrane of primary hepatocytes from rat, rabbit, dog and human. No binding to cynomolgus monkey hepatocytes was observed. Bulevirtide inhibited the sodium taurocholate co-transporting polypeptide (NTCP)-mediated transport of taurocholate with an IC_{50} of 0.32 µM in human and 0.068 µM in rat. In HepaRG cells, bulevirtide inhibited infection with hepatitis B virus (HBV) genotypes B, C, D, E and G, as well as with hepatitis D virus (HDV) clinical isolates, with EC_{50} values ranging from 0.015 to 0.834 nM without any cytotoxicity at concentrations up to 50 µM. Moreover, infection of HuH7 cells stably expressing human NTCP with HDV genotype 8 enveloped with all HBV genotypes (A, B, C, D, E, F, G and H) was inhibited by bulevirtide, with EC_{50} values ranging between 0.023 and 0.747 nM. A further study in primary human hepatocytes confirmed the anti-viral activity of bulevirtide against all eight genotypes of HDV enveloped with HBV genotypes A to H, including strains with most prevalent genotype A-D polymorphisms (mean EC_{50} values between 0.21 and 0.68 nM).

In urokinase-type plasminogen activator (uPA)/SCID mice transplanted with human hepatocytes and infected with HBV, subcutaneous (s.c.) treatment with bulevirtide at 2 mg/kg/day initiated either 3 days or 3 weeks post infection prevented HBV spread from initially infected hepatocytes. Since HDV needs the envelope proteins of HBV for secretion and viral propagation, bulevirtide is expected to also block HDV dissemination. In the same mouse model, treatment with 2 mg/kg/day s.c. bulevirtide initiated before HBV and HBV inoculation prevented *de novo* HDV infection. Finally, in transgenic mice expressing human NTCP, delivered an HBV genome and infected with HDV, bulevirtide (67.6 µg/kg/day intraperitoneally) efficiently suppressed HDV viraemia but failed to cure HDV infection, as evidenced by a rebound of viraemia upon treatment stop.

In conclusion, the pharmacology of bulevirtide as an inhibitor of NTCP for the treatment of HDV infection has been sufficiently characterised from a nonclinical perspective.

The applicant did not conduct any *in vitro* secondary/off-target pharmacology screen, which is acceptable for a 47-amino acid peptide.

The safety pharmacology studies in the rat did not reveal any effects of bulevirtide on the central nervous or respiratory system at plasma concentrations >23 and >7-fold human C_{max}, respectively. In the 13-week repeat-dose toxicity study in the dog, bulevirtide did not show any effects on electrocardiograms or blood pressure at plasma concentrations >30-fold human C_{max}.

In vitro pharmacodynamic drug interaction studies demonstrated that tenofovir disoproxil fumarate and entecavir (nucleotide/nucleoside analogues for first-line treatment for chronic hepatitis B) do not impair the inhibitory effect of bulevirtide on HDV infection.

5.2 Pharmacokinetics

The estimated bioavailability of bulevirtide after s.c. administration is approximately 80% in rat. Elimination half-life ($t_{1/2}$) of bulevirtide in rat was 1 to 2 hours. However, bulevirtide could be detected in the liver up to 72 hours post dose.

After repeated s.c. doses of 0.25-2.5 mg/kg/day, plasma exposure to bulevirtide increased with the dose. Accumulation (up to 50-fold after 26 weeks in the rat and up to 8-fold after 13 weeks in the dog) occurred after repeated daily administration. There were no clear sex-related differences in exposure. Liver concentrations were not dose-dependent, and there were no sex-related differences in any species.

Formation of ADAs in rats and dogs had no clear impact on plasma or liver exposure to bulevirtide and was not associated with any toxicity.

In vitro plasma protein binding of bulevirtide was very high, with estimated bound fractions of >99.9% in rat, dog, rabbit and human. Biodistribution studies showed a rapid and specific distribution to the liver in mice, rats and dogs but not in cynomolgus monkeys. This is consistent with the expression/localisation of NTCP in the liver and the observation that bulevirtide does not bind to cynomolgus monkey hepatocytes.

The applicant did not conduct any metabolism studies with bulevirtide, which is acceptable for a peptide and in line with ICH S6(R1).

Only small peptide fragments, but no full-length bulevirtide, were detected in the urine from rat and dogs.

5.3 Toxicology

Since bulevirtide is a peptide, the applicant conducted a toxicology programme in line with ICH S6(R1). The repeat-dose toxicity studies were conducted in the rat and dog, both being pharmacologically relevant animal species. Bulevirtide was administered s.c., in line with the intended clinical route of administration. The duration of the repeat-dose toxicity studies (up to 26 weeks in the rat) is appropriate for a peptide drug intended for long-term use.

There was no acute toxicity in the rat after a single intravenous administration of bulevirtide at 12.5 mg/kg (>23-fold human C_{max}) or s.c. doses up to 25 mg/kg (>47-fold human C_{max}). Bulevirtide did not induce any cytokine release from human peripheral blood mononuclear cells or in rats. The pivotal repeat-dose toxicity studies in rat and dog did not reveal any test item-related toxicity at exposures 46- and 82-fold human AUC. As expected from an inhibitor of NTCP, bulevirtide increased bile acid concentration in blood. Increases in bile salts were also observed in clinical studies and are listed as a side effect in the information for healthcare professionals. Although the nonclinical studies did not identify any safety issue, given the limited clinical safety data, long-term safety of bile acid elevation is included under missing information in the RMP and is the subject of additional pharmacovigilance activities.

The applicant did not conduct any genotoxicity studies with bulevirtide, which is acceptable for a peptide and in line with ICH S6(R1).

No carcinogenicity studies were conducted. In line with ICH S6(R1), the applicant provided an assessment of the carcinogenic potential of bulevirtide based on a weight of evidence approach. This assessment does not suggest any carcinogenic potential for bulevirtide.

Bulevirtide did not impair fertility or early embryonic development in rat at exposures approximately 10-fold human AUC in both sexes. No embryofetal toxicity or teratogenicity was noted in the rat (at an exposure 12-fold human AUC) or in the rabbit (at an exposure 124-fold human AUC). The pre- and postnatal development study in rats did not identify any maternal or reproductive toxicity to the F0 generation or effects on pre- or postnatal development of the F1 generation (including reproductive performance) at exposures approximately 10-fold human AUC. There were no findings in the reproductive organs at histopathology in any of the repeat-dose toxicity studies. Although bulevirtide did not show any reproductive or developmental toxicity, it is preferable to avoid the use of bulevirtide during pregnancy and in women of child-bearing potential not using contraception.

There were no concerns with excipients or impurities. All relevant nonclinical safety findings are included in the nonclinical part of the safety specification of the RMP. Due to its peptide nature, bulevirtide is not expected to pose any risk to the environment.

5.4 Nonclinical conclusions

The submitted nonclinical documentation is considered adequate to support the approval of bulevirtide for the proposed indication. All safety-relevant nonclinical data are included in the information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The PK of BLV was investigated over a dose range of 100 µg – 20 mg i.v. and 0.5 – 10 mg s.c. in healthy subjects and patients with HDV infection.

The commercial dose strength of “Bulevirtide for injection, 2 mg” is defined based on the content of a vial. Taking into account losses due to product hold-up in the vial, syringe, and needles during dose preparation and administration, the delivered dose is 1.7 mg BLV.

ADME

Absorption
Following s.c. administration, BLV was rapidly absorbed, with T_{max} occurring between 0.5 and 3 hours post dose in healthy subjects and patients with HDV infection.
The absolute bioavailability of BLV at the therapeutic dose (2 mg) has not been determined. Following s.c. administration, the absolute bioavailability at 5 mg and 10 mg was approximately 48% and 57%, respectively. However, these values should not be extrapolated to the 2 mg dose level due to the non-linear PK of BLV.

Distribution
The volume of distribution (Vd) of BLV was dose-dependent and decreased with increasing doses of BLV. Following multiple administrations of 2 mg BLV as a subcutaneous injection, the mean apparent volume of distribution was estimated to be 133 L.
In vitro, BLV was highly bound (99.9%) to human plasma proteins. The N-terminal myristic acid was thought to mediate the high degree of BLV protein binding.

Metabolism and elimination
The metabolism of BLV was not studied specifically. As a peptide, BLV is assumed to be degraded to amino acids by endogenous peptide catabolism.
BLV was not excreted in urine. The high protein binding is assumed to limit renal excretion. BLV clearance decreased with increasing dose. Following multiple administrations of 2 mg BLV as a s.c. injection, the mean apparent systemic clearance was 12.8 L/h. The mean half-life of BLV after a single dose of 2 mg s.c. ranged from 3 to 7 hours.

Dose-proportionality and time-dependency
The PK of BLV is non-linear with respect to dose and time. Both after single and multiple dosing, drug exposure increased more than proportionally with increasing doses, which is likely linked to target mediated drug disposition (TMDD).
Upon multiple dosing, accumulation of BLV of approximately 2-fold was observed (based on C_{max} and AUC). As BLV has a short half-life, there is currently only a limited understanding of the underlying reasons for the observed non-linearity in BLV PK. Possibly the accumulation reflects changes in the abundance and /or activity of the target NTCP.

Special populations / Intrinsic factors

Impaired hepatic function
The influence of impaired hepatic function on the BLV PK has not been studied in a dedicated PK study. In a PopPK analysis, participants with cirrhosis (Child-Pugh A, mild hepatic impairment (n = 154)) had increased BLV exposures (approximately 38% and 42% increases in Cmax and AUC, respectively) compared to participants without cirrhosis (n=230). The efficacy and safety profile in cirrhotic patients indicated that, since this increase in exposure is not clinically relevant, no dose adjustment is required.

The PK of BLV has not been evaluated in patients with moderate or severe hepatic impairment (Child-Pugh B and C).

Impaired renal function
The influence of impaired renal function on BLV exposure was not studied in a dedicated study, which is acceptable as BLV was not excreted in urine. In a PopPK analysis, mild renal impairment (creatinine clearance (CrCl) ≥ 60 and < 90 mL/min, n=60) had no significant influence on the PK of BLV, which is consistent with theoretical expectations. BLV has not been studied in subjects with CrCl < 60 mL/min.

Other demographic factors
Potential effects of other factors on the PK of BLV were assessed using a PopPK analyses approach. Overall, the PopPK analyses indicated that no dose adjustments are required based on weight, gender, race and age, with the limitation that BLV was not studied in subjects >65 years of age.

Interactions

The interaction potential of BLV was investigated *in vitro* and in clinical studies with the common co-medication tenofovir disoproxil fumarate (TDF), with the OATP1B1/3 substrate pravastatin and the CYP3A substrate midazolam.

The *in vitro* studies to assess the interaction potential of BLV were conducted according to current regulatory guidelines with regard to the CYPs/transporters and BLV concentrations investigated. No *in vitro* inhibitory signals or induction potential for CYP enzymes were detected. The *in vitro* results for transporters indicated an inhibitory potential for OATP1B1/3, but no clinically relevant interactions are expected for MDR1, BCRP, BSEP, MATE1, MATE2K, OATP2B1, OAT1, OAT3, OCT1 and OCT2.

Effect of other drugs on BLV
In vitro, it has been shown that certain drugs can inhibit NTCP, the target of BLV. Therefore, the co-administration of such drugs is not recommended.

Effect of BLV on other drugs
Following concomitant administration of a single dose of 40 mg pravastatin (OATP1B1/3- und NTCP-substrate) with BLV at steady-state (5 mg BID for 7 days), the pravastatin AUC_{0-inf} and C_{max} were increased to 1.34-fold. These results indicated a mild inhibition of OATP1B1/3 and/or NTCP by BLV at steady-state exposure following 5 mg BID, which is in accordance with the inhibitory potential observed *in vitro*. The BLV dose tested in this study was 5 times higher than the therapeutic dose (2 mg QD). Thus, the study represents a worst-case scenario, and the interaction effect at the therapeutic dose is likely less pronounced – although the exact extent remains uncertain. Therefore, cautionary measures for co-administration of OATP1B1/3 substrates are recommended also at the therapeutic dose.

Although in *vitro data* indicated no signals of inhibition or induction of CYP3A4, BLV might still indirectly impact the CYP3A activity by alterations in bile acid metabolism. A potential interaction was investigated in clinical studies with midazolam as CYP3A4 substrate. The respective studies had limitations in terms of design, but allowed the conclusion that BLV does not have a strong effect on midazolam clearance. However, it remained difficult to exclude a mild effect. As a precautionary measure, close clinical monitoring is recommended when sensitive CYP3A4 substrates are co-administered with BLV.

The clinical interaction study with the common co-medication TDF indicated no relevant interaction.

Pharmacodynamics

Mechanism of action and primary pharmacology
Bulevirtide is a 47-amino acid, N-terminally myristoylated, HBV large envelope protein–derived, synthesised lipopeptide that binds to NTCP and acts as an entry inhibitor of HDV into hepatocytes.
The antiviral effect of bulevirtide was assessed based on the change in HDV RNA from baseline and viral response rates in the phase 2 dose-finding studies. The results are summarised in section 2.10.3.

Secondary pharmacology (safety)
Bile acids
Conjugated bile salts are endogenous substrates of NTCP. Thus, an increase in plasma bile salt concentrations is expected as a consequence of NTCP inhibition. Changes in plasma bile salt concentrations have been thoroughly characterised throughout the clinical study programme, and the results are summarised in section 2.10.5.

QTc prolongation
No thorough QT/QTc study has been conducted. As the available non-clinical and clinical safety data did not indicate a risk for QTc prolongation, the lack of a dedicated QT/QTc study is acceptable.

6.2 Dose finding and dose recommendation

Study MYR202 randomised adult HBV-HDV coinfected patients (who had either failed previous interferon treatment or were considered interferon-intolerant) to four treatment groups: three doses of bulevirtide (2 mg/day, 5 mg/day, 10 mg/day) versus no HDV-targeted therapy (control group). All patients also received the nucleotide analogue tenofovir (TDF, 245 mg/day) for the HBV infection. Patients on bulevirtide were co-treated for 24 weeks then received TDF only for 24 weeks.

The primary efficacy endpoint was HDV RNA response (negativation or decrease by ≥ 2 $\log_{10}$ IU/mL) from baseline to week 24. Secondary endpoints included durability of response (week 24 to week 48), changes in transaminases (ALT), combined treatment response (virological HDV RNA response and normal ALT), changes in HBsAg, as well as assessment of fibrosis markers.

110 patients completed the study. Two thirds were males with a median age of 38 years and a median baseline HDV viraemia of 5.5 $\log_{10}$ IU/mL. 100% were HbsAg positive, 90% HBeAg negative. Median ALT levels were 130 UI/L. The median liver elasticity was 14.94 kPa. Half of the patients were considered to have hepatic cirrhosis. The characteristics were well balanced between the treatment groups except for a slightly lower percentage of males (53.6%), ALT level (74 UI/L), and liver stiffness (13.8 kPa) in the BLV 2 mg group.

In the mITT (randomised patients who received at least one dose of the study treatment) the primary efficacy endpoint was achieved for the BLV 2 mg, 5 mg, and 10 mg groups in 53.6% (15/28), 50.0% (16/32), and 76.7% (23/30) of subjects, respectively ($p<0.0001$ for all BLV groups in comparison to TDF). Response in the TDF alone group was 3.6% (1/28). Only a few patients achieved undetectable RNA levels (1/28, 2/32 and 1/30 in the BLV 2 mg, 5 mg and 10 mg groups) and, of the 4 patients with undetectable RNA levels at week 24, only 2 remained undetectable at week 48. In consequence, the majority of responders were due to a ≥ 2 $\log_{10}$ IU/mL HDV RNA decrease.

Regarding mean HDV RNA levels after 24 weeks of treatment, these declined by -1.92 $\log_{10}$ IU/mL, -1,76 $\log_{10}$ IU/mL and -2.59 $\log_{10}$ IU/mL in the 2 mg, 5 mg, and 10 mg BLV groups, whereas in the TDF control group there was no significant decrease (-0.18 $\log_{10}$ IU/mL). After cessation of treatment, HDV RNA levels essentially rebounded to baseline values. When durability of HDV RNA response was analysed (persistence of an at least ≥ 2 $\log_{10}$ IU/mL decrease in HDV RNA levels), the response levels at week 48 were 7.1% (n=2/28, CI 0.9-23.5), 3.1% (n=1/32, CI 0.1 to 16.2) and 10% (n=3/30,

CI 2.1 to 26.5) in the 2 mg, 5 mg, 10 mg BLV groups, respectively. In the subgroup of subjects with cirrhosis at baseline, response rates were similar.

Regarding normalisation of ALT levels at week 24, the proportions of patients in the mITT set were 42.9% (12/28), 50% (16/32) and 40% (12/30) in the 2 mg, 5 mg, 10 mg BLV groups, respectively. The proportion in the TDF group was 7.1% (2/28). At the end of follow-up at week 48, ALT normalisation rates were 14.3% (4/28), 3.1% (1/32) and 10% (3/30) in the 2 mg, 5 mg, 10 mg BLV groups, respectively, compared to 14.3% (4/28) in the TDF group. This means that there was no significant difference in the BLV groups and the TDF control group at this timepoint.

Regarding combined treatment response (HDV RNA response accompanied by a normal transaminase level) at week 24, the proportions of patients in the mITT set were 21.4% (6/28), 28.1% (9/32) and 36.7% (11/30) in the 2 mg, 5 mg, 10 mg BLV groups, respectively. In contrast, no case of combined treatment response at week 24 was observed in the TDF group. At the end of follow-up at week 48, combined treatment response rates were 7.1% (2/28), 3.1% (1/32) and 3.3% (1/30) in the 2 mg, 5 mg, 10 mg BLV groups, respectively. This means that there was no significant difference in the BLV groups and the TDF control group at this timepoint.

Regarding fibrosis, elastometry measurement indicated changes from baseline at week 24 of -2.85 ± 2.65 kPa, -2.52 ± 6.21 kPa, -3.38 ± 3.83 kPa and -0.78 ± 3.17 kPa in the 2 mg BLV, 5 mg BLV, 10 mg BLV, and TDF only groups, respectively. Similar results were observed in the subgroup of subjects with cirrhosis at baseline. Overall, there is a trend towards a decrease in liver stiffness from baseline to week 24 in the BLV groups. However, since stiffness can arise from oedema or inflammation (not only fibrosis), interpretation of the results is difficult regarding the evolution of fibrosis versus improvement in inflammation/oedema, especially within a short time span of 24 weeks. Some patients had paired liver biopsies at baseline and week 24, but data are inconclusive due to the low number.

Regarding HBsAg levels, these were essentially unchanged from baseline in all groups, and there were no statistically significant changes in HBV DNA from baseline to week 24 or 48 in the BLV group in comparison to the TDF group (the mean decline of HBV viral load was approx. -0.3 $\log_{10}$ IU/mL). In consequence, no specific synergistic effect of bulevirtide with TDF was shown.

From a safety perspective, in MYR202 there was no dose dependency in the AE profile. However, the increase in bile acids was less pronounced in the BLV 2 mg group, in comparison to the BLV 5 mg and 10 mg groups.

Overall, MYR202 study results indicated that bulevirtide is efficacious for the treatment of chronic hepatitis D. Results are not significantly different between groups, but there was a slight dose effect in favour of the 10 mg dosing.

Study MYR203 investigated the efficacy of BLV in chronic hepatitis D patients with compensated liver disease either (i) in monotherapy at daily 2 mg dosing or (ii) in combination with PEG-IFNα at BLV daily 2 mg, 5 mg or 10 mg dosing or (iii) in combination with TDF at BLV 5 mg BID dosing, in comparison to monotherapy with PEG-IFNα. All patients were treated for 48 weeks, and there was a follow-up period of 24 weeks (patients who had received TDF continued this treatment).

The primary efficacy endpoint was the proportion of patients with a negative HDV RNA PCR at week 72. Secondary efficacy endpoints included the proportion of patients with a negative HDV RNA PCR at weeks 24 and 48, as well as ALT normalisation, combined response (virological and ALT response), HBsAg response and changes in liver fibrosis.

79 subjects completed the study. Two thirds were males with a median age of 38 years. HDV viraemia (median levels of ca. 6.0 $\log_{10}$ UI/ml) and ALT (median levels of 79 U/l) were quite similar

between groups, with some variability given the small numbers of participants. The median liver elasticity was 10.15 kPa. 100% of subjects were HbsAg positive, 90% HBeAg negative.

For the primary endpoint in the full analysis set at week 72 (24 weeks after end of treatment), the primary efficacy endpoint was achieved by 6.7% (1/15) in BLV 2 mg monotherapy, 53.3% (8/15) in BLV 2 mg + PEG-IFNα, 26.7% (4/15) in BLV 5 mg + PEG-IFNα, 6.7% (1/15) in BLV 10 mg + PEG-IFNα, 33.3% (5/15) in BLV 5 mg BID + TDF. No patient (0/15) treated with PEG-IFNα only met the primary endpoint.

At the end of treatment at week 48, HDV RNA response rates in the same groups were 13.3% (2/15) in BLV 2 mg monotherapy, 80% (12/15) in BLV 2 mg + PEG-IFNα, 86.7% (13/15) in BLV 5 mg + PEG-IFNα, 80% (12/15) in BLV 10 mg + PEG-IFNα, 46.7% (7/15) in BLV 5 mg BID + TDF. The response was 13.3% (2/15) in the PEG-IFNα group. Regarding normalisation of ALT levels, this was 73.3% (11/15) in BLV 2 mg monotherapy, 26.7% (4/15) in BLV 2 mg + PEG-IFNα, 46.7% (7/15) in BLV 5 mg + PEG-IFNα, 26.7% (12/15) in BLV 10 mg + PEG-IFNα, 40% (6/15) in BLV 5 mg BID + TDF, and 26.7% (4/15) in the PEG-IFNα group. Regarding combined response (undetectable HDV RNA and ALT normalisation) levels at the end of treatment (week 48), these were 13.3% (2/15) in BLV 2 mg monotherapy, 20% (3/15) in BLV 2 mg + PEG-IFNα, 33.3% (3/15) in BLV 5 mg + PEG-IFNα, 20% (3/15) in BLV 10 mg + PEG-IFNα, 13.3% (2/15) in BLV 5 mg BID + TDF, and 6.7% (1/15) in the PEG-IFNα group. It should be noted that in MYR203, the combined response used an undetectable HDV RNA criterion, whereas in MYR301 (pivotal study described below), the combined response assessment included an updated acceptance criterion that was undetectable HDV RNA or a ≥ 2 $\log_{10}$ reduction, which renders inter-study comparisons difficult.

In consequence, even though there were significantly fewer undetectable HDV RNA responses in the BLV 2 mg monotherapy arm in comparison to the other groups, normalisation of ALT levels was numerically better. Thus, the normalisation of ALT does not seem to be fully correlated to the evolution of HDV viral load, which could be related to the mechanism of action of BLV, which is not an antiviral directly interfering with virus replication, but rather an inhibitor of viral entry that blocks *de novo* infection of the hepatocytes. As well, the pro-inflammatory effect of PEG-IFNα might contribute to this observation.

Regarding the degree of liver fibrosis at week 48 and 72, elastometry results in MYR203 showed no significant differences in the change from baseline for any group.

In terms of response to HBV (HBsAg negativation or HBV DNA decline > 1 $\log_{10}$ IU/mL, below the limit of detection), the proportions of responders were not statistically significantly different in the BLV-containing groups in comparison to the PEG-IFNα group.

From a safety perspective, in MYR203 there was no BLV dose dependency in the AE profile apart from the increase in bile acids.

Overall, while there appears to be a dose-response relationship from 2 mg to 10 mg for antiviral efficacy, the limitations of the MYR202 and MYR203 studies suggest that it cannot be conclusively determined which dose of BLV is most appropriate for antiviral efficacy leading to ALT normalisation. The potential emergence of resistance (not observed in MYR202 and MYR203) at a lower dose versus a potential increase in AEs at a higher dose also had to be considered. For all these reasons, the sponsor conducted the pivotal Phase 3 study of MYR301 with BLV 2 mg and 10 mg doses, which was an acceptable approach.

6.3 Efficacy

Clinical efficacy for the requested indication was supported by the interim Week 48 results from the ongoing pivotal phase 3 **study MYR301**, which will continue until Week 144. This is a multicentre, open-label, randomised phase 3 clinical trial to assess the efficacy and safety of bulevirtide in patients with chronic hepatitis D.

Participants were randomised (1:1:1) among 3 treatment groups, and randomisation was stratified for liver cirrhosis status.

Treatment Group A: Delayed treatment with BLV 10 mg/day for 96 weeks after an observational period of 48 weeks, with an additional follow-up period of 96 weeks.

Treatment Group B: Immediate treatment with BLV 2 mg/day for 144 weeks, with a further follow-up period of 96 weeks.

Treatment Group C: Immediate treatment with BLV 10 mg/day for 144 weeks, with a further follow-up period of 96 weeks.

The primary efficacy endpoint was the proportion of participants achieving combined response at Week 48. Combined response was defined as fulfilment of 2 conditions simultaneously:

- Undetectable HDV RNA or decreased by ≥ 2 $\log_{10}$ IU/mL from baseline

- ALT normalisation

This is indeed considered, in guidance issued by the FDA in October 2019, to be an appropriate surrogate endpoint reasonably likely to predict clinical benefit.

The key secondary efficacy endpoint was the proportion of participants with undetectable RNA at week 48. Other secondary efficacy endpoints include the proportion of participants with ALT normalisation at Week 48, the proportion of participants with undetectable HDV RNA 24 weeks and 48 weeks after scheduled end of treatment (sustained virological response), and change from baseline in liver stiffness as measured by elastography. A number of exploratory efficacy endpoints were also assessed (e.g. proportion of participants with HBsAg loss, resistance testing).

Participants were adults over 18 years old, with positive serum anti-HDV antibody or PCR for serum/plasma HDV RNA for at least 6 months before screening and a positive PCR for serum/plasma HDV RNA at screening. They were required to have liver inflammation with ALT level > 1 × upper limit of normal (ULN), but less than 10 × ULN. Participants could have a Child-Pugh hepatic insufficiency score up to 6 points (Child-Pugh A). They could not have additional known primary or secondary causes of liver disease, other than hepatitis B and D infection.

Multiple group comparisons for the primary endpoint and the inclusion of a main secondary endpoint were to be handled with a hierarchical testing procedure. All other analyses were considered exploratory, and no adjustment for multiple testing was performed. In analyses using a mixed-effects model for repeated measures (MMRM), missing values were handled by means of built-in maximum-likelihood based methods, under the “missing at random” assumption.

Planned analyses of efficacy endpoints were performed using the full analysis set for the main analysis (FAS, which included all participants either randomised to the delayed treatment group or randomised to BLV and receiving BLV at least once after randomisation, based on the planned treatment). Supportive analysis was performed in the per protocol analysis set (PP, defined as all

participants in the FAS for whom no protocol deviation judged as having an impact on the primary efficacy analysis was reported or identified). All evaluations of safety data were performed on the Safety Analysis Set.

150 patients were randomised, and both demographics and baseline disease characteristics were generally similar among the 3 study groups. The majority of participants were male (57.3%), and the median age was 41.0 years (range: 19 to 62 years). 47.3% of the participants had cirrhosis at the time of enrolment (Child-Pugh Class A with a mean [SD] score of 5.3 [0.4]). All participants except one had HDV Genotype 1 (98.7%). The median (IQR) HDV RNA was 5.26 (1.69) $\log_{10}$ IU/mL. Regarding HBV, genotype was identifiable in 136 participants and Genotype D was the most common overall (84.0%). 90% of participants were HBeAg-negative at baseline. HBV viraemia was low at approx. 1.1 $\log_{10}$ IU/mL. The median (IQR) ALT at baseline was 91.5 (70) U/L. Median (IQR) liver stiffness by elastometry was 11.90 (9.30) kPa.

Before the study, 56% of the patients had previously received interferon therapy. During the first 48 weeks of treatment, 60% of patients received a concomitant HBV medication, which was mainly tenofovir and, in some cases, entecavir.

The proportions of participants who achieved combined response (pEP) at Week 48 of treatment in the FAS were:

Delayed treatment:	2.0% (95% CI: 0.0% to 10.4%), that is 1/51 participants
BLV 2 mg:	44.9% (95% CI: 30.7% to 59.8%), that is 22/49 participants
BLV 10 mg:	48.0% (95% CI: 33.7% to 62.6%), that is 24/50 participants

The differences of responders between each of the BLV treatment groups and the delayed treatment group were statistically significant ($P < 0.0001$).

Results for the pEP indicated that the high BLV 10 mg dose did not lead to an increased combined response. Between weeks 24 and 48, there was an increase in responders for both BLV treatment groups, but half of the subjects did not meet the pEP. Normalisation of ALT levels is regarded as an important goal for chronic HDV/HBV treatment, but the correlation between the evolution of HDV RNA and ALT levels is not straightforward. A subanalysis showed that patients with < 2 $\log_{10}$ reduction in HDV RNA at Week 48 had a significantly lower ALT normalisation than participants with ≥ 2 $\log_{10}$ reduction, 33%, n=9/27 vs 63%, n=60/95. No participant across the treatment groups experienced HBsAg loss or HBsAg seroconversion. Because the study is ongoing, it is currently difficult to determine at which stage a patient can be classified as a non-responder and the treatment potentially stopped for futility. The information for healthcare professionals regarding treatment duration indicates that personalised treatment durations may be considered based on ALT, HDV RNA, HBsAg kinetics, treatment tolerability, and the medical assessment provided by the treating physician.

At week 48 in the FAS, subgroup analysis of the primary efficacy endpoint indicated that, for patients without cirrhosis, the proportion of participants who achieved a combined response was numerically higher for the BLV 2 mg group (53.8%, n=14/26) than the BLV 10 mg group (46.2%, n=12/26). In patients with cirrhosis, the proportion of participants who achieved a combined response was numerically lower for the BLV 2 mg group (34.8%, n=8/23) than the BLV 10 mg group (50.0%, n=12/24). Of note, there was a difference in ALT normalisation at Week 48 in participants without and with cirrhosis (61.5% vs 39.1%), which was not observed in an updated Week 96 interim data analysis provided by the applicant.

The proportions of participants who achieved an HDV RNA decrease by ≥ 2 log_{10} IU/mL from baseline or undetectable HDV RNA at Week 48 were:

Delayed treatment:	3.9% (95% CI: 0.5% to 13.5%), that is 2/51 participants
BLV 2 mg:	71.4% (95% CI: 56.7% to 83.4%), that is 35/49 participants
BLV 10 mg:	76.0% (95% CI: 61.8% to 86.9%), that is 38/50 participants

The proportions of participants who achieved undetectable HDV RNA at Week 48 (Key secondary endpoint) were:

Delayed treatment:	0.0% (95% CI: 0.0% to 10.4%), that is 0/51 participants
BLV 2 mg:	12.2% (95% CI: 4.6% to 24.8%, that is 6/49 participants
BLV 10 mg:	20.0% (95% CI: 10.0% to 33.7%), that is 10/50 participants

Only a small proportion of subjects achieved undetectable HDV levels, and it is not known whether patients who achieved undetectable levels have actually cleared their HDV infection. Deep sequencing of HDV samples up to Week 48 from patients who were non-responders (HDV RNA decline <1 log10 IU/mL, n=6) or experienced virologic breakthrough (2 consecutive increases in HDV RNA of ≥1 log_{10} IU/mL from nadir or 2 consecutive HDV RNA values ≥LLOD if previously <LLOD, n=5) did not reveal mutations leading to a decreased susceptibility to BLV. As well, in vitro assays indicated that BLV EC_{50} values from baseline samples of participants were found to be similar across non-responders, partial responders and responders. Genomic database sequence alignment of the BLV sequence 9-NPGLFFP-15 in the PreS1 region of the HBV genome (crucial for binding to the NTCP receptor) indicated that it is highly conserved among all eight HBV genotypes. As well, BLV showed potent antiviral activity against HDV genotypes 1-8 enveloped with HBV genotypes A-H and a panel of HDV clinical isolates. Overall, host factors, non-compliance and changes in viral reproduction rate may be responsible for fluctuations of the viral load under therapy, independently of resistance development.

The proportions of participants who achieved alanine aminotransferase (ALT) normalisation at Week 48 (secondary efficacy endpoint) were:

Delayed treatment:	11.8% (95% CI: 4.4% to 23.9%), that is 6/51 participants
BLV 2 mg:	51.0% (95% CI: 36.3% to 65.6%, that is 25/49 participants
BLV 10 mg:	56.0% (95% CI: 41.3% to 70.0%), that is 28/50 participants

These results indicate that, independently from reaching an undetectable HDV level, ALT normalisation is significantly more frequently achieved in BLV-treated participants. There was no significant difference at Week 48 between the 2 mg and 10 mg dosing.

The changes from baseline in liver stiffness by Fibroscan (in kPa) at Week 48 (secondary efficacy endpoint) were:

Delayed treatment:	0.88 kPa (95% CI: -0.80, 2.56) in 45 analysed participants
BLV 2 mg:	-3.08 kPa (95% CI: -4.7, -1.46) in 48 analysed participants
BLV 10 mg:	-3.17 kPa (95% CI: -4.9, -1.44) in 42 analysed participants

Reduction of liver inflammation was accompanied by an improvement in liver stiffness parameters at Week 48. The long-term evolution of this outcome will be of paramount importance since, in the short term, the decrease in stiffness can represent more the decline in liver inflammation than the actual improvement of liver fibrosis.

6.4 Safety

Pooled safety data from studies MYR203, MYR204 and MYR301 included a total of 414 adults in the safety analysis set, 324 of whom received at least 1 dose of BLV. For the monotherapy indication, a total of 64 participants and 115 participants received BLV 2 mg and BLV 10 mg, respectively, with 63 participants receiving 48 weeks of 2 mg dosing and 111 participants receiving 48 weeks of 10 mg dosing. Data were analysed both by combined and separated dosage groups. Comparisons were made with patients receiving either no treatment (or delayed treatment, n=51) or PEG-IFNα only (n=39).

Of note, in the clinical studies of BLV, many participants received anti-HBV treatment with tenofovir disoproxil fumarate (TDF) or other nucleoside/nucleotide analogues. The safety profiles of TDF and other anti-HBV nucleosides/nucleotides are well described and, for the purposes of the pooled analyses, regardless of whether BLV was given alone or with TDF or other nucleoside/nucleotide analogues, it was considered as monotherapy for HDV treatment, and this is agreed.

In the combined monotherapy dosing groups (BLV 2 mg and 10 mg), 61.5% of participants experienced AEs considered related to BLV treatment, which was higher than the rate in the BLV + Peg-IFNα group (52.4%). In contrast, higher percentages of participants experienced AEs considered related to Peg-IFNα treatment: 87.2% of participants in the Peg-IFNα group and 97.2% of participants in the BLV + Peg-IFNα group. A similar percentage of participants experienced AEs considered related to BLV treatment in the BLV 2 mg (59.4%) and BLV 10 mg group (62.6%).

In the combined monotherapy dosing groups, the proportion of participants experiencing a Grade 3 or higher AE was 11.2%. This was higher than in the control group (5.9%), and markedly lower than the rates of Grade 3 or higher AEs in the Peg-IFNα monotherapy and BLV + Peg-IFNα groups (51.3% and 56.6%, respectively). Overall, 10.9% participants in the BLV 2 mg group experienced a Grade 3 or higher AE, which was similar to the 11.3% rate in the BLV 10 mg group. Of these, Grade 3 or higher AEs considered as related to BLV were 3.1% and 4.3% in the BLV 2 mg and 10 mg groups, respectively. Across all treatment groups, SAEs were infrequently reported. Two participants (one case of asthenia/depression, one case of foot fracture) in the BLV 2 mg group and 2 participants (one case of COVID-19 pneumonia, one case of urinary tract infection) in the BLV 10 mg group had an SAE during the 48-week assessment period.

A total of 2 participants experienced an AE leading to premature discontinuation of BLV, neither of whom were in the BLV 2 mg or 10 mg groups. One participant in the BLV 10 mg + Peg-IFNα group experienced a Grade 3 SAE of drug-induced liver injury (assessed as related to Peg-IFNα) and 1 participant in the BLV 2 mg + Peg-IFNα group had a Grade 5 SAE of anaplastic astrocytoma.

Up to the data cutoff, no deaths occurred in the BLV development programme while on study. One death due to an anaplastic astrocytoma reported for a participant from Study MYR204 receiving BLV 2 mg + Peg-IFNα whose treatment had been discontinued was not considered related to the study drug.

The rates of headache were higher in the BLV monotherapy groups (BLV 2 mg, 15.6%; BLV 10 mg, 16.5%) relative to the control group where no participants reported this AE. All events of headache were reported as nonserious and all were mild or moderate in severity.

The rates of pruritus were higher in the BLV monotherapy groups (BLV 2 mg, 10.9%; BLV 10 mg, 9.6%) than in the control group where no participants reported this AE. All events of pruritus were reported as non-serious and the majority were of mild intensity. While pruritus could be expected to be associated with increased bile salt levels in BLV-treated participants, there was no difference in reported rates of pruritus when observations were stratified by bile salt levels. The mechanism behind pruritus observed with BLV treatment is unknown.

Plasmatic bile salt elevations are mechanistically linked to BLV binding to the NTCP receptor, which is how it blocks entry of HDV into hepatocytes, since NTCP is primarily responsible for the recycling and uptake of bile acids. Therefore, increased bile salts is an expected outcome in participants treated with BLV. In the combined dosing groups, 17.9% (32 of 179) of participants in the BLV monotherapy group had an AE of total bile acids increased. Incidences of AE were comparable when BLV was dosed at 2 mg and 10 mg, indicating no dose dependency. No instances of total bile acids increased were reported in the control group. Of the 32 reported AEs of total bile acids increased in the BLV monotherapy group, only 2 were Grade 3 and none were Grade 4. The duration of bile salt elevation lasted as long as participants were receiving BLV therapy, and normalised once BLV treatment was discontinued.

BLV was injected subcutaneously, and 15.6% in the BLV 2 mg group experienced injection site reactions, which was less than the 20.0% in the BLV 10 mg group (likely due to the higher injection burden of 2 vs. 1). None were above Grade 2 and, for the 2 mg dosing, the median (Q1, Q3) duration of the injection site reactions was 9 (2, 42) days.

Some AEs with incidences < 10% were observed more frequently in the BLV monotherapy group than in the control group. These were dizziness (BLV monotherapy 5.6%, control 0%), fatigue (BLV monotherapy 7.8%, control 2.0%), nausea (BLV monotherapy 6.7%, control 3.9%) asthenia (BLV monotherapy 5.0%, control 0%), eosinophilia (BLV monotherapy 6.1%, control 0%). The incidences of these were lower in the BLV 2 mg group compared with the BLV 10 mg group, except for eosinophilia (9.4% vs 4.3%). The vast majority (approx. 85%) of eosinophilia cases were mild (<1.5 G/l absolute eosinophils) with a minority (approx. 15%) of cases categorised as moderate (>1.5 – 5 G/l absolute eosinophils). None were severe (>5 G/l absolute eosinophils). The majority of cases were single observations and counts normalised while on BLV treatment. Eosinophilia was not associated with drug-induced liver disease (DILI).

There are concerns about the risk of hepatitis exacerbation during treatment or after drug discontinuation. The applicant reviewed SAEs indicative of this in the week 48 integrated summary of safety and in all prior studies involving BLV use. It must be taken into account that most participants from ongoing Studies MYR204 and MYR301 are continuing on treatment at the Week 48 interim cut-off and therefore no data are available for these patients.

In MYR203, MYR204 and MYR301, the applicant identified a number of potential on-treatment hepatic flares that were slightly higher in the BLV monotherapy groups (BLV 2 mg, 17.2%, BLV 10 mg, 15.7%) than in the control group (7.8%). The review of narratives indicated that 3 patients exhibited hepatitis flares with ALT > 5 x ULN that were not related to BLV therapy, but rather due to fluctuations in liver function tests during the course of the disease. Post-treatment events potentially associated with hepatic exacerbations in study MYR202 for the BLV 2 mg, 5 mg and 10 mg treatment groups were 14.3%, 25.8% and 34.5%, respectively, which was higher than the incidence in the TDF-only group (16.0%). In Study MYR203, these were 57.1% and 7.1% for the BLV 2 mg and 10 mg groups, respectively. There were a number of cases of hepatic flares with > 5 x the ULN after treatment completion in studies MYR202 and MYR203. Focusing on the BLV 2 mg dosing groups (n=28 in MYR202, n=14 in MYR203 for a total of 42 subjects), these flares with ALT >5 x ULN, in MYR202, occurred in 2/28 (7.1%) of subjects and, in MYR203, in 4/14 (28.5%) of subjects. Among these patients, there were no cases of liver decompensation. Flares usually correlated with rebounds in HDV and HBV viraemia.

The development of ADAs against BLV was evaluated throughout the clinical programme. At week 48, in the BLV 2 mg group 28.1% of the evaluable participants were positive for ADA prevalence (4.7% were positive for ADA at baseline). Analyses of AEs, combined response, viral response and ALT normalisation are limited by low numbers, but do not show a deleterious effect of ADA on treatment safety or efficacy.
Overall, the safety profile was not influenced by age, sex, race or the presence of cirrhosis.

6.5 Final clinical benefit risk assessment

Chronic hepatitis D caused by HDV/HBV co-infection is a debilitating liver disease. Compared with HBV monoinfection, chronic HBV/HDV hepatitis has an accelerated clinical course with a relative risk of cirrhosis, liver decompensation and hepatocellular carcinoma that is approximately three times higher. Treatment options for HDV are limited and essentially consist of weekly PEG IFN-α injections for 48 weeks with partial efficacy (30-40%), late relapses and significant side effects.

The PK of BLV has been characterised in healthy subjects as well as the intended patient population. The available data indicate a complex, non-linear PK with respect to dose and time. TMDD likely explains the more than dose-proportional increase in exposure. In addition, BLV accumulates with multiple dosing, but the underlying mechanism remains poorly understood. No dose adjustment based on demographic factors is required. However, lack of data in subjects with moderate and severe renal or hepatic impairment currently prevents use in these subpopulations. Additional studies in these subpopulations are ongoing (post authorisation requirements). Overall, BLV has a low potential for DDIs, but currently there remains uncertainty with respect to potential interaction effect on CYP3A4 or OATP1B transporters. However, these uncertainties could be addressed by cautionary wording in the information for healthcare professionals.

In a Phase 3 study, BLV daily subcutaneous injections at a dose of 2 mg were shown to result in a significant ≥ 2 $\log_{10}$ reduction in HDV viral load in 44.9% of participants at week 48, associated with normalisation of ALT (combined response primary endpoint). Liver elastometry results showed an improvement in stiffness parameters at the same timepoint.

There are a number of unknowns regarding the optimal place of BLV in the therapeutic armamentarium. Firstly, the optimal duration and long-term efficacy of BLV monotherapy is unknown. A finite duration of BLV monotherapy does not appear to be an attractive option, as very few patients remain relapse-free off treatment, so patients may require long-term BLV therapy. In this respect, it is not yet known what the treating physician should do after a certain period of treatment if no biological or clinical benefit is observed. Interestingly, results from the Phase 2 study MYR203 suggest that BLV + PEG IFNα combination treatment may provide the best response (in terms of HDV RNA below the limit of detection, ALT normalisation, HBsAg response). This is particularly important as prolonged off-treatment HDV RNA responses are only observed in patients who achieve an HBsAg response. Therefore, for patients eligible for PEG-IFNα treatment, a curative approach (i.e. a sustained viral response at 6 months off-therapy) with a finite duration of combination treatment is an attractive option, on which the results of an ongoing study (MYR204) may provide more information.

Second, it is agreed that it is currently reasonable to base approval of HDV therapies on a surrogate endpoint that is reasonably predictive of clinical benefit, and the combined response assessed as the primary efficacy endpoint is consistent with both FDA and EASL/AASLD guidelines. However, it should be noted that the ≥ 2 $\log_{10}$ reduction does not take into account the baseline level of HDV RNA and therefore does not distinguish between an undetectable viral load (as would occur with cure) and a reduction that may persist at high viral load levels. The correlation of clinical benefit with the level of HDV RNA load is not known, and ALT normalisation may be a more important parameter. An ideal biological endpoint of chronic hepatitis D treatment might be the loss of HBsAg (i.e. similar to functional HBV cure), as it better correlates with the perspective of event-free survival, or alternatively the clearance of HDV. In this regard, BLV monotherapy did not affect HBsAg levels. Subsequent confirmation of the surrogate endpoint by demonstrating an improvement in clinical outcomes (reduction in fibrosis/cirrhosis progression, decompensated liver disease, liver transplantation, hepatocellular carcinoma, liver-related death) over long-term follow-up remains crucial.

BLV has been well tolerated in clinical trials and the safety profile is reassuring. The majority of adverse events were mild. There is a clear dose-related increase in bile acid levels which returned to

baseline levels when BLV was stopped. No clinical symptoms were associated with this increase, but the long-term safety of elevated bile acid levels is unknown. There is no evidence of the development of treatment-emergent resistance. As BLV is administered daily by subcutaneous injection, there may be concerns about long-term adherence and patient discontinuation. Significant liver flares following treatment interruptions have not been observed in the clinical programme.

BLV reduces HDV viraemia and normalises ALT levels in nearly 44.9% of compensated chronic hepatitis D patients on treatment at week 48, which may improve long-term prognosis. Questions remain regarding the exact strategy of antiviral treatment, in particular the duration of treatment and the combination of BLV with PEG-IFNα. The benefit/risk of BLV for the requested indication is considered positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Hepcludex was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

HEPCLUDEX®

Composition

Active substances

Bulevirtide as bulevirtide acetate

Excipients

Sodium carbonate anhydrous, sodium hydrogen carbonate, mannitol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment).

One 2.0 mg single-dose vial of Hepcludex contains 0.63 mg sodium.

Pharmaceutical form and active substance quantity per unit

Sterile, preservative-free, white to off-white lyophilized powder that is to be reconstituted with 1 mL of sterile water for injection prior to administration by subcutaneous injection. Each vial contains 2 mg bulevirtide. Following reconstitution, each vial contains 2 mg/mL of bulevirtide solution.
The administered dose of bulevirtide is 1.7 mg due to the solution hold up in the syringe and the needle.

Indications/Uses

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in adults with compensated liver disease.

Dosage/Administration

Therapy should be initiated by a physician experienced in the management of patients with HDV infection.
In all patients, manage the underlying hepatitis B virus (HBV) infection simultaneously as clinically appropriate according to the official guidelines.

Recommended Dosage

The recommended dosage in adults is Hepcludex 2 mg once daily corresponding to a delivered dose of 1.7 mg administered by subcutaneous injection.

Duration of treatment

The optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit. Long-term treatment may be considered with the duration of treatment being

individualized based on the kinetics of ALT, HDV-RNA and HBsAg, the tolerability of the treatment and the medical assessment by the treating physician.
Consideration to discontinue the treatment should be given in case of sustained (6 months) HBsAg seroconversion.

Mode of administration

For subcutaneous use only. Hepcludex may be administered into upper thigh or lower abdomen.

Healthcare professionals should train patients in the proper technique for reconstituting Hepcludex with sterile water for injection and self-administering subcutaneous injections using a syringe.

Please see “Other Information” for instructions on reconstitution of Hepcludex before administration and the package leaflet including Instructions for Use for details on the preparation and administration of Hepcludex.

Missed dose

If a dose is missed, that dose should be taken as soon as possible on that day. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

Special dosage instructions

Patients with hepatic disorders

No dosage adjustment of Hepcludex is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of Hepcludex in patients with Child-Pugh B or C hepatic impairment or patients with decompensated liver disease have not been evaluated (see “Pharmacokinetics”).

Patients with renal disorders

No dosage adjustment of Hepcludex is required in patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 and < 90 mL/min). The safety and efficacy of Hepcludex in patients with CrCl < 60 mL/min have not been evaluated (see “Pharmacokinetics”).

Elderly patients

No data are available on which to make a dose recommendation for patients over the age of 65 years (see “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of Hepcludex in patients under 18 years of age have not been evaluated.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Exacerbation of hepatitis after discontinuation of treatment

Severe acute exacerbations of HDV and HBV infection may occur after Hepcludex is discontinued. Monitor hepatic function closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Hepcludex. In certain circumstances, resumption of antiviral therapy may be warranted.

HDV and HBV genotype

HDV genotype 1 was largely predominant in the clinical trial population. It is not known whether HDV or HBV genotype affects the clinical efficacy of Hepcludex.

Co-infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV)

No data are available from HIV or HCV co-infected patients.

Decompensated liver disease

The pharmacokinetics, safety and efficacy of Hepcludex in patients with decompensated cirrhosis have not been established. The use in patients with decompensated liver disease is not recommended.

Co-infection with HBV

The underlying HBV infection should be simultaneously managed according to current treatment guidelines. Close monitoring of HBV DNA levels is recommended.

Excipients

A 2 mg Hepcludex vial contains less than 1 mmol of sodium (23 mg) per injection, which means it is almost “sodium-free”.

Interactions

Effect of other agents on bulevirtide

Concomitant use not recommended

NTCP inhibitors

In vitro, it has been shown that certain medicinal products can inhibit the therapeutic target molecule of bulevirtide, the sodium taurocholate co-transporting polypeptide (NTCP). The co-administration of such medicinal products (e.g. sulfasalazine, irbesartan, ezetimibe, ritonavir, and ciclosporine A) is not recommended.

Effect of bulevirtide on other agents

Caution with simultaneous intake

OATP1B1/3 und NTCP substrates

In vitro bulevirtide inhibited the organic anion transporting polypeptides, OATP1B1 and OATP1B3, with IC_{50} values of 0.5 and 8.7 µM, respectively. A clinical drug drug interaction (DDI) study of bulevirtide (administered at 5 mg twice daily) showed a 1.34 fold increase of C_{max} and AUC of the OATP1B1/3 and NTCP substrate, pravastatin (40 mg single dose). Based on bulevirtide exposures at the recommended 2 mg dose, the risk for clinically relevant interactions with OATP1B1/OATP1B3 and/or NTCP substrates is considered to be low.
However, use with caution if OATP1B1/OATP1B3 and/or NTCP substrates (eg. estrone-3-sulfate, fluvastatin, atorvastatin, pitavastatin, pravastatin, rosuvastatin, thyroid hormones, bosentan, docetaxel, fexofenadine, glecaprevir, glyburide (glibenclamide), grazoprevir, nateglinide, paclitaxel, repaglinide, simvastatin, olmesartan, telmisartan, valsartan and voxilaprevir) are administered in combination with bulevirtide.

CYP3A4 substrates

In clinical DDI studies, no strongly pronounced interaction effects of bulevirtide on the clearance of the CYP3A4 substrate midazolam were observed; however, weak interaction effects of bulevirtide on CYP3A4 substrates cannot be ruled out. As such, close monitoring is recommended as a precautionary measure if sensitive CYP3A4 substrates with a narrow therapeutic index (eg. cyclosporine, carbamazepine, sirolimus and tacrolimus) are administered in combination with bulevirtide.

Other interactions

In vitro studies have shown that no clinically relevant interactions are expected for the most common efflux transporters (MDR1, BCRP, BSEP, MATE1 and MATE2K) and uptake transporters (OATP2B1, OAT1, OAT3, OCT1 and OCT2).
In vitro studies have shown that bulevirtide does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. No *in vitro* induction of CYP1A2, CYP2B6 or CYP3A4 by bulevirtide was observed.
In a clinical pharmacokinetic drug interaction study in healthy volunteers, there was no significant effect of bulevirtide on the pharmacokinetics of tenofovir disoproxil fumarate (TDF), a potential concomitant medication for the treatment of HBV infection.

Pregnancy, lactation

Women of childbearing potential/Pregnancy

There are no or limited amount of data from the use of bulevirtide in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section “Preclinical data”).

As a precautious measure, it is preferable to avoid the use of bulevirtide during pregnancy and in women of child-bearing potential not using contraception.

Lactation

It is unknown whether bulevirtide is excreted in human milk. However, due to its high protein binding, bulevirtide is not likely to be secreted in milk. A decision must be made whether to breastfeed/discontinue breastfeeding or to discontinue / abstain from treatment with bulevirtide, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of bulevirtide on fertility are available. In animal studies, no effects of bulevirtide on male or female mating and fertility were noted (see section “Preclinical data”).

Effects on ability to drive and use machines

No studies on the effects of Hepcludex on the ability to drive and use machines have been performed. Inform patients that dizziness has been reported during treatment with Hepcludex.

Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on pooled data from 64 patients with HDV who received 48 weeks of treatment with Hepcludex 2 mg in a Phase 2 study (MYR203) and a Phase 3 study (MYR301), 28 patients with HDV who received 24 weeks of treatment with Hepcludex 2 mg in a Phase 2 study (MYR202), and from post-marketing experience.

List of adverse reactions

A tabulated list of adverse reactions is presented in Table 1. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and not known (frequency cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions

Frequency[a]	Adverse reaction
Blood and lymphatic system disorders	
Common	eosinophilia
Immune system disorders	
Not known	hypersensitivity, including anaphylactic reaction[b]
Nervous system disorders	
Very Common	headache (15,6%)
Common	dizziness
Gastrointestinal disorders	
Common	nausea
Hepatobiliary disorders	
Very Common	total bile salts increased (20,3%)
Skin and subcutaneous tissue disorders	
Very common	pruritus (10,9%)
General disorders and administration site conditions	
Very Common	injection site reactions (15,6%)[c]
Common	fatigue

a Frequency based on all patients receiving bulevirtide 2 mg (with or without a nucleoside/nucleotide analog for HBV treatment) through Week 48 in the MYR203 and MYR301 clinical studies .

b Adverse reaction identified through post-marketing surveillance.

c Includes injection site erythema, injection site reaction, injection site pruritus, injection site hematoma, injection site swelling, injection site pain, injection site induration and injection site rash.

Description of specific adverse reactions and additional information

Eosinophil Count Increased

Increases in eosinophil counts were commonly observed in patients receiving Hepcludex 2 mg; there were no associated clinical sequelae, hepatic adverse reactions or significant liver-related laboratory abnormalities.

Total Bile Salts Increased

Asymptomatic bile salt elevations, associated with the mechanism of action of Hepcludex, were reported as adverse events very commonly in 20.3% of patients in clinical studies of Hepcludex 2 mg; the bile salt elevations resolved upon discontinuation of Hepcludex.

Due to renal excretion of bile salts, elevation of bile salts may be greater in patients with renal impairment.

As there are only limited data available on the long-term use of Hepcludex, the long-term consequences of bile salt elevations induced by Hepcludex in humans are unknown.

Immunogenicity

Hepcludex has the potential to induce antidrug antibodies (ADA), as detected in clinical studies using an enzyme-linked immunosorbent assay (ELISA). In studies MYR203 and MYR301, a total of 64 patients who were treated with Hepcludex 2 mg monotherapy for 48 weeks were eligible for assessment of ADA prevalence; 18 of these patients (28.1%) were positive for ADA prevalence, of which 3 patients (4.7%) were positive for ADA at baseline. There is no evidence that the safety or effectiveness of Hepcludex were altered in these patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There are no data on human overdose with bulevirtide. If overdose occurs, the patient must be monitored for evidence of toxicity and given standard supportive treatment as necessary.

Properties/Effects

ATC code

J05AX28

Mechanism of action

Bulevirtide is a 47-amino acid, N-terminally myristoylated, HBV-L-protein derived, syntheticlipopeptide. Bulevirtide blocks the entry of HBV and HDV into hepatocytes by binding to and inactivating the essential HBV and HDV entry receptor NTCP.

Pharmacodynamics

Antiviral activity in cell culture

Bulevirtide potently inhibited HDV infection in all the combinations of HBV and HDV genotypes tested in a primary human hepatocytes infectious system. The mean bulevirtide EC_{50} values ranged from 0.26 to 0.64 nM across HDV-1 to HDV-8 and from 0.21 to 0.68 nM for HDV carrying envelopes across HBV genotype A-H. Similarly, the mean bulevirtide EC_{50} values against HDV-1 viruses pseudotyped with multiple strains of HBV genotype A-D were 0.57 nM (genotype A), 0.59 nM (genotype B), 0.43 nM (genotype C), and 0.33 nM (genotype D). For 137 clinical isolates, bulevirtide had mean EC_{50} values of 0.40 nM, 0.45 nM, and 0.70 nM against HDV-1, HDV-5 and HDV-6, respectively. The mean EC_{50} values were 0.58 nM, 0.38 nM and 0.45 nM against HDV clinical isolates carrying the envelopes from HBV genotype A, genotype D and genotype E, respectively.

Resistance

In Clinical Studies

In Study MYR301, resistance analysis was performed on 6 patients at Week 24 and 9 patients at Week 48 in the bulevirtide 2 mg group who experienced virologic breakthrough (2 consecutive increases in HDV RNA of ≥ 1 $\log_{10}$ IU/mL from nadir or 2 or more consecutive positive (target detected) HDV RNA values if previously HDV RNA was undetectable (target not detected) at 2 or more consecutive time points; 4 patients at Week 48) or HDV RNA decline < 1 $\log_{10}$ IU/mL (6 patients

at Week 24 and 5 patients at Week 48). In Study MYR202, resistance analysis was performed on 5 patients in the bulevirtide 2 mg group who experienced virologic breakthrough (a single patient) or HDV RNA decline < 1 log_{10} IU/mL (4 patients) at Week 24. No amino acid substitutions tested at HBV bulevirtide sequence positions or HDV HDAg associated with reduced susceptibility to Hepcludex were identified in these isolates from any of these patients at baseline, Week 24 and Week 48. All substitutions tested remained susceptible to bulevirtide *in vitro*. No resistance to Hepcludex was observed.

Clinical efficacy

The efficacy and safety of Hepcludex 2 mg once daily in the treatment of adults with chronic hepatitis D and compensated liver disease is based on data through 48 weeks of treatment from one randomised, open-label Phase 3 study, Study MYR301 (N=150) and from data through 24 weeks and 48 weeks of treatment from two randomised open-label Phase 2 studies, Study MYR202 (N=118) and Study MYR203 (N=90), respectively. Additional data at 24 weeks of follow up (corresponding to Week 72) are provided for Study MYR203. A total of 92 patients in Studies MYR301, MYR202 and MYR203 received Hepcludex 2 mg once daily.

Across Studies MYR301, MYR202 and MYR203, combined response was defined as undetectable HDV RNA or decrease in HDV RNA by ≥ 2 log_{10} IU/mL from baseline and ALT normalisation. Undetectable HDV RNA was defined as < lower limit of quantification [LLOQ] (target not detected) in Study MYR301; and < limit of detection [LOD], where LOD was 14 and 10 IU/mL in Studies MYR202 and MYR203, respectively.

Study MYR301

In Study MYR301, 100 of 150 patients with chronic HDV infection were randomised to receive immediate treatment with once daily Hepcludex 2 mg (N=49) or to have treatment delayed for 48 weeks (N=51). Randomisation was stratified by the presence or absence of compensated cirrhosis.

Of the 49 patients in the immediate treatment group, mean age was 44 years; 61% were male, 84% were White and 16% were Asian. Of the 51 patients in the delayed treatment group, mean age was 41 years; 51% were male, 78% were White and 22% were Asian. All patients had infection with HDV genotype 1. Baseline characteristics were balanced among the immediate and delayed treatment groups. Of the patients in the immediate treatment group, at baseline, mean plasma HDV RNA was 5.1 log_{10} IU/mL, mean ALT was 108 U/L, 47% of patients had a history of cirrhosis and 53% were interferon experienced. Patients were treated according to the standard care for their underlying HBV infection: the most common concomitant medications were TDF-containing or tenofovir alafenamide-containing products (49%) and entecavir (14%).

Table 2 presents the virologic and biochemical outcomes for immediate treatment with Hepcludex 2 mg once daily and delayed treatment at Week 24 and Week 48.

Table 2: Study MYR301: HDV RNA (virologic) and ALT (biochemical) outcomes at Week 24[a,b] and Week 48[b] in patients with chronic HDV infection and compensated liver disease (Full Analysis Set)

	Week 24		Week 48	
	Hepcludex 2 mg (Immediate Treatment) (N=49)	Delayed Treatment (N=51)	Hepcludex 2 mg (Immediate Treatment) (N=49)	Delayed Treatment (N=51)
Undetectable[c] HDV RNA or decrease in HDV RNA by ≥ 2 log_{10} IU/mL and ALT normalisation[d]	37%[e]	0%	45%[e]	2%
Undetectable[c] HDV RNA or decrease in HDV RNA by ≥ 2 log_{10} IU/mL	55%[f]	4%	71%[f]	4%
ALT normalisation[d]	53%[f]	6%	51%[f]	12%

a Interim results.
b For the first endpoint, for missing values, the last observation carrying forward (LOCF) was used if COVID-19 related; otherwise, missing = failure; for the second and third endpoints, missing = failure.
c < lower limit of quantification [LLOQ], target not detected.
d Defined as an ALT value within the normal range: Russian sites, ≤ 31 U/L for females and ≤ 41 U/L for males; all other sites, ≤ 34 U/L for females and ≤ 49 U/L for males.
e p-value < 0.0001.
f Nominal p-value < 0.0001.

Study MYR202

In Study MYR202, 56 of 118 patients with chronic HDV infection and ongoing viral replication who were interferon experienced, had a contraindication to interferon or were cirrhotic, were randomised to receive Hepcludex 2 mg + TDF (N=28) or TDF alone (N=28) for 24 weeks. At Week 24, 21% of patients in the Hepcludex 2 mg + TDF group achieved a combined response, 54% achieved undetectable HDV RNA or decrease by ≥ 2 log_{10} IU/mL, and 43% achieved ALT normalization. At Week 24, no patients in the TDF group achieved a combined response, 4% achieved undetectable HDV RNA or decrease in HDV RNA by ≥ 2 log_{10} IU/mL, and 7% achieved ALT normalisation (normal ALT was defined as ≤ 31 U/L for females and ≤ 41 U/L for males).

Study MYR203

In Study MYR203, 15 of 90 patients with chronic HDV infection were randomised to receive once daily Hepcludex 2 mg for 48 weeks. The primary efficacy endpoint was defined as the proportion of patients with undetectable HDV RNA at Week 72 (end of the 24-week treatment-free follow-up period). At Weeks 24 and 48, respectively, 33% and 53% of patients achieved a combined response;

47% and 60% achieved undetectable HDV RNA or decrease in HDV RNA by ≥ 2 log_{10} IU/mL; and 64% and 73% achieved ALT normalisation (normal ALT was defined as ≤ 31 U/L for females and ≤ 41 U/L for males). At Week 72, one patient (7%) who had received Hepcludex 2 mg achieved the primary endpoint of undetectable HDV RNA; an additional 4 patients (27%) achieved decrease in HDV RNA by ≥ 2 log_{10} IU/mL. Three patients who had received Hepcludex 2 mg achieved ALT normalization and combined response at Week 72.

Pharmacokinetics

Pharmacokinetic Properties

The pharmacokinetic (PK) properties of bulevirtide were characterised after intravenous and subcutaneous administration. The exposure of bulevirtide increased in a more than proportional manner with increasing doses (dose range: 100 mcg to 20 mg intravenous; 800 mcg to 10 mg subcutaneous). Following 14 days of dosing, accumulation ratios for the recommended 2 mg dose for C_{max} and AUC_{0-24h} were approximately 2-fold. Based on clinical results and population PK analysis, no relationship could be identified between presence of ADA and bulevirtide PK.

The steady state PK parameters of bulevirtide in Study MYR301 (based on population PK analysis) are provided in Table 3.

Table 3: Steady state pharmacokinetic parameters of bulevirtide following subcutaneous administration of Hepcludex 2 mg in HDV-Infected Adults[a]

Parameter[b]	Bulevirtide
Cmax (ng/mL)	24 (20-30)
AUC0-24h (ng•h/mL)	261 (216-315)

a From Population PK analysis exposure estimates of MYR301 study participants, N = 49.
b Values refer to geometric mean (90% confidence interval).

Absorption

After subcutaneous injection, bulevirtide reached maximum plasma concentrations between 0.5 and 3 hours.

The absolute bioavailability of 2 mg bulevirtide after subcutaneous injection has not been estimated. Bioavailability following subcutaneous doses of 5 mg and 10 mg is estimated to be 48% and 57%, respectively. As bulevirtide demonstrates non-linear PK, extrapolation of bioavailability at other dose levels should be done with caution.

Distribution

In vitro protein binding is high with > 99.9% of bulevirtide bound to plasma proteins.

Following multiple dosing with bulevirtide 2 mg subcutaneous injection, the mean apparent volume of distribution was estimated to be 133 L in Study MYR203.

Metabolism

No biotransformation study was performed for bulevirtide. Bulevirtide is a linear peptide consisting of L-amino acids, and it is expected to be catabolized by peptidases to amino acids. No active metabolites are expected.

Elimination

No bulevirtide excretion into urine was detected in healthy volunteers. Following multiple dosing with bulevirtide 2 mg subcutaneous injection, total mean apparent systemic clearance was estimated at 12.8 L/h in Study MYR203. After reaching peak concentrations, plasma levels declined with $t_{1/2}$ of 3-7 hours.

Kinetics in specific patient groups

Age, gender, and race

Based on population PK modelling, age (years; median [min, max]: 39.0 [18.0, 65.0]), gender (n, male=277; female=137, race (n; White=367; Black or African American=9, Asian=37; other=1) or body weight (kg; median [min, max]: 74.3 [39.7, 110]) did not have a clinically relevant impact on the systemic exposure of bulevirtide.

Hepatic impairment

Population PK modeling characterised a 41.5% increase in AUC_{tau} and 38.3% increase in C_{max} in patients with mild hepatic impairment (Child-Pugh A) (n=154) compared to patients with normal liver function (n=230). The pharmacokinetics of bulevirtide have not been evaluated in patients with moderate and severe hepatic impairment (Child-Pugh B and C, respectively) (see “Posology/Administration”).

Renal impairment

In a population PK analysis, mild renal impairment (CrCL ≥ 60 and < 90 mL/min, n = 60) did not significantly affect the pharmacokinetics of bulevirtide. The pharmacokinetics of bulevirtide have not been evaluated in patients with moderate and severe renal impairment (CrCl < 60 mL/min), or in patients with end-stage renal disease, including those on dialysis (see “Posology/Administration”). As bulevirtide is > 99.9% protein bound, dialysis is not expected to alter exposures of bulevirtide.

Elderly patients

The pharmacokinetics of bulevirtide have not been evaluated in the elderly (65 years of age and older).

Children and adolescents

No data is available in patients younger than 18 years of age.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and toxicity to reproduction and development. Carcinogenicity and genotoxicity studies have not been conducted with bulevirtide.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicinal product after the expiry date ("EXP") stated on the pack.

Shelf life after opening

The reconstituted injection preparation is not preserved. After reconstitution, chemical and physical in-use stability has been demonstrated for 2 hours at room temperature (up to 25°C). From a microbiological point of view, it is recommended that the product be used immediately.
Do not reuse or save reconstituted Hepcludex for future use.

Special precautions for storage

Keep out of reach of children.
Store in a refrigerator (2–8°C).
Store in the original packaging in order to protect from light.

Instructions for handling

Dose preparation and administration

Healthcare professionals should train patients in the proper technique for reconstituting Hepcludex with sterile water for injection and self-administering subcutaneous injections using a syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Instruct the patient to read the “Instructions For Use” at the time they receive a prescription for Hepcludex and as needed for ongoing administration of Hepcludex.

Emphasize the following instructions to the patient:

- Hepcludex must be stored in the refrigerator prior to preparation and administration.
- Hepcludex needs to be reconstituted with sterile water for injection prior to administration.
- The sterile water for injection and syringe and needles for preparation and injection are provided separately from Hepcludex; they should be stored out of the reach of children.
- Hepcludex must be administered by subcutaneous injection. Do not administer by any other route.

Reconstitution Instructions

- Aseptically reconstitute Hepcludex lyophilized powder by adding 1 mL of sterile water for injection to the Hepcludex vial.
- Carefully tap and then roll the vial between the hands to dissolve the powder. Complete dissolution might take up to 3 minutes.
- Completely dissolved Hepcludex should be clear without foam. If the Hepcludex solution appears foamy, allow more time for the powder to dissolve.
- If there are bubbles in the solution, gently tap the vial until they disappear.
- If there are particles in the solution once the powder is (completely) dissolved, do not use that vial of solution.
- Use reconstituted product immediately, however if this is not possible, it can be stored for up to 2 hours at a temperature of up to 25°C. Do not refrigerate.

Administration Instructions

- Administer by subcutaneous injection into the upper thigh or lower abdomen.
- If a dose is missed, that dose should be taken as soon as possible on that day. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.
- Change the injection site with each injection.

Do not reuse the vials, syringe, needles or any remaining sterile water for injection.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Full instructions for use and handling of Hepcludex are provided in the package leaflet (see “Instructions for Use”).

Authorisation number

68338 (Swissmedic)

Packs

Hepcludex, powder for solution for injection: 30 single-dose vials [A]

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug

Date of revision of the text

November 2023