28 May 2020
EMA/326446/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hepcludex

International non-proprietary name: bulevirtide

Procedure No. EMEA/H/C/004854/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Administrative information

Name of the medicinal product:	Hepcludex
Applicant:	MYR GmbH Hessenring 89 61348 Bad Homburg GERMANY
Active substance:	bulevirtide acetate
International Non-proprietary Name:	bulevirtide
Pharmaco-therapeutic group (ATC Code):	direct acting antivirals, (J05AX28)
Therapeutic indication:	Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.
Pharmaceutical form:	Powder for solution for injection
Strength:	2 mg
Route of administration:	Subcutaneous use
Packaging:	vial (glass)
Package size:	30 vials

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List of abbreviations

AAS	Atomic Absorption Spectrometry
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
AP	Applicant's Part (or Open Part) of a ASMF
AS	Active substance
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	Area under the curve
cccDNA	Covalently closed circular DNA
CHB	Chronic Hepatitis B
CHD	Chronic Hepatitis D
CHMP	Committee for Medicinal Products for Human use
CFU	Colony Forming Units
CMA	Conditional Marketing Authorisation
CMC	Critical micelle concentration
CoA	Certificate of Analysis
CPM	Counts per minute
CPP	Critical process parameter
CYP	Cytochrome
DDI	Drug-Drug Interaction
DLS	Dynamic light scattering
EA	elemental analysis
EDQM	European Directorate for the Quality of Medicines
EC	European Commission
ELISA	Enzyme-linked immunoabsorbent assay
EMA	European Medical Agency
EP	European Pharmacopoeia
ESI-MS	Electrospray ionisation-mass spectrometry
EU	European Union
FDA	Food and Drug Administration
GC	Gas Chromatography
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HbeAg	HBV e antigen
HBV L protein	HBV large protein
HbsAg	HBV surface antigen
HDPE	High Density Polyethylene
HDV	Hepatitis D virus
HPLC	High performance liquid chromatography
HPLC-DAD	High performance liquid chromatography- Diode Array detector
HPLC-MS/MS	High-performance liquid chromatography-tandem mass spectrometry
i.v.	Intravenous(ly)
IC50	Inhibitory concentration 50

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared spectroscopy
IU	International Units
IUPAC	International Union of Pure and Applied Chemistry
KF	Karl Fischer titration
LCMS	Liquid chromatography mass spectrometry
LDPE	Low Density Polyethylene
LOD	Limit of detection
LOQ	Lower limit of quantification
LT	Less than
MBHA resin	4-methylbenzhydrylamine resin
mITT	Modified intention to treat
MRT	Mean Residence Time
MS	Mass Spectrometry
NLT	Not less than
NOEL	No-observed-effect level
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NTCP	Sodium Taurocholate Cotransporting Polypeptide
PD	Pharmacodynamic
PDCO	Paediatric Committee
PDE	Permitted Daily Exposure
PEG-IFNα	Pegylated interferon alpha
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PTFE	polytetrafluoroethylene
PVC	Polyvinyl chloride
QWP	Quality Working Party
RH	Relative Humidity
RI	Renal impairment
RIA	Radioimmunoassay
s.c.	Subcutaneous(ly)
SD	Standard deviation
SmPC	Summary of Product Characteristics
TFA	Trifluoroacetic acid
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
UPLC	Ultra high performance liquid chromatography
US	United States of America
USP	United States Pharmacopoeia
UV	Ultraviolet spectrometry
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYR GmbH submitted on 10 October 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Hepcludex, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 May 2017.

Hepcludex, was designated as an orphan medicinal product EU/3/15/1500 on 19/06/2015 in the following condition: *Treatment of hepatitis delta virus infection*

Hepcludex was granted eligibility to PRIME on 18 May 2017 in the following indication: treatment of chronic hepatitis D infection.

Eligibility to PRIME was granted at the time in view of the following:

- Hepatitis delta virus infection remains a major health problem, particularly in low income countries where the diagnosis is suboptimal. There is no specific therapy for hepatitis D and currently treatment is limited to alpha-interferon therapy or nucleos(t)ide analogues.
- In study MYR201, bulevirtide showed antiviral activity in the target population by decreases in viral load of ≥ $1\log_{10}$ from baseline, supporting proof of concept.

The applicant applied for the following indication:

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0296/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0296/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Conditional marketing authorisation and Accelerated assessment

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance bulevirtide contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

PRIME support

Upon granting of eligibility to PRIME, Filip Josephson was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 27 November 2017. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

Manufacturing of the active substance and finished medicinal products, selection of doses in non-clinical studies, plans for pre- and post-natal development toxicology studies, secondary pharmacology studies, rationale for dose selection for phase 3 study, assay for HDV RNA analysis, discussion on treatment strategy, target patient population, choice of endpoints, registry, post-authorisation planning, conditional marketing authorisation submission strategy, paediatric investigation plan.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 June 2015	EMA/CHMP/SAWP/382780/2015/SME/III	Dr Mair Powell and Dr Elmer Schabel
31 May 2018	EMA/CHMPS/SAWP/301457/2018/PA/SME/HTA/PR/III	Prof. Fernando de Andrés Trelles and Dr Filip Josephson

The Protocol assistance pertained to the following aspects:

EMEA/H/SA/3074/1/2015/SME/III:

- Comparability exercise to support manufacturing scale-up
- Adequacy of the manufacturing process description, analytical methods, specifications and stability data
- Release and stability specifications and tests
- The strategy on self-reconstitution and administration by patients
- The non-clinical strategy
- Phase 2 trials in patients with established HBV- HDV-co-infection. After receipt of the list of issues the original plan was amended, and the company proposed one Ph2 trial in combination with TFV and a second Ph2 with PEG-INF
- The use of HDV RNA as endpoint and its correlation with clinical endpoints
- The HDV RNA assay
- The plan for antibody determination
- CMA based on the proposed phase 2 study

EMEA/H/SA/3074/2/2018/PA/SME/HTA/PR/III (included a parallel consultation with HTA bodies):

- The registration strategy for the two new Drug Substance manufacturers
- The use of Phase 2 API and Phase 3 API for the proposed Phase 3 clinical trial?
- Analytical methods and specifications for Drug Substance and drug product
- Omission of a bioassay and use only of HPLC analysis
- The suitability of the device that will be used for reconstitution and administration of the drug product
- The preclinical package for CMA, especially regarding embryofoetal toxicity and lack of carcinogenicity studies
- The design, the selected dose and the country distribution of the study sites for the proposed phase 3 clinical trial
- The strategy of the applicant for investigating viral resistance
- The HDV RNA analysis assay
- The wording of the indication
- Proposed primary endpoint with respect to virological and biochemical response and timing of assessment
- The prevalence of the disease and the scarcity of patient population in Europe
- The plan for additional evidence generation with a patient registry
- The plan to file for a CMA based on phase 2 data and the timing for initiation of the proposed confirmatory phase 3 study
- The safety database
- The plan not to study Hepcludex in children
- The plan to identify potential predictors of response

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Daniela Melchiorri

The application was received by the EMA on	10 October 2019
Accelerated Assessment procedure was agreed-upon by CHMP on	19 September 2019

The procedure started on	31 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	6 January 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	6 January 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	7 January 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 January 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 February 2020
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at one investigator site and the sponsor, both in Russia, took place between 20-31 January 2020. The outcome of the inspection carried out was issued on	13 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	12 March 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	24 March 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 May 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
An *Ad Hoc* Expert Group was convened to address questions raised by the CHMP on The CHMP considered the views of the *Ad Hoc* Expert Group as presented in the minutes of this meeting.	20 May 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	28 May 2020

a conditional marketing authorisation to Hepcludex on	

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

2.1.2. Disease or condition

HDV is a satellite virus of HBV which requires the presence of HBV for its replication. Chronic HBV/HDV infection is associated with an increased risk of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) (Rizzetto 2009, Wedemeyer et al. 2010).

2.1.3. Epidemiology

Worldwide, an estimated 5-10 % of chronic Hepatitis B virus (HBV) carriers are co-infected with Hepatitis delta virus (HDV), corresponding to 10-25 million individuals. Since HDV is an incomplete virus requiring the presence of HBsAg for its life-cycle, the epidemiology of HDV is necessarily linked to HBV epidemiology. In 2015, the HBV prevalence in the European Union (EU) is estimated to be 0.9% corresponding to 4.7 million chronic HBV cases. The applicant's assumption of an HDV co-infection prevalence of 1-2% in the European Hepatitis B patient population results in an estimated range of minimum 6.909 to 20.492 patients with HDV infection.

2.1.4. Clinical presentation and diagnosis

The liver disease associated with HDV runs a more progressive course than chronic hepatitis B (CHB) and may lead to cirrhosis within 2 years in 10–15% of patients (Yurdaydin et al. 2010). Chronic HDV infection is associated with faster progression to fibrosis and cirrhosis, earlier onset of hepatic complications and likelihood of liver transplantation (Niro et al. 2010, Buti et al. 2011, Heidrich et al. 2013). Liver cirrhosis and cancer occur on average earlier in HBV/HDV co-infection and the 5-year mortality of co-infected individuals is twice that of HBV mono-infection (Cornberg et al. 2007). Chronic HDV infection has been described to cause cirrhosis and HCC with annual rates of 4% and 2.7%, respectively (Romeo et al. 2009, Gordien 2015).

2.1.5. Management

Worldwide, no therapeutic regimen or drug is currently approved for the treatment of chronic hepatitis D (CHD). PEG-IFNα is used however, based on limited data, and remains the only available therapeutic option recommended by treatment guidelines (EASL 2017). In CHD patients with ongoing HBV DNA replication therapy with nucleos(t)ide analogue (NA) should be considered (EASL 2017, AASLD 2018). NAs approved for treatment of HBV infection show negligible antiviral effects on HDV since they neither affect HDV replication nor suppress HBsAg production (Wedemeyer et al. 2011).

Current clinical results, however, demonstrate limited efficacy of interferon and are based on a few clinical studies. In general, clinical trials showed sustained virological response in 25-30% of patients treated with PEG-IFNα (Heidrich et al. 2013). Recent trials demonstrated that PEG-IFNα lead to undetectable HDV RNA 24 weeks after therapy in 31% of patients treated for 48 weeks (HIDIT-I) (Wedemeyer et al. 2011) and that even prolonged treatment duration of 96 weeks did not increase response rates (23% of patients in HIDIT-II) (Wedemeyer et al. 2011). Moreover, late relapse occurred in >50% of patients treated with PEG-IFNα (Heidrich et al. 2014).

Additionally, only ~50% of patients are eligible for PEG-IFNα therapy e.g. due to contraindications, intolerabilities or advanced liver disease as demonstrated in the French deltavir cohort where only 52.5% of patients were eligible for treatment (Brichler et al. 2015). Furthermore, it has to be considered that AEs under interferon therapy are frequent and may be severe, so that these side effects result in 10-14% premature withdrawals from therapy (Fried 2002).

In conclusion, current clinical experience indicates that only ~50% of patients are eligible for interferon treatment. 25% thereof achieve a response; ~ 50% of these patient's relapse. Thus, interferon therapy is only helpful for around 10% of patients and the benefit-risk in chronic HDV infection is not established.

Patients with CHD have an unmet medical need.

2.1.6. About the product

Bulevirtide is a 47-amino acid long, N-terminally myristoylated, HBV-L-protein derived lipopeptide that binds specifically to the sodium taurocholate co-transporting polypeptide (NTCP) and blocks HBV and HDV entry. The natural function of NTCP within the enterohepatic circulation is to exert the hepatic re-uptake of conjugated bile salts into the hepatocytes. Due to bulevirtide ability to bind to NTCP an inhibition of the bile salt transport at saturating concentrations is the consequence. The proposed treatment regimen for treatment of patients with CHD is 2 mg bulevirtide per day administered subcutaneously.

2.1.7. Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the lack of approved therapies for HDV infection, and the existence of a subset of patients at risk of progressing to life-threatening liver disease where new treatment options are urgently needed. The applicant has shown, in the MYR202 study, supported by the MYR203 study, that bulevirtide as monotherapy has a promising antiviral effect with apparently generally durable decreases in HDV RNA accompanied by ALT reductions that are expected to provide on-treatment clinical benefit in terms of reducing the rate of progression of liver disease.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as the accelerated assessment timelines could not accommodate the consultation of experts in the context of an *ad hoc* Expert Group meeting, as requested by the CHMP.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data on safety and efficacy through

the MYR301 study. Furthermore, the applicant has proposed a post-marketing cohort study to characterise the frequency of hepatic decompensation, hepatocellular cancer, liver transplantation, liver related- and overall mortality and long-term safety in patients treated with bulevirtide.

- Unmet medical needs will be addressed, as there are presently no approved products for the treatment of HDV, which is associated with a higher rate of disease progression and end-stage liver disease compared to HBV mono-infection.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a lyophilised powder for solution for injection, containing 2 mg per vial bulevirtide (as acetate) as active substance.

Other ingredients are sodium carbonate anhydrous, sodium hydrogen carbonate, mannitol, hydrochloric acid and sodium hydroxide.

The product is available in a colourless glass vial with bromobutyl rubber stopper, sealed with a flip off cap (aluminium with plastic disc).

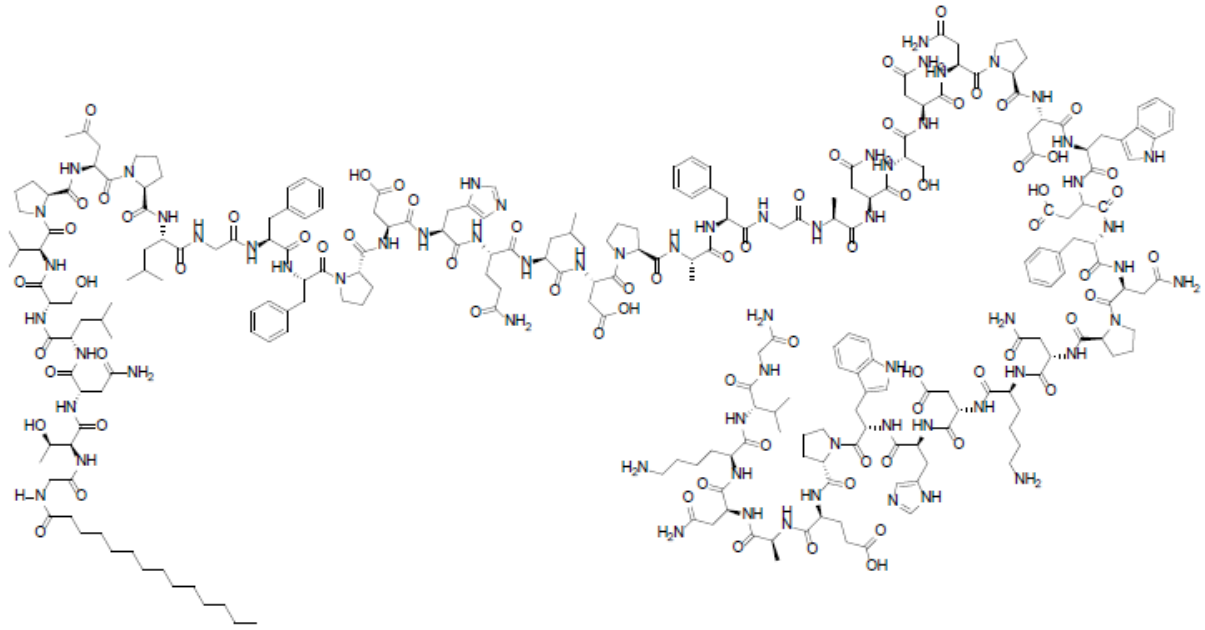
2.2.2. Active Substance

General information

Bulevirtide is a 47-amino acid peptide with a fatty acid, a myristoyl residue, at the N-terminus and an amidated C-terminus. The active substance is available as acetate salt. The counter ion acetate is bound in ionic form to basic groups of the peptide molecule and is present in a non-stoichiometric ratio.

The chemical name of bulevirtide is (N-Myristoyl-glycyl-L-threonyl-L-asparaginyl-L-leucyl-L-seryl-L-valyl-L-prolyl-L-asparaginyl-L-prolyl-L-leucyl-glycyl-L-phenylalanyl-L-phenylalanyl-L-prolyl-L-aspartyl-L-histidyl-L-glutaminyl-L-leucyl-L-aspartyl-L-prolyl-L-alanyl-L-phenylalanyl-glycyl-L-alanyl-L-asparaginyl-L-seryl-L-asparaginyl-L-asparaginyl-Lprolyl-L-aspartyl-L-tryptophanyl-L-aspartyl-L-phenylalanyl-L-asparaginyl-L-prolyl-L-asparaginyl-L-lysyl-L-aspartyl-L-histidyl-L-tryptophanyl-L-prolyl-L-glutamyl-L-alanyl-L-asparaginyl-L-lysyl-L-valylglycinamide, acetate salt. It corresponds to the molecular formula $C_{248}H_{355}N_{65}O_{72}$, its relative molecular mass is 5398.9 g/mol and it has the structure shown in Figure 1.

Figure 1. Structure of bulevirtide



Bulevirtide appears as a white or off-white hygroscopic powder. It is practically insoluble in water and soluble at concentrations of 1 mg/ml in 50% acetic acid and about 7 mg/ml in carbonate buffer solution at pH 8.8, respectively.

The structure of the active substance (AS) was elucidated by a combination of infrared spectroscopy (IR), mass spectrometry (MS), amino acid analysis and sequence analysis

Other characteristics studied included ultraviolet (UV) spectrum, higher order structure (1D- and 2D- nuclear magnetic resonance spectroscopy (NMR)) and aggregation (Dynamic Light Scattering). Neither tertiary structure nor aggregation states of bulevirtide have been identified.

With regard to enantiomeric purity, all amino acids are used in L-configuration except glycine, which is achiral by nature. Two batches of bulevirtide acetate were evaluated for enanatiomeric purity and no relevant change in configuration during synthesis was detected.

Manufacture, characterisation and process controls

Bulevirtide is manufactured by a single manufacturer. It is a chemically synthesised linear peptide containing only naturally occurring amino acids. The manufacturing of this peptide is achieved using standard solid-phase peptide synthesis (SPPS) on a 4-methylbenzhydrylamine resin (MBHA resin) derivatised with Rink amide linker in order to obtain a crude peptide mixture. This crude mixture is purified through a series of washing and preparative chromatography steps. Finally, the purified peptide is freeze-dried prior to final packaging and storage.

The process involves further four main steps: synthesis of the protected peptide on the resin while side-chain functional groups are protected as applicable; cleavage of the peptide from the resin, together with the removal of the side chain protecting groups to obtain the crude peptide; purification; and lyophilisation. Two chromatographic systems are used for purification. No design space is claimed. Resin, Linker Fmoc protected

amino acids and myristic acid are starting materials in line with ICH Q11. Sufficient information is provided on the source and the synthetic route of the starting materials. The active substance is obtained as a non-sterile, lyophilised powder.

All critical steps and parameters were presented and clearly indicated in the description of the manufacturing process. The process description includes also sufficient information on the type of equipment for the SPPS, in-process controls (IPCs). The circumstances under which reprocessing might be performed were clearly presented. No holding times are proposed. Overall the process is sufficiently described.

Manufacturing process development is very brief, but it is acknowledged that SPPS is in itself a standardised procedure and that the properties and characteristics of the input materials are known.
The manufacturing process development history and the process changes have been presented. Comparative data from the three different manufacturers were provided. The impurity profiles indicate that impurity levels are generally equal or lower for active substance manufactured by the proposed manufacturer compared to substance manufactured by the development sites.

A process validation study was conducted at the intended commercial manufacturing facility. The validation results were provided in the dossier although this is not mandatory since the substance is not sterile. Process validation data concerned three commercial scale batches of active substance including a reprocessed batch. Based on the validation results the process parameters were adjusted in line with what was investigated during the process validation studies. The information presented is considered satisfactory.

The active substance is packaged in amber, wide mouth, type III soda-lime glass bottle, closed by a white polypropylene screw cap with a polytetrafluoroethylene (PTFE) liner. Prior to use, the bottles are depyrogenated. The bottles are packed in sealed aluminium composite bags (polyester/aluminium/polyethylene). Compliance with relevant European quality standards are confirmed for the primary packaging, i.e. Ph. Eur. 3.2.1 Glass containers for pharmaceutical use and EU 10/2011.

Specification

Bulevirtide active substance specification includes appropriate tests and limits for appearance (visual), molecular weight (ESI-MS, Ph. Eur.), amino acid analysis (UPLC), appearance of solution (Ph. Eur.), water content (Ph. Eur.), acetic acid (HPLC), trifluoroacetic acid (HPLC), residual solvents (GC), elemental impurities (Ph. Eur.), related substances (HPLC), bacterial endotoxins (Ph. Eur.), microbial quality (Ph. Eur.) and bulevirtide assay (HPLC).

Impurities are controlled according to the limits for synthetic peptides in Ph. Eur. Substances for pharmaceutical use. The presence of elemental impurities (Class 1 and 2A according to ICH Q3D) were analysed and found to be well below the proposed specification levels. All other proposed specification limits are also acceptable based on guidelines, pharmacopoeial requirements and batch data.

The potential for higher order structure of bulevirtide acetate has been investigated and it was demonstrated that bulevirtide acetate has a linear structure. In the absence of a higher structure peptide, a bioassay is not considered as relevant.

The analytical procedures have been sufficiently described. Non-compendial analytical methods have been successful validated according to ICH guidance. In-house reference standards are used to qualify working standards of active substance and its impurities. Satisfactory certificates of analysis of reference and working standards of active substance and its impurities have been presented.

Batch analysis data was reported for three commercial scale batches, used for process validation. The batches were tested according to the proposed specification. Overall, the results demonstrate that the active substance can be manufactured consistently and meeting the specification limits.

Stability

Stability data on four production scale batches of active substance stored in the intended commercial packaging for up to 12 months under long term conditions -20 ± 5°C and for up to 6 months under accelerated conditions (5 ± 3°C), were provided according to the ICH guidelines. Potential effects of short-term excursions were evaluated in the 6 months study at 5 ± 3°C, also in line with ICH Q1A. Supportive data for 24 months at long term conditions was also included from a batch by one of the manufacturers during the development phase. Samples were tested for appearance, water content, acetic acid content, related substances, assay and microbial quality.

All results are within their respective specification limits, with one exception for the 6 months sampling of one impurity in one batch at accelerated conditions, which has been satisfactorily investigated and explained, thus raising no concern. In addition, there are no trends in the submitted stability data, only some fluctuations are observed.

Regarding photostability, tests were performed on one commercial scale batch according to ICH Q1B. A change in appearance (to slightly brownish and brownish, respectively) and increased amounts of impurities were observed indicating light sensitivity of the active substance.

Based on the outcome of a forced degradation study, it was concluded that bulevirtide is degraded in alkaline solutions, water and oxidative solutions, but less susceptible to degradation in acidic solution. It is noted that for the forced degradation study a different analytical method was used.

Considering the overall stability data, the proposed re-test period of 12 months for the active substance when stored at -20°C ± 5°C is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

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.

The components of the formulation were selected by literature review and knowledge of compositions of similar products available on the market at that time, containing HCl, water, mannitol, sodium carbonate, sodium hydrogen carbonate and sodium hydroxide. All excipients are normally used in the manufacture of lyophilisates. The quality of the excipients complies with their respective Ph. Eur monographs. The intrinsic properties of the active substance and the compounding formulation do not support microbiological growth as demonstrated by the stability data. No additional preservatives are therefore needed.

The final formulation, the target pH and the osmolality were determined. Various buffer solutions were added to the suspension of bulevirtide acetate in water and the resulting solutions were analysed by microscopical evaluation. The solubility of bulevirtide acetate in aqueous solution increases by rising pH values.

The maximal solubility of bulevirtide acetate in the carbonate buffer/mannitol was determined. Thus, the intended concentrations of active substance per vial are below the maximal solubility of bulevirtide acetate in the proposed formulation and in consequence the solubilisation of the active substance in the reconstituted solution for injection is fully guaranteed.

Inorganic salts are used in the formulation for pH adjustment and to maintain the isotonicity of the re-hydrogenated formulation.

The formulation of bulevirtide should be administered subcutaneously. Therefore, the pH should be as neutral as possible (pH 3.5 to pH 9.5) and the solution should be isotonic.; the painless range for the subcutaneous injection is between 225 and 430 mOsmol/kg. The established buffer mixture is within both the pH and he osmolality range suitable for painless subcutaneous use.

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 entire preclinical and clinical development. The active substance and product batches used during development were presented in the dossier.

The results of the compatibility study performed on bulevirtide lyophilised powder for solution for injection 1 mg were presented. As no significant changes occurred, it can be concluded that the lyophilised finished product is compatible with the intended reconstitution solution (water for injection) and that the reconstituted solutions of bulevirtide in the vials are stable for 120 minutes at room temperature. The results are considered representative and indicative for bulevirtide lyophilised powder for solution for injection 2 mg and 5 mg (the latter strength not applied for).

A further in-use stability of a 1 mg/ml solution of bulevirtide acetate in the selected buffer was conducted at different temperatures. The results are considered representative for bulevirtide lyophilised powder for solution for injection 2 mg. In summary, bulevirtide acetate in solution is stable when stored at 4°C up to 96 h and at 25°C up to 24 h. The claim in the SPC 6.3 is that after reconstitution, chemical and physical in-use stability has been demonstrated for at least 2 h at room temperature (up to 25°C). This is a shorter time than the demonstrated stability, however the in-use period of 2 h stated in the SmPC is seen as the applied in-use period and is thus accepted.

An extractable volume determination study was performed as per Ph. Eur. 2.9.17 for lyophilised products. The results indicate that the intended volume can be extracted from the vial after reconstitution.

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 three registration batches of the 2 mg strength. The commercial manufacturing process is identical to the manufacturing process used by the Phase 2 clinical batches manufacturer. Starting from the development's composition, an industrial scale manufacturing process following cGMP regulation and guidelines, using a sterile filtration, aseptic processing and lyophilisation, was developed. Considering that the preparation of bulevirtide solution is a standard process, the manufacturing process development focused on the adequacy of the filter for sterilisation and the process parameters for lyophilisation step. The assessment of impact of the manufacturing site and batch size change has been evaluated through comparison of the manufacturing processes and has been satisfactorily discussed. As a conclusion, no

difference can be noticed between both manufacturing processes, the Phase 2 clinical batches manufacturer and the commercial batches manufacturer. Both processes are considered as equivalent.

The container closure system for Hepcludex consists of a 2R injection colourless 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). The glass vials are washed and depyrogenised, rubber stoppers are autoclaved prior filling, 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. Compliance with Ph. Eur. requirements and European legislation is stated for the primary packaging materials.

Manufacture of the product and process controls

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 regarded to be a non-standard process. A flowchart of the process together with the proposed in-process controls was presented.

Sterilisation of all material and equipment that come into contact with product is done as per standard operation procedure. Equipment for compounding and filling as well as filters is autoclaved. Stoppers are autoclaved and dried directly after sterilisation inside the autoclave in a fractionised vacuum. Vials are washed, sterilised and depyrogenised according to a validated procedure in the hot air sterilisation tunnel.

A 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. No design spaces were claimed for the manufacturing process of the finished product. Overall the proposed control strategy is deemed satisfactory.

Process validation has been performed on three consecutive full production scale batches and the results have been presented. A decrease in assay values observed in two batches has been investigated and justified. The sources of variation for assay value and root causes were identified. After implementation of the corrective actions using the corrected sample preparation method, the results from the re-testing demonstrate, that all values for the process validation batches at release are in the expected range. The process is considered successfully validated and that it is adequately under control in order to consistently obtain a product that complies with the specifications.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), primary packaging material (visual), identification (HPLC-DAD), water content (Ph. Eur.), assay (HPLC-DAD), uniformity of dosage units (Ph. Eur.), related substances (HPLC), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), colour and clarity of solution (Ph. Eur.),osmolality (Ph. Eur.), reconstitution time, visible and subvisible particles (Ph. Eur.) and pH of solution (Ph. Eur.).

The limits for impurities are based on available release and stability data. In addition, the limit for impurities A and C corresponds to the qualification threshold established for peptides obtained by chemical synthesis. The limit for the main impurity is supported by toxicity studies. Referring to the acceptance criteria established for unidentified impurities, these are consistent with the limits recommended in Ph. Eur. monograph "substances for pharmaceutical use" for peptides obtained by chemical synthesis, with an identification threshold at 0.5%.

The assay limits range has been tightened for finished product batches at release and for stability data. In addition, the CHMP requested re-assessment of batch data, once batch release data from additional ten finished product batches with corrected sample preparation method will be available, in order to possibly further tighten the release specification limit for assay. The Applicant committed to this.
The limits for the pH have been justified based on literature and clinical studies tolerability 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 30% threshold of the respective PDE value. Therefore, it is acceptable not to control residual solvents 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 for nitrosamine impurities formation and no risk for 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 three commercial scale batches. The data demonstrate that all parameters are well within their specifications and therefore indicate consistent manufacture of the finished product.

Stability of the product

The stability studies were carried out on three commercial scale batches manufactured at the proposed manufacturing site stored at long term conditions (-20°C) for 12 months and at accelerated conditions (5°C, and 25°C / 60% RH) for 12 months according to the ICH guidelines. The tested batches were packaged in the container closure systems intended for marketing.

Samples were tested for appearance, primary packaging material, identification, water content, assay, related substances, colour and clarity of solution, visible and subvisible particles and pH. No significant changes were observed, and the results are found to be well within the specification limits.

Moreover, supportive stability data for two approximately commercial scale batches of 2 mg and 5 mg strengths (the latter strength not applied for) manufactured by the development manufacturer used in clinical studies covering up to 36 months of storage were presented as supportive data. Details on the stability protocol applied to those batches were presented; samples were tested according to the specifications valid at time of testing and met the acceptance criteria.

An in-use stability study was performed on bulevirtide lyophilised powder for solution for injection after reconstitution, the 2 mg and 5 mg batches (the latter strength not applied for) were manufactured by the proposed manufacturer. The solutions were tested for appearance (clarity and colour of solution), pH, 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 h 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 carton boxes protected from light and stored in a refrigerator at -20° C prior dispensing from the pharmacy; they are subsequently stored in a refrigerator protected from light in the patient´s home, providing additional light protection barrier. In addition, the time in solution after reconstitution has been limited to 2-hour time frame (SmPC 6.3) as discussed above, during which the product maintains its chemical-physical properties.

Based on the overall stability data the proposed shelf-life of 1 years when stored at -20°C and stored in the original package in order to protect from light as described in SmPC sections 6.3 and 6.4 can be accepted. The storage conditions concerning the reconstituted product as stated in SmPC sections 6.3 and 6.4 are also accepted.

Adventitious agents

There are no excipients of human or animal origin used in the manufacture of Hepcludex 2 mg powder for solution for injection.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The manufacturing process for the finished product is non-standard and the required validation data has been provided. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- re-assess batch data, once batch release data from an additional ten finished product batches with corrected sample preparation method is available, in order to possibly tighten the release specification limit for assay and update the information about new batch release data from next production batches, on a regular basis.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Mechanism of action

Bulevirtide is stated to block the entry of HBV and HDV into hepatocytes by binding to and inactivating NTCP (sodium taurocholate co-transporting polypeptide), a transmembrane sodium-dependent uptake transporter expressed on the basolateral (blood-side) membrane of hepatocytes. NTCP is primarily responsible for the recycling and uptake of bile acids but is also a functional receptor for viral (HBV/HDV) entry. It is known from the literature that peptides comprising the first 47 amino acids (HBVpreS/2-48myr) of the preS1 domain of the HBV large (L) surface protein inhibits viral infection *in vitro* and *in vivo*. The full inhibitory functionality of HBVpreS/2-48myr relies on the integrity of the essential amino acid region 9´-NPLGFFP-15´ and the presence of an acylation. Mutation within this essential region (amino acids 11, 12 and 13) or the removal of the myristoylation render HBV particles non-infectious. There was an absence of binding of bulevirtide to cynomolgus monkey hepatocytes which is likely due to an NTCP sequence variation at amino acid 157 to 165 in cynomolgus monkeys. Limited *in vitro* and *in vivo* studies were conducted to pharmacologically characterise bulevirtide.

Primary pharmacology

Bulevirtide is claimed to be a selective and specific inhibitor of NTCP. Binding studies are limited to microscopy and FACS analysis showing that bulevirtide binds to hepatocytes in the selected species. However, no quantitative data regarding, for example, binding specificity, potency or affinity to the NTCP receptor has been provided to allow a comparison of the binding profile of bulevirtide in rats, dogs, rabbits and humans.

In cellular uptake transporter inhibition assays, bulevirtide inhibits human NTCP function *in vitro* in a dose-dependent manner with a maximum inhibition of 90% (IC90) at 5 µM and an IC50 of 0.32 µM, while a maximum inhibition of 99% (IC99) at 5 µM and an IC50 of 0.068 µM were obtained for rat NTCP.

In HBV and HDV *in vitro* infection assays, bulevirtide inhibited the infectivity potential of several HBV genotypes and HDV isolates with IC50 values ranging from 14.5 to 834.0 pM in human hepatic HepaRG cells.

Based on a limited number of published literature studies, inhibition of HDV entry into hepatocytes by bulevirtide (2 mg/kg/day, SC) was demonstrated in a transgenic uPA/SCID mouse model transplanted with human hepatocytes after HDV infection *in vivo*.

Secondary pharmacology

In secondary pharmacodynamic studies *in vitro*, bulevirtide showed no effect on the peripheral blood mononuclear cells (PBMC) metabolism or on their cytokine response (TNFα and IL-6 production) at any of the tested doses (1, 5, 10 and 50 µg/ml,). These data were confirmed *in vivo* in the 4-week repeat-dose toxicity study in rats, where there was no influence on serum cytokine levels (i.e. IL-2, IL-6, IL-10, TNFα and IFN-γ) after bulevirtide treatment (0.25, 1, 2.5 mg/kg/day, SC).

In separate secondary pharmacodynamic studies the effect of bulevirtide on the hepatic stellate cells (HSC) was investigated. A non-specific binding to the primary rat stellate cells was observed independently of the peptide sequence of bulevirtide (i.e. wildtype, mutated or scrambled peptides). *In vitro*, bulevirtide did not show any cytotoxicity in the stellate cells (LDH release and ATP content). Furthermore, in the repeated dose toxicity studies, the administration of bulevirtide to rats did not lead to any immunotoxicities and no bulevirtide-related changes in the liver were observed (see toxicology section, Study 24197). The applicant considers therefore that the non-specific binding of bulevirtide to the HSC is of low relevance. This is agreed.

By blocking the primary target, the NTCP (sodium taurocholate co-transporter polypeptide) receptor, bulevirtide inhibits the transport of bile acids from portal blood to hepatocytes, leading to elevation of serum bile salts, which is commonly observed in both animals and in man. Information on increase of bile salts is provided in section 4.4 and 4.8 of the SmPC document.

Safety pharmacology

In line with ICH S6 (R1), the safety pharmacology studies *in vivo* were incorporated into the toxicology program in studies 23467 (rat) and 24196 (dog). An additional separate study (27084) was performed in rats to address the effect of bulevirtide on the respiratory system. The applicant did not conduct an *in vitro* hERG assay. This is considered acceptable given the nature of the product (a peptide) and a hERG test is thus normally not appropriate for biologics. In addition, there is a lack of cardiovascular safety findings in the CV studies *in vivo* (see below).

In the safety pharmacology studies *in vivo*, which were incorporated in the repeat-dose toxicity studies, there were no bulevirtide-related effects on any CNS parameters (IRWIN screen) in female and male rats at single intravenous dose of 12.5 mg/kg or on cardiovascular functions (ECG in female and male dogs) or respiratory functions (male rats) at doses up to 2.5 mg/kg providing exposure margins of > 15-fold for CV function in dogs and > 6.6- fold for respiratory function in rats compared to clinical C_{max}, respectively.

Pharmacodynamic drug interaction

The applicant provided one non-clinical pharmacodynamics drug interaction study with entecavir, as an example of a coadministration of an approved nucleoside/nucleotide analogue together with bulevirtide. During HDV infection in human hepatic HepaRG cells *in vitro*, entecavir (20 µM) did not affect the inhibitory activity of bulevirtide up to 100 nM. Thus, entecavir had no impact on the antiviral activity of bulevirtide against HDV infection *in vitro*.

Except for the combination study of entecavir and bulevirtide *in vitro*, no formal PD drug interaction study was conducted in animals. This is acceptable.

2.3.2. Pharmacokinetics

A program of absorption, distribution and excretion studies has been carried out with bulevirtide in mice, rats, dogs, cynomolgus monkeys and chimpanzees.

Methods

In pharmacokinetic and toxicity studies, plasma bulevirtide concentrations were measured with HPLC-MS/MS methods. The methods to determine bulevirtide in plasma in rats and rabbits have been validated to fulfil contemporary regulations in compliance with GLP. The method for the determination of bulevirtide in dog plasma, however, was not validated in compliance with GLP.

Liver concentration of bulevirtide was determined by a non-GLP HPLC-MS/MS method. Validity of the method during analysis of study test samples was ensured by assaying quality control (QC) samples with known concentrations of bulevirtide in the liver. The method seems adequate for its purpose.

A competitive radioimmunoassay for the determination of specific antibodies against bulevirtide in plasma samples from animals (and humans) was developed and validated to show the binding capacity of the rabbit antiserum against bulevirtide (09022). The method seems adequate for its purpose.

Absorption

Bulevirtide is rapidly absorbed after subcutaneous administration with maximum plasma concentrations (C_{max}) being reached within 4-6 h. Exposure (AUC) to bulevirtide generally increased in approximate proportion to dose in rats and dogs (0.25-2.5 mg/kg dose). After a single subcutaneous dose, the bioavailability of bulevirtide was large and estimated at 81.44% in rats, consistent with the bioavailability observed in humans. In the entity of conducted studies, no clear trend for gender-related differences in exposure could be identified.

Distribution

The tissue distribution of radiolabelled bulevirtide was examined in several species; mouse, rat, dog, cynomolgus monkey and chimpanzee. Bulevirtide was either labelled at the C-terminus or in the middle of the peptide (amino acid position 23). Radiolabelled bulevirtide was rapidly distributed to the liver in all tested species with exception of the cynomolgus monkey. The maximum radioactivity was observed rapidly following IV administration (about 10 minutes) and more slow following SC administration (around 4 to 6 hours).

Radioactivity signals were also detected in the GI tract and in kidneys/urinary bladder (see excretion). Low levels of radioactivity were also detected in the thyroid gland (mouse, rat and dog), likely representing uptake of free iodine.

In cynomolgus monkeys, no specific liver targeting of bulevirtide-y-^{123}I was observed. Apart from the injection site, the highest radioactivity was observed in the bladder with a peak at 8 hours post dose. In other organs, a rather distribution at all time points was observed. Bulevirtide is highly plasma-protein bound. In dogs, binding to plasma proteins was investigated by size exclusion chromatography. The radioactivity peak of bulevirtide-y-^{123}I overlapped with the main plasma protein peak indicating bulevirtide binding. *In vitro*, the bound fraction % ranges in the studied species (rat, dog, rabbit and human) from >99.90% to >99.92%, which can be considered as a very high binding.

Metabolism

No specific metabolism studies were conducted. This is acceptable.

Excretion

Studies performed with radiolabelled bulevirtide have shown accumulation of radioactivity in the urinary bladder and/or kidney in rats and dogs. However, radio-HPLC measurements of urine samples obtained from the rat and dog suggest that free iodine or a small labelled C-terminal fragment but not the full-length peptide is excreted. Low levels of radioactivity were also detected in the GI tract indicating some excretion through the biliary pathway.

2.3.3. Toxicology

The toxicological profile of bulevirtide has been evaluated in a set of non-clinical studies including a single dose study in rat, repeat-dose studies up to 13 weeks (dog) and 26 weeks (rat), developmental and reproductive toxicity studies in rat and rabbit (FEED in rat, EFD in rat and rabbit and PPND in rat), an antigenicity study in rat and *in vitro* cytotoxicity studies. Safety pharmacology parameters were included in the single-dose rat study and in the 13- and 26-week studies in dogs and rats, respectively.

In all studies with exception of the single-dose study, bulevirtide was administered via the SC route, which is in accordance with the clinical route of administration.

Rat and dog were selected as species for repeat-dose toxicity studies while rat and rabbit were used in the reproductive toxicity study package. The selection of species is questioned as there are no adequate data supporting that bulevirtide is a specific and selective inhibitor of NTCP in the species used for safety evaluation (see further discussion in section 3.2.5.).

Single-dose toxicity

The single-dose toxicity of bulevirtide was evaluated in rats at a dose-level of 12.5 mg/kg (IV administration). No mortality or bulevirtide-related effects were observed in any of the investigated parameters (clinical signs, neuropharmacological parameters, body weight or gross pathology).

Repeat-dose toxicity

Repeat-dose toxicity studies of up 13 weeks in dogs and 26 weeks in rats have been performed. A 4-week recovery period was included in the 26-week rat study. No bulevirtide-related toxicity was observed in any of the investigated parameters in the repeat-dose studies. In dogs, a tendency for an increase of bile salts was detected at week 13 in comparison to baseline; however, according to the study report, the values remained in the normal range and the alteration were not statistically significant. This bile salt elevation was not accompanied by any liver symptoms or histopathological changes in the dogs. Thus, the NOAEL was set at 2.5 mg/kg in both rats and dogs corresponding to AUC exposure margins of >30 in rats and >60 in dogs.

Genotoxicity and carcinogenicity

As the clinical treatment duration is >6 months, the carcinogenic potential of bulevirtide should be considered. In line with ICH S6(R1), genotoxicity or carcinogenicity studies were not performed with bulevirtide. As recommended by CHMP (EMA/CHMP/SAWP/301457/2018) it is agreed that life-long rodent

studies are not appropriate and instead, a weight of evidence approach has been provided which is an acceptable strategy.

Reproductive and developmental toxicity

Bulevirtide was evaluated in a complete reproductive and developmental toxicity program consisting of fertility and early embryonic development studies in male and female rats, a preliminary enhanced EFD study in rats, embryofoetal development studies in rats and rabbits, and a prenatal and postnatal development study in rats. Only one bulevirtide dose level (2.5 mg/kg/day) was included in these studies.

Fertility and early embryonic development

In the FEED study, no bulevirtide-related signs of local or systemic effects were noted. In male rats, no influence was noted on the fertility index or on sperm parameters. In females, the fertility index, the estrus cycles and the reproductive performance (resorption rate, pre-and post-implantation loss, number of corpora lutea, implantation sites and foetuses) were not influenced by bulevirtide. For both general and reproductive toxicity, the NOAEL was 2.5 mg/kg/day, corresponding to 9- and 10-fold the clinical AUC exposure in male and female rats, respectively.

Additionally, there were no bulevirtide-related histopathological changes in male and female reproductive organs in the repeat-dose studies where higher bulevirtide exposures were studied.

Embryo-foetal development

In the preliminary enhanced EFD study in rats, administration of bulevirtide was well tolerated in pregnant rats and there were no effects on reproduction data or on foetal examinations. The NOAEL for maternal toxicity and embryofoetal development was 2.5 mg/kg/day. In this study, an evaluation of maternal and foetal bulevirtide concentrations in liver was included. In the test item-treated dams, bulevirtide was detected in all animals with a group mean of 116 ng/g liver. Bulevirtide could not be detected in any of the investigated foetuses indicating that the peptide does not pass the placental barrier.

The definitive EFD studies in rats and rabbits did not reveal any embryotoxic or teratogenic properties of bulevirtide. In rats, the NOAEL for maternal toxicity and embryofoetal development was 2.5 mg/kg/day, corresponding to 12-fold the clinical AUC exposure. In rabbits, a slight reduction in the body weight and food intake was observed in pregnant dams at 2.5 mg/kg/day. Such effects were no seen in other species and may be explained by the fact that exposures were higher in rabbits than to the other species tested. Thus, a NOAEL for maternal toxicity was not identified. Despite the slight maternal toxicity, there were no bulevirtide-related embryo-foetal effects. Thus, the NOAEL for embryofoetal development in rabbits was 2.5 mg/kg/day.

Prenatal and postnatal development

In the prenatal and postnatal development study, pregnant rats (F0 generation) were treated with bulevirtide from implantation (6th day of gestation) until weaning (the 21st day of lactation). There were no bulevirtide-related effects noted in the treated F0 generation, nor in the F1 or F2 generations. The NOAEL in this study was 2.5 mg/kg/day for the F0, F1 and F2 generations.

Juvenile toxicity

The currently sought indication only includes only adult patients. The PDCO has granted a waiver for the paediatric population from birth to less than 3 years of age and deferral (EMEA-002399-PIP01-18).

Local tolerance

The local tolerance of bulevirtide was evaluated within toxicology studies using SC administration which is considered acceptable.

Antigenicity

The immunogenic potential (i. e. development of ADAs) of bulevirtide was evaluated as part of the toxicokinetic evaluation in the 26-week rat and 13-week dog repeat-dose studies. ADAs were detected in the plasma samples of 12 out of 53 rats (23%), and in 8 out of 18 dogs (44%) treated with bulevirtide with no clear dose-dependency. The presence of ADAs did not cause any apparent changes in the systemic exposure to bulevirtide or associated toxicity.

The study investigating the tissue distribution of bulevirtide-y-^{125}I in the presence of anti-drug antibodies (i. e. in immunised rats) indicate that the presence of ADAs does not impact the distribution of bulevirtide-y-^{125}I to the liver.

Impurities

One major impurity (with RRT at 1.05 using the optimised HPLC method or with RRT at 1.047 using the UPLC method) was identified and elucidated as a process-related modification of bulevirtide. This impurity, denoted assu^{16}-bulevirtide, is considered toxicologically qualified up to or above the proposed specification limit.

Cytotoxicity

The cytotoxicity of bulevirtide was investigated in primary human hepatocytes, stellate cells, renal proximal tubule cells and ChoK1 cells from the medium samples after 24 h exposure by measuring membrane integrity (LDH leakage). In parallel, the cell viability was measured by the means of ATP content indicating the metabolically competent cells. ATP content was measured based on luciferase catalysed reaction generating bioluminescent signal. LDH leakage and ATP content did not indicate cytotoxicity in comparison with the vehicle control within 24 hours at any tested concentration up to 92.6 µM of bulevirtide.

2.3.4. Ecotoxicity/environmental risk assessment

The active substance, bulevirtide, is a 47-amino acid long, N-terminally myristoylated, HBVL-protein derived lipopeptide, for the treatment of chronic HDV infection. Bulevirtide is manufactured by solid phase synthesis and has the following chemical name: *N-tetradecanoylglycyl-L-threonyl-L-asparaginyl-L-leucyl-Lseryl- L-valyl-L-prolyl-L-sparaginylL-prolyl-L-leucylglycyl-Lphenylalanyl-L-phenylalanyl-L-prolyl-L-α-aspartyl-L-histidyl-Lglutaminyl-L-leucyl-L-α-aspartyl-L-prolyl-L-alanyl-Lphenylalanylglycyl-L-alanyl-Lasparaginyl-L-seryl-Lasparaginyl-L-asparaginyl-L-prolyl-L-α-aspartyl-L-tryptophyl-L-αaspartyl-L-phenylalanyl-L-asparaginyl-L-prolyl-Lasparaginyl-L-lysyl-L-α-aspartyl-L-histidyl-Ltryptophyl-Lprolyl-L-α-glutamyl-L-alanyl-L-asparaginyl-L-lysyl-Lvalylglycinamide*.

Bulevirtide contains only naturally occurring amino acids, and no modifications were introduced to increase its stability. The peptide, including the N-terminal myristic acid moiety, is identical in sequence to a conserved part of the large (L) viral envelope protein of hepatitis B virus (HBV). Bulevirtide can therefore be regarded

as naturally occurring in the environment with a biostability equivalent to that of naturally occurring peptides. In addition, it should be considered that bulevirtide is intended for the orphan indication chronic hepatitis D, such that environmental entry can be expected to remain very low. In accordance with the EMA "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 Rev. 1), ecotoxicity and environmental fate studies are not required for an active pharmaceutical ingredient that is a peptide as peptides are extensively degraded and unlikely to result in significant risk to the environment. Thus, ecotoxicity and environmental studies were not performed by the applicant. This is acceptable. Bulevirtide is not expected to pose a risk to the environment

2.3.5. Discussion on non-clinical aspects

The non-clinical studies were, in general, performed in accordance with legal requirements and available guidelines. Scientific advice on non-clinical developmental aspects has been received and the CHMP advice have been followed to a large extent.

Pharmacology

In the first round, the absence of quantitative data on binding and functional activity on NTCP in the animal species used for safety evaluation was considered a weakness. Whereas bulevirtide is claimed to be a specific inhibitor of NTCP, the binding data is limited to microscopy and FACS analysis showing the relative binding of bulevirtide to primary hepatocytes in the selected species (rat, rabbit, dog, cynomolgus and human). In the response to this question, the applicant states in their response that the NTCP receptor structure is conserved across the species tested including humans and the physiological function of NTCP is similar in animals as in humans. Since NTCP is a primary transporter for bile salt uptake from portal blood into the liver following NTCP blockade by bulevirtide an increase in plasma bile salts is an expected consequence. In order to demonstrate pharmacologic target-driven for activity bulevirtide *in vivo*, the applicant submitted data on the measurement of plasma bile salt levels, as an PD marker for bulevirtide, in rats and rabbits. The results show an elevation of total bile salt levels in plasma following administration of bulevirtide in both rats and rabbits, thus indicating that bulevirtide binds to NTCP and leads to a functional inhibition leading to increases of total bile salts in animals *in vivo*. In addition, published functional *in vitro* experiments indicate that the TC uptake, which is mediated by the respective NTCP homologues from human, rat and dog was inhibited by bulevirtide. Taken together, its agreed that the presented data shows that the physiological NTCP function including bile acid uptake function in animals including, rodents, rabbits and dogs, is existing and that the inhibition of NTCP with bulevirtide in the animal species tested leads to an expected increase in bile salts similarly to what is observed in humans, indicating that the species used for toxicity assessment are pharmacologically relevant. However, a potential contribution to the elevation of bile acids through interaction with other transporters by bulevirtide cannot be completely excluded.

Concerning secondary pharmacology, the applicant did not perform a conventional off-target screen, including common receptors, enzymes and transporters, with bulevirtide. This is considered acceptable given the nature of the product (a peptide) and a receptor off-target screen is, in general, considered of low value for biologics. The interaction of bulevirtide with other liver transporters (e.g. BSEP, MDR1, OATP1B1, OATP1B3) as well as its potential clinical relevance is considered adequately assessed and discussed in the Clinical Pharmacology section. Even though distribution studies with radiolabelled bulevirtide *in vivo* show a high distribution to liver, kidneys and intestine, there were no toxicology findings (in two species) in these tissues and an absence of adverse effects in these organs in patients following bulevirtide treatment,

indicating a low safety risk related to potential interactions with NTCP-related transporters in liver and other tissues.

Hepatic bile acid metabolism is tightly regulated, including at both the transcriptional level and by post-translational mechanisms. Since downregulation of NTCP expression in the human liver has been implicated in several liver pathologies, the applicant should discuss potential physiological consequences and clinical relevance following inhibition of NTCP after bulevirtide treatment and a possible suppression of NTCP expression. In a CHMP advice (EMA/CHMP/SAWP/382780/2015) the applicant was initially asked to discuss the physiological function of the NTCP transporter and the implications of its blockage by bulevirtide. Given the limited clinical safety data, long term safety of bile acid elevation is included as a potential important risk in the RMP and will be further investigated in the ongoing trials MYR301 and MYR204, and in the Myr-HDV registry study. A warning is also included in the SmPC section 4.4. The concern of long-term effects of bile acid increase is further discussed in the clinical section.

In accordance with the provisions of ICH S6(R1) guidance documents, safety pharmacology endpoints were incorporated into the design of toxicology studies with bulevirtide. The safety pharmacology studies revealed no safety issues regarding cardiovascular (including ECG), respiratory and central nervous system (CNS, Irwin screen) systems at the tested doses. In addition, no obvious adverse safety concerns related to CNS or respiratory function were found in the assessment of the clinical studies for bulevirtide. Furthermore, no adverse CV effects were observed in the clinical phase I study and, in general, the results from ECG measurements in phase II trials showed few clinically changes and no trends were observed (see Clinical section).

Pharmacokinetics

The scope of pharmacokinetic program is considered adequate.

The bioanalytical methods for analysis of bulevirtide in rat and rabbit plasma are considered adequate. The method for the determination of bulevirtide in dog plasma, however, was not validated in compliance with GLP. According to Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2) aspects of method validation not performed according to GLP should be clearly identified and their potential impact on the validation status of the method indicated. It was further clarified by the applicant that the bioanalytical method validation was performed between 2009 and 2010 in agreement with recommendations in Guidance for Industry, U.S. Department of Health and Human Services (FDA 2001). The validation was not performed under GLP conditions as this was not a formal requirement. A study director was formally responsible for the validation, and the methods and results are documented in a study report and subsequent report amendments. Relevant validation parameters were investigated, and the method seems valid and suitable for the measurement and quantification of bulevirtide in dog plasma. The bioanalysis of bulevirtide in plasma in the 13-week repeat-dose dog study was performed in compliance with GLP. Overall, it is agreed that there is no impact on the integrity of the results obtained in the pivotal dog study.

The tissue distribution studies showed that bulevirtide rapidly and specifically distributed to the liver in mice, rats, dogs, and chimpanzees but not in cynomolgus monkeys. The absence of specific liver targeting in monkeys is consistent with the absence of bulevirtide binding to cynomolgus monkey hepatocytes *in vitro*.

It is noted that one of the distribution studies used chimpanzees as a test species. The use of great apes raises serious ethical concerns and is not in agreement with the guiding principles of the 3R´s. The added

scientific value of the chimpanzee study is questioned. Thus, the applicant was asked to ethically and scientifically justify the use of chimpanzees. It was clarified that the chimpanzee study report was completed shortly after the ban on the use of chimpanzee animal model (Directive 2010/63/EU), but prior to the directive came into force across EU in 2013. From a scientific perspective, it was argued that efforts were made to select a relevant animal model for the PK/PD studies and that that the chimpanzee model is the only primate animal model to investigate all aspects of an HBV and HDV infection given the restricted host range of the viruses. Additionally, the NTCP residues that are identified as critical for binding of the HBV preS1 domain are identical between chimpanzee and man. However, HBV/HDV infection were not studied in the chimpanzee model. From an ethical perspective, the study was limited to evaluation of pharmacokinetics and tolerability following a single IV infusion in 3 animals.

Toxicology

The scope of toxicology program is largely in agreement with ICH S6(R1) which is acceptable as bulevirtide is a large peptide. While ICH S6(R1) generally recommends repeat-dose studies of 26-weeks in duration in both rodents and non-rodents for chronic use products, the bulevirtide repeat-dose studies are considered sufficient and no further repeat dose toxicity studies should be required as previously concluded by CHMP (EMA/CHMP/SAWP/382780/2015).

CHMP also recommended that a justification for the dose levels in the repeat-dose studies should be provided. However, no such justification has been found in the documentation. In the 7-day dose-range-finding study in rats, bulevirtide was well tolerated up to a SC dose of 25 mg/kg/day. However, in subsequent repeat-dose toxicity studies in both rat and dog the following doses were used: 0.25; 1; 2.5 mg/kg/day. Thus, the applicant was asked to justify the choice of the selected doses for the toxicology program in line with what requested in SA EMA/CHMP/SAWP/382780/2015. The applicant argued that the 2.5mg bulevirtide dose was considered an acceptable maximum dose for dogs and rats since it provided sufficient safety margins of above 50-fold to the systemic exposure expected in humans in line with ICH M3(R2).

As further discussed in the pharmacology section, the pharmacological relevance of the toxicology species was questioned in the first round. After further clarifications by the applicant, it is agreed that the species used for toxicity assessment are likely pharmacologically relevant. Although bile salt levels were not measured in the rat repeat-dose studies, it seems reasonable to assume that the response in non-pregnant rats is similar to that in pregnant rats. The plasma bile salt elevations caused no adverse effects under the conditions of the non-clinical studies. Given the limited clinical safety data, long term safety of bile acid elevation is included as a potential important risk in the RMP and will be further investigated in the ongoing trials MYR301 and MYR204, and in the Myr-HDV registry study. A warning is also included in the SmPC section 4.4. The concern of long-term effects of bile acid increase is further discussed in the clinical section.

In the repeat-dose studies in rats and dogs, bulevirtide treatment was well tolerated with exception of a few events of injection site toxicity. In the 4- and 26-week studies in rats, macroscopic inspection at necropsy revealed subcutaneous haemorrhage at the injection sites in 3/54 treated rats and in 5/80 animals (1M of the control group, 1M and in 2F of the low dose group and 1M of the high dose group), respectively. Similar effects have been observed in the 13-week dog study, in which 5/24 treated animals showed subcutaneous haemorrhages at the injection sites. Moreover, histologically examinations, revealed inflammatory changes in dermis and/or subcutis (like subcutis granulomatous inflammation and haemorrhages) for most of the animals, with no gender or treatment-dependence. The applicant stated that due to the low incidence, the

lacking dose-relationship and as also animals of the control group were affected, these findings should be considered to be related to the technical procedure of the repeated subcutaneous infusion and not to the treatment with the test item. However, these events of skin damage and irritation could be related to the subcutaneous administration of a solution with an alkaline pH, that in these three studies was more than two units above the physiological one (about 8.8 and 8.9). The applicant was asked to discuss the relationship between the alkaline pH of the administered solution and the observed adverse effects at the injection sites. The applicant states that the haemorrhages were observed only at necropsy and were limited to a small number of animals and with no dose-dependency. Additionally, considered that also animals in the control group were affected, this finding is considered associated with the technical procedure of the repeated subcutaneous infusions rather than to the treatment with the test item. However, even if we agree to consider low the incidence because in the 1-month and 6-month repeated dose toxicity studies in rat, subcutaneous haemorrhages at the injection sites were observed in 3/54 and in 5/80 treated animals respectively, while during 13-week study haemorrhage affected 5/24 treated dogs, the incidence in the control group, was not comparable with the one observed in the treated group. About the possible correlation between the mild local toxicity and the pH values of the batches (about 8.8 and 8.9) it is concluded that the mild injection site toxicity is likely not related to the pH of the formulation.

In the 13-week dog study, a decrease in food consumption was observed for all dogs of control and treatment-groups following test Week 13. The applicant justified this reduction as a result of a very warm weather in June and July. However, in order to minimise the effects of environmental variables on the animal, the facility has to be designed and operated to control selected parameters (such as temperature). The applicant was asked to clarify this deviation from study protocol and GLP principles. The applicant declared that the very warm weather recorded in June and July 2009 is solely responsible for the decrease in food consumption observed in rats in study 24196 and that this decrease in food consumption was not accompanied by a decrease in body weight or body gain and had no impact on the conduct of the study. In accordance with Appendix A of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes: guidelines for accommodation and care of animals, the temperature in the outdoor areas provided for animals to exercise and interact did not have strict temperature regulation, therefore, according to the applicant, it was not reported as a GLP deviation. However, section 2.2.4 of the above-mentioned guideline specified also that: Animals should not be restricted to such areas under climatic conditions which may cause them distress. However, except for the mean group bodyweight of the female animals treated with 2.5 mg/kg that it was below the body weight of the control group by -16% and -20% in test weeks 7 and 8 respectively, due to the reduced body weight in female no.22, none of the treated rats revealed significative changes in body weight and food consumption.

Bulevirtide was evaluated in a complete reproductive and developmental toxicity program in rats and rabbits. As previously discussed, the pharmacological relevance of rat and rabbit is questioned. Only one bulevirtide dose level (2.5 mg/kg/day) was included in these studies. The strategy for evaluating reproductive risk was discussed in a scientific advice (EMA/CHMP/SAWP/301457/2018). CHMP commented that if effects are observed in the bulevirtide-treated group, it might be necessary to study lower dose levels. Apart from a mild maternal toxicity seen as slight reductions in body weight and food consumption observed in pregnant rabbits, there were no findings considered bulevirtide-related in the reproductive toxicity studies. It is therefore considered acceptable that only one dose level was studied. Given the molecular weight of bulevirtide, 5398.9 Da, a low or no transplacental passage seems likely.

2.3.6. Conclusion on the non-clinical aspects

In general, the non-clinical characterisation of bulevirtide appears adequate and approval can be recommended from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

Note that the bulevirtide was previously named "Myrcludex B". This name is used in most/all reports described but was replaced by the now approved international non-proprietary name "bulevirtide" in this document except in study titles, where the original wording is retained.

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A routine GCP inspection has been performed for the clinical study MYR202. Compliance with GCP and applicable regulations was to be verified, in particular where it had an impact on the validity of the data or the ethical conduct of the study. No specific concerns were known or had been identified by the assessment at the time of adoption of the inspection request.

During the inspection an assessment of the sponsor and an investigator site were conducted. There were no critical findings noted during the inspection. 6 findings were graded as major and 6 as minor for the sponsor and 3 major and 13 minor for the investigator site.

Despite major findings noted during the inspection there are no elements to doubt the overall reliability of data provided for MAA and it can be concluded that the study has generally been conducted in compliance with GCP and internationally accepted ethical standards.

- Tabular overview of clinical studies

Table 1. Overview of pharmacokinetic trials with bulevirtide

Study number	Clinical phase	Subjects	Treatment groups	# Subjects included in PK analysis
MYR101	1a	healthy volunteers	bulevirtide i.v. at doses from 300 ng to 20 mg	27
			bulevirtide s.c. at doses from 800 µg to 10 mg	9
MYR102	1	healthy volunteers	10 mg bulevirtide s.c. + 245 mg tenofovir oral	12
MYR201 (HBV)	1b/2a	patients with HBeAG negative chronic hepatitis B	bulevirtide s.c. at doses of 0.5 mg, 1 mg, 2 mg, 5 mg and 10 mg	16
MYR202*	2	chronic hepatitis D	bulevirtide s.c. at doses of 2 mg, 5 mg and 10 mg + tenofovir 245 mg oral	25
MYR203*	2	chronic hepatitis D	bulevirtide s.c. at doses of 2 mg and 5 mg + PEG-IFN 180 µg s.c. per week	20
Total				**109**

* in addition to the patients mentioned in this table, a PK main study was performed in which single plasma samples were collected from all study participants to investigate accumulation over time
Abbreviations: i.v. = intravenous; PEG-IFN = peginterferon alfa-2a; s.c. = subcutaneous

Table 2. Overview of clinical studies and compassionate use in chronic HDV infection contributing to the evaluation of efficacy

Clinical study code	Study Title	Number of patients with available efficacy data
MYR202 / phase II	A Multicenter, Open-label, Randomized Clinical Study to Assess Efficacy and Safety of 3 Doses of Myrcludex B for 24 Weeks in Combination with Tenofovir Compared to Tenofovir Alone to Suppress HBV Replication in Patients with Chronic Hepatitis D	90
MYR203 main study / phase II	A Multicenter, Open-label, Randomized, Comparative, parallel-arm phase II study to Assess efficacy and safety of Myrcludex B in combination with Peginterferon alfa-2a versus Peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent	45
MYR201 (HDV)	Randomized open-label substudy of daily Myrcludex B plus pegylated interferon-alpha-2a in patients with HBeAg negative chronic hepatitis B co-infected with hepatitis delta	16
Supportive efficacy data		
CUP	Compassionate use of 10 mg bulevirtide	4

2.4.2. Pharmacokinetics

Methods

Quantification of bulevirtide

The concentrations of bulevirtide in human plasma and urine were determined using three validated high-performance or ultrahigh-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS or UPLC-MS/MS).

Bile acids

Bile acids in human plasma were analysed using liquid chromatography quadropoly time-of-flight mass spectrometry (LC-QTOF-MS) in the DDI studies.

In the safety and efficacy studies, a standard enzyme-linked immunosorbent assay (ELISA) method was used.

Detection of anti-drug antibodies (ADA)

Development of anti-drug antibodies against bulevirtide was analysed in the clinical trials MYR101, MYR201 HBV, and MYR201 HDV using a validated competitive radioimmunoassay (RIA), and in MYR202 and MYR203 with an ELISA.

The RIA method is based on the binding of specific antibodies against bulevirtide to both 125I-Tyr-bulevirtide (tracer) and bulevirtide in plasma calibration standards. The separation of the antibody bound 125I-Tyr-bulevirtide from the unbound was achieved following the addition of an aqueous polyethyleneglycol solution and rabbit IgG. Radioactivity is measured in the precipitate. Rabbit antiserum was used as a positive control.

The described ELISA method used unmyristoylated bulevirtide for ADA capture and detection occurred colorimetrically after binding of a peroxidase-coupled secondary antibodies goat-anti-human IgA + IgG + IgM and its substrate tetramethylbenzidine-dihydrochloride. The confirmation assay used an excess of bulevirtide

to inhibit the signal. A manufactured monoclonal IgG1 "MYR-Ab" against bulevirtide was used as positive control, the method is thus semi-quantitative. Cut-off points were selected for a 5% false positive rate in the screening step and 0.1% in the confirmation step.

ADAs were detected in all multiple dose clinical trials and in all dose groups (see Table 3). In trial MYR203, the incidence of ADA was significantly higher in the patients that received combined treatment with bulevirtide and PEG-IFNα compared to bulevirtide alone. The mean concentrations of ADAs were consistently higher in the bulevirtide 5 mg + PEG-IFNα group. After the cessation of bulevirtide treatment, there was a significant decline of anti-drug antibody titers in trials MYR201 HDV, and MYR202. In study MYR203, there was a slow decrease of the mean ADA concentrations, but the mean values were still above baseline values at week 72.

Table 3. Development of anti-drug antibodies.

Clinical trial	**Time after first administration**	**n positive subjects/n subjects with measurement (%)**				
		0.5 mg	**2 mg**	**5 mg**	**10 mg**	**Total**
MYR101	up to 6 months	-	-	-	-	0[#]/36
MYR201 HBV	up to 12 weeks	4/8 (50.0%)	-	5/8 (62.5%)	5/8 (62.5%)	14/24 (58.3%)
MYR202	12 weeks	-	1/28 (3.6%)	5/32 (15.6%)	5/30 (16.7%)	11/90 (12.2%)
	24 weeks	-	5/28 (17.9%)	6/30 (20.0%)	7/28 (25.0%)	18/86 (20.9%)
	36 weeks	-	2/28 (7.1%)	1/29 (3.4%)	1/29 (3.4%)	4/86 (4.7%)
	48 weeks	-	1/28 (3.6%)	1/29 (3.4%)	0/29 (0%)	2/86 (2.3%)
		2 mg	**2 mg + PEG-IFNα**	**5 mg + PEG-IFNα**		**Total**
MYR201 HDV	12 weeks	2/8 (25%)	6/7 (85.7%)	**-**		8/15b (53.3%)
	24 weeks	3/8 (37.5%)	7/7 (100%)	**-**		10/15 (66.7%)
	48 weeks	1/7 (24.3%)	n/a	**-**		1/7 (24.3%)
	72 weeks	n/a	0/6 (0%)	**-**		0/6 (0%)
	96 weeks	0/7 (0%)	n/a	**-**		0/7 (0%)

MYR203	12 weeks	1/15 (6.7%)	14/15 (93.3%)	13/15 (86.7%)		28/45 (62.2%)
	24 weeks	2/14 (14.3%)	14/15 (93.3%)	12/15 (80.0%)		28/44 (63.6%)
	48 weeks	0/15	13/15 (86.7%)	13/15 (86.7%)		26/45 (57.8%)
	72 weeks	0/13	5/13 (38.5%)	7/15 (46.7%)		12/41 (29.3%)

Source: study reports MYR101, MYR201 HBV, MYR201 HDV, MYR202, MYR203

[#] dose range from 3 µg i.v. to 10 mg s.c.

[*] Treatment arm A (therapy with 2 mg/day bulevirtide for 24 weeks followed by therapy with PEG-IFNα for 48 weeks): 4/8 (50.0%); treatment arm B (combination therapy with 2 mg/day bulevirtide plus PEG-IFNα for 24 weeks followed by therapy with PEG-IFNα for another 24 weeks): 7/7 (100%)

The Applicant provided results showing that ADA concentration obtained in the screening assay are comparable with the ADA titer measured within the titer assay, the proposal to not develop a specific method to measure titer is acceptable.

The virological and biological response is similar between subjects positive to ADA and subjects negative, and consequently the conclusion that neutralising potential of ADA is negligible may be considered acceptable.

Clinical studies addressing bulevirtide PK

The pharmacokinetics of bulevirtide was investigated in a total of 5 clinical phase 1 and phase 2 trials, namely MYR101, MYR102, MYR201 (HBV), MYR202 and MYR203. Two phase 1 trials in healthy volunteers aimed to gain first information on the safety and tolerability of bulevirtide, to identify a reasonable dose of bulevirtide and investigated a possible drug interaction with tenofovir (MYR101 and MYR102). Trial MYR201 (HBV) included patients with HBeAg-negative CHB. Pharmacokinetics in the target population, i.e. patients with CHD, has been evaluated in the two pivotal phase 2 trials MYR202 and MYR203. An overview of the clinical trials raising PK data, as well as an overview of obtained PK parameters with the proposed dose of bulevirtide 2 mg s.c. is given in the tables below.

Table 4. Overview of clinical studies containing pharmacokinetic aspects of bulevirtide in the submitted clinical pharmacology package.

Study number	Clinical phase	Subjects	Treatment groups	# Subjects included in PK analysis
MYR101	1a	healthy volunteers	bulevirtide i.v. at doses from 300 ng to 20 mg	27
			bulevirtide s.c. at doses from 800 µg to 10 mg	9
MYR102	1	healthy volunteers	10 mg bulevirtide s.c. + 245 mg tenofovir oral	12
MYR201 (HBV)	1b/2a	patients with HBeAG negative chronic hepatitis B	bulevirtide s.c. at doses of 0.5 mg, 1 mg, 2 mg, 5 mg and 10 mg	16
MYR202*	2	chronic hepatitis D	bulevirtide s.c. at doses of 2 mg, 5 mg and 10 mg + tenofovir 245 mg oral	25
MYR203*	2	chronic hepatitis D	bulevirtide s.c. at doses of 2 mg and 5 mg + PEG-IFNα 180 µg s.c. per week	20
Total				**109**

* in addition to the patients mentioned in this table, a PK main study was performed in which single plasma samples were collected from all study participants to investigate accumulation over time

Abbreviations: i.v. = intravenous; PEG-IFNα = peginterferon alfa-2a; s.c. = subcutaneous

Table 5. PK parameters of bulevirtide (s.c. 2 mg dose) across the clinical trials.

Study number	Comment	PK parameter					
		C_{max}*	T_{max}~	AUC_{0-24}*	$AUC_{0-\infty}$*	$t_{1/2}$#	Cl/F#
		[ng/mL]	[h]	[ng*h/mL]	[ng*h/mL]	[h]	[L/h]
Single dose (day 1)							
MYR201 (HBV) (n=4)	patients with HBeAg negative chronic hepatitis B	11.55 (27.91)	0.5 (0.0, 1.0)	45.84 (15.25)	n.c.	4.13 (1.45)	44.02 (7.06)
MYR202 (n=9)	patients with chronic hepatitis D bulevirtide + tenofovir	73.3 (24.0)	1.0 (0.27, 26.77)	n.c.	339.9 (56.6)	6.8 (2.1)	6.6 (3.1)
MYR203 (n=10)	patients with chronic hepatitis D bulevirtide + PEG-IFNα	22.4 (74.4)	0.5 (0.50, 2.00)	n.c.	117.3 (81.9)	6.6 (4.4)	20.2 (10.2)
Multiple dose (day 14)							
MYR201 (HBV) (n=4)	patients with HBeAg negative chronic hepatitis B	17.76 (37.26)	1.0 (0.5, 1.0)	88.25 (17.45)	n.c.	6.22 (4.90)	22.92 (3.99)
MYR202 (n=9)	patients with chronic hepatitis D bulevirtide + tenofovir	139.5 (80.5)	0.5 (0.08, 1.50)	574.1 (84.9)	n.c.	n.c.	4.2 (2.6)
MYR203 (n=10)	patients with chronic hepatitis D bulevirtide + PEG-IFNα	30.1 (87.1)	1.2 (0.50, 3.02)	n.c.	n.c.	n.c.	12.8 (8.9)

* data presented as geometric mean (geometric CV%)
# data presented as mean (SD)
~ data presented as median (range)
Abbreviations: AUC_{0-24} = area under the concentration-time curve up to 24 hours; $AUC_{0-\infty}$ = area under the concentration-time curve up to infinity; Cl/F = apparent clearance; C_{max} = peak plasma concentration; CV = coefficient of variance; n.c. = not calculated; SD = standard deviation; $t_{1/2}$ = elimination half-life; t_{max} = time to reach C_{max}; V_d = apparent volume of distribution

Absorption and distribution

The bioavailability (F) in study MYR101 after s.c. administration estimated based on non-compartmental analysis for doses of 5 and 10 mg was 48% and 57%, respectively. Applicant has performed non-linear mixed effects modelling approach and estimated F to be 85%, i.e. a higher value in comparison to F from the non-compartmental PK estimation. However, the currently presented data/estimations are considered insufficient to provide a precise and reliable value on the bioavailability of bulevirtide. Furthermore, Applicant has stated that the release after subcutaneous administration was best described by a parallel slow and fast first-order process, where 49% of the bioavailable dose was absorbed fast and the remaining 51% of the dose was absorbed slowly with absorption half-lives of 1.3 h and 5.3 h, respectively.

Data about the exact injection site were only available from studies MYR101 and MYR102, in which the drug was administered subcutaneously at the same injection site, i.e. in the lower quadrants of the abdomen. According to the Applicant, in all later trials, it was left to the discretion of the patient where to inject the drug, and no data on particular injection sites are available. Therefore, it is unclear if (and how many) study subjects have used injection sites other than the abdomen (e.g. upper thighs or upper arms). Furthermore, Applicant has decided to remove the "upper arms" as a potential injection site from the initial SmPC 4.2, assuming that patients were unlikely to self-administer the drug into the upper arm. Therefore, proposed injection sites in the SmPC 4.2 include the abdomen as well as upper thighs.

Vd parameter was dose-dependent and decreased with increasing doses of bulevirtide. Vd parameter was not presented/estimated in all clinical study addressing PK aspects of bulevirtide. In study MYR101 conducted in healthy volunteers, Vd obtained by non-compartmental analysis after s.c. single doses ranged from 247 L (±86.5) after the dose of 800 µg, to 43 L (±13.2) after the dose of 10 mg. In study MYR202 conducted in target population, Vd obtained after 2 mg s.c. single dose was 63.2 L (±27.2) (n=9), and after repeated dosing 2 mg s.c. o.d. on day 14 it was 40.3 L (±52.9) (n=9).

The Applicant has conducted plasma protein binding study of bulevirtide (study denoted as ADM-19-2633) by implementing cross filtration technique described in the provided reference by Taylor and Harker, 2006. The plasma protein binding of bulevirtide was studied at single concentration of 10 µM using three replicates in rat, dog, rabbit, and human plasma. Applicant has concluded that bulevirtide shows high plasma protein binding and that no clear difference in binding between species can be determined. Moreover, the Applicant stated – "As the obtained binding values were obtained using the limit of detection observed in the calibrator samples, it is critical to keep in mind that the binding values are borderline values and that the bound fractions are in fact even higher (p.e > 99 90% in rat)". The N-terminal myristic acid was pointed out as the structural determinant responsible for a high degree of bulevirtide binding to the human albumin.

Elimination

The mean half-life ($t_{1/2}$) of bulevirtide after its single dose of 2 mg s.c. in all PK studies ranged approximately from 4 up to 7 hours. As bulevirtide is a synthetic peptide, no liver metabolism was assumed, but rather an elimination through catabolism to amino acids by peptidases. In MYR102 study, no full-length peptide was detected in urine samples, and Applicant has concluded that significant renal elimination is unlikely.

Clearance after s.c. administration (CL/F) generally showed a tendency to decrease with increasing doses of bulevirtide. In study MYR101 conducted in healthy volunteers, CL/F ranged from 62 L/h (±16.7) after s.c. dose of 800µg, to 7.98 L/h (±2.02) after s.c. dose of 10 mg.

Moreover, there were big differences in CL/F observed between different studies conducted in patients where CL/F after s.c. single dose of 2 mg was 44.02 (±7.06), 6.6 (±3.1) and 20.2 (±10.2) L/h in study MYR201, MYR202 and MYR203, respectively. CL/F after repeated dosing of 2 mg s.c. o.d. was 22.92 (±3.99), 4.2 (±2.6) and 12.8 (±8.9) L/h in MYR201, MYR202 and MYR203, respectively.

Dose-proportionality

In general, all clinical studies have pointed towards non-linear pharmacokinetics of bulevirtide. Drug exposure increased more than proportionally with increasing doses.

According to the Applicant, bulevirtide showed nonlinear pharmacokinetics after intravenous and subcutaneous administration. Clearance and volume of distribution decreased with increasing dose, while the AUC increased more than proportionally. This phenomenon was described by a target-mediated drug disposition (TMDD) for which a mathematical model was developed. There was no significant influence of ADAs on bulevirtide PK that would require a dose adjustment.

Pharmacokinetics in target population

There were three clinical studies conducted addressing the pharmacokinetic aspects of bulevirtide in the target population - MYR201, MYR202 and MYR203.

Study subjects in MYR201 only had a HBV infection without HDV co-infection, unlike the study subjects in MYR202 and MYR203 who were co-infected with HDV. However, it is not expected that these differences in viral agents could result in PK differences between the studied patient populations.

A brief description of PK aspects examined in clinical studies MYR201, MYR202 and MYR203 is given below. For more detailed assessment of respective studies please see Pharmacokinetics AR.

MYR201

Systemic exposure of bulevirtide was studied in an explorative phase 1b/2a study in patients with HBeAg negative CHB following 0.5, 1, 2, 5 and 10 mg s.c. once daily for two weeks. PK profiles were described at Day 1 and Day 14.

Relatively limited number of study subjects was included in the PK analysis (n=3 per treatment group with the exception of treatment arm C (2 mg) with n=4) with relatively high inter-individual variability.

PK parameters were estimated using non-compartmental analysis. The exposure of bulevirtide increased more than dose-proportionally with increasing doses. A trend towards increase of elimination half-life with the dose increase was observed for both Day 1 and Day 14. Moreover, this was accompanied with corresponding decrease in total body clearance (with increasing doses).

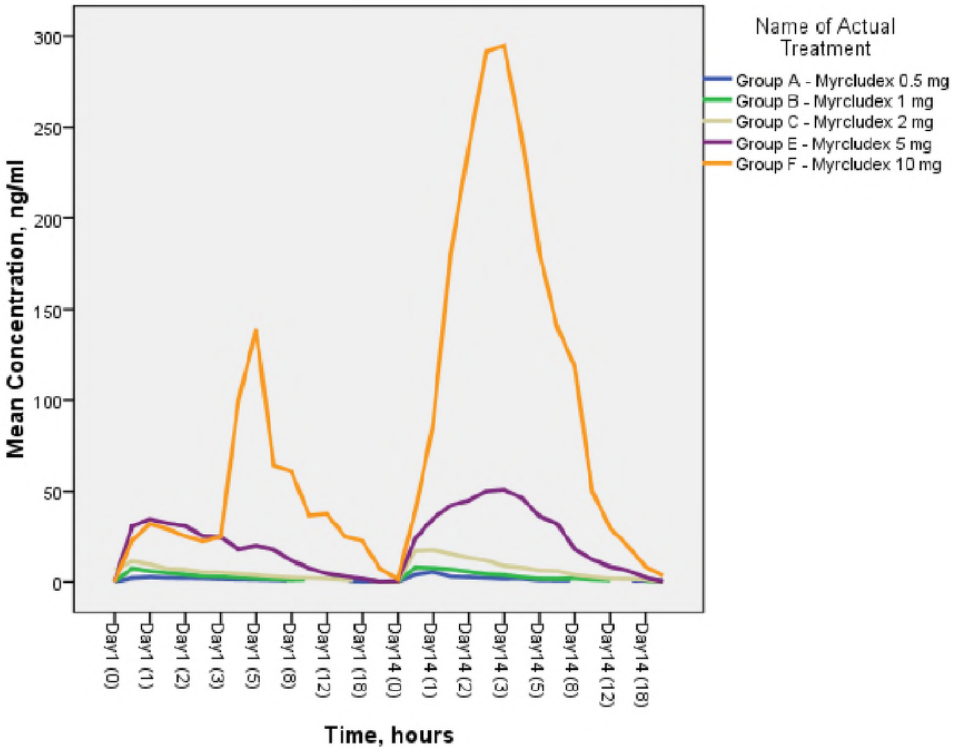
Systemic exposure of bulevirtide increased following repeated treatment with a R_{AC} of about 2-fold.

Table 6. Mean (SD) basic PK of bulevirtide on day 1 and Day 14 following 0.5-10 mg s.c. once daily in MYR201.

	0.5 mg	**1 mg**	**2 mg**	**5 mg**	**10 mg**
Day 1					
C_{max} (ng/ml)	2.9(0.5)	7.4(2.1)	11.9(3.6)	35(16)	150(126)
t_{max}[a] (h)	1.0 (1.0, 1.5)	0.5 (0.5, 1.0)	0.5 (0.0, 1.0)	1.0 (0.5, 1.0)	5.0 (1.0, 6.0)
AUC_{τ} (ng/ml.h)	8.8(1.3)	24(14)	46(6)	222(83)	897(470)
CL/F (L/h)	57(8)	54(36)	44(7)	25(11)	15(10)
$t_{1/2}$ (h)	4.1(0.6)	4.0(0.6)	4.1(4.5)	5.3(3.1)	5.6(1.3)
Day 14					
C_{max} (ng/ml)	8.5(2.0)	8.8(3.2)	19(8)	52(20)	305(162)
t_{max}[a] (h)	0.75 (0.5, 1.0)	1.0 (0.5, 1.5)	1.0 (0.5, 1.0)	3.0 (2.5, 3.0)	3.0 (2.5, 8.0)
AUC_{τ} (ng/ml.h)	21(12)	28(7)	89(15)	374(122)	1783(581)
CL/F (L/h)	30(16)	38(11)	23(4)	15(6)	6.1(2.2)
$t_{1/2}$ (h)	1.4(0.0)	3.4(1.5)	6.2(4.9)	4.2(2.8)	4.1(0.5)

[a] median (min, max)

Figure 4. Mean PK profiles of bulevirtide after single and multiple doses by treatment arm in study MYR201. (X-axis not continuous)



MYR202

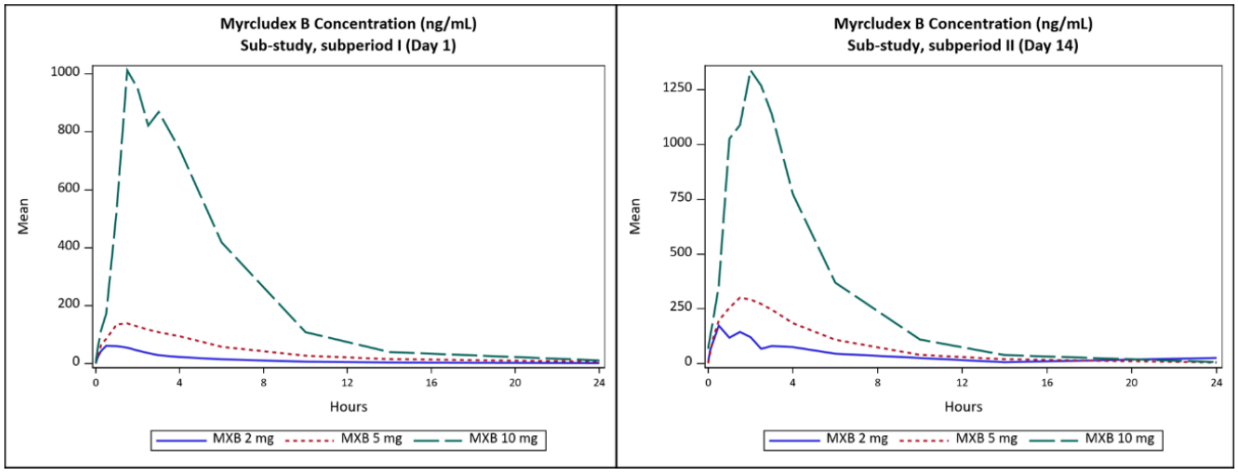
Systemic exposure of bulevirtide in combination with tenofovir was investigated in CHD patients at bulevirtide doses of 2, 5 or 10 mg s.c. once daily in the PK "sub study". All study subjects received concomitant tenofovir treatment at the dose of 245 mg p.o. once daily. Rich PK sampling was performed after the first dose (Day 1) and after repeated dosing (Day 14).

The systemic exposure of bulevirtide increased more than dose-proportionally after a single dose and following repeated treatment. According to the applicant, R_{AC} was determined to 1.7-, 1.8- and 1.4-fold following 2, 5 and 10 mg bulevirtide s.c. once daily.

Table 7. Basic PK of bulevirtide on Day 1 and day 14 following 2, 5 and 10 mg s.c. once daily in combination with tenofovir for 24 weeks in patients with CHD in study MYR202.

Pharmacokinetic parameter		Group A 2 mg	Group B 5 mg	Group C 10 mg
Number of patients		**9**	**7**	**9**
Single dose (day 1)				
C_{max}*	ng/mL	73.3 (24.0)	103.2 (111.4)	641.7 (221.6)
t_{max}#	h	1.0 (0.27-26.77)	1.5 (0.52-24.55)	3.0 (1.52-6.02)
AUC_{τ}*	h*ng/mL	320.9 (56.8)	761.2 (82.5)	3831.3 (97.1)
$AUC_{0-\infty}$*	h*ng/mL	339.9 (56.6)	878.8 (73.6)	3926.8 (94.0)
$t_{1/2}$+	h	6.8 (2.1)	8.1 (4.5)	3.9 (1.6)
Cl/F+	L/h	6.6 (3.1)	6.7 (3.4)	2.7 (1.8)
V_d+	L	63.2 (27.2)	81.4 (52.7)	17.3 (17.1)
Multiple dose (day 14)				
Number of patients		**8**	**7**	**9**
C_{av}*	ng/mL	23.9 (84.9)	65.5 (47.9)	226.5 (55.7)
C_{max}*	ng/mL	139.5 (80.5)	261.5 (88.3)	1193.8 (82.5)
C_{min}*	ng/mL	0.9 (195.7)	2.7 (62.0)	3.6 (48.7)
t_{max}#	h	0.5 (0.08-1.50)	1.5 (0.07-4.02)	2.5 (1.00-4.00)
AUC_{τ}*	h*ng/mL	574.1 (84.9)	1572.0 (47.9)	5435.1 (55.7)
Cl/F+	L/h	4.2 (2.6)	3.5 (1.6)	1.8 (1.1)
V_d+		40.3 (52.9)	25.0 (19.4)	9.1 (5.8)

Figure 1. Mean plasma concentrations of bulevirtide after the first dose (Day 1, left) and after multiple doses (Day 14, right) (PK "sub-study") in MYR202.



MYR203

Results from PK "sub-study" which was performed as a part of the **MYR203** study were presented for study groups B, C receiving bulevirtide (s.c. o.d. at 2 and 5 mg, respectively) together with concomitant PEG-IFNα 180 µg. Rich blood sampling for the assessment of the bulevirtide concentration was performed in these patients after the first dose (Day 1) and after multiple doses (Day 14). Blood samples were taken for up to 24h post-dose.

Figure 6. Mean plasma concentrations of bulevirtide over time (PK "sub-study" of MYR203) after the first dose on Day 1 (left) and at steady-state on Day14 (right) in MYR203.

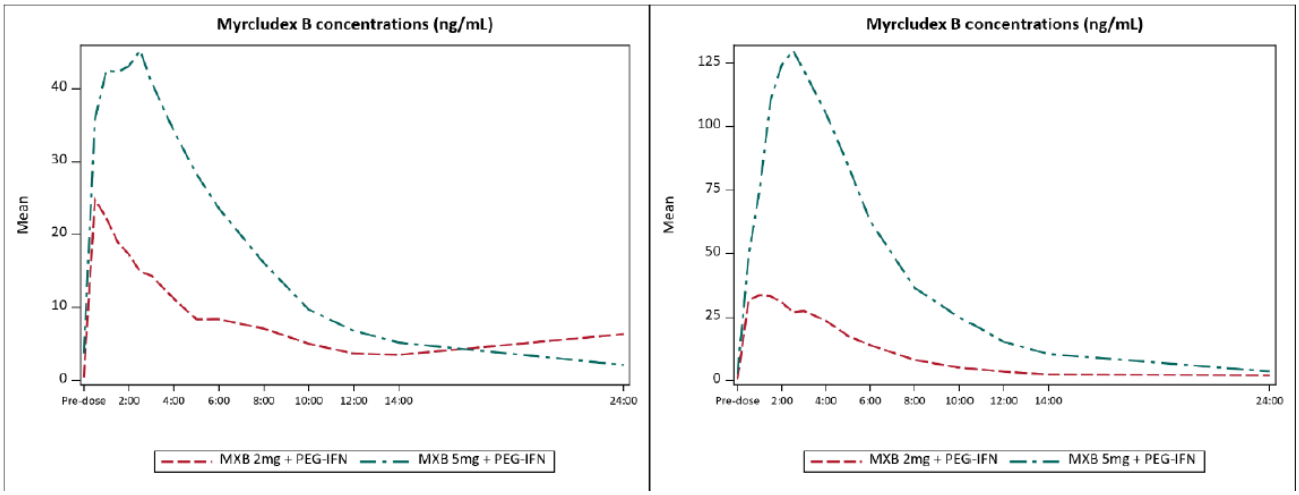


Table 8. Pharmacokinetic parameters of bulevirtide in clinical trial MYR203.

Pharmacokinetic parameter		Group B 2 mg + PEG-IFNα	Group C 5 mg + PEG-IFNα
Number of patients		**10**	**10**
Single dose (day 1)			
C_{max}*	ng/mL	22.4 (74.4)	42.9 (65.7)
t_{max}#	h	0.5 (0.50, 2.00)	1.5 (0.50, 5.02)
$AUC_{0-\infty}$*	h*ng/mL	117.3 (81.9)	326.4 (38.7)
$t_{1/2}$+	h	6.6 (4.4)	5.1 (1.5)
Cl/F+	L/h	20.2 (10.2)	16.3 (6.1)
Multiple dose (day 14)			
Number of patients		**10**	**10**
C_{max}*	ng/mL	30.1 (87.1)	130.3 (44.4)
t_{max}#	h	1.2 (0.50, 3.02)	2.5 (1.50, 4.02)
Cl/F+	L/h	12.8 (8.9)	6.5 (1.9)

Special populations

Regarding the special patient populations, no dedicated studies were conducted with bulevirtide in subjects with renal impairment (RI). According to the Applicant, the RI is unlikely to influence bulevirtide PK when considering its probable elimination pathways involving catabolism to amino acids by peptidases. However, impact on elevated bile salts (observed with bulevirtide treatment) which are renally excreted might be expected in this patient population, and SmPC warning is proposed.

When it comes to patients with hepatic impairment (HI), a significant proportion of patients participating in Phase II trials (40%) had mild hepatic impairment (Child-Pugh class A). The safety profile in this population was not different in comparison to overall population. Therefore, no dose adjustments in these patients is

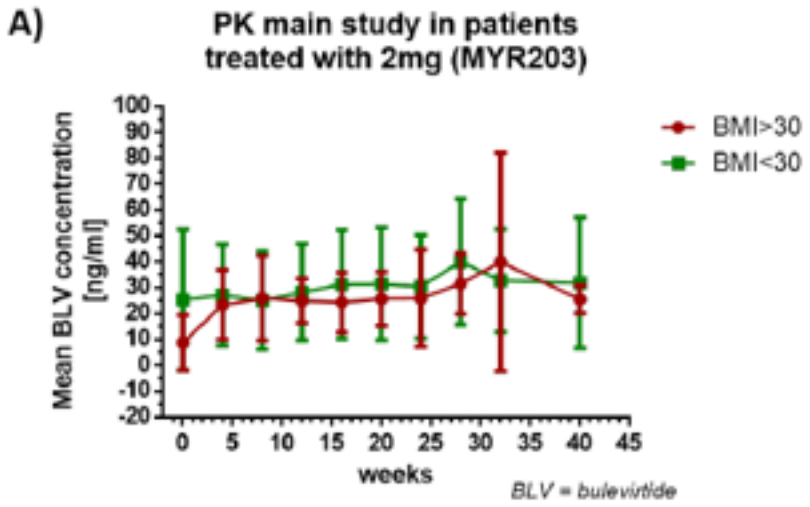
required according to proposed SmPC text. Importantly, no safety and efficacy data for bulevirtide in patients with decompensated cirrhosis have been presented, and corresponding text is included in the SmPC.

No clinical studies with bulevirtide were performed in elderly patients (aged above 65 years) nor paediatric population. No data is available.

BMI>30

No significant difference to overall population could be observed in terms of drug concentrations for patients with BMI>30.

Figure 7 – PK main study in patients with BMI > 30 and BMI < 30



Interactions

Applicant has conducted all DDI *in vitro* experiments with bulevirtide concentrations of up to at least 5 µM, which is considered appropriate and in accordance with EMA's DDI guideline requirement.

The highest mean C_{max} for bulevirtide at the proposed dose of 2 mg s.c. o.d. was observed in a clinical study MYR202 (conducted in target population with concomitant administration of tenofovir) and it was 139.5 ng/mL (µg/L). When considering bulevirtide's MW = 5399 g/mol (µg/µmol), the observed C_{max} corresponds to the molar concentration of 0.026 µM. The *in vitro* estimated fu values showed almost complete binding to plasma proteins (i.e. fu of bulevirtide was less than 0.01). Therefore, it can be concluded that the presented *in vitro* DDI package has investigated sufficiently high bulevirtide concentrations (up to 5 µM) and it is considered adequate according to the EMA 's DDI guideline (i.e. when calculating the concentration cut-off as 50 x $C_{max,u}$).

The Applicant has conducted *in vitro* experiments in human liver microsomes looking at the direct inhibitory potential of bulevirtide towards several CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) at concentrations of up to 5 µM. No *in vitro* inhibitory signals for CYP enzymes were detected. Moreover, no induction potential was observed *in vitro* for CYP1A2, CYP2B6 and CYP3A4 in cryopreserved hepatocytes from 3 human donors.

Based on the obtained *in vitro* results with transporters, the applicant has drawn the following conclusions:

• Bulevirtide is an inhibitor of BSEP and MDR1 efflux transporters, as well as an inhibitor of NTCP, OATP1B1 and OATP1B3 uptake transporters.

• Bulevirtide is not an inhibitor of BCRP efflux transporter. Furthermore, it is not an inhibitor of MATE1, MATE2-K, OAT1, OAT3, OATP2B1, OCT1 and OCT2 uptake transporters.

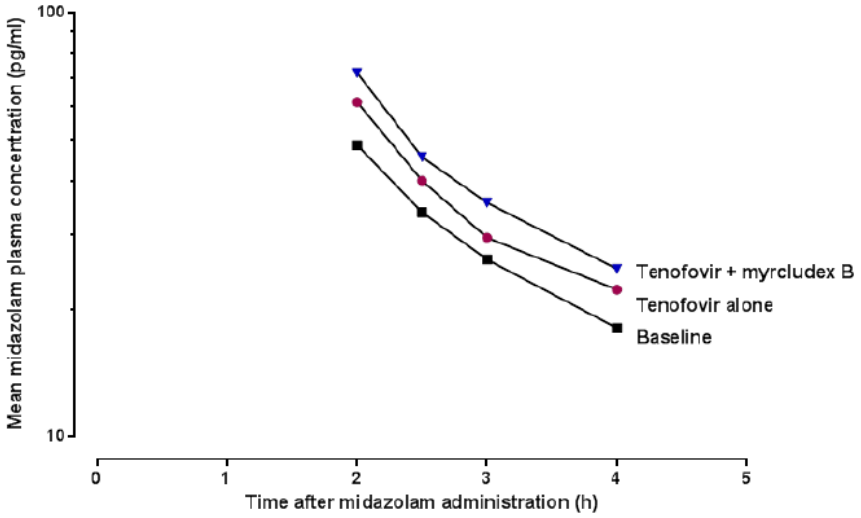
According to the Applicant, the clinical relevance of *in vitro* interaction signal with OATPs will be further investigated in a clinical DDI study between bulevirtide and the OATP-substrate pravastatin. A corresponding SmPC warning is proposed regarding concomitant OATP substrate administration until clinical DDI data become available. Based on the *in vitro* IC50 values for BSEP (1.99 µM) and MDR1 (4.29 µM), no clinical DDI studies are needed. IC50 for NTCP *in vitro* was 0.32 µM (and for rat Ntcp 0.068 µM) which was expected based on the proposed pharmacodynamics/mechanism of action of bulevirtide.

In vivo interaction studies with bulevirtide were conducted within the MYR102 study in healthy volunteers as well as in MYR202 study in the target population. Both clinical studies included concomitant administration of bulevirtide, tenofovir and midazolam. Moreover, in the clinical study MYR203 bulevirtide was administered together with PEG-IFN alfa-2a, however no DDI aspects were discussed within this study.

Midazolam was used in two DDI clinical studies (as a victim drug investigating potential changes in CYP3A activity) despite the fact that all *in vitro* data with bulevirtide showed no signals of inhibition nor induction of CYP3A4. However, the Applicant has explained the reason for conducting DDI studies with midazolam by stating that bulevirtide might still impact the CYP3A activity by alterations in bile acid metabolism, and also mentioned several bile acids as ligands of nuclear receptor PXR. In addition, literature references were also presented to justify investigation of tenofovir as a potential inhibitor of CYP3A4.

In the study MYR102, sparse sampling of midazolam following its oral micro dose of 30 µg showed an indication of statistically non-significant decrease in CL/F *i.e.* CYP3A inhibition when co-administered with tenofovir and tenofovir+bulevirtide. The difference between midazolam $AUC_{2\text{-}4h}$ without comedication and with combined tenofovir plus bulevirtide medication was statistically significant (p-value 0.02). Since only sparse sampling of midazolam was implemented, i.e. between 2 and 4h post-dose, no complete AUC nor precise C_{max} were available in this study. Based on the obtained results, SmPC warning concerning the concomitant administration of bulevirtide and sensitive CYP3A4 substrates is included.

Figure 8. Mean plasma concentration midazolam versus time after an oral dose of 30 µg alone, in combination with tenofovir and in combination tenofovir+bulevirtide in study MYR102.



The MYR202 clinical study conducted in target population included a PK "sub-study" also looking at the potential interaction with midazolam (victim) together with bulevirtide (perpetrator). Midazolam as well as its metabolite 1-hydroxymidazolam (1-OHMDL) were quantified during the pre-treatment period Day -13 (with no concomitant drugs), and later on two more occasions (firstly on Day 1, and secondly on Day 14) with the co-administration of bulevirtide + tenofovir. However, according to the Applicant, the obtained results of MYR202 study were considered inconclusive. Midazolam $AUC_{0-\infty}$ values had a high variability between the treatment groups, leading to both decreases and increases in midazolam exposure when compared with the corresponding baseline values. According to the Applicant, this was attributed to technical difficulties with the administration of microdose of midazolam solution and/or sampling. Overall, DDI study MYR202 is considered inconclusive and it was not used as a basis for any treatment recommendations.

Evaluation and Qualification of Models

Data handling for modelling

The data source employed to inform modelling and parameter estimation is derived from MYR-202. All patients had completed the treatment phase of the trial. The planned follow up was not complete in all patients. The data provided for this analysis was supplied on 31 Oct 2017. There were 120 study participants enrolled in the study. One patient (43-002) assigned to the standard of care (tenofovir) group had no observations. All observations provided in the data from Hepatera were used for the analysis. The time and dose of each sub-cutaneous (SC) administration of bulevirtide was recorded for all patients who participated in the PK sub-study and some patients who were not in the PK sub-study. For all other patients doses were imputed based on the nominal protocol start and date of treatment with bulevirtide. Missing covariates were imputed from observed values using both first observation carried backwards and last observation carried forwards. No observations were removed because they appeared to be outliers. The total number of observations of each type (count), statistics for individuals (median, %iles, min, max) and % of BLQ observations for each type are shown in Table 9. Covariates tested in the model analysis are shown in Table 10.

Table 9. Observation counts for model dataset.

Observation	count	median	2.5% ile	97.5% ile	min	max	% blq
HDV	1446	10.5	0	15	0	15	
HDV blq	186	0	0	8.675	0	15	11%
MXB total	1254	5	0	34	0	34	
MXB main	597	5	0	7	0	7	
MXB blq	56	0	0	2	0	7	3%

blq=Below Limit of Quantitation

Table 10. Covariates at study entry.

Covariate	average	2.5% ile	97.5% ile	min	max
Age (y)	40.4	26	62.05	21	64
WT (kg)	75.8	53.5	104.1	50.5	109.5
FFM (kg)	54.3	36.4	71.8	34.6	75.0
Renal Function	1.1	0.7	1.5	0.6	1.6
ALT (U/L)	115.5	40.8	381.8	32.0	469.0
GGT U/L)	70.5	17.8	231.7	13.0	277.0
Total Bile Acids (umol/L)	10.0	0.8	25.3	0.1	148.8
Albumin (g/L)	43.3	35.0	50.0	31.0	53.0
Platelets (10^9/L	159.8	91.5	244.1	8.0	277.0
HBSAG (IU/mL)	15869	327	47401	12	77885

Sex	female	33%
	male	67%
Race	Caucasian	85%
	Asian	13%
	Euro-Asian	0.8%
	Black	0.8%

popPK structure model and model evaluation

The model structure was obtained from a previously reported model in healthy subjects. The plasma concentrations of MXB were described using a first-order input with two compartment distribution. Elimination was described by a first-order process combined with a saturable target mediated disposition (TMD) process (Figure 9). The pharmacokinetics of bulevirtide were estimated independently of HDV. The runtime for the PK sub- and main-study model was too long to perform a bootstrap analysis and the asymptotic estimates of standard error were not obtainable for numerical reasons within NONMEM. Bootstrap estimates of the parameters and 95% confidence intervals obtained from the PK sub-study are shown in Table 10. The VPCs over the full 24-week period of treatment show that concentrations at each dose rate remain stable from week 4. The predictions for the 2 mg/day dose rate (Figure 10) are somewhat higher than the observations which may reflect mis-specification of the treatment dependent elimination process model. There is better agreement between the observed and predicted median concentrations for the 5 mg/day (Figure 11) and 10 mg/day (Figure 12) dose rates.

Figure 9. bulevirtide popPK model structure, originally developed for healthy subjects and used for patients here.

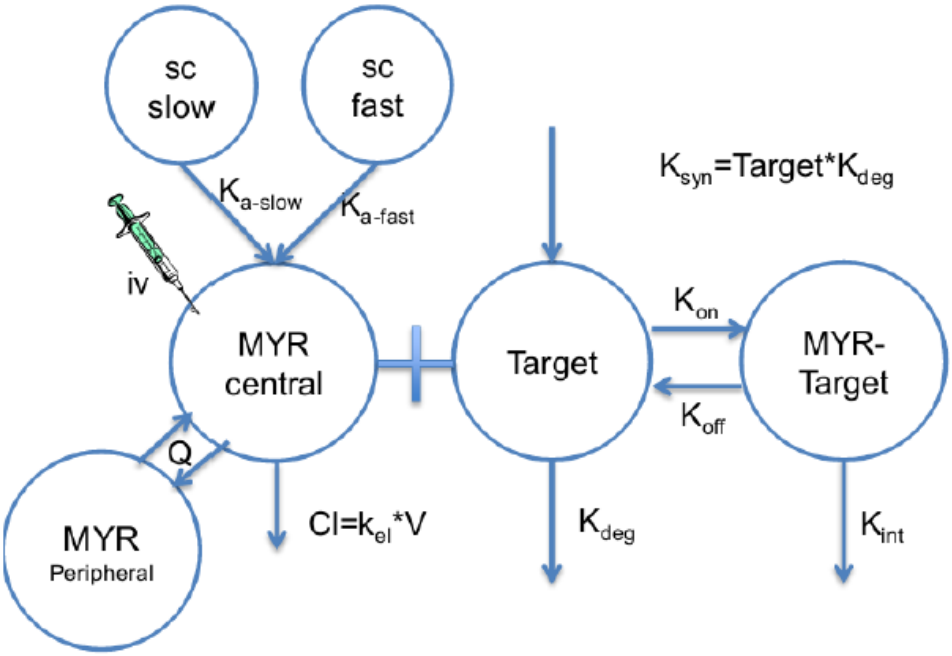


Table 11. Bootstrap parameter estimates (100 replicates) for study 202 (PK-sub study only).

Parameter	Description	Units	Original	Bootstrap average	2.5% ile	97.5% ile	RSE
POP_VCENTRAL	Central volume of distribution of MXB	L/70kg	1.55	1.69	1.36	2.63	22%
POP_CL	First-order clearance of MXB	L/h/70kg	1.71	1.72	1.19	2.26	13%
POP_VPERIPHERAL	Peripheral volume of distribution of MXB	L/70kg	0.46	0.50	0.40	0.75	17%
POP_Q	Intercompartmental clearance of MXB	L/h/70kg	0.04	0.05	0.02	0.08	26%
POP_KA_FAST	First-order rate constant for fast absorption	1/h	0.525	0.548	0.402	0.801	18%
POP_KA_SLOW	First-order rate constant for slow absorption	1/h	0.127	0.134	0.102	0.236	23%
POP_F_BIOAV	Bioavailability	.	0.845	FIXED	.	.	.
POP_FDOSE_FAST	Fraction of dose absorbed by fast process	.	0.420	0.424	0.262	0.550	16%
FFAT_V	Ffat for volumes of distribution	.	1.000	FIXED	.	.	.
FFAT_CL	Ffat for clearances	.	1.000	FIXED	.	.	.
BSV_VC	BSV of central volume for MXB	.	0.669	0.683	0.416	0.963	18%
BSV_CL	BSV of clearance for MXB	.	0.157	0.158	0.128	0.227	16%
BOV_VC1	BOV of central volume for MXB	.	1.17	1.28	1.02	1.95	18%
BOV_CL1	BOV of clearance for MXB	.	0.437	0.457	0.370	0.802	23%
PPV_Q	PPV of intercompartmental clearance of MXB	.	0.212	0.224	0.154	0.380	27%
PPV_VP	PPV of peripheral volume of MXB	.	0.070	0.077	0.049	0.127	21%
BSV_KA	BSV of first-order rate constant	.	0.338	0.350	0.249	0.560	20%
BOV_KA1	BOV of first order rate constant	.	0.139	0.174	0.124	0.451	52%
BSV_F	BSV of bioavailability	.	0.409	0.425	0.340	0.626	17%
BOV_F1	BOV of bioavailability	.	0.135	0.142	0.102	0.230	22%
PPV_RUV_CMXB	PPV of RUV for MXB	.	0.371	0.362	0.262	0.475	14%
RUV_CV_CMXB	Proportional residual error for MXB	.	0.307	0.311	0.260	0.381	11%
RUV_SD_CMXB	Additive residual error for MXB	ng/mL	1.23	1.33	0.93	1.86	19%
POP_FREE	Unbound target concentration	nmol/L	676	684	554	875	9%
POP_KON	MXB association rate constant	1/(h*nmol/L)	0.00737	0.00734	0.00663	0.00798	4%
POP_KOFF	MXB dissociation rate constant	1/h	0.0548	0.0541	0.0364	0.0677	13%
POP_T2OFF	MXB dissociation half-life	h	12.6	12.8	10.2	19.0	13%
POP_KD	MXB equilibrium binding constant	nmol/L	7.44	7.38	4.71	9.48	14%
POP_KD	MXB equilibrium binding constant	ng/mL	40.1	39.8	25.4	51.2	14%
POP_KDEG	Target elimination rate constant	1/h	0.0157	0.0143	0.0067	0.0186	19%
POP_KINT	MXB-Target elimination rate constant	1/h	0.144	0.130	0.072	0.151	17%

Model=4038_PK_TargetBi_FreeEst_CMXB_tbwVCL_B
PPV=Population Parameter Variability; RUV=Residual Unidentified Variability
RSE=Relative standard error

Figure 10.

prediction corrected VPC for 2mg/Day for study 202. (data only left, pcVPC right).

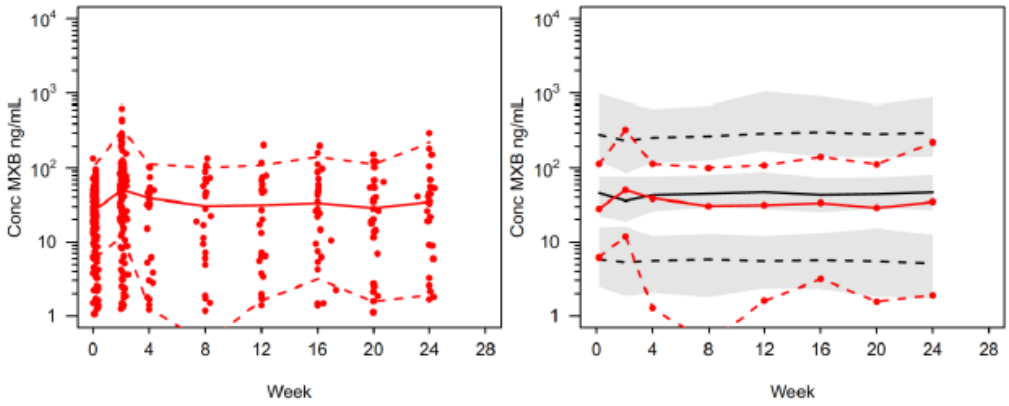


Figure 11. prediction corrected VPC for 5mg/Day for study 202.

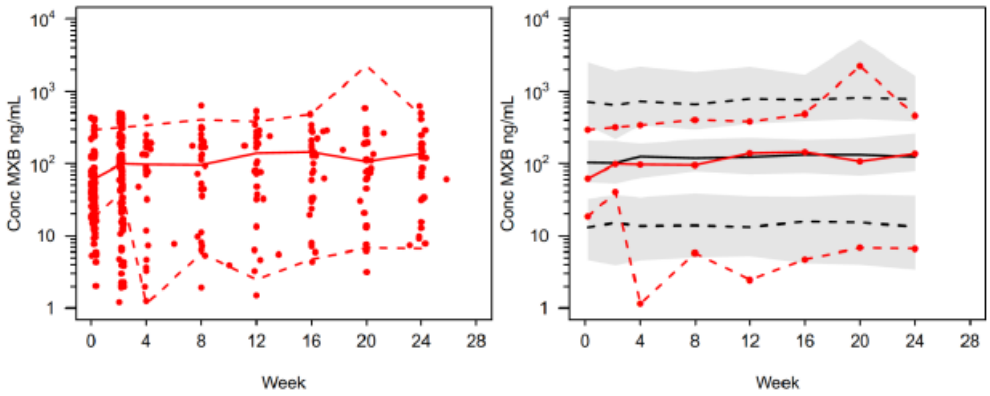
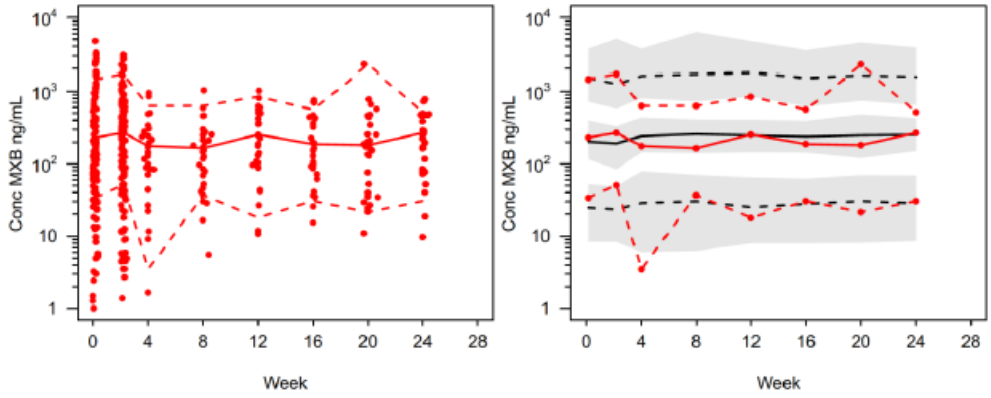


Figure 12. prediction corrected VPC for 10mg/Day for study 202.



2.4.3. Pharmacodynamics

Mechanism of action

Bulevirtide is a 47-amino acid long, N-terminally myristoylated, HBV-L-protein derived lipopeptide. It blocks the entry of HBV into hepatocytes by binding to and inactivating NTCP/SLC10A1 (sodium taurocholate co-transporting polypeptide), a bile salt liver transporter serving as essential HBV and HDV entry receptor.

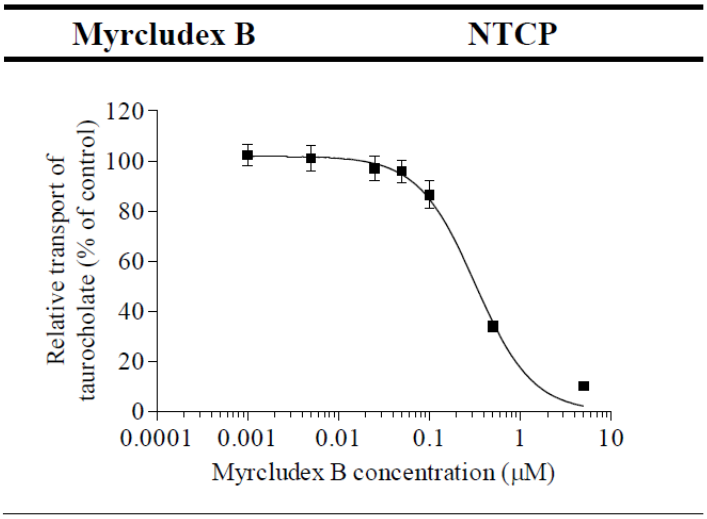
Two regions of NTCP, one located on the first extracellular loop (residues 84-87) and the other likely more buried (residues 157-165), are required for viral infection and largely determine HBV species specificity at the entry level.

Bulevirtide acts at a post attachment step probably misdirecting the entry route of HBV to an unproductive cellular pathway. Bulevirtide does not directly interfere with viral production or elimination of the virus. By blocking the essential entry receptor, the de novo infection of liver cells is decreased, viral spread is inhibited, and the life cycle of HDV is disrupted. By preventing viral spread, the number of the infected cells in the liver is expected to decline through immunological mechanisms and viral cytopathic effects.

Inhibition of NTCP by bulevirtide

The interaction of bulevirtide with the human NTCP has been investigated in an uptake transporter inhibition assay. Bulevirtide inhibited the NTCP-mediated probe substrate (taurocholate) accumulation in a dose-dependent manner (0.001, 0.005, 0.025, 0.05, 0.10, 0.50 and 5.00 µM) with a maximum inhibition of 90%; the calculated IC_{50} was 0.32 µM.

Figure 13. Effect of NTCP-mediated probe substrate (taurocholate) transport by bulevirtide in the uptake transporter inhibition assay – Human NTCP



In addition, the interaction of bulevirtide with the rat NTCP was investigated in an uptake transporter inhibition assay using CHO-K1 cells overexpressing the transporter. Bulevirtide inhibited the rat NTCP-mediated taurocholate transport in a dose-dependent manner (0.001, 0.005, 0.025, 0.05, 0.10, 0.50 and 5.00 µM) with a maximum inhibition of 99% at 5 µM. The calculated IC_{50} value was 0.068 µM.

Antiviral activity

The non-GLP study OMZ-201 addressed its antiviral activity in cells susceptible to HBV infection *in vitro*; HepaRG cells. To determine IC50, cells were pre-incubated with different concentrations of bulevirtide and subsequently infected with HBV carrying the large envelope proteins from different genotypes (B, C, D, E and G), or with sera from HDV infected patients. At day 14 post infection, the secreted HBsAg an HBeAg in the cell culture supernatant was measured by ELISA. In parallel, infection outcome was analysed by HBcAg-specific immunofluorescence (IF). In order to determine the efficacy and inhibitory activity of bulevirtide on HDV, an HDAg-specific IF was performed, and HDAg-positive cells were counted by fluorescence microscopy. A potential drug-drug interaction with entecavir was also investigated using the same experimental procedure.

Bulevirtide successfully inhibited all tested HBV genotypes and HDV isolates with IC50 values ranging from 14.5 to 834.0 pM, depending on the virus titer and cell culture conditions and did not show any signs of cytotoxicity in concentrations up to 50 µM.

Table 12. Inhibition of HBV genotypes (B, C, D, E and G) and HDV by bulevirtide in HepaRG cells

Virus/Genotype	System	Virus input titer	Method	IC_{50}
HBV / B	HepaRG	1.1 x 10^6 ge	HBsAg, IF	158.5 pM
HBV / C	HepaRG	5.3 x 10^6 ge	HBsAg, IF	77.5 pM
HBV / D	HepaRG	1.0 x 10^{10} ge	HBsAg, HBeAg, IF	14.5 pM
HBV / D	HepaRG	3.2 x 10^{10} ge	HBsAg, HBeAg, IF	< 66 pM
HBV / E	HepaRG	6.7 x 10^8 ge	HBsAg, IF	834.0 pM
HBV / G	HepaRG	6.7 x 10^8 ge	HBsAg, IF	540.6 pM
HDV serum 1	HepaRG	Not determined	IF	45.9 pM
HDV serum 2	HepaRG	Not determined	IF	331.9 pM

HBV = Hepatitis B virus, HDV = Hepatitis delta Virus, ge = genome equivalents, HBsAg = HBV surface antigen, HBeAg = HBV e antigen, IF = immunofluorescence; Table was taken form study report OMZ-201.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Quantification of bulevirtide

Bulevirtide does not have a stable tertiary structure, therefore a LC-MS/MS based quantification is acceptable. Overall, the provided LV-MS/MS methods are adequately validated for the intended purpose, despite the lack of cross-validation.

Bile acids

The MS based methods were found adequately validated for the intended use. Bile acid concentrations used for efficacy and safety analyses were based on data generated with ELISA based methods.

Immunogenicity

Two different methods were used, and since they have different positive controls, their results should not be compared directly. Analysis reports from the clinical studies were not initially submitted, but these were provided by the Applicant upon the assessor's request.

Since bulevirtide is a 47-amino acid peptide with a fatty acid chain, it is considered a therapeutic protein. Therefore, a multi-tiered immunogenicity assessment strategy (screening, confirmation, titer, neutralising capacity) would be required or the lack of it should be justified.

The Applicant provided a justification for the lack of titration by including a standard in the confirmation assay, thus providing concentrations of ADAs. This is still to be viewed as semi-quantitative, since ADAs are polyclonal, but is adequate in place of a titration assay. Regarding the lack of assay for the neutralising potential of these ADAs, the Applicant compared the HDV RNA response, the ALT and bile acids stratified by ADA status. In all cases, this was in a similar range in both groups, thus showing that if NAbs are present, their effect is not clinically significant.

The radioimmunoassay was found adequately validated for the intended purpose.

The ELISA assay was validated for the intended purpose. The fatty acid was removed for the capture of ADAs in the ELISA (report 16028), thus ADAs directed towards the fatty acid component of bulevirtide could not be detected by the present assay. However, the Applicant has further discussed this aspect and justified the lack of anticipated impact on the immunogenicity results. Myristic acid is saturated long-chain fatty acid with a 14-carbon backbone, which is naturally found in palm oil, coconut oil, butter fat, bovine and breast milk. According to the Applicant, in the dose range in which the Hepcludex is intended to be administered, no additional biological effects or myristic acid (such as toxicity or immunogenicity) can be expected, compared with those which may occur with the dietary uptake. No further information was required in this regard. The cut-point selected for the confirmation assay was lower (0.1%) than the usually accepted 1% false positive rate. The use of this tighter false-positive coefficient increases the rate of false-negative results and is not recommended. Therefore, a report with data using a cut point of 1 % was requested. The Applicant has provided a new amendment to the validation report 16028 with the requested cut-point at 1% false negative rate. The Applicant also presented a summary table of all immunogenicity results presenting the number of patients that were positive in the screening and became negative in the confirmation assay after the change of cut-point from 0.1% to 1% false positive rate, stratified per study, dose and timepoint

PK properties

In general, the characterisation of bulevirtide pharmacokinetics appears adequate. All clinical studies have indicated non-linear pharmacokinetics of bulevirtide. Clearance and volume of distribution decreased with increasing doses, while the AUC increased more than proportionally. This phenomenon was attributed to target-mediated drug disposition (TMDD) and corresponding model was developed by the Applicant describing it mathematically. Overall, it appeared that there was no significant influence of ADAs on bulevirtide PK that would require a dose adjustment (e.g. see figure below from the MYR202 study).

Figure 14 – MYR202 mean bulevirtide PK level presented by treatment group and bulevirtide ADA status

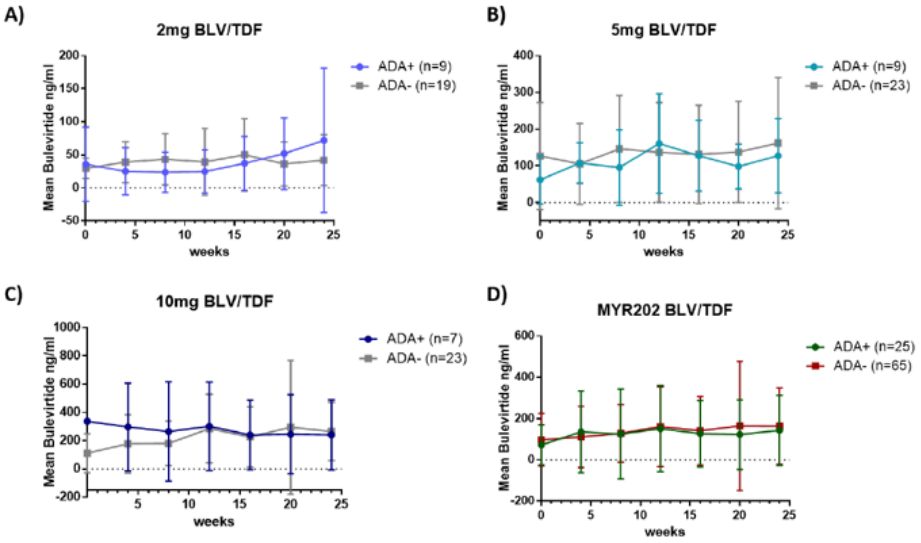


Figure 2. MYR202 mean Bulevirtide PK levels presented by treatment group and bulevirtide ADA status. Bulevirtide PK levels were taken from the PK main study. (A) Mean bulevirtide concentration in plasma during treatment with 2mg bulevirtide. (B) Mean bulevirtide concentration in plasma during treatment with 5mg bulevirtide. (C) Mean bulevirtide concentration in plasma during treatment with 10mg bulevirtide. (D) Pooled mean bulevirtide PK levels in patients positive for bulevirtide-specific ADA compared to patients being ADA negative in MYR202 over 24 weeks.

The bioavailability (F) after s.c. administration in study MYR101 estimated (by the Assessor) based on non-compartmental analysis for doses of 5 and 10 mg was 48% and 57%, respectively. The applicant has performed non-linear mixed effects modelling approach and estimated F to be 85%, i.e. a higher value in comparison to F from the non-compartmental PK estimation. There is no popPK report from the analysis of MYR101. Without a complete report, the F parameter derived from a model described only in a publication, with limited details on model development and validation, should not be used as fix parameter. This represent an issue for the model reliability and the 85% F may not be a reliable estimate.

No mass balance study with radio labelled bulevirtide was performed. No *in vitro* studies investigating bulevirtide as CYP substrate were performed. Lack of these studies is considered acceptable when considering its structure - 47-amino acid synthetic peptide with a fatty acid (MW 5398.9 g/mol) and an expected elimination pathway via catabolism to amino-acids by peptidases.

The lack of dedicated clinical study in renally impaired subjects was justified by the Applicant. Given that small proteins (e.g. bulevirtide's MW is only about 5 kDa) often are renally excreted followed by tubular re-absorption and subsequent renal metabolism (EMA's Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins), the Applicant was asked to address whether renal filtration/metabolism may be of importance for bulevirtide elimination. All relevant aspects of bulevirtide in this regard such as e.g. molecular size, plasma protein binding and its possible catabolic pathways needed to be considered. Furthermore, reliability of urine data in study MYR102 (which indicated no presence of bulevirtide in urine) was also questioned in terms of the applied bioanalytical method and its low recovery. The Applicant has acknowledged the drawback of the applied bioanalytical method in terms of low recovery values of bulevirtide (36-46%) from the urine samples. However, in general, it is agreed with the Applicant's

argument that due to the almost complete plasma protein binding, the glomerular filtration is most probably not a relevant factor for the elimination of bulevirtide.

The mean half-life ($t_{1/2}$) of bulevirtide after its single dose of 2 mg s.c. in all PK studies ranged approximately from 4 up to 7 hours.

No study of the impact of moderate or severe hepatic impairment on bulevirtide PK has been performed. Presently, therefore, there are no data to support the use in decompensated liver disease. The Applicant has stated the following timeline regarding this study: "it is planned to initiate the study (first patient enrolled) latest in 2021, and to have the PK data available in 2022".

Plasma protein binding estimated *in vitro* by cross filtration technique indicted a very low fu < 0.1%. Reason for such a high (almost complete) plasma protein binding of bulevirtide was explained by its chemical structure, i.e. the presence of the N-terminal myristic acid as the key determinant for a high degree of bulevirtide binding to the human albumin.

Interactions

Applicant has conducted all *in vitro* DDI studies (concerning relevant CYP enzymes and transporters) with bulevirtide concentrations of up to at least 5 µM, which is considered adequate and in accordance with the EMA's DDI guideline.

Positive *in vitro* inhibitory signals were observed for NTCP, BSEP, MDR1, OATP1B1 and OATP1B3 transporters. Importantly, clinical DDI study investigating bulevirtide effect on OATPs is currently ongoing, and a corresponding SmPC warning for potential DDI is proposed until the results become available. Based on the obtained *in vitro* IC50 values for BSEP and MDR1 transporters, no *in vivo* studies were considered necessary. Inhibition of NTCP *in vivo* was expected as it represents the proposed mode of bulevirtide pharmacodynamic effect. No induction nor direct inhibitory *in vitro* signals were detected for all tested CYP enzymes. Overall, the submitted *in vitro* program for bulevirtide appears sufficient.

Apart from the *in vitro* DDI experiments, the Applicant has conducted *in vivo* DDI study in healthy volunteers within MYR102. This study investigated bulevirtide's DDI potential as a "perpetrator" on tenofovir (victim; drug expected to be used concomitantly) exposure. No significant changes in the tenofovir exposure were observed with and without bulevirtide treatment.

In addition, in the same MYR102 study, midazolam was also included as the victim drug (CYP3A4 substrate) even though no *in vitro* signals were observed for bulevirtide regarding CYP enzymes. The reason for conducting clinical DDI study with midazolam was explained by the Applicant by stating that the elevated levels of bile acids (as observed with bulevirtide treatment) could still influence the CYP activity levels. Obtained DDI results with midazolam were not fully conclusive (no AUC profiles nor C_{max} were available for midazolam) because of its sparse sampling which covered only a short time period between 2 and 4h post-dose (i.e. only partial AUCs). However, it is worth noting that there was a significant increase in midazolam $AUC_{2\text{-}4h}$ as a consequence of the concomitant therapy, and therefore an inclusion of corresponding information in the SmPC was implemented. Finally, the Applicant has conducted another clinical DDI study (MYR202) with midazolam and bulevirtide in the target population. Unlike the study MYR102 which only looked at the partial AUCs of midazolam, study MYR202 included rich sampling of midazolam up to 24h post-dose. However, the obtained results were considered inconclusive. One of the reasons for inconclusive data might be technical difficulties which occurred during this study, as stated by the Applicant.

No studies investigating bulevirtide as a victim drug in potential DDIs were conducted.

Exposure in overweight patients was plotted and discussed by the applicant. Only 6 patients had a BMI>30, overall exposure were largely overlapping with patients with BMI<30.

popPK

The plasma concentrations of MXB were described using a first-order input with two compartment distribution. Elimination was described by a first-order process combined with a saturable target mediated disposition (TMD) process. The pharmacokinetics of bulevirtide were estimated independently of HDV.

The applicant was asked to justify only using MYR-202 data in popPK analysis or update the dataset and update the popPK model. The applicant explained that with several ongoing studies, it was not a strategy to constantly update the model with any incoming data. The applicant plans the next update upon availability of 301/204 interim data. The rapporteur considers it good practice to include all relevant data. Using only MYR202 data may restrict the conclusions made on the modelling results. The PKPD modelling has been deemed to uncertain, thus the use of the popPK model is to describe PK. Using only the MYR202 data at this stage is not optimal but deemed adequate. The commitment to update the model in the future is encouraged.

The applicant has discussed the model structure and using a model structure including TMDD is considered adequate, however the model cannot be deemed mechanistic. The VPCs for the popPK model are deemed adequate.

Pharmacodynamics

Initially, the applicant was asked to provide a figure plotting bulevirtide plasma concentration against NTCP occupancy rate and to clarify whether a specific cut-off of receptor saturation is required for optimal anti-viral activity but instead provided a plot estimated using the PK/PD model to estimate only receptor occupancy. The model cannot be used to provide evidence supporting the minimal clinical effect required for the intended clinical response. Currently, no reassurance has been provided that the minimal activity predicted for the 2 mg BLV is sufficient from a clinical/efficacy point of view and it has been confirmed that the dose of 10 mg allows higher target saturation rate and leads to an increment of the plasma drug concentration. The model provided by the Applicant cannot be considerate supportive of the dose selection, which is thus based only on clinical efficacy and safety data.

SmPC

Section 5.2 in the SmPC was sparse. The following information in the SmPC: Potential influence of concomitant therapies, relevant patient factors, accumulation ratios (C_{max} and AUC), typical value and variability in PK parameters between studies (e.g. CL, Vd, $t_{1/2}$) was provided by the Applicant.

2.4.5. Conclusions on clinical pharmacology

In general, the characterisation of bulevirtide pharmacokinetics appears adequate. There are no issues concerning the PK of bulevirtide which would require further studies/explanations.

The PK/PD model provided cannot be considered supportive of the dose selection, which is thus based only on clinical efficacy and safety data.

2.5. Clinical efficacy

2.5.1. Dose response study and main clinical studies

Bulevirtide blocks the entry of hepatitis B virus (HBV) and hepatitis delta virus (HDV) into hepatocytes by binding to and inactivating sodium taurocholate co-transporting polypeptide NTCP/SLC10A1, a bile salt liver transporter serving as essential HBV and HDV entry receptor.

The clinical development program of bulevirtide has been designed to investigate the potential for treatment of chronic HBV and HDV infection in adult patients. Bulevirtide was evaluated in Hepatitis e-antigen (HBeAg) negative chronic Hepatitis B (CHB) patients. However, the activity in HBV infection was insufficient to motivate further study given the present treatment landscape. However, a sub-study of MYR201 (HDV) in CHD patients revealed significant potential for antiviral efficacy of bulevirtide against HDV infection. In MYR202, no major differences in HDV RNA decrease across treatment arms (2 mg, 5 mg, and 10 mg) are observed at W4 (-0.59, -0.39, -0.54, respectively) and W8 (-1.01, -0.92, -1.14, respectively). For bulevirtide 2 mg/day, median viral decay from baseline to W4 and W8 was consistent in MYR202 and MYR203 studies.

The application is based on limited data given the unmet medical need in the target disease. Further studies are ongoing.

Table 13. Overview of clinical studies and compassionate use in chronic HDV infection contributing to the evaluation of efficacy

Clinical study code	**Study Title**	**Number of patients with available efficacy data**
MYR202 / phase II	A Multicenter, Open-label, Randomized Clinical Study to Assess Efficacy and Safety of 3 Doses of Myrcludex B for 24 Weeks in Combination with Tenofovir Compared to Tenofovir Alone to Suppress HBV Replication in Patients with Chronic Hepatitis D	90
MYR203 main study / phase II	A Multicenter, Open-label, Randomized, Comparative, parallel-arm phase II study to Assess efficacy and safety of Myrcludex B in combination with Peginterferon alfa-2a versus Peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent	45
MYR201 (HDV)	Randomized open-label substudy of daily Myrcludex B plus pegylated interferon-alpha-2a in patients with HBeAg negative chronic hepatitis B co-infected with hepatitis delta	16
Supportive efficacy data		
CUP	Compassionate use of 10 mg bulevirtide	4

Main studies

Clinical efficacy in chronic HDV infection has been studied in two phase 2 studies: MYR202 (completed) and MYR203 (ongoing). In the MYR203 study, the evaluation of a first 4 cohorts is completed, these cohort are referenced as MYR203 study in the application. Two additional cohorts are ongoing (MYR203 extension); however, only information on deaths, SAEs and pregnancies are included into this application.

All studies that contribute to the efficacy evaluation of bulevirtide were open-label, randomised, controlled trials with a parallel-group design.

The MYR202 study has compared three doses of bulevirtide versus no HDV-targeted therapy. Patients of the control group received nucleotide analogue tenofovir (TDF) for control of underlying HBV infection. In the MYR203 study, patients of the control group received pegylated interferon alpha 2a (PEG-IFNα), which is used in HDV patients per recommendation of the current treatment guidelines (EASL 2017).

The study endpoints included the occurrence of at least 2 log10 decline to baseline and/or undetectable HDV ribonucleic acid (RNA), alanine aminotransferase (ALT) normalisation and hepatitis B virus surface antigen (HBsAg) response at different treatment time points (e.g. end of treatment, end of follow-up).

In MYR202, the patients received combined treatment with bulevirtide and TDF for 24 weeks followed by a period of 24 weeks of continued TDF treatment alone. The control group received TDF only for the complete period of 48 weeks.

The treatment period was 48 weeks in MYR203 where the patients were treated either with bulevirtide + PEG-IFNα, with bulevirtide only, or with PEG-IFNα only, followed by 24 weeks without treatment.

Note that the bulevirtide was previously named "Myrcludex B". This name is used in most/all reports described but was replaced by the now approved international non-proprietary name "bulevirtide" in this document except in study titles, where the original wording is retained.

The design of the MYR202 and MYR203 studies suggest two different treatment approaches; one using bulevirtide as continuous monotherapy of indefinite duration aiming at on-treatment virological control and ALT normalisation (along with NUC therapy for HBV control) and the other using bulevirtide in combination with PEG-IFN for finite duration therapy, with the purpose of inducing a sustained off-treatment response.

MYR202 - A multicenter, open-label, randomized clinical study to assess efficacy and safety of 3 doses of Myrcludex B for 24 weeks in combination with Tenofovir compared to Tenofovir alone to suppress HBV replication in patients with chronic hepatitis D

Methods

Study Participants

This study was performed at four sites in Germany and 12 sites in the Russian Federation. Inclusion and exclusion criteria are presented below.

Both HBeAg positive and negative patients were allowed in the study. Patients failing previous treatment with IFN or were considered IFN-intolerant were included, as well as patient with compensated cirrhosis. Patients with decompensated liver disease were not studied.

Of note, patients with previous IFN treatment could only be enrolled 30 days after the last IFN dose and NUC therapy for HBV was to be ongoing or initiated no later than 12 weeks prior to start of study therapy.

Key inclusion criteria

In order to be enrolled in the MYR202 study, participants had to meet all the inclusion criteria listed below.

1. Age from 18 to 65 years at the time of the ICF signature.
2. Positive serum HBsAg for at least 6 months before screening.
3. Positive serum anti-HDV antibody for at least 6 months before screening.
4. Positive PCR results for serum HDV RNA at screening.
5. Patients with liver cirrhosis, irrespective of previous interferon treatment.
6. Patients without liver cirrhosis, who failed prior interferon treatment or for whom, in the opinion of the Investigator, such treatment is currently contraindicated (including history of interferon intolerance).
7. ALT level >1 x ULN, but less than 10 x ULN.
8. Previous nucleotide/nucleoside analogue treatment within at least 12 weeks prior to the planned start of study treatment or patient's willingness to take Tenofovir for at least 12 weeks prior to the planned start of study treatment.

Key exclusion criteria

Participants who met any of the following exclusion criteria were not eligible for the study.

1. Child-Pugh score of B-C or over 6 points.
2. HCV or HIV coinfection. Patients with anti-HCV antibodies can be enrolled, if screening HCV RNA test is negative.
3. Creatinine clearance <60 mL/min.
4. Total bilirubin ≥ 2mg/dL. Patients with higher total bilirubin values could be included after the consultation with the medical monitor, if such elevation could be clearly attributed to Gilbert's syndrome associated with low-grade hyperbilirubinaemia.
5. Any previous or current malignant neoplasms, including hepatic carcinoma.
6. Current or previous decompensated liver disease, including coagulopathy, hyperbilirubinaemia, hepatic encephalopathy, hypoalbuminaemia, ascites, and oesophageal varices haemorrhage.

Treatments

Three different doses of bulevirtide for 24 weeks in combination with TDF for 48 weeks are compared to TDF only for 48 weeks. However, see further comments below regarding the randomisation algorithm.

The doses of Myrcludex B used in the study were 2, 5 or 10 mg. Patients performed subcutaneous self-injections of Myrcludex B. Subcutaneous injections had to be performed every 24±1 hours after the first dose. The total duration of the therapy was 24 weeks.

Patients were randomised to four treatment groups:

• Group A (n=28): Myrcludex B 2 mg/day + Tenofovir 245 mg

• Group B (n=32): Myrcludex B 5 mg/day + Tenofovir 245 mg

• Group C (n=30): Myrcludex B 10 mg/day + Tenofovir 245 mg

• Group D (n=28): Tenofovir 245 mg

Objectives

Primary objective

To investigate the efficacy of Myrcludex B and to compare three doses of Myrcludex B versus observation on background therapy with Tenofovir in patients with CHD.

Secondary objectives

To investigate additional efficacy parameters, safety and tolerability, as well as to assess pharmacokinetics (PK) and immunogenicity, of three doses of Myrcludex B in in patients with CHD.

Outcomes/endpoints

Primary variable

The primary variable was HDV RNA response, defined as HDV RNA negativation or a decrease in HDV RNA by ≥2 log10 IU/mL from baseline to week 24.

Secondary efficacy variables

- Durability of HDV RNA response to 24 weeks post treatment (from week 24 to week 48)
- Combined treatment response, defined as HDV RNA response (HDV RNA negativation or ≥2 log10 IU/mL decline) and normal ALT at treatment week 24 and week 48 (analysis at week 48 added in SAP)
- Changes in ALT values at week 24 and week 48 compared to baseline
- Lack of fibrosis progression based on transient elastometry (fibroscan) at week 24 compared to baseline (Germany specific protocol)
- Changes (absence of increase) in fibrosis marker: serum alpha-2-macroglobulin at week 24 and week 48 compared to baseline
- Changes in HBsAg (defined as decline in HBsAg levels, disappearance of HBsAg and HBsAg seroconversion to anti-HBsAg) at week 24 and week 48 compared to baseline
- Change in HBV DNA levels at week 24 and week 48 compared to baseline
- Improvement of the histological findings (reduction of necroinflammation, absence of fibrosis progression, etc.) according to the liver biopsy study results or the absence of a fibrosis progression according to the findings of transient elastometry (fibroscan) at week 24 compared to baseline (Russia specific protocol)

The primary and secondary efficacy variables are considered relevant for evaluating the study objectives. The secondary efficacy variable of combined response (HDV RNA and ALT response) is key to the regulatory evaluation, based on CHMP scientific advice. It should be noted that the statistical analysis plan was not locked before the study was completed and the database had been opened.

Sample size

As stated above, HDV RNA response, defined as HDV RNA negativation or a decrease in HDV RNA by ≥2 log10 IU/mL from baseline to week 24 was the primary efficacy parameter. Using a two-sided test with a power of 80%, a significance level of $\alpha = 0.05/3 \approx 0.0167$ (using Bonferroni correction to adjust for multiple testing; the three active treatment groups will be tested separately against the control group), and a superiority limit (test margin) of 5%, a sample size of 28 patients per group was assumed be sufficient to detect a 34% increase in response compared to the control group, assuming a response rate of 3% for the control group.

Assuming a drop-out rate of 5%, a total number of 30 patients per treatment group were needed.

Randomisation and blinding (masking)

This was an open-label study.

Randomisation was performed in a ratio of 1:1:1:1 using an Interactive Web Response System (IWRS). The randomisation was stratified by country (Russia/Germany), PK sub-study consent signing and the presence of liver cirrhosis.

The initial randomisation list based on Clinical Study Protocol version 4.0, was generated using permuted block randomisation. After implementation of Clinical Study Protocol version 5.0 which introduced a PK sub-study a second randomisation was superimposed on the randomisation list for Russia. 25 patients who gave their consent to participate in the PK sub-study were administered with midazolam during pre-treatment and were subsequently randomised with the IWRS to one of the Myrcludex B treatment groups (groups A-C) in a 1:1:1 ratio. Patients who didn't give their consent for PK sub-study were randomised to groups A-D up to the overall ratio in the study 1:1:1:1. This randomisation was done without using permuted blocks. To increase the recruitment to the PK sub-study, randomisation numbers which were linked to the PK sub-study participation were allocated primarily in the final phase of the study circumventing the sequence of randomisation numbers.

The randomisation with respect to giving consent for the PK sub-study is a confounding factor, possibly steering patients with better overall health and clinical outcome to the bulevirtide arms. Also, the linking of randomisation numbers to the PK sub-study late in the study is at risk of intervening with randomisation as it could then be expected that patients included at this time would receive bulevirtide rather than tenofovir only. Of 120 randomised patients, only 93 were randomised between all four study groups. Hence, a post hoc sensitivity analysis has been performed on this subset of patients.

Randomisation outside the PK sub-study, after CSP version 5.0, was done without using permuted blocks which probably caused the slight imbalance in the numbers of patients in the treatment groups; this is however of no concern.

Description of the randomisation and stratification are referenced to the Randomisation Plan that cannot be found in the application file. According to the SAP, the stratification factor used was presence of cirrhosis,

while also country and PK sub-study were mentioned in the CSR. Details provided on request confirmed stratification by all three factors, however, with uncertainties around the PK group.

Statistical methods

Analysis populations

The modified intention-to-treat (mITT) analysis was defined as all randomised subjects who received at least one dose of study treatment. Analysis was based on the planned treatment (i.e. subjects analysed 'as randomised').

The per-protocol analysis set (PPAS) was defined as the subset of subjects in the mITT analysis set who completed the 24-week treatment period with efficacy results for Week 24 and for whom no major protocol deviations were reported. Per-protocol analysis was based on the actual treatment (i.e. subjects analysed 'as treated').

Safety analysis set was defined as all subjects who received at least one dose of the study treatment.

Efficacy analyses were performed on both the mITT (main analysis) and the per-protocol analysis set (supportive analysis).

The primary endpoint analysis

A null hypothesis of no clinically significant difference in proportion of HDV RNA response in each of the three MXB treatment groups (A, B and C), compared to the tenofovir only group (D), at Week 24, was tested using the one-sided Wald test for superiority, at a one-sided overall significance level of 0.05 adjusted for multiple testing according to Bonferroni–Holm. As supportive analysis, Fisher's exact test was used to test a null hypothesis of no difference in proportions against a two-sided alternative hypothesis separately for each of the three MXB treatment groups against the control group, at Week 24.

Secondary analyses

A null hypothesis of no difference between the MDX treatment groups and the control group in the change from baseline in HDV RNA levels was planned to be tested against a two-sided alternative hypothesis using a mixed-effects model for repeated measures (MMRM). Assessments from all post-baseline analysis visits up to Week 48 were considered for the dependent variable, and tests were performed at Weeks 24 and 48. The model was to include baseline HDV RNA as a fixed covariate, and treatment group, analysis visit, the interaction between treatment group and analysis visit, and presence of cirrhosis (the stratification factor) as fixed factors. An appropriate covariance structure was to be selected based on the Akaike information criterion, AIC. If the assumptions for the MMRM were not-fulfilled, a non-parametric analysis was to be performed instead, using two-sided van Elteren test (stratified Wilcoxon rank-sum test) adjusted for the stratification factor. All analyses on HDV RNA levels were based on log-10 transformed data.

Continuous secondary endpoints were planned to be analysed using MMRM or van Elteren test as described above, while differences in proportions were analysed using Fisher's exact test. Categorical data were presented using absolute frequency and percentage and Clopper–Pearson exact confidence intervals for binomial proportions.

Missing values

In general, no imputations of missing data were performed, unless stated otherwise. For all response

parameters, the missing equals failure (MEF) approach were used for the main analysis (i.e., subjects with missing data were considered as non-responders).

For the virology results, the following rules were applied:

- Values below the limit of detection were collected in the database as zero values.
- Values reported as '<x' (below the lower limit of quantification, LLOQ), were imputed as half the LLOQ value.
- 'Non-measurable' data were considered as missing data.
- Values reported as '>x' (above the upper limit of quantification, ULOQ), were imputed as the ULOQ value.
- For the log-10 transformed data, missing values due to untransformed values of zero were imputed as zero.

Multiplicity

Correction for multiple testing of 3 treatment groups (A, B, and C) vs control group (D) was done using the Bonferroni-Holm method for the primary and secondary efficacy variables, why adjusted p-values were presented in addition to the raw unadjusted p-values.

Interim analyses

An interim safety analysis was performed when 10 subjects of each arm had completed 28 days of treatment. Based on the results of the analysis, it was decided that cirrhotic subjects could be included in the study.

When all randomised subjects had completed the 24-week treatment period, an interim analysis on efficacy and safety of the study treatment was performed and documented in an interim study report.

Subgroup analysis

The following subgroups were defined:

- patients with cirrhosis at baseline
- patients with no cirrhosis at baseline
- patients with normal ALT levels at baseline
- patients with abnormal ALT levels at baseline
- patients who attended at least one follow-up visit
- patients who tested positive for HBeAg at screening.

The baseline value for a parameter was defined as the last non-missing value before the first dose of the study treatment.

SAP composition

The SAP was initially authored on 2018-10-24, and updated on 2018-11-13 (version 2.0, final). Date of the database lock is unknown. Analysis database was run 2019-05-20. The last patient's last visit was on 2018-01-31.

Changes from the planned analysis that was specified in the protocol included addition and analysis of secondary endpoints Change from baseline in HDV RNA levels at Week 24 and 48, and analysis of combined response at Week 48, as well as omitting analysis of anti-HBsAG as no patients had HBsAG loss.

Changes from pre-specified analysis after finalisation of the SAP

Changes in the planed analyses included change in the definition of baseline value for Tenofovir arm, and omitting some analyses for various reasons, as presented in Table 14.

Table 14 – Changes in planned analyses after finalisation of the statistical plan

Planned analysis	Details of change
Country and site level disposition of patients	It was decided after the finalisation of the SAP not to present the disposition of patients on a country or site level.
Subgroup analysis of combined response	It was decided after the finalisation of the SAP not to perform the planned subgroup analyses for combined response.
Myrcludex B terminal elimination half-life	It was discovered during the development of analysis datasets, that data for the Myrcludex B terminal elimination half-life were not available for subperiod II, and the planned analyses/presentations based on these data were thus omitted.
Midazolam and 1-OHMDL PK	It was discovered during the development of analysis datasets, that data for the Midazolam and 1-OHMDL AUC to infinity, AUC to the last measurable concentration, and terminal elimination half-life were not available for subperiods I and II, and the planned analyses/presentations based on these data were thus omitted.
Subgroup analysis	It was decided by the sponsor during the analysis of safety data, that the Early Termination visit for subject 01018-R049 was to be considered as a follow-up visit for the purpose of including the patient in the analysis of AEs for the subgroup of patients attending at least one follow-up visit.
Change in the baseline definitions	It was decided on 2019-02-18 to change the baseline definition for group D (Tenofovir only), since the date of first dose was reported for the three Myrcludex B arms only and thus could not be used to identify baseline values for group D. The impact of having different baseline definitions for the Myrcludex B groups and the control group was judged to be negligible. Baseline was thus defined as follows in the analysis of data: Unless stated otherwise, the baseline value for a parameter was defined as the last non-missing value before the first dose of the study treatment **for the Myrcludex B treatment groups. For group D (Tenofovir only), the baseline value for a parameter was defined as the last non-missing value before or on the date of randomisation.** **For the classification of medical history and concomitant medications as prior/concomitant, the date of first Myrcludex B treatment (groups A–C) or date of randomisation (group D) was considered as baseline.**

Performing the main efficacy analysis based on the mITT analysis set instead of all randomised subjects is not considered an issue as there are only 2 subjects (in the control group) who did not receive the study medication and exclusion of these subjects from the mITT analysis set yields a conservative approach in the comparative analysis.

One-sided testing on overall 5% significance level was performed. However, in the regulatory assessment, 2-sided tests on 5% level and 95% confidence intervals (2-sided) are considered in the interpretation of the results. The primary analysis was not stratified by the randomisation stratification factors, but a subgroup analysis was performed for subjects with/without cirrhosis.

The analysis of secondary continuous variables involved adaptive data-driven elements in the choice of the analysis method (parametric vs non-parametric) and covariance structure (in case MMRM was performed) adding to uncontrolled Type I error rate. The results of the normality tests that preceded justified a non-parametric analysis. In the responder analyses, subjects with missing data were considered as non-responders which is appropriate. The MMRM analysis method was not used. The interim efficacy analysis was performed when all subjects completed the 24-week treatment period, which allowed assessment of the primary endpoint for all subjects with no impact on the Type I error rate. The SAP was authored after the study completion, which is problematic in general, and particularly in open label studies, but this is not surprising considering that the initial purpose of the study was dose-finding and not pivotal. It can be noted that no changes from the protocol were made on the primary endpoint definition and analysis, and that the changes of the secondary analyses do not appear as crucial. Study design and the statistical analysis applied are flawed considering the low number of subjects and the methodological elements (such as open label, second randomisation, data-driven selection of the analysis type) that add to bias and uncertainty in the results. Due to these circumstances, efficacy is potentially overestimated to an unknown extent.

Results

Participant flow

The study participant flow is presented in the disposition table below.

Table 15 – Disposition of patients

	MXB 2 mg	MXB 5 mg	MXB 10 mg	Tenofovir	MXB total	Total
Screened						171
Screening failures						51
Randomised	28	32	30	30	90	120
Did not receive study medication	0	0	0	2 (6.7%)	0	2 (1.7%)
Received study medication	28 (100.0%)	32 (100.0%)	30 (100.0%)	28 (93.3%)	90 (100.0%)	118 (98.3%)
Completed the treatment period	28 (100.0%)	30 (93.8%)	29 (96.7%)	25 (83.3%)	87 (96.7%)	112 (93.3%)
Completed the study	28 (100.0%)	29 (90.6%)	28 (93.3%)	25 (83.3%)	85 (94.4%)	110 (91.7%)
Prematurely withdrawn from the study	0	3 (9.4%)	2 (6.7%)	5 (16.7%)	5 (5.6%)	10 (8.3%)
Analysis sets						
Safety analysis set	28 (100.0%)	32 (100.0%)	30 (100.0%)	28 (93.3%)	90 (100.0%)	118 (98.3%)
Modified intention-to-treat analysis set	28 (100.0%)	32 (100.0%)	30 (100.0%)	28 (93.3%)	90 (100.0%)	118 (98.3%)
Per-protocol analysis set	23 (82.1%)	26 (81.3%)	23 (76.7%)	20 (66.7%)	72 (80.0%)	92 (76.7%)
Pharmacokinetic concentrations analysis set	28 (100.0%)	32 (100.0%)	30 (100.0%)	1 (3.3%)	90 (100.0%)	91 (75.8%)
Pharmacokinetic analysis set	9 (32.1%)	7 (21.9%)	9 (30.0%)	0	25 (27.8%)	25 (20.8%)

Percentages are based on the number of randomised subjects within each treatment group.
Program: \Subprogs\Tables\DS Disposition.sas
Date and time program was run: 2019-05-23T08:34. Date and time analysis database was run: 2019-05-20T14:24

Reasons for screening failures were violations of one or several eligibility criteria, most commonly ALT levels outside the pre-determined range (inclusion criteria no 7), too low WBC and too low neutrophil count.

Two patients were randomised before all eligibility criteria were properly confirmed and one of those two patients together with 14 other patients were randomised and treated in violation of one or more eligibility criteria. These deviations were judged as major for all these 16 patients.

There were eight withdrawals from the study. All other patients (n=110) completed the study. The primary reasons for withdrawal were withdrawal by subject (four patients), progressive disease (one patient), lost to follow-up (one patient), AE (one patient) and other (one patient, did not wish to participate in the study).

The first patient's first visit in the study (first patient screened) was on 2016-02-16 and the last patient's last visit was on 2018-01-31.

Withdrawals from the study were slightly higher in the TDF-only arm compared to the bulevirtide-containing arms. Of note, two patients in the TDF-only arm did not receive study medication and 5/30 (16.7%) of patients withdrew from the study, in comparison with 5/90 (5.6%) in total in the bulevirtide-containing arms.

Baseline data

Demographics

Patient demographics are summarised below in Table 16.

Table 16. Demographics (safety analysis set)

	MXB 2 mg (N=28)	MXB 5 mg (N=32)	MXB 10 mg (N=30)	Tenofovir (N=28)	MXB total (N=90)	Total (N=118)
Age (years)						
n/nmiss	28/0	32/0	30/0	28/0	90/0	118/0
Mean (SD)	39.4 (8.3)	40.9 (9.5)	41.8 (11.3)	38.5 (8.7)	40.7 (9.8)	40.2 (9.5)
Median	38.0	39.0	39.0	37.0	39.0	38.0
Q1, Q3	35.5, 43.0	35.5, 44.0	33.0, 51.0	32.5, 44.5	35.0, 45.0	34.0, 45.0
Min, Max	21, 64	20, 61	26, 63	26, 63	20, 64	20, 64
Age groups						
<65 years	28 (100.0%)	32 (100.0%)	30 (100.0%)	28 (100.0%)	90 (100.0%)	118 (100.0%)
≥65 years	0	0	0	0	0	0
Sex						
Female	13 (46.4%)	11 (34.4%)	7 (23.3%)	8 (28.6%)	31 (34.4%)	39 (33.1%)
Male	15 (53.6%)	21 (65.6%)	23 (76.7%)	20 (71.4%)	59 (65.6%)	79 (66.9%)
Race						
American Indian or Alaska Native	0	0	0	0	0	0
Asian	7 (25.0%)	1 (3.1%)	3 (10.0%)	5 (17.9%)	11 (12.2%)	16 (13.6%)
Black or African American	0	1 (3.1%)	0	0	1 (1.1%)	1 (0.8%)
Native Hawaiian or Other Pacific	0	0	0	0	0	0
White	21 (75.0%)	30 (93.8%)	27 (90.0%)	23 (82.1%)	78 (86.7%)	101 (85.6%)
Height (cm)						
n/nmiss	28/0	32/0	30/0	28/0	90/0	118/0
Mean (SD)	168.5 (8.3)	172.9 (7.4)	173.8 (9.8)	172.8 (9.4)	171.8 (8.8)	172.0 (8.9)
Median	168.0	173.5	176.0	174.5	172.5	173.0
Q1, Q3	163.5, 174.5	167.5, 178.0	167.0, 180.0	163.5, 180.5	164.0, 178.0	164.0, 178.0
Min, Max	154, 188	159, 185	152, 188	156, 189	152, 188	152, 189
Body Weight (kg)						
n/nmiss	28/0	32/0	30/0	28/0	90/0	118/0
Mean (SD)	70.19 (13.54)	75.09 (12.54)	77.59 (13.72)	79.15 (17.21)	74.40 (13.45)	75.53 (14.49)
Median	68.00	73.55	78.45	76.05	72.65	73.85
Q1, Q3	62.00, 77.65	65.05, 85.00	65.30, 88.60	63.55, 93.50	64.50, 85.00	64.30, 87.00
Min, Max	52.0, 110.0	52.8, 95.0	51.0, 103.0	53.2, 105.2	51.0, 110.0	51.0, 110.0
BMI (kg/m²)						
n/nmiss	28/0	32/0	30/0	28/0	90/0	118/0
Mean (SD)	24.63 (3.65)	25.03 (3.19)	25.57 (3.22)	26.38 (4.63)	25.08 (3.33)	25.39 (3.70)
Median	23.96	24.92	25.58	27.17	25.09	25.21
Q1, Q3	21.78, 26.35	23.21, 27.39	23.49, 27.40	22.62, 29.87	23.27, 27.33	23.15, 28.09
Min, Max	17.7, 34.7	18.1, 31.8	18.3, 32.7	19.0, 33.9	17.7, 34.7	17.7, 34.7
BMI categories						
<30 kg/m²	27 (96.4%)	31 (96.9%)	28 (93.3%)	22 (78.6%)	86 (95.6%)	108 (91.5%)
≥30 kg/m²	1 (3.6%)	1 (3.1%)	2 (6.7%)	6 (21.4%)	4 (4.4%)	10 (8.5%)

n/nmiss = number of subjects with evaluable/missing data, Q1 = first quartile, Q3 = third quartile, SD = standard deviation
Percentages are based on the number of subjects within each treatment group.
Program: \Subprogs\Tables\DM.sas
Date and time program was run: 2019-05-23T08:34. Date and time analysis database was run: 2019-05-20T14:24

Table 17. Baseline characteristics MYR202

mITT population	**Arm A: (n=28) (n=19) BLV 2 mg/day + TDF**	**Arm B: (n=32) (n=25) BLV 5 mg/day + TDF**	**Arm C: (n=30) (n=21) BLV 10 mg/day + TDF**	**Arm D: (n=28) (n=28) TDF (245 mg/day)**	**Total: (n=118) (n=93)**
Age (years): Mean (SD)	39.4 (8.3) 40.7 (8.7)	40.9 (9.5) 40.6 (10.0)	41.8 (11.3) 38.7 (10.2)	38.5 (8.7) 38.5 (8.7)	40.2 (9.5) 39.6 (9.3)
Sex: Male (N, %) **Female (N, %)**	15 (53.6) 10 (52.6) 13 (46.4) 9 (47.4)	21 (65.6) 16 (64.0) 11 (34.4) 9 (36.0)	23 (76.7) 18 (85.7) 7 (23.3) 3 (14.3)	20 (71.4) 20 (71.4) 8 (28.6) 8 (28.6)	79 (66.9) 64 (68.8) 39 (33.1) 29 (31.2)
Race: Caucasian (N, %) **Asian (N, %)** **Black (N, %)**	21 (75.0) 15 (78.9) 7 (25.0) 4 (21.1) - -	30 (93.8) 24 (96.0) 1 (3.1) - 1 (3.1) 1 (4.0)	27 (90) 18 (85.7) 3 (10.0) 3 (14.3) - -	23 (82.1) 23 (82.1) 5 (17.9) 5 (17.9) - -	101 (85.6) 80 (86.0) 16 (13.6) 12 (12.9) 1 (0.8) 1 (1.1)
Cirrhosis: With cirrhosis (N, %) **Without cirrhosis (N, %)**	15 (53.6) 9 (47.4) 13 (46.4) 10 (52.6)	15 (46.9) 11 (44.0) 17 (53.1) 14 (56.0)	16 (53.3) 12 (57.1) 14 (46.7) 9 (42.9)	13 (46.4) 13 (46.4) 15 (53.6) 15 (53.6)	59 (50.0) 45 (48.4) 59 (50.0) 48 (51.6)
Previous IFN therapy: >30 days prior to screening N (%)	20 (71.4) 14 (73.7)	15 (46.9) 11 (44.0)	14 (46.7) 11(52.4)	18 (64.3) 18 (64.3)	67 (56.8) 54 (58.1)
Previous NUC therapy (days, mean (SD)) prior to screening	234.1 (347.1) 271.7 (385.0)	239.0 (412.4) 242.7 (440.4)	229.9 (518.0) 304.8 (608.0)	172.1 (311.7) 172.1 (311.7)	219.6 (402.0) 240.7 (434.8)
HBeAg positive (N, %)	6 (21.4) 4 (21.1)	1 (3.1) 1 (4.0)	3 (10.0) 3 (14.3)	1 (3.6) 1 (3.6)	11 (9.3) 9 (9.7)
ALT: U/ml, Mean, (SD) **3xULN (N, %)**	97.1 (65.2) 97.7 (71.7) 8 (28.6)	123.1 (80.2) 126.4 (87.6) 11 (34.4)	122.7 (84.1) 116.8 (82.7) 12 (40·0)	118.6 (87.6) 118.6 (87.6) 11 (39.3)	115.8 (79.5) 116.0 (82.7) 42 (35.6)
HDV RNA: Median log IU/ml **(range)**	5.60 5.613 (1.70, 7.11)	5.07 5.041 (1.0, 7.30) (1.70, 7.30)	5.85 5.925 (3.71, 7.36) (4.34, 7.36) 23 (76.6)	5.98 5.987 (1.70, 7.18) (1.70, 7.18) 20 (71.4)	5.59 5.602 (1.70, 7.36)

mITT population	Arm A: (n=28) (n=19) BLV 2 mg/day + TDF	Arm B: (n=32) (n=25) BLV 5 mg/day + TDF	Arm C: (n=30) (n=21) BLV 10 mg/day + TDF	Arm D: (n=28) (n=28) TDF (245 mg/day)	Total: (n=118) (n=93)
% > 100.000 IU/ml (n,%)	(3.84, 6.86) 19 (67.9)	17 (53.1)			(1.70, 7.36) 79 (66.9)
HDV genotype **Gen 1 (N, %)** **Gen 2 (N, %)** **Missing** Missing	 25 (89.3) 17 (89.5) 2 (7.1) 2 (10.5) 1 (3.6) 0	 28 (87.5) 22 (88.0) - - 4 (12.5) 3 (12)	 23 (76.7) 19 (90.5) 2 (6.7) 1 (4.8) 5 (16.7) 1 (4.8)	 27 (96.4) 27 (96.4) 1 (3.6) 1 (3.6) 0 0	 103 (87.3) 85 (91.4) 5 (4.2) 4 (4.3) 10 (8.5) 4 (4.3)
HBsAg **Mean log IU/ml (SD)**	 4.10 (0.40) 4.145 (0.276)	 3.87 (0.73) 3.856 (0.797)	 3.98 (0.42) 4.007 (0.468)	 3.97 (0.62) 3.970 (0.627)	 3.98 (0.57) 3.981 (0.598)
Fibroscan kPa **(N)** **Mean (SD)** **patients with >14 (N, %)**	19 12 14.45 (6.37) 12.31 (4.65) 9 (47.3)	25 19 17.18 (11.49) 17.31 (12.38) 13 (52.0)	20 16 16.00 (7.37) 16.46 (7.62) 12 (60.0)	18 18 16.20 (7.83) 16.20 (7.83) 9 (50.0)	82 65 16.05 (8.65) 15.87 (8.94) 43 (52.4)

The baseline characteristics appear comparable between study groups, but arm A has a higher proportion of female subjects, numerically lower ALT levels and slightly better liver elasticity (Fibroscan).

The Applicant has provided data on prior NUC therapy and HBeAg status and has clarified that MELD and BEA scores could not be calculated due to lack of INR data.

The number of HBeAg-positive subjects is overall low, indicating that the slight imbalance is not expected to substantially affect the assessment of study endpoints.

Overall, baseline demographic and disease characteristics appear comparable between the mITT and the subset of 93 patients randomised to the whole cohort.

When comparing the duration of previous NUC therapy, the TDF control group clearly deviates from the bulevirtide groups. This indicates that randomisation was not sufficient to balance this parameter. This imbalance appears to be a stochastic event and is not expected to affect the study results.

Medical history

Based on the documented fulfilment of the inclusion criteria, all patients had HBV/HDV coinfection on inclusion in the study. Other common ongoing conditions at inclusion in the study were hepatic cirrhosis (reported by 50% of the patients), chronic cholecystitis (reported by 22.9% of the patients), chronic

pancreatitis (reported by 16.1% of the patients), chronic gastritis (reported by 14.4% of the patients) and gastroduodenitis (reported by 9.3% of the patients).

Pancreatitis was not allowed in the Germany specific protocol. In total, 19 patients with chronic pancreatitis were enrolled in the study. All of these 19 patients were enrolled at Russian sites.

One patient had ongoing chronic hepatitis C infection recorded as medical history. This was not considered a violation of exclusion criterion no. 2 since the patient had negative results for HCV RNA at screening. Two patients developed hyperbilirubinaemia between screening and randomisation in the study, which was recorded as medical history. For one of these patients, the abnormal laboratory value was below the limit for exclusion (<34.2 µmol/L) and the patient could therefore be randomised as planned. For the other patient, the abnormal value was unknown at the time of randomisation (sample taken on Day 1) and inclusion in the study was based on the normal value at screening. This was not recorded as a protocol deviation.

Concomitant medications

The most common concomitant medications used during the study treatment period were oral contraceptives (Certostat, Drospirenone w/ethinylestradiol or Diane), used by 5.9% of patients overall, antivirals for systemic use (Tenofovir, Lamivudine, Tenofovir disoproxil or Entecavir), used by 5.1% of patients overall, and immunostimulants (interferon alfa-2A, peginterferons alfa-2A/alfa-2B or cepeginterferon alfa-2B), used by 5.9% of patients overall. Although reported as concomitant medications in the CSR due to unknown stop date in the database, as per the rules for handling missing data in SAP, the immunostimulants (i.e. interferon treatments) were confirmed via queries to the sites to have been stopped in all patients before randomisation.

Numbers analysed

All treated patients (118) were included in the Safety analysis set and the mITT. Ninety-two patients were included in the PPAS. All patients who completed the 24-week treatment period without major protocol deviations and with efficacy results for the 24-week time point were included in the PPAS. For six patients, randomisation visit assessments were performed after randomisation and first dose which meant that they were excluded from most of the efficacy analyses, due to lack of baseline values.

Ninety-one patients had at least one measured bulevirtide concentration and were included in the PKCAS, and 25 patients were included in the PK sub-study and were thus included in the PKAS.

Outcomes and estimation

Primary efficacy variable: HDV RNA response at week 24

A statistically significant superiority of p<.0001 (mITT) in the proportion of responders was found in all three Myrcludex B/Tenofovir treatment groups compared to treatment with Tenofovir alone. Similar results were obtained when the analysis was performed on the PP analysis set (PPAS; p<.0001).

Table 18. Frequency table on HDV RNA response (mITT)

HDV RNA response	MXB 2 mg (N=28)	MXB 5 mg (N=32)	MXB 10 mg (N=30)	Tenofovir (N=28)	MXB total (N=90)	Total (N=118)
Week 24						
Responder	15 (53.6%)	16 (50.0%)	23 (76.7%)	1 (3.6%)	54 (60.0%)	55 (46.6%)
95% CI	(33.9%, 72.5%)	(31.9%, 68.1%)	(57.7%, 90.1%)	(0.1%, 18.3%)	(49.1%, 70.2%)	(37.4%, 56.0%)
Non-responder	13 (46.4%)	16 (50.0%)	7 (23.3%)	27 (96.4%)	36 (40.0%)	63 (53.4%)
95% CI	(27.5%, 66.1%)	(31.9%, 68.1%)	(9.9%, 42.3%)	(81.7%, 99.9%)	(29.8%, 50.9%)	(44.0%, 62.6%)

Percentages are based on the number of subjects within each treatment group.
CI = confidence interval. Clopper–Pearson (exact) confidence intervals are presented for the proportions.
Program: \Subprogs\Tables\EFF1 Response.sas
Date and time program was run: 2019-05-23T08:35. Date and time analysis database was run: 2019-05-20T14:24

Table 19. HDV RNA response: statistical analysis on the difference in proportions, using Fisher's exact test (mITT)

HDV RNA response	MXB 2 mg (N=28)	MXB 5 mg (N=32)	MXB 10 mg (N=30)	Tenofovir (N=28)
Week 24				
Number of subjects in analysis	28	32	30	28
Difference in proportions	0.5000	0.4643	0.7310	
95% confidence interval	(0.2712, 0.6943)	(0.2438, 0.6528)	(0.5133, 0.8782)	
Raw p-value	<.0001	<.0001	<.0001	
Adjusted p-value	<.0001	<.0001	<.0001	

HDV RNA response is defined as HDV RNA negativation or a decrease by at least 2 log 10 from baseline.
Exact unconditional Chan–Zhang confidence intervals are presented for the difference in proportions.
Two-sided Fisher's exact tests were used to test null hypotheses of no difference in the proportion of responders compared to the Tenofovir only group.
Separate comparisons were made for each of the three MXB groups versus the control group, and adjusted p-values were computed using the Bonferroni–Holm method.
A test is considered as statistically significant if the adjusted p-value is smaller than 0.05.
Program: \Subprogs\Tables\EFF1 Response.sas
Date and time program was run: 2019-05-23T08:34. Date and time analysis database was run: 2019-05-20T14:24

In patients with cirrhosis the primary endpoint was achieved by 8/15 (53.3%, 95% CI 26.6 to 78.7), 8/15 (53.3%, 95% CI 26.6-78.7), and 13/16 (81.3%, 95% CI 54.4-96.0) of patients treated with Myrcludex B in the 2 mg, 5 mg and 10 mg groups, respectively. Only one patient in the Tenofovir group achieved the primary endpoint (1/13, 7.7%, 95% CI 0.2-36.0).

There is a trend, indicating a virologic dose-response relationship in the dose range between 2 and 10 mg of bulevirtide daily.

A total of 12 HBeAg positive patients were included in the study. In the 2 mg group, 1/6 patients reached the composite endpoint, compared to 1/1 in the 5 mg group and 2/3 in the 10 mg group. The number of HBeAg positive patients is however too low to allow any conclusion regarding the effect of HBeAg serostatus on dose-response.

Secondary variables

Change in HDV RNA

Mean HDV RNA levels over time for all four treatment groups are presented below. A statistically significant reduction in HDV RNA levels from baseline to week 24 was observed in all Myrcludex B groups compared to Tenofovir treatment (mITT; p<.0001). HDV RNA levels rebounded after cessation of Myrcludex B with no significant difference between the Myrcludex B and Tenofovir groups at week 48 post treatment initiation. Per protocol set analysis revealed similar results.

A subgroup analysis, separately investigating patients with cirrhosis revealed that change in HDV RNA from baseline to week 24 was comparable with the full mITT population.

Table 20. Summary statistics on log-10 transformed HDV RNA levels

Log 10(HDV RNA [IU/mL])	MXB 2 mg (N=28)	MXB 5 mg (N=32)	MXB 10 mg (N=30)	Tenofovir (N=28)	MXB total (N=90)	Total (N=118)
Baseline						
n/nmiss	27/1	32/0	29/1	28/0	88/2	116/2
Mean (SD)	5.345 (1.157)	4.874 (1.398)	5.688 (0.983)	5.393 (1.351)	5.287 (1.235)	5.312 (1.259)
Median	5.602	5.078	5.857	5.987	5.496	5.591
Q1, Q3	4.602, 5.973	4.255, 6.097	5.204, 6.477	4.589, 6.286	4.415, 6.130	4.480, 6.204
Min, Max	1.70, 7.11	1.70, 7.30	3.71, 7.36	1.70, 7.18	1.70, 7.36	1.70, 7.36
Week 24						
n/nmiss	28/0	30/2	29/1	25/3	87/3	112/6
Mean (SD)	3.478 (1.613)	3.114 (1.659)	3.040 (1.118)	5.099 (1.394)	3.206 (1.479)	3.629 (1.656)
Median	3.633	2.923	3.146	5.462	3.279	3.633
Q1, Q3	1.699, 4.701	1.699, 4.663	2.279, 3.806	4.505, 6.279	2.079, 4.362	2.290, 4.914
Min, Max	0.00, 6.51	0.00, 5.69	0.00, 5.18	1.70, 6.79	0.00, 6.51	0.00, 6.79
Change from Baseline to Week 24						
n/nmiss	27/1	30/2	28/2	25/3	85/5	110/8
Mean (SD)	-1.918 (1.186)	-1.758 (1.149)	-2.594 (0.652)	-0.175 (0.806)	-2.084 (1.078)	-1.650 (1.298)
Median	-2.140	-2.021	-2.702	-0.176	-2.301	-1.957
Q1, Q3	-2.716, -1.208	-2.511, -0.859	-3.009, -2.282	-0.456, 0.137	-2.735, -1.426	-2.699, -0.634
Min, Max	-3.70, 1.86	-3.86, 0.60	-3.75, -1.12	-2.72, 1.91	-3.86, 1.86	-3.86, 1.91
Week 48						
n/nmiss	28/0	29/3	29/1	24/4	86/4	110/8
Mean (SD)	5.092 (1.426)	4.483 (1.823)	5.055 (1.358)	5.368 (1.568)	4.874 (1.558)	4.982 (1.566)
Median	5.060	4.531	5.114	5.851	5.041	5.097
Q1, Q3	4.540, 6.060	3.431, 5.851	4.322, 6.000	4.585, 6.614	4.301, 6.000	4.322, 6.176
Min, Max	0.00, 6.98	0.00, 7.23	1.70, 7.38	1.70, 7.34	0.00, 7.38	0.00, 7.38
Change from Baseline to Week 48						
n/nmiss	27/1	29/3	28/2	24/4	84/6	108/10
Mean (SD)	-0.239 (0.951)	-0.408 (1.289)	-0.611 (1.073)	0.085 (0.608)	-0.421 (1.114)	-0.309 (1.043)
Median	-0.269	-0.131	-0.331	0.068	-0.273	-0.176
Q1, Q3	-0.790, 0.306	-0.911, 0.490	-1.339, 0.072	-0.276, 0.533	-1.011, 0.286	-0.807, 0.366
Min, Max	-2.37, 2.20	-3.48, 1.72	-3.05, 1.24	-1.38, 1.14	-3.48, 2.20	-3.48, 2.20

CI = confidence interval, n/nmiss = number of subjects with evaluable/missing data, Q1 = first quartile, Q3 = third quartile, SD = standard deviation

Baseline is defined as the last valid evaluation prior to the first dose of study medication.

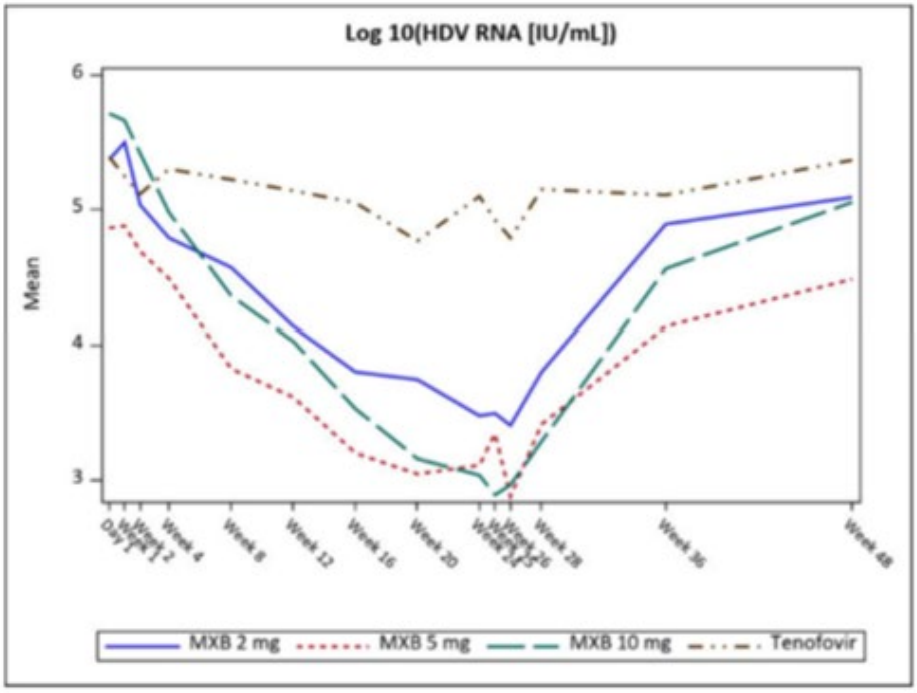
Raw values of zero were imputed as zero after log transformation.

Program: \Subprogs\Tables\EFF2 HDV RNA.sas

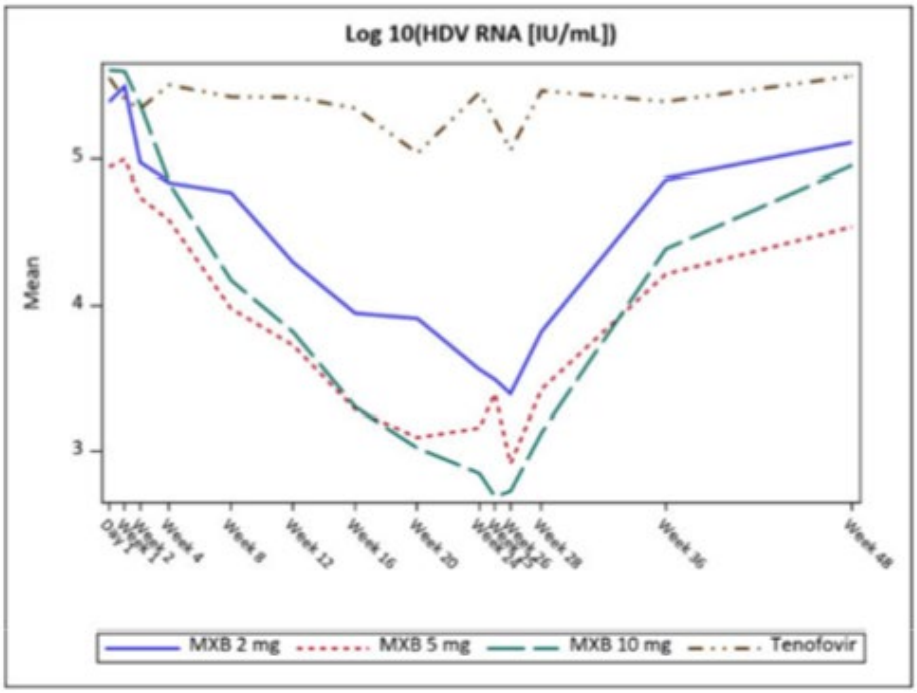
Date and time program was run: 2019-05-23T08:35. Date and time analysis database was run: 2019-05-20T14:24

Figure 15. Mean log-10 transformed HDV RNA levels over time

A. mITT analysis set



B. PPAS



As expected, analyses of change in HDV RNA levels is in line with the primary analysis and indicate that bulevirtide is more effective than tenofovir in lowering HDV RNA levels. Similar to the proportion of protocol-defined virologic responders, the separation of curves efficacy at 24 weeks indicate a virologic dose-response is seen in the interval 2-10 mg. There are no signs of a clinically relevant virologic post-treatment effect with the regimens used in this study.

Change in ALT

ALT normalisation (ALT response) at week 24, defined as ALT values ≤31 U/L for female patients and ≤41 U/L for male patients, was observed in 12/28 (42.9%, 95% CI 24.5 to 62.8) of patients in the 2 mg group, 16/32 (50.0%, 95% CI 31.9 to 68.1) of patients in the 5 mg group, 12/30 (40.0%, 95% CI 22.7 to 59.4) of patients in the 10 mg group, and in 2/28 (7.1%, 95% CI 0.9 to 23.5) of patients treated with tenofovir alone. Thus, a significantly higher proportion of patients treated with Myrcludex B had normal ALT levels at week 24 compared to patients receiving only Tenofovir (mITT; p<.05).

At week 48, no relevant difference in the proportion of patient with normal ALT values between the treatment groups was demonstrated.

ALT normalisation at week 24 in patients with liver cirrhosis occurred in 6/15 (40.0 %, 95% CI 16.3 to 67.7) of patients in the 2 mg group, 6/15 (40.0 %, 95% CI 16.3 to 67.7) of patients in the 5 mg group and in 9/16 (56.3 %, 95% CI 29.9 to 80.2) of patients in the 10 mg group. No ALT normalisation was achieved in cirrhotic patients treated with Tenofovir alone. At week 48, no significant difference in the proportion of patient with normal ALT values between the treatment groups was demonstrated.

Figure 16 – Mean ALAT levels over time. Modified intention-to-treat analysis set

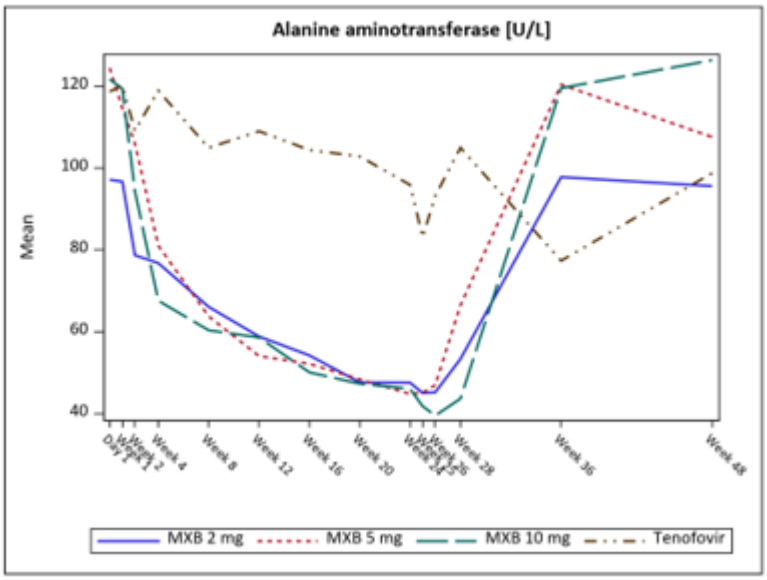
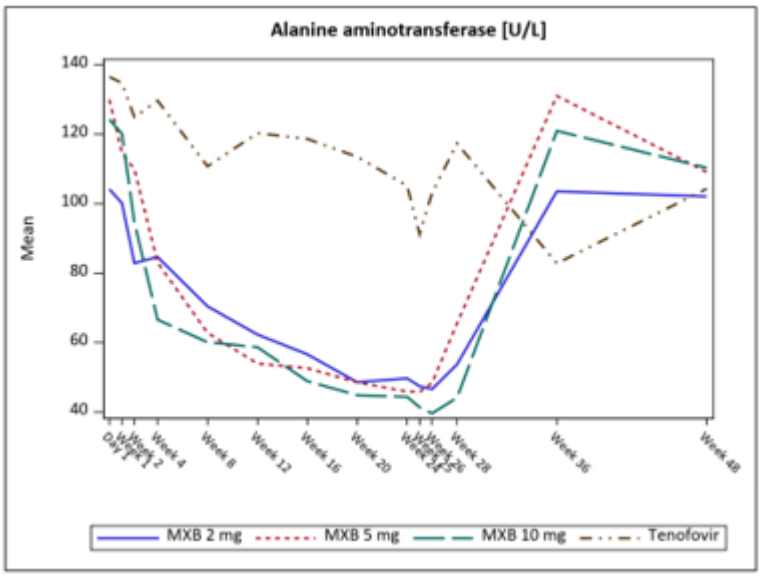


Figure 17 – Mean ALAT levels over time. Per-protocol analysis set



ALT normalisation is clearly more common in the bulevirtide groups compared to tenofovir only.

Combined treatment response

A combined treatment response was defined as the fulfilment of two criteria (i) HDV RNA negativation or a decrease in HDV RNA by ≥2 log10 IU/mL and (ii) normalisation of ALT levels. At week 24, the proportion of patients in the mITT analysis set with a combined treatment response, was significantly higher in all groups receiving Myrcludex B/Tenofovir compared to treatment with Tenofovir only (mITT; p<.05). At week 48, there were no significant difference in the proportion of patients achieving a combined treatment response between the Myrcludex B treatment groups and the Tenofovir only group.

Similar results were obtained when analyses were performed on the PP analysis set, except that the difference in proportions of patients with combined a response at week 24 did not reach statistical significance in the Myrcludex B 2 mg/day group versus Tenofovir only (p=.0511, PPAS).

The subgroup analysis on patients with cirrhosis at baseline, revealed that a combined treatment response at week 24 was achieved by 3/15 (20.0%, 95% CI 4.3 to 48.1) patients in the 2 mg group, 4/15 (26.7%, 95% CI 7.8 to 55.1) patients in the 5 mg group, and 9/16 (56.3%, 95% CI 29.9 to 80.2) patients in the 10 mg group. No such response was observed in the Tenofovir only group. At week 48, no combined treatment response was observed in any of the treatment groups (mITT subgroup cirrhosis at baseline).

Table 21. Frequency table on combined response (mITT)

Combined Response	MXB 2 mg (N=28)	MXB 5 mg (N=32)	MXB 10 mg (N=30)	Tenofovir (N=28)	MXB total (N=90)	Total (N=118)
Week 24						
Responder	6 (21.4%)	9 (28.1%)	11 (36.7%)	0	26 (28.9%)	26 (22.0%)
95% CI	(8.3%, 41.0%)	(13.7%, 46.7%)	(19.9%, 56.1%)	(0.0%, 12.3%)	(19.8%, 39.4%)	(14.9%, 30.6%)
Non-responder	22 (78.6%)	23 (71.9%)	19 (63.3%)	28 (100.0%)	64 (71.1%)	92 (78.0%)
95% CI	(59.0%, 91.7%)	(53.3%, 86.3%)	(43.9%, 80.1%)	(87.7%, 100.0%)	(60.6%, 80.2%)	(69.4%, 85.1%)
Week 48						
Responder	2 (7.1%)	1 (3.1%)	1 (3.3%)	0	4 (4.4%)	4 (3.4%)
95% CI	(0.9%, 23.5%)	(0.1%, 16.2%)	(0.1%, 17.2%)	(0.0%, 12.3%)	(1.2%, 11.0%)	(0.9%, 8.5%)
Non-responder	26 (92.9%)	31 (96.9%)	29 (96.7%)	28 (100.0%)	86 (95.6%)	114 (96.6%)
95% CI	(76.5%, 99.1%)	(83.8%, 99.9%)	(82.8%, 99.9%)	(87.7%, 100.0%)	(89.0%, 98.8%)	(91.5%, 99.1%)

Percentages are based on the number of subjects within each treatment group.
CI = confidence interval. Clopper–Pearson (exact) confidence intervals are presented for the proportions.
Program: \Subprogs\Tables\EFF2 Combined response.sas
Date and time program was run: 2019-05-23T08:36. Date and time analysis database was run: 2019-05-20T14:24

Figure 18. Change from baseline in log HDV RNA and ALT at week 24 in bulevirtide treatment groups - Scatterplot with linear regression line and 95%-confidence intervals for mean predicted value - Pearson correlation coefficient = -0.05 (N = 85)

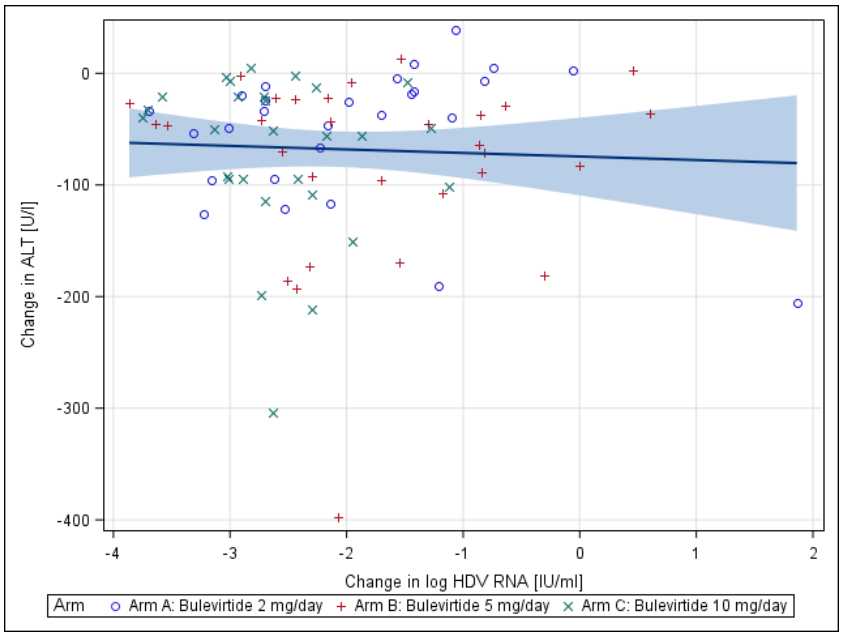


Figure 19. Measured values at week 24 of log HDV RNA and ALT in bulevirtide treatment groups Scatterplot with linear regression line and 95%-confidence intervals for mean predicted value - Pearson correlation coefficient = 0.33 (N = 87)

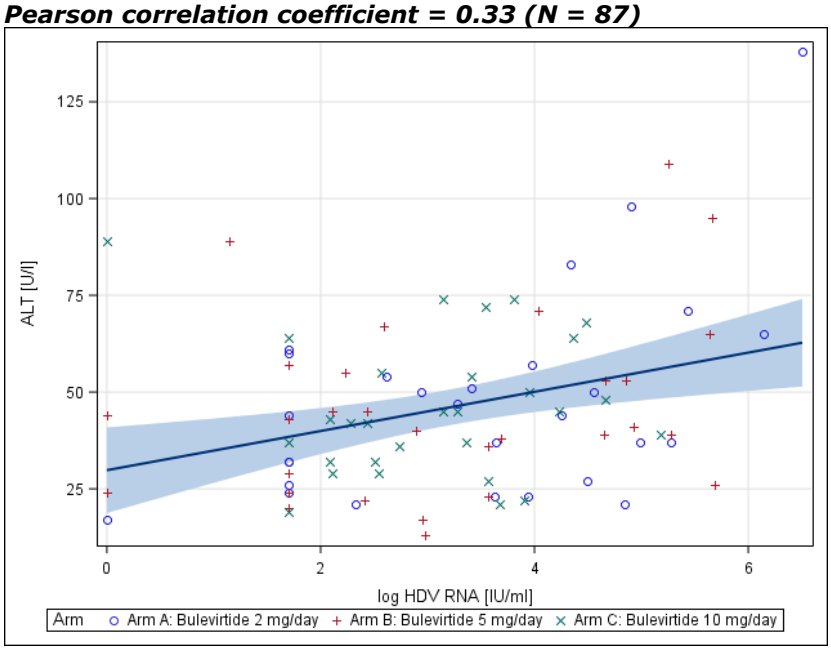
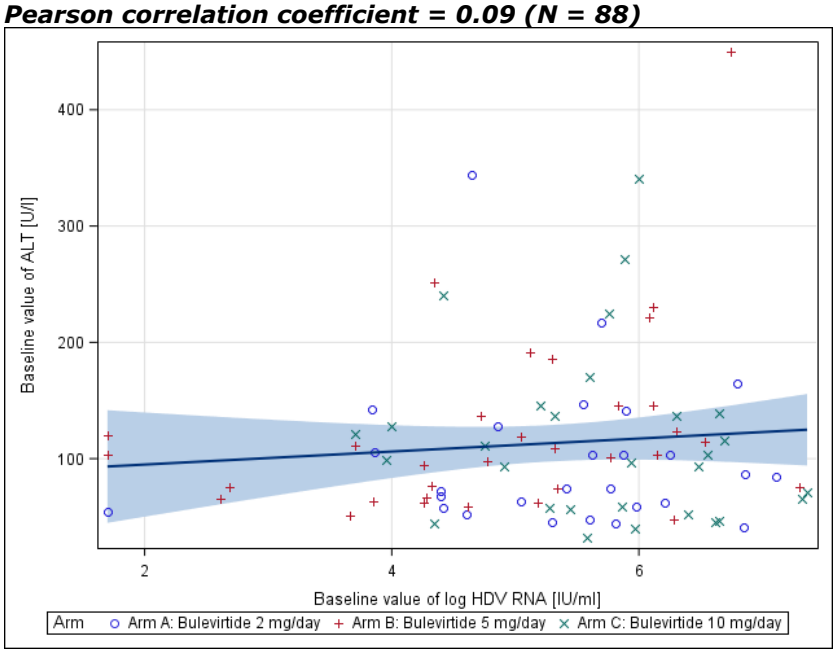


Figure 20. Baseline values of log HDV RNA and ALT in bulevirtide treatment groups Scatterplot with linear regression line and 95%-confidence intervals for mean predicted value - Pearson correlation coefficient = 0.09 (N = 88)



The tabulated analysis of combined treatment response indicates a connection between the virologic and biochemical effects observed in the bulevirtide groups. However, the plot of change (baseline vs. week 24) in HDV RNA (log10) vs. change in ALT indicates that there is no correlation between the magnitude of HDV RNA decline and reduced necroinflammation.

The correlation between virologic and biochemical response is pivotal for the assumption of clinical benefit, and the data presented raise the question whether the evidence of efficacy from this relatively small and open label study meets criteria of internal consistency required for an approval based on a single pivotal trial. Although there is bibliographic evidence from observational studies of a qualitative relation between HDV RNA positivity and clinical outcome, the lack of HDV RNA vs ALT correlation at baseline further is of concern since the quantitative surrogacy of viremia is currently not established for HDV. It is acknowledged that the on-treatment correlation at week 24, together with previously presented data on combined HDV-RNA/ALT response would be indicative of a beneficial effect but the there is remaining uncertainty.

There is a remaining lack of understanding of the relationship between antiviral effect and impact on necro-inflammation, which is the presumed chain of causation whereby bulevirtide would provide clinical benefit. This issue will be further discussed by the SAG before a potential approval.

Sensitivity analysis

With regards to the primary endpoint and the secondary endpoints related to HDV RNA decline, the analyses of the subset of 93 patients randomised neutrally between the full set of cohorts appear comparable to the full mITT set. However, mainly indicating an overall scarcity of data, the combined HDV RNA/ALT response is no longer significantly different (p=0.060) between the 2 mg bulevirtide group and the control group.

Ancillary analyses

Change in hepatitis B surface antigen

After 24 weeks of treatment with Myrcludex B, no change in mean HBsAg levels were noted; the same pertains to study week 48, post discontinuation.

At week 48, there were two subjects with at least 1 log10 HBsAg decrease (or loss).

Change in HBV DNA

As indicated by the very low levels of HBV DNA during the study, the TDF background treatment in all groups is already very effective in this aspect. Within the timeframe of the MYR202 study, the addition of bulevirtide to tenofovir does not seem to provide any additional virologic activity against HBV.

Fibrosis biomarkers and elastometry

After 24 weeks of treatment, only small changes in alpha-2-macroglobulin values were noted. There were no statistically significant changes in the fibrosis marker alpha-2-macroglobulin from baseline to week 24 or week 48 in any treatment group (mITT).

Median FIB-4 index value was 1.75 at baseline. The distribution between groups was well balanced with regard to this score. Values at the end of treatment (study week 24) slightly declined in comparison to baseline (10-25%) in all groups, returning to approximately baseline levels at week 48.

Median baseline values of APRI score ranged from 1 to 1.4 in different groups. The values declined in all treatment arms with a tendency to a more pronounced decline in the bulevirtide dosing groups 5 mg and 10 mg. At the end of follow up (week 48), the values returned to baseline in all bulevirtide groups and stayed at approximately the same level in the TDF group, reflecting the dynamics of the inflammatory markers observed in the trial.

Values at baseline, end of treatment (study week 24), and follow-up (study week 48) are presented in the table below.

Table 22 and 23. MYR202 safety analysis sets

Table 7. MYR 202. Fibrosis-4 (FIB-4) score. Safety analysis set

Fibrosis-4 (FIB-4) score	BLV 2 mg (N=28)	BLV 5 mg (N=32)	BLV 10 mg (N=30)	Tenofovir (N=28)	BLV total (N=90)	Total (N=118)
Baseline						
n/nmiss	28/0	32/0	30/0	28/0	90/0	118/0
Median	1.821	1.695	1.707	1.824	1.716	1.750
Week 24						
n/nmiss	27/1	30/2	29/1	24/4	86/4	110/8
Median	1.646	1.279	1.585	1.443	1.524	1.500
Week 48						
n/nmiss	27/1	29/3	28/2	23/5	84/6	107/11
Median	2.071	1.775	2.039	1.621	1.908	1.773

Table 8. MYR 202. AST to Platelet Ratio Index (APRI). Safety analysis set

AST to Platelet Ratio Index (APRI)	BLV 2 mg (N=28)	BLV 5 mg (N=32)	BLV 10 mg (N=30)	Tenofovir (N=28)	BLV total (N=90)	Total (N=118)
Baseline						
n/nmiss	28/0	32/0	30/0	28/0	90/0	118/0
Median	1.0845	1.1773	1.2042	1.4562	1.1207	1.2368
Week 24						
n/nmiss	27/1	30/2	29/1	24/4	86/4	110/8
Median	0.8119	0.5639	0.6675	0.9773	0.6381	0.7072
Week 48						
n/nmiss	27/1	29/3	28/2	23/5	84/6	107/11
Median	1.2728	1.1466	1.3599	1.0798	1.2567	1.2500

Results from the transient elastometry are presented below. After 24 weeks of treatment, there were numerically larger mean decreases in liver stiffness compared to baseline values in all Myrcludex B groups than in the Tenofovir only group.

Table 24 – Liver stiffness (transient elastometry) Modified intention-to-treat analysis set

Table 14.2.9.1 Liver stiffness (transient elastometry). Modified intention-to-treat analysis set

Liver stiffness (kPa)	MXB 2 mg (N=28)	MXB 5 mg (N=32)	MXB 10 mg (N=30)	Tenofovir (N=28)	MXB total (N=90)	Total (N=118)
Baseline						
n/nmiss	19/9	25/7	20/10	18/10	64/26	82/36
Mean (SD)	14.45 (6.37)	17.18 (11.49)	16.00 (7.37)	16.20 (7.83)	16.00 (8.92)	16.05 (8.65)
95% CI for the mean	(11.38, 17.52)	(12.44, 21.92)	(12.55, 19.45)	(12.30, 20.10)	(13.77, 18.23)	(14.15, 17.94)
Median	13.80	15.00	16.80	13.90	15.55	14.95
Q1, Q3	9.60, 17.00	8.00, 21.30	9.20, 19.80	10.20, 19.10	8.75, 20.75	9.00, 20.40
Min, Max	4.3, 28.4	5.8, 46.4	7.0, 36.9	5.8, 34.8	4.3, 46.4	4.3, 46.4
Week 24						
n/nmiss	22/6	26/6	22/8	17/11	70/20	87/31
Mean (SD)	11.31 (5.29)	14.12 (9.96)	12.00 (6.19)	12.35 (6.14)	12.57 (7.59)	12.53 (7.30)
95% CI for the mean	(8.96, 13.66)	(10.09, 18.14)	(9.26, 14.75)	(9.19, 15.51)	(10.76, 14.38)	(10.97, 14.08)
Median	10.25	11.00	10.80	11.80	10.50	10.50
Q1, Q3	6.60, 14.50	6.60, 17.30	7.40, 14.10	7.80, 13.40	6.80, 16.30	6.90, 14.90
Min, Max	4.5, 22.3	5.1, 46.4	5.8, 28.8	3.9, 28.3	4.5, 46.4	3.9, 46.4
Change from Baseline to Week 24						
n/nmiss	19/9	23/9	20/10	14/14	62/28	76/42
Mean (SD)	-2.85 (2.65)	-2.52 (6.21)	-3.38 (3.83)	-0.78 (3.17)	-2.90 (4.55)	-2.51 (4.39)
95% CI for the mean	(-4.13, -1.58)	(-5.21, 0.17)	(-5.17, -1.59)	(-2.61, 1.05)	(-4.05, -1.74)	(-3.51, -1.51)
Median	-2.90	-1.60	-3.15	-1.00	-2.85	-2.55
Q1, Q3	-4.90, -1.60	-5.10, 0.10	-6.55, -0.15	-3.50, 1.10	-5.10, -0.20	-4.80, 0.10
Min, Max	-8.3, 2.9	-12.6, 11.8	-9.1, 3.5	-6.6, 5.3	-12.6, 11.8	-12.6, 11.8

CI = confidence interval, n/nmiss = number of subjects with evaluable/missing data, Q1 = first quartile, Q3 = third quartile, SD = standard deviation
Baseline is defined as the last valid evaluation prior to the first dose of study medication.
Program: \Subprogs\Tables\EFF2 Histological.sas
Date and time program was run: 2019-05-23T08:37. Date and time analysis database was run: 2019-05-20T14:24

There is a trend towards a decrease in liver stiffness from baseline to week 24 that is numerically larger in the bulevirtide treatment groups. However, given the high proportion of missing data, especially in the TDF group, no firm conclusions can be drawn. Within a 24-week period, it is expected that changes in liver stiffness are driven by changes in inflammation and hepatic oedema rather than a true reduction of fibrosis.

HBV and HDV genotyping

HDV genotyping revealed that 103/118 (87.3%) of patients were infected with HDV genotype 1 and 5/118 (4.2%) of patients were infected with HDV genotype 2. Ten patients (8.5%) had missing values for HDV genotyping.

Due to low HBV DNA levels at baseline, HBV genotyping was only possible in 10/118 patients (8.5%) demonstrating that all ten patients were infected with HBV genotype D. No apparent difference in proportion of patients with HDV genotype 1 and 2 were noted depending on cirrhosis status at baseline.

Due to the integrated life cycle of the HBV/HDV coinfection, both HBV and HDV genotypes could potentially affect response to treatment. The MYR202 study mainly included HDV GT1 patients along with a limited number of GT2 patients. The HBV genotyping dataset is, due to the study design, unfortunately very limited.

Summary of main efficacy results

Table 25 – HDV RNA response

HDV RNA response	**Arm A:** **(n=28)** **2mg bulevirtide + TDF**	**Arm B:** **(n=32)** **5mg bulevirtide + TDF**	**Arm C:** **(n=30)** **10mg bulevirtide +** **TDF**	**Arm D:** **(n=28)** **TDF**
Patients with undetectable HDV RNA or decrease by ≥2log$_{10}$ from baseline to week 24,	53.6 %*	50.0% *	76.7%*	3.6%
Patients with undetectable HDV RNA or decline by >2log$_{10}$ and normal ALT at week 24	21.4%*	28.1% *	36.7% *	0.0%
Patients with ALT normalisation	42.9%*	50.0%*	40.0%*	7.1%

Although the MYR202 study has not been optimally designed or conducted to serve as a pivotal clinical trial, it provides ground for the following conclusions regarding the clinical efficacy of bulevirtide:

- Bulevirtide is effective in reducing HDV RNA with 53.6% of patients treated reaching the primary endpoint of a 2 log10 HDV RNA reduction or becoming negative, when treated with the 2 mg daily dose proposed by the Applicant, significantly superior to TDF only.
- There is an apparent dose-response up to at least 10 mg, which was the highest dose group, where 76.7% of patients reached the primary endpoint.
- Along with virologic response, a superior biochemical response is seen in the bulevirtide groups compared to TDF only, with 40-50% of patients in the each of the bulevirtide groups normalising their ALT levels after 24 weeks of therapy compared to 7% of TDF patients, suggesting a reduction of hepatic necroinflammation in the bulevirtide groups. However, there is a lack of consistency between virologic and biochemical response, questioning the mechanism of ALT reduction and extrapolation to expected long-term clinical benefit.
- A modest numerical improvement in liver stiffness (estimated by elastometry) and non-invasive scores (FIB-4 and APRI) was observed at Week 24. Within a 24-week period, it is expected that changes in liver stiffness are driven by changes in inflammation and hepatic oedema rather than a true reduction of fibrosis.

MYR203 – A multicentre, open-label, randomized, comparative, parallel-arm phase II study to assess efficacy and safety of Myrcludex B in combination with peginterferon alfa-2a versus peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent

Methods

Study Participants

Patients were included at 7 centres in Russia. Key inclusion and exclusion criteria are presented below.

Key inclusion criteria

1. Male and female patients aged from 18 through 65 years (inclusive)
2. Patients with chronic hepatitis B (HBeAg positive or negative) and presence of HBsAg for at least 6 months prior to screening
3. Positive results on anti-HDV antibodies for at least 6 months prior to screening
4. Positive result of HDV RNA during screening
5. ALT ≥1 ULN but <10 ULN

Patients who were previously treated with interferon drugs were allowed to be included in the study

Key exclusion criteria

1. Antiviral therapy to treat chronic viral hepatitis B with delta-agent during the previous 6 months
2. Total bilirubin >34.2 µmol/L. Patients with a higher level of total bilirubin could be enrolled into the study after consultation with the study Medical Monitor, if it had been clearly established that such an increase was a manifestation of Gilbert's syndrome.
3. Decompensated liver disease in the current or past medical history, including blood-clotting disorder, hyperbilirubinaemia, hepatic encephalopathy, hypoalbuminaemia, ascites and bleeding oesophageal varices; B/C class or Child-Pugh-Score ≥6
4. Co-infection with the hepatitis C or HIV (Patients with presence of anti- HCV antibodies at screening but absence of HCV RNA were allowed to participate in the study)
5. Hepatocellular carcinoma
6. Contraindications to liver biopsy

Treatments

In part 1 of the MYR203 study which is currently presented by the Applicant, doses of 2 mg and 5 mg of bulevirtide were used in combination with PEG-IFN (groups B and C) and compared to PEG-IFN monotherapy (group A) and 2 mg bulevirtide monotherapy (group D). In these groups, no background therapy with TDF was used.

The test product was MXB. PEG-IFN was the reference product. All presently relevant treatment groups had a treatment period of 48 weeks with a treatment free follow-up period of 24 weeks after the treatment.

The duration of the therapy was 48 weeks.

Patients performed self-injections of MXB, except for the visits on the days of PK blood sampling. For patients also receiving injection(s) with PEG-IFN, the injection of MXB should be done first, followed by the injection of PEG-IFN. The s.c. injections of MXB and PEG-IFN were to be performed in different anatomical regions.

Objectives

Primary objective

To investigate the efficacy of MXB in monotherapy and in combination with PEG-IFN and with Tenofovir compared to monotherapy with PEG-IFN, based on the achievement of undetectable viral load at the end of the follow-up period 6 months (24 weeks) after the end of treatment.

Secondary objective(s)

- To investigate the efficacy of MXB in monotherapy and in combination with PEG-IFN and with Tenofovir as compared with monotherapy with PEG-IFN, based on the secondary efficacy endpoints.
- To investigate the safety of MXB in monotherapy and in combination with PEG-IFN and with Tenofovir compared with PEG-IFN monotherapy.
- To investigate the pharmacokinetics (PK) of MXB when administered in monotherapy and in combination with PEG-IFN and with Tenofovir
- To investigate the immunogenicity of MXB

Outcomes/endpoints

Primary variable

The primary variable was the occurrence of a negative polymerase chain reaction (PCR) result of HDV RNA (HDV RNA negativation) at week 72 (end of the follow up period).

Secondary variables

The secondary variables are the occurrence of (where proportions will be assessed):

- Negative PCR result of HDV RNA (HDV RNA negativation) at Weeks 24 and 48;
- ALT normalisation at Weeks 24, 48 and 72;
- Combined treatment response (negative PCR result of HDV RNA and ALT normalisation) at Weeks 24, 48 and 72;
- HBsAg response HBsAg negativation or >1 log10 IU/mL decline) at Weeks 24, 48 and 72;
- HBsAg negativation with the appearance of anti-HBsAg antibodies at Weeks 48 and 72;
- HBsAg negativation without appearance of anti-HBsAg antibodies at Weeks 48 and 72;
- Negative PCR result of HBV DNA at Weeks 24, 48 and 72.
- The intensity of liver fibrosis based on results of transient elastometry of liver at Weeks 48 and 72;
- Changes in the results of liver biopsy before and after the treatment as part of the study of efficacy;
- HBV, HDV genotyping, resistance assay and study of NTCP polymorphism.

In this finite therapy approach, the combined (HDV RNA negativity and ALT normalisation) off-treatment response at week 72 is key to regulatory evaluation. It should be noted that the statistical analysis plan was not locked before the study was completed and the database had been opened.

Sample size

The study size was informed by the very small MYR201 study. Notably, the trial was exploratory in nature, and not powered for inferential testing.

Randomisation and blinding (masking)

This was an open-label study.

Randomisation was performed using the Interactive Web Response System (IWRS) provided by DataMATRIX. Patients were assigned to treatments using separate randomisation lists in the two phases of the study (for groups A-D and for groups E-F).

In the 1st, presently relevant phase, 60 patients were assigned to the following groups:

- Group A (n=15): PEG-IFN (180 µg)
- Group B (n=15): MXB (2 mg) + PEG-IFN (180 µg)
- Group C (n=15): MXB (5 mg) + PEG-IFN (180 µg)
- Group D (n=15): MXB (2 mg)

The study started with only groups A-C using a software setting to assign patients preferably into groups B and C if they had signed the consent for the PK sub-study. The randomisation list contained groups A-D, but group D was blocked in the system. As soon as new protocol amendment (version 2.0) was approved, group D was unblocked for further patients` randomisation into four groups A-D.

The randomisation with respect to giving consent for the PK sub-study could be a confounding factor, possibly steering patients with better overall health and clinical outcome to the bulevirtide arms.

Statistical methods

Analysis populations

The full analysis set (FAS) was defined as all randomised subjects who received at least one dose of the study medication. Analysis of the full analysis set was based on the planned treatment (i.e. subjects analysed 'as randomised').

The per-protocol analysis set (PPAS) was defined as the subset of subjects in the full analysis set for whom no major protocol deviation judged as having an impact on the primary efficacy analysis was reported or identified. Per-protocol analysis was based on the actual treatment (i.e. subjects analysed 'as treated').

Safety analysis set was defined as all subjects who received at least one dose of the study medication.

Efficacy analyses were performed on both the full analysis set (main analysis) and the per-protocol analysis set (supportive analysis).

The primary endpoint analysis

The proportions of negative HDV RNA response at Week 72 in each of the Myrcludex treatment groups (B-D) was compared with the control group (A) of Peginterferon alfa-2a by using Fisher's exact test and by

presenting exact unconditional 95%-confidence intervals based on scores for the proportion differences. FAS using missing equals failure (MEF) was used for the main analysis.

Secondary analyses
The secondary efficacy variables involving proportions were analysed in the same way as the primary efficacy variable. For each comparison Arm B-D versus Arm A, the hypotheses of equal proportions were tested using Fisher's exact test and by presenting exact unconditional 95%-confidence intervals based on scores for the proportion differences.

Wilcoxon Mann-Whitney test (also called Wilcoxon rank-sum test) was used to compare change from baseline in intensity of liver fibrosis at week 48 and 72, between each of groups B-D versus group A. HDV RNA levels and HBV DNA levels (on log-10 scale) were analysed using MMRM with time-point estimates. Descriptive statistics of molecular and gene expression parameters were presented based on log-10 transformed data as well as untransformed data.

Multiplicity

Considering the explorative nature of the study, no adjustment for multiple testing was performed.

Interim analyses

There were two interim analyses in the study before the final analysis of all treatment arms.

1) Phase I: When groups A-D have finished, final analysis was performed for these groups (presented in this report);

2) 24 weeks interim for Phase II (groups E-F), described separately in an Interim Analysis Plan.

SAP composition

The SAP was initially authored on 2018-12-13, and updated on 2019-01-22 (version 2.0, final), with 2 amendments dated 2019-05-17 and 2019-08-13, respectively. Date of the database lock is unknown. Analysis database was run 2019-06-03. The last patient's last visit was on 2018-05-29.

Changes from pre-specified analysis after finalisation of the SAP

Changes in the planned analyses were described in SAP amendments 1 and 2. In summary, the updates were made to handling of missing data and non-quantifiable values regarding values below LLoD and LLOQ, definition of HDV negativation, calculation of compliance to Myrcludex treatment; also, a few secondary variables are added and analysed *post-hoc*. Most of the changes were done in order to harmonise with the analysis of study MYR202.

Performing the main efficacy analysis based on the full analysis set and utilising Fisher's exact test and exact unconditional 95% confidence intervals is acceptable. The exploratory purpose of the study is apparent through the repeated substantial changes of the study design and the statistical analyses without adjusting for multiple testing. A potential discussion on the Type I error rate *post-hoc* is not deemed relevant for a pilot study intended for efficacy signal detection. In the responder analyses, subjects with missing data were considered as non-responders which is appropriate. Authoring the SAP and its amendments late after the study completion is noted but understood in the context of the exploratory nature of the study. The reason for most of the changes in the two SAP amendments was to harmonise the methods with the analysis of study MYR202. Considering the statistical methodology, the quality of the study is low due to the low number

of subjects and the methodological shortcomings such as open label, corrupted randomisation procedure, and unaddressed multiplicity issue.

Results

Participant flow

Study participant flow and reasons for withdrawals are presented below.

Table 26. Disposition of patients

	PEG-IFN	MXB 2mg + PEG-IFN	MXB 5mg + PEG-IFN	MXB 2mg	Total
Screened					60
Randomised	15	15	15	15	60
Received study medication	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	60 (100.0%)
Completed the study	10 (66.7%)	13 (86.7%)	15 (100.0%)	13 (86.7%)	51 (85.0%)
Prematurely withdrawn from the study	5 (33.3%)	2 (13.3%)	0	2 (13.3%)	9 (15.0%)
Analysis sets					
Safety analysis set	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	60 (100.0%)
Full analysis set	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	60 (100.0%)
Per protocol analysis set	8 (53.3%)	12 (80.0%)	12 (80.0%)	11 (73.3%)	43 (71.7%)
Pharmacokinetic analysis set - sub-study	0	10 (66.7%)	10 (66.7%)	0	20 (33.3%)
Pharmacokinetic analysis set - main study	0	15 (100.0%)	15 (100.0%)	15 (100.0%)	45 (75.0%)

Percentages are based on the number of randomised subjects within each treatment group.
Subjects are presented in the treatment groups as treated (i.e. actual treatment).
Program: \Subprogs\Tables\DS Disposition.sas
Date and time program was run: 2019-06-27T07:53. Date and time analysis database was run: 2019-06-03T14:32

Table 27. Reason for premature withdrawals. Full analysis set.

	PEG-IFN (N=15)	MXB 2mg + PEG-IFN (N=15)	MXB 5mg + PEG-IFN (N=15)	MXB 2mg (N=15)	Total (N=60)
Prematurely withdrawn from the study[a]	5 (33.3%)	2 (13.3%)	0	2 (13.3%)	9 (15.0%)
Primary reason for withdrawal[b]					
Withdrawal by subject	1 (20.0%)	2 (100.0%)	0	1 (50.0%)	4 (44.4%)
Pregnancy	1 (20.0%)	0	0	0	1 (11.1%)
Lost to follow-up	1 (20.0%)	0	0	1 (50.0%)	2 (22.2%)
Adverse event	2 (40.0%)	0	0	0	2 (22.2%)

[a] Percentages are based on the number of subjects within each treatment group.
[b] Percentages are based on the number of prematurely withdrawn subjects within each treatment group.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\DS Withdrawals.sas
Date and time program was run: 2019-06-27T07:54. Date and time analysis database was run: 2019-06-03T14:32

The first patient's first visit in the study was on 2016-06-29, the first patient was randomised on 2016-07-28 and the last patient's last visit was on 2018-05-29.

Due to a substantial number of withdrawals and protocol violations, only 43 patients in total and 8/15 in the PEF-IFN comparator arm are available for per protocol-analyses.

Baseline data

Demographics and clinical characteristics

In the PEG-IFN group (group A) the majority was females (67%), compared to the opposite in the MXB 2 mg + PEG-IFN group (group B) and the MXB 2 mg group (group D) (27% females) and a more even distribution in the MXB 5 mg + PEG-IFN group (group C) (53% females).

Due to the limited size of the study, there are imbalances in several of the baseline disease characteristics. Overall, subjects in arm B have lower HDV RNA, lower proportion of cirrhotic patients, lower ALT and HBV DNA compared to groups C and D.

Table 28. Baseline characteristics MYR203

mITT population	**Arm A: (n=15) PEG-IFNα**	**Arm B (n=15): BLV 2mg/day + PEG-IFNα**	**Arm C (n=15): BLV 5mg/day + PEG-IFNα**	**Arm D (n=15): BLV 2mg/day**	**Total: (n=60)**
Age (years): Mean (SD)	34.1 (7.0)	37.1 (5.5)	36.9 (7.5)	42.1 (9.4)	37.6 (7.8)

mITT population	Arm A: (n=15) PEG-IFNα	Arm B (n=15): BLV 2mg/day + PEG-IFNα	Arm C (n=15): BLV 5mg/day + PEG-IFNα	Arm D (n=15): BLV 2mg/day	Total: (n=60)
Gender: **Male (n, %)** **Female (n, %)**	5 (33.3) 10 (66.7)	11 (73.3) 4 (26.7)	7 (46.7) 8 (53.3)	11 (73.3) 4 (26.7)	34 (56.7) 26 (43.3)
Race: **Caucasian (n, %)** **Asian (n, %)**	14 (93.3) 1 (6.7)	15 (100) -	15 (100) -	15 (100) -	59 (98.3) 1 (1.7)
Cirrhosis (%)	4 (26.6)	2 (13.2)	5 (33.3)	3 (19.8)	14 (23.3)
ALT at BL (n): **U/L, Median (range)**	15 90.0 (39 - 176)	15 70.0 (44 - 311)	15 79.0 (30 - 1810)	15 84.0 (27 - 434)	60 79.0 (27 - 1810)
HDV RNA at BL (n): **Median log IU/ml (range)** **>100.000 IU/ml (n,%)**	15 5.44 (2.96 - 6.69) 10 (66.7)	15 5.48 (2.00 - 7.01) 10 (66.7)	15 6.24 (4.12 - 7.83) 13 (86.7)	15 6.39 (2.00 - 7.09) 12 (80.0)	60 5.92 (2.00 - 7.83) 45 (75.0)
HBsAg at BL: **Median log IU/ml**	4.13 (3.50, 4.71)	4.04 (2.90, 4.43)	4.26 (3.78, 5.30)	4.27 (3.42, 4.66)	4.17 (2.90, 5.30)

mITT population	Arm A: (n=15) PEG-IFNα	Arm B (n=15): BLV 2mg/day + PEG-IFNα	Arm C (n=15): BLV 5mg/day + PEG-IFNα	Arm D (n=15): BLV 2mg/day	Total: (n=60)
(Min, Max)					
HBV DNA at BL: Median (Min, Max)	10.0 (0, 20380)	10.0 (0, 1469)	28.0 (0, 309600000)	29.0 (0, 36090)	25.0 (0,309600000)
HDV genotype detected (n): Gen 1 (n,%)	14 14 (100)	14 14 (100)	14 14 (100)	15 15 (100)	57 57 (100)
HBV genotype detected (n): Gen C n, (%) Gen D n, (%) Gen H n, (%)	2 - 2 (100) -	1 - 1 (100) -	5 - 4 (80) 1 (20)	3 1 (33.3) 2 (66.6) -	11 1 (9.09) 9 (81.81) 1 (9.09)
Fibroscan kPa (N) Mean kPA (SD)	13 11.01 (4.66)	14 9.98 (4.98)	14 11.34 (6.03)	9 13.78 (5.09)	50 11.31 (5.23)

Outcomes and estimation

Primary efficacy variable: HDV RNA response at week 72

HDV RNA response data are provided below for the FAS and the PPAS. HDV RNA response, was defined as having an HDV RNA value below the lower level of detection (LLoD), where LLoD=10 IU/mL.

Figure 21 – Mean log-10 transformed HDV RNA levels over time. Full analysis set.

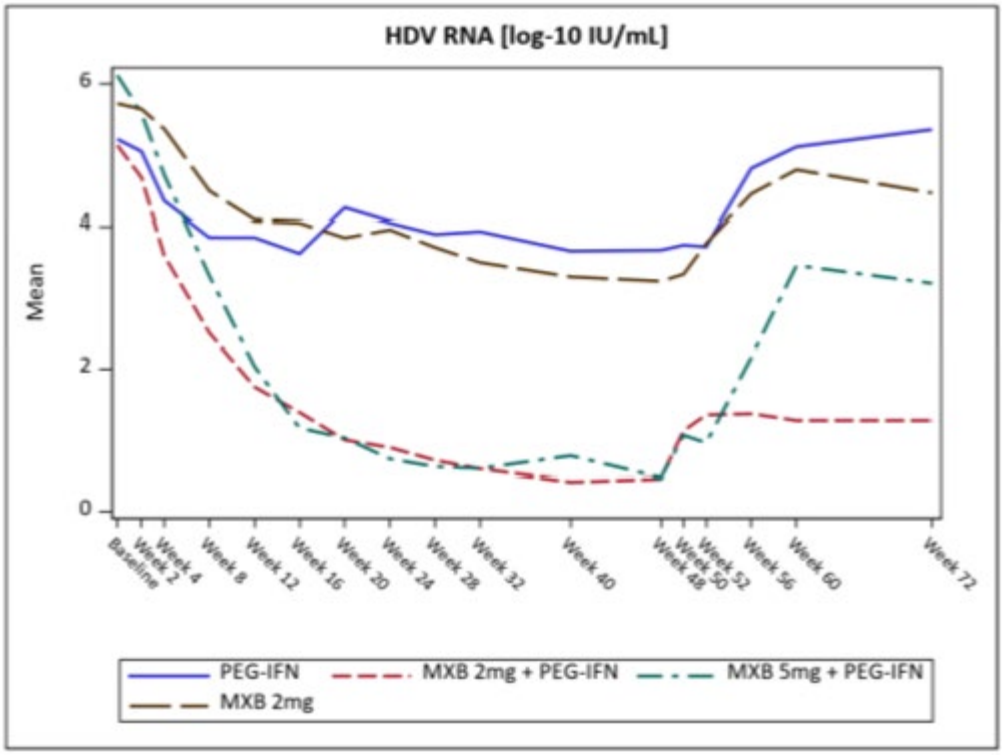


Table 29 - Primary efficacy variable: HDV RNA response at week 72. Statistical analysis on the difference in proportions, using Fisher's exact test. Full analysis set

HDV RNA response	PEG-IFN (N=15)	MXB 2mg + PEG-IFN (N=15)	MXB 5mg + PEG-IFN (N=15)	MXB 2mg (N=15)
Week 72				
Number of subjects in analysis	15	15	15	15
Number of responders	0	8	4	1
Proportion Responders (95% CI)	0 (0.0%, 21.8%)	53.3% (26.6%, 78.7%)	26.7% (7.8%, 55.1%)	6.7% (0.2%, 31.9%)
Difference in proportions (95% CI)		53.3 (25.1, 78.7)	26.7 (0.9, 55.1)	6.7 (-16.0, 31.9)
p-value		0.0022	0.0996	1.0000

HDV RNA response is defined as HDV RNA value below lower level of detection (LLoD), where LLoD=10.
Proportions in percent are based on the number of subjects in analysis within each treatment group.
CI = Confidence interval, calculated using Clopper-Pearson (exact) for within group proportions and exact unconditional for difference in proportions.
Fisher's exact test was used for the comparison of respective MXB group and PEG-IFN alfa-2 only group.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF1 HDV RNA Response.sas
Date and time program was run: 2019-06-27T12:39. Date and time analysis database was run: 2019-06-03T14:32

Table 30 - Primary efficacy variable: HDV RNA response at week 72. Statistical analysis on the difference in proportions, using Fisher's exact test. Per protocol analysis set

HDV RNA response	PEG-IFN (N=8)	MXB 2mg + PEG-IFN (N=12)	MXB 5mg + PEG-IFN (N=12)	MXB 2mg (N=11)
Week 72				
Number of subjects in analysis	8	12	12	10
Number of responders	0	7	3	1
Proportion Responders (95% CI)	0 (0.0%, 36.9%)	58.3% (27.7%, 84.8%)	25.0% (5.5%, 57.2%)	10.0% (0.3%, 44.5%)
Difference in proportions (95% CI)		58.3 (12.7, 84.8)	25.0 (-13.7, 57.5)	10.0 (-29.7, 44.5)
p-value		0.0147	0.2421	1.0000

HDV RNA response is defined as HDV RNA value below lower level of detection (LLoD), where LLoD=10.
Proportions in percent are based on the number of subjects in analysis within each treatment group.
CI = Confidence interval, calculated using Clopper-Pearson (exact) for within group proportions and exact unconditional for difference in proportions.
Fisher's exact test was used for the comparison of respective MXB group and PEG-IFN alfa-2 only group.
For the per protocol analysis set, subjects are analysed as treated (i.e. actual treatment).
Program: \Subprogs\Tables\EFF1 HDV RNA Response.sas
Date and time program was run: 2019-06-27T12:39. Date and time analysis database was run: 2019-06-03T14:32

Secondary efficacy variables

HDV RNA response at week 24 and week 48

HDV RNA response at week 24 and 48, defined as having an HDV RNA value below LLoD (where LLoD=10 IU/mL), are described below.

The results were comparable at week 48 when excluding patients with early termination at visit 13. Similar results were observed when the analyses were performed on the PPAS.

Table 31 - HDV RNA response at week 24 and week 48. Statistical analysis of difference in proportions, using Fisher's exact test. Full analysis set.

HDV RNA response	PEG-IFN (N=15)	MXB 2mg + PEG-IFN (N=15)	MXB 5mg + PEG-IFN (N=15)	MXB 2mg (N=15)
Week 24				
Number of subjects in analysis	15	15	15	15
Number of responders	1	9	9	2
Proportion Responders (95% CI)	6.7% (0.2%, 31.9%)	60.0% (32.3%, 83.7%)	60.0% (32.3%, 83.7%)	13.3% (1.7%, 40.5%)
Difference in proportions (95% CI)		53.3 (18.2, 78.9)	53.3 (18.2, 78.9)	6.7 (-20.3, 34.4)
p-value		0.0052	0.0052	1.0000
Week 48				
Number of subjects in analysis	15	15	15	15
Number of responders	2	12	13	2
Proportion Responders (95% CI)	13.3% (1.7%, 40.5%)	80.0% (51.9%, 95.7%)	86.7% (59.5%, 98.3%)	13.3% (1.7%, 40.5%)
Difference in proportions (95% CI)		66.7 (30.3, 88.7)	73.3 (37.0, 92.5)	0.0 (-28.9, 28.9)
p-value		0.0007	0.0001	1.0000

HDV RNA response is defined as HDV RNA value below lower level of detection (LLoD), where LLoD=10.
Proportions in percent are based on the number of subjects in analysis within each treatment group.
CI = Confidence interval, calculated using Clopper-Pearson (exact) for within group proportions and exact unconditional for difference in proportions.
Fisher's exact test was used for the comparison of respective MXB group and PEG-IFN alfa-2 only group.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF2 HDV RNA Response.sas
Date and time program was run: 2019-06-27T12:39. Date and time analysis database was run: 2019-06-03T14:32

The on-treatment virologic efficacy of the bulevirtide+PEG-IFN combination appears superior to that of monotherapy with either PEG-IFN or bulevirtide. However, when analysing data at 72 weeks according to the primary endpoint, the picture is less clear. Patients in study group B treated with 2 mg bulevirtide + PEG-IFN maintain virologic control 24 weeks after cessation of therapy, but not patients in group C who have received 5 mg bulevirtide + PEG-IFN. These conflicting findings, together with the overall scarcity of data, raise the question whether a clinically relevant post-treatment effect has been shown to the level of certainty required for establishing clinical efficacy for finite duration therapy.

The Applicant has clarified that they do not intend to make any labelling claims regarding the efficacy of the bulevirtide+PEG-IFN at this time.

ALT normalisation and combined response (undetectable HDV RNA and ALT normalisation)

Results regarding ALT normalisation at weeks 24, 48 and 72 are provided below.

Similar results were observed when the analyses were performed on the PPAS, except there was no statistically significant result (MXB 2 mg group/group D vs. PEG-IFN group/group A) at week 48.

Results for ALT normalisation at weeks 24, 48 and 72 were comparable in the subgroup analysis performed on patients with abnormal ALT values at baseline.

Table 32- ALT normalisation at weeks 24, 48 and 72. Statistical analysis of difference in proportions, using Fisher's exact test. Full analysis set.

ALT normalisation	PEG-IFN (N=15)	MXB 2mg + PEG-IFN (N=15)	MXB 5mg + PEG-IFN (N=15)	MXB 2mg (N=15)
Week 24				
Number of subjects in analysis	15	15	15	14
Number with ALT normalisation	0	1	3	9
Proportion (95% CI)	0 (0.0%, 21.8%)	6.7% (0.2%, 31.9%)	20.0% (4.3%, 48.1%)	64.3% (35.1%, 87.2%)
Difference in proportions (95% CI)		6.7 (-16.0, 31.9)	20.0 (-5.6, 48.1)	64.3 (33.9, 87.2)
p-value		1.0000	0.2241	0.0002
Week 48				
Number of subjects in analysis	15	15	15	15
Number with ALT normalisation	4	4	7	11
Proportion (95% CI)	26.7% (7.8%, 55.1%)	26.7% (7.8%, 55.1%)	46.7% (21.3%, 73.4%)	73.3% (44.9%, 92.2%)
Difference in proportions (95% CI)		0.0 (-32.8, 32.8)	20.0 (-16.0, 52.6)	46.7 (8.2, 75.4)
p-value		1.0000	0.4497	0.0268
Week 72				
Number of subjects in analysis	10	13	15	13
Number with ALT normalisation	1	7	5	3
Proportion (95% CI)	10.0% (0.3%, 44.5%)	53.8% (25.1%, 80.8%)	33.3% (11.8%, 61.6%)	23.1% (5.0%, 53.8%)
Difference in proportions (95% CI)		43.8 (1.2, 74.3)	23.3 (-15.2, 54.6)	13.1 (-24.8, 46.0)
p-value		0.0743	0.3449	0.6036

ALT normalisation is defined as normal ALT value (value within the normal range).
One withdrawn subject in the MXB 2mg group with normal ALT at week 48, used this visit (visit 13) as early termination visit.
Proportions in percent are based on the number of subjects in analysis within each treatment group.
CI = Confidence interval, calculated using Clopper-Pearson (exact) for within group proportions and exact unconditional for difference in proportions.
Fisher's exact test was used for the comparison of respective MXB group and PEG-IFN alfa-2 only group.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF2 ALT.sas
Date and time program was run: 2019-06-27T12:40. Date and time analysis database was run: 2019-06-03T14:32

Results of the combined response at weeks 24, 48, and 72 are provided below.

Table 33 - Combined response (negative HDV RNA and ALT normalisation) at weeks 24, 48 and 72. Statistical analysis of difference in proportions, using Fisher's exact test. Full analysis set.

Combined Response	PEG-IFN (N=15)	MXB 2mg + PEG-IFN (N=15)	MXB 5mg + PEG-IFN (N=15)	MXB 2mg (N=15)
Week 24				
Number of subjects in analysis	15	15	15	15
Number of responders	0	1	3	2
Proportion Responders (95% CI)	0 (0.0%, 21.8%)	6.7% (0.2%, 31.9%)	20.0% (4.3%, 48.1%)	13.3% (1.7%, 40.5%)
Difference in proportions (95% CI)		6.7 (-16.0, 31.9)	20.0 (-5.6, 48.1)	13.3 (-10.1, 40.5)
p-value		1.0000	0.2241	0.4828
Week 48				
Number of subjects in analysis	15	15	15	15
Number of responders	1	3	5	2
Proportion Responders (95% CI)	6.7% (0.2%, 31.9%)	20.0% (4.3%, 48.1%)	33.3% (11.8%, 61.6%)	13.3% (1.7%, 40.5%)
Difference in proportions (95% CI)		13.3 (-14.9, 43.3)	26.7 (-4.2, 55.6)	6.7 (-20.3, 34.4)
p-value		0.5977	0.1686	1.0000
Week 72				
Number of subjects in analysis	15	15	15	15
Number of responders	0	7	2	1
Proportion Responders (95% CI)	0 (0.0%, 21.8%)	46.7% (21.3%, 73.4%)	13.3% (1.7%, 40.5%)	6.7% (0.2%, 31.9%)
Difference in proportions (95% CI)		46.7 (19.2, 73.4)	13.3 (-10.1, 40.5)	6.7 (-16.0, 31.9)
p-value		0.0063	0.4828	1.0000

Combined response is defined as HDV RNA response and ALT normalisation.
Proportions in percent are based on the number of subjects in analysis within each treatment group.
CI = Confidence interval, calculated using Clopper-Pearson (exact) for within group proportions and exact unconditional for difference in proportions.
Fisher's exact test was used for the comparison of respective MXB group and PEG-IFN alfa-2 only group.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF2 Combined Response.sas
Date and time program was run: 2019-06-27T12:40. Date and time analysis database was run: 2019-06-03T14:32

In comparison to the reference PEG-IFN arm, the bulevirtide monotherapy arm shows a statistically significant difference in the proportion of subjects with on-treatment ALT normalisation, replicating the findings in the 202 study. This is not seen in the bulevirtide+PEG-IFN combination arms, likely due to the proinflammatory interferon effect. At 24 weeks post therapy (week 72), there is a numerically higher but non-significant proportion of responders in the 2 mg bulevirtide + PEF-IFN arm but in line with the virologic response the 5 mg combination arm performs less well.

The analysis of combined virologic/biochemical response is mainly of interest at week 72 as this biomarker profile, if found to be stable, raises hope for a long-term reduction of clinical events such as cirrhosis and hepatocellular cancer. Unfortunately, similar to the virologic response, the 5 mg bulevirtide+PEG-IFN arm performs less well than the 2 mg arm. Additional data are required to establish whether the bulevirtide + PEG-IFN combination yields clinically relevant rates of sustained virological and biochemical responses post treatment.

Fibrosis biomarkers

In the MYR203 study the median FIB-4 index was 1.32. A slight decrease from baseline to week 48 was observed under bulevirtide monotherapy, whereas an increase was detected in all PEG-IFNα containing arms. In the follow up, the values remained stable for bulevirtide monotherapy arm and returned to approximately baseline values in the PEG-IFNα containing arms.

Median baseline APRI values ranged from 0.7 to 1. An increase in all PEG-IFNα containing arms was detected at week 48, whereas a pronounced decline (from 1 to 0.4) was observed in the bulevirtide monotherapy arm. During the follow up, the values in the PEG-IFNα containing arms declined, and the score slightly increased in the bulevirtide monotherapy arm.

Tables 34 and 35. MYR203 safety analysis sets

Table 9. MYR 203. Fibrosis-4 (FIB-4) score. Safety analysis set

Fibrosis-4 (FIB-4) score	PEG-IFN (N=15)	BLV 2mg + PEG-IFN (N=15)	BLV 5mg + PEG-IFN (N=15)	BLV 2mg (N=15)	Total (N=60)
Baseline					
n/nmiss	15/0	15/0	15/0	15/0	60/0
Median	1.232	1.042	1.392	1.583	1.327
Week 48					
n/nmiss	14/1	15/0	15/0	15/0	59/1
Median	2.421	2.228	1.983	1.181	1.847
Week 72					
n/nmiss	10/5	13/2	15/0	13/2	51/9
Median	1.069	1.295	0.956	1.204	1.083

Table 10. MYR 203. AST to Platelet Ratio Index (APRI). Safety analysis set

AST to Platelet Ratio Index (APRI)	PEG-IFN (N=15)	BLV 2mg + PEG-IFN (N=15)	BLV 5mg + PEG-IFN (N=15)	BLV 2mg (N=15)	Total (N=60)
Baseline					
n/nmiss	15/0	15/0	15/0	15/0	60/0
Median	1.1991	0.6909	1.0994	1.0161	1.0252
Week 48					
n/nmiss	14/1	15/0	15/0	15/0	59/1
Median	1.2594	1.2218	0.8726	0.4467	0.8907
Week 72					
n/nmiss	10/5	13/2	15/0	13/2	51/9
Median	0.7376	0.5991	0.7422	0.6336	0.6600

Transient elastometry and liver biopsy

There were no statistically significant differences in the change from baseline between the groups receiving MXB alone or in combination with PEG-IFN (groups B, C and D) compared to the PEG-IFN group (group A) at any time-point. Similar results were observed when the analyses were performed on the PPAS population.

HBV and HDV genotyping

Samples from all patients were analysed; however due to low HBV DNA levels at baseline, the HBV genotyping gave no results for 49 patients (81.7%). The HBV genotyping that was successful in eleven patients (18.3%), revealed that one patient (1.7%) was infected with HBV genotype C, nine patients (15.0%) were infected with HBV genotype D and one patient (1.7%) was infected with HBV genotype H.

The HDV genotyping revealed that 57/60 patients (95.0%) were infected with HDV genotype 1. Three patients (5.0%) had missing values for HDV genotyping.

Similar to MYR202, the HBV genotyping dataset is very limited, and patients were almost exclusively of HDV GT 1.

Summary of main efficacy results

Table 36 – HDV RNA response

HDV RNA response	PEG-IFN (N=15)	MXB 2mg + PEG-IFN (N=15)	MXB 5mg + PEG-IFN (N=15)	MXB 2mg (N=15)
Week 72				
Number of subjects in analysis	15	15	15	15
Number of responders	0	8	4	1
Proportion Responders (95% CI)	0 (0.0%, 21.8%)	53.3% (26.6%, 78.7%)	26.7% (7.8%, 55.1%)	6.7% (0.2%, 31.9%)
Difference in proportions (95% CI)		53.3 (25.1, 78.7)	26.7 (0.9, 55.1)	6.7 (-16.0, 31.9)
p-value		0.0022	0.0996	1.0000

- The aim of the MYR203 study was to investigate the efficacy of MXB in monotherapy and in combination with PEG-IFN and with Tenofovir compared to monotherapy with PEG-IFN, based on the achievement of undetectable viral load at the end of the follow-up period 6 months (24 weeks) after the end of treatment. The small sample size (n=60) is explained by the clearly stated exploratory nature of the study.
- The on-treatment efficacy of the bulevirtide+PEG-IFN combination appears superior to that of monotherapy with either PEG-IFN or bulevirtide. When analysing data at 72 weeks according to the primary endpoint, the picture is less clear. A statistically significant higher proportion of subjects (8/15) in study group B treated with 2 mg bulevirtide + PEG-IFN maintain virologic control 24 weeks after cessation of therapy, compared to monotherapy with PEF-IFN or bulevirtide. However, the results in group C who have received 5 mg bulevirtide + PEG-IFN are less convincing (4/15) and not significantly better than PEG-IFN (0/15) or bulevirtide 2 mg monotherapy (1/15). This raises the question on whether a clinically relevant post-treatment effect has been shown to the level of certainty required for establishing clinical efficacy for finite duration therapy.
- In comparison to the reference PEG-IFN arm, the bulevirtide monotherapy arm shows a statistically significant difference in the proportion of subjects with on-treatment ALT normalisation, confirming

the findings in the -202 study. This is not seen in the bulevirtide+PEG-IFN combination arms, likely due to the proinflammatory interferon effect. At 24 weeks post therapy (week 72), there is a numerically higher but non-significant proportion of responders in the 2 mg bulevirtide + PEF-IFN arm but in line with the virologic response the 5 mg combination arm performs less well.

- The analysis of combined virologic/biochemical response is mainly of interest at week 72 as this biomarker profile, if found to be stable, raises hope for a long-term reduction of clinical events such as cirrhosis and hepatocellular cancer. Unfortunately, similar to the virologic response, the 5 mg bulevirtide+PEG-IFN arm performs less well than the 2 mg arm.
- Median non-invasive biomarkers (FIB-4 and APRI scores) in the bulevirtide 2 mg arm showed a reduction at EOT, that worsened after treatment cessation, without however returning to baseline values.
- The Applicant has clarified that they do not intend to make any labelling claims regarding the use of the bulevirtide+PEG-IFN at this time.

Resistance testing

A functional *in vitro* cell based resistance assay was developed based on the plasma infectivity potential of HDV. HuH7-hNTCP cells stably transfected with hNTCP were inoculated with patient plasma containing patient derived HDV isolates. To test the *in vitro* susceptibility of bulevirtide on patient plasma serum infectivity, cells were pre-treated for 30 minutes with serial dilution of bulevirtide (0.0078, 0.156, 0.312, 3.125, 62.5, 125, 250, and 500nM) At day 5 post infection, cells were fixed and stained for HDAg. HDV infected cells were detected using immunofluorescent microscopy. Quantification of infected cells was performed by means of automated cell counting using Image J software. There appears to have been no available positive control of bulevirtide-resistant virus.

Virological breakthrough was defined as a confirmed increase of $\geq 2\log_{10}$ IU/ml HDV RNA from the nadir on two consecutive visits under treatment and/or until the end of treatment, assuming the nadir was previously at least $\geq 1\log_{10}$ IU/ml below the HDV RNA baseline value at two consecutive visits.

In MYR202, no virologic breakthroughs occurred.

In the MYR203 trial, two patients receiving 2 mg bulevirtide as monotherapy and one patient receiving 5 mg bulevirtide in combination with PEG-IFNα experienced virological breakthrough. An overview on these patients is presented below.

Table 37. MYR203. Overview of patients with virological breakthroughs.

	MYR203		
Treatment regimen	Arm D: BLV 2 mg/day	Arm C: BLV 2 mg/day	Arm C: BLV 5 mg/day + PEG-IFNα
Virological breakthrough: **log increase in HDV RNA from nadir to timepoint of endpoint assessment** **[$\log_{10}$ IU/ml]**	+ $2.3\log_{10}$	+ $3.2\log_{10}$ [1]	+ $1.98\log_{10}$

HDV genotype	1	1	1
HBV genotype	n.d.	n.d.	n.d.
***In vitro* phenotypic resistance determinable:** **EC50 at baseline** **EC50 at end of treatment**	 0.39 nM 0.40 nM	 n.d. 0.41 nM[1]	 0.43 nM 0.25 nM
***Δresistance:* from EC50 reference strain** **BL** **End of treatment**	 0.1 0.1	 n.d. 0.1	 0.11 0.06
Δ*resistance:* from BL EC50	1.022	n.d.	0.5

n.d. = not detectable, BLV = bulevirtide, BL = baseline, EC50 = effective concentration 50

[1]patient 18313 withdrew ICF at treatment week 24, log increase is calculated for week 24 and EC50 of week 24 patient plasma was determined

Source: MYR-VB-001

Virological breakthroughs were also identified in five patients treated with PEG-IFNα only.

The phenotypic assessment of patients experiencing virological breakthroughs demonstrated that all patient-derived HDV from baseline, week 24 and week 48 were still susceptible to *in vitro* application of bulevirtide with EC50 values within the picomolar range.

NTCP polymorphisms testing for the two most prominent single nucleotide polymorphism (SNP), Arg252His and Ser267Phe was performed as part of the resistance testing strategy, i.e. in patients who either showed no response to treatment or experienced a virological breakthrough. In total, samples from three patients were examined and all five NTCP exons were sequenced and inspected for SNP. In general, no known SNPs were detected in comparison to the WT NTCP sequence. With respect to the two prominent SNPs in exon 4, all three patients showed a homozygous genotype, the individual chromatogram nucleotide triplets were unique for both Arg252 and Ser267.

Analysis performed across trials (pooled analyses and meta-analysis)

Given the different treatment strategies in the MYR202 and MYR203 studies, pooling of efficacy data does not contribute to further characterisation of the efficacy of bulevirtide.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

General comments

The present application rests on the outcome of two small phase II studies, MYR202 and MYR203

MYR202 studied patients with chronic hepatitis delta and quantifiable HDV virus replication, failing previous treatment with IFN or were considered IFN-intolerant were included, as well as patient with compensated cirrhosis. Patients with decompensated liver disease were not studied. Patients received 2 mg, 5 mg or 10 mg bulevirtide s.c. once daily, or no treatment for chronic hepatitis delta. All patients received tenofovir to treat underlying chronic hepatitis B. The primary variable was HDV RNA response, defined as HDV RNA negativation or a decrease in HDV RNA by ≥2 log10 IU/mL from baseline to week 24.

The MYR203 study included patients with compensated liver disease who were eligible for interferon therapy. This trial had pegIFN as the reference therapy, investigated 2 mg or 5 mg bulevirtide s.c. once daily as an add-on to pegIFN, or 2 mg bulevirtide s.c. alone. The primary variable was the occurrence of a negative polymerase chain reaction (PCR) result of HDV RNA (HDV RNA negativation) at week 72 (end of the follow up period).While the duration of treatment in the MYR202 study was 24 weeks, it was clearly demonstrated that this does not induce a sustained off-treatment virological response. Therefore, this study is representative of a strategy of continuous treatment of indefinite duration, such as with nucleos(t)ide analogues for chronic hepatitis B or HIV infection. Contrariwise, the treatment strategy in the MYR203 refers to a treatment of finite duration, where the aim is to induce a sustained virological response after the end of therapy. This is analogous to pegIFN treatment on chronic hepatitis B, or the treatment strategy for chronic hepatitis C.

In both cases the studies were exploratory. As results emerged, the applicant sought and received PRIME status for bulevirtide. Since chronic hepatitis delta is virgin territory from a regulatory point of view, fundamental issues on how to define clinical benefit were discussed in CHMP scientific advice. As opposed to the case for HIV and chronic hepatitis B and C, it was not considered that the surrogacy of reduction of viremia with respect to reducing the risk of relevant clinical endpoints such as liver failure, hepatocellular carcinoma, liver transplantation, liver death or overall mortality had been established. Therefore, the actual primary endpoints of the performed studies are not appropriate for registration, and the entire program is seen as purely exploratory in its design.

However, it has long been recognised that in chronic hepatitides, ALT elevations are indicative of ongoing necro-inflammation, and ALT normalisation is associated with a decrease in the rate of progression to cirrhosis. Therefore, ALT normalisation is considered a surrogate of clinical benefit, in a situation where the duration and size of studies to directly demonstrate an impact on clinical endpoints, make randomised controlled trials for this purpose not feasible.

Preliminary assessment of data from the bulevirtide program in the scope of PRIME indicated that virological response was indeed associated with decreases in ALT. Since sustained virological activity is necessary to sustain effects on ALT, the CHMP agreed that a combined endpoint of HDV RNA negativation or a decrease in HDV RNA by ≥2 log10 IU/mL AND ALT normalisation, is appropriate to assess clinical benefit in the present setting. This endpoint has been implemented in the ongoing randomised phase III MYR301 study, investigating 2 mg or 10 mg of bulevirtide compared to no treatment for chronic hepatitis delta. The primary endpoint is at 48 weeks.

In case a finite treatment duration is studied, the primary endpoint needs to demonstrate sustained virological response in order to indicate clinical benefit. In analogy with what was used for chronic hepatitis C until earlier surrogate measurements were validated, the CHMP considered that sustained response at 24 weeks after the discontinuation of therapy was appropriate as primary endpoint, provided that this is supported by further data on the durability of response in subsets at the time of a MAA.

Thus, both trials are viewed from the point of view of an endpoint defined post-hoc. In the absence of statistical rigor, convincing antiviral effects linked to ALT normalisation would be wanted to establish efficacy

in the context of a serious chronic viral hepatitis for which no treatments are approved and for which clinical benefit has not been firmly established for any treatment – although an antiviral effect of pegIFN, which is the only therapy recommended per guideline, has been shown, as exemplified by on-treatment outcomes in the control arm of MYR203.

Apart from this fundamental weakness in the available data, rendering the efficacy demonstration non-comprehensive, it is notable that in neither study was randomisation was completely neutral, since patients agreeing to participate in PK sub-studies were not eligible for randomisation to the control arms. A GCP inspection is pending. Furthermore, neither study was large enough to produce truly balanced randomisation.

The main factor mitigating these grave deficiencies is the fact that clinically relevant virological and/or biochemical response is anticipated to be uncommon in patients with chronic hepatitis delta, with transaminitis and quantifiable viremia, as demonstrated by the behaviour of the control arm in the MYR202 study. While calibration is deficient and true effect sizes remain uncertain, it remains possible to identify combined virological and biochemical response as defined above, as effects of bulevirtide treatment.

MYR202

The above-mentioned deficiencies are outstanding.

In this open label study, there was some imbalance across the treatment arms in the rate of premature withdrawals from the study, with more missing data in the control arm.

The primary analysis was not stratified by the randomisation stratification factors; instead, a subgroup analysis was performed for subjects with/without cirrhosis. In the responder analyses, subjects with missing data were considered as non-responders which is supported.

The SAP was authored after the study completion, which is problematic in general, and particularly in open label studies. This should be seen, however, in the light of the exploratory nature of the study and the aspects discussed above.

MYR203

The general consideration mentioned above are relevant also here. The randomisation with respect to giving consent for the PK sub-study could be a confounding factor, possibly steering patients with better overall health and clinical outcome to the bulevirtide arms. Also, after implementation of CSP amendment 2, patients not participating in the PK sub-study were "mainly randomised in arm D".

The exploratory purpose of the study is apparent through the repeated substantial changes of the study design and the statistical analyses without adjusting for multiple testing.

Authoring the SAP and its amendments late after the study completion is problematic, but not surprising considering the exploratory nature of the study. The reason for most of the changes in the two SAP amendments was to harmonise the methods with the analysis of study MYR202.

Considering the statistical methodology, the quality of the study is low due to the low number of subjects and the methodological shortcomings such as open label, corrupted randomisation procedure, and unaddressed multiplicity issue. These are deviations from basic statistical principles required to enable unbiased estimation.

Efficacy data and additional analyses

The MYR202 study, including 90 patients treated with bulevirtide (with background TDF) for 24 weeks in comparison with 30 patients treated with TDF only, provides ground for the following conclusions regarding the clinical efficacy of bulevirtide:

- Bulevirtide is effective in reducing HDV RNA with 53.6% of patients treated reaching the primary endpoint of a 2 log10 HDV RNA reduction or becoming negative, when treated with the 2 mg daily dose proposed by the Applicant, significantly superior to TDF only.
- There is an apparent dose-response up to at least 10 mg, which was the highest dose group, where 76.7% of patients reached the primary endpoint.
- Along with virologic response, a superior biochemical response is seen in all bulevirtide groups compared to TDF only, with 40-50% of patients in the bulevirtide group normalising their ALT levels after 24 weeks of therapy compared to 7% of TDF patients, suggesting a reduction of hepatic necroinflammation in the bulevirtide groups. It is notable that the dose-response relation appears substantially stronger for the antiviral effect compared to the effect on ALT. Some information has been provided concerning the relation of plasma HDV-RNA and ALT response: At baseline, serum HDV RNA levels did not correlate with ALT levels with mean HDV RNA serum levels were 4.84 ± 2.75 log10, 5.22 ± 1.36 log10, 5.38 ± 1.01 log10, and 5.72 ± 0.74 log10 for ALT CTC grade 0, 1, 2, and 3. While at baseline, no correlation between HDV RNA and ALT levels was observed, a significant association between HDV RNA and ALT CTC grades appeared at the end of treatment (week 24, $p<.0001$).
- The Applicant has provided a plot showing the change from baseline in log HDV RNA and ALT at week 24 in bulevirtide treatment groups (see below). Although there is bibliographic evidence from observational studies of a qualitative relation between HDV RNA positivity and clinical outcome, the lack of HDV RNA vs ALT correlation at baseline further shows that the quantitative surrogacy of viremia is currently not established for HDV. It is acknowledged that the on-treatment correlation at week 24, together with previously presented data on combined HDV-RNA/ALT response supports a beneficial effect but there is some residual uncertainty.

There are also uncertainties about the relative efficacy oi the 2 mg dose, given that baseline ALT is lower in this group, illustrating that the study is not large enough to produce balanced randomisation.

- A modest numerical improvement in liver stiffness (estimated by elastometry) and non-invasive scores (FIB-4 and APRI) was observed at Week 24. Within a 24-week period, it is expected that changes in liver stiffness are driven by changes in inflammation and hepatic oedema rather than a true reduction of fibrosis.

The MYR203 study included 30 patients treated for 48 weeks with bulevirtide in combination with PEG-IFN, 15 patients treated with bulevirtide only and 15 patients treated with PEG-IFN only.

- Due to a substantial number of withdrawals and protocol violations, only 43 patients in total and 8/15 in the PEF-IFN arm are available for per protocol-analyses. Due to the small study size, it cannot be ascertained that randomisation is balanced (see e.g. proportion of the respective genders in each arm).
- The on-treatment efficacy of the bulevirtide+PEG-IFN combination appears superior to that of monotherapy with either PEG-IFN or bulevirtide. However, when analysing data at 72 weeks, the

picture is less clear. While no patients in the pegIFN control arm exhibited a sustained combined response, 7/15 patients in the 2 mg bulevirtide + pegIFN arm did, as did 2/15 in the 5 mg+ bulevirtide arm, and 1/15 in the bulevirtide 2 mg only arm. Given the severe methodological caveats, it cannot be inferred that the clinical benefit of using bulevirtide in a finite therapy setting, alone or in combination with pegIFN, has been demonstrated. A larger study of the use of bulevirtide in combination with pegIFN (MYR204) is ongoing and will hopefully shed further light on the usefulness of this treatment paradigm.

- Importantly, the MYR203 study indicates that the on-treatment antiviral effect of bulevirtide is similar to that of pegIFN, which while not being regulatorily approved, is recommended in treatment guidelines based on sparse data supporting such an antiviral effect. Moreover, 9/15 patients treated with 2 mg bulevirtide alone showed normalised ALT at week 24, and 11/15 patients at week 48 (end of therapy). Thus, the results from this study corroborate the finding from the MYR202 study indicating that the 2 mg dose of bulevirtide may produce clinical beneift.
- Median non-invasive biomarkers (FIB-4 and APRI scores) in the bulevirtide 2 mg arm showed a reduction at EOT, that worsened after treatment cessation, without however returning to baseline values.

Dose selection and viral drug resistance

Despite the substantial deficiencies of MYR202 and MYR203, data are considered sufficient to establish the antiviral effect of bulevirtide. While there appears to be a dose-response relation from 2 mg to 10 mg with regards to antiviral efficacy, it is not clear that this translates into higher rates of ALT normalisation. Furthermore, the ability of the 2 mg bulevirtide dose alone to provide meaningful rates of ALT normalisation is supported by both studies. However, see above concerning imbalanced randomisation with respect to baseline ALT, which makes it difficult to fully understand the relative efficacy of 2 mg ant 10 mg.

In the general case for an antiviral, given similar tolerability, the 10 mg dose would seem to be relevant for approval. The reason for this would be the wish to maximise the barrier to resistance, whereby activity against escape variants as well as wild-type virus would need to be considered. However, as will be elaborated below on clinical safety, the safety database to support a 5 mg or 10 mg dose would arguably be prohibitively small. This issue was extensively discussed within the PRIME deliberations, and the applicant decided to seek approval for the 2 mg dose, pending the further investigations of the 2 mg and 10 mg doses in the MYR301 study.

Bulevirtide on-treatment virological breakthrough was observed in none of the MYR202 study subjects and in 3 of the of the MYR203 participants (two in 2 mg/day and one in 5 mg/day + PegIFN). In order to evaluate impact of non-adherence behaviour on treatment efficacy and virological breakthrough, the Applicant provided data showing in the 2 mg treatment arm of MYR203 study a mean number of missed doses of 1.1 (SD 2.3). Among subjects with virological breakthrough 1 out of 3 (patient 18313) displayed clear non-adherence behaviour characterised by missed doses and irregular drug administration.

None of these patients received a subsequent bulevirtide treatment. In samples obtained from these subjects based on serum infectivity assay no evidence of the selection of resistant variants was found. The Applicant states that no HBV nucleotide sequencing was performed in the study for technical reasons, due to very low HBV DNA levels (for patients with VB, HBV DNA levels were very low ranging from 10-29 IU/ml at baseline). This is understandable, although level of viraemia (between 10 and 29 IU/ml) does not exclude that, with

appropriate technical measures (e.g. through nested-PCR), a good number of positive responses can be obtained.

Based on the mechanism of action, a high barrier to resistance may be anticipated. Here it is notable that the selection pressure would likely be exerted on HBV rather than HDV, insofar as the viral entry receptor for HDV, which interacts with NTCP, is HBsAg, which is encoded by HBV.

Altogether, the view is that the 2 mg dose, albeit not optimal from an antiviral point of view, will not be associated with viral resistance and potential loss of chance.

Additional efficacy data needed in the context of a conditional MA

For the reasons elaborated above, as well as due to the limited safety database, data are deemed non-comprehensive in the sense of the CMA legislation. To corroborate the efficacy of bulevirtide, complete data from the MYR301 (150 subjects, monotherapy approach) study is needed.

Additional expert consultation

Final answers of the *ad hoc* Expert Group meeting for He AHEG ANSWERS FOR HEPCLUDEX

1. **Does the SAG think that there is a patient population with chronic HDV infection that is in urgent need of treatment and whose prognosis would be negatively affected by delay of approval? In case of affirmative answer, what size are estimates for this patient population?**

The experts agreed that there is an unmet medical need for bulevirtide and that chronic hepatitis delta virus (HDV) infected, HDV-RNA positive adult patients with compensated liver cirrhosis or advanced/ rapidly progressive liver fibrosis with undetectable HBV-DNA on nucleo(s)(t)ide treatment for HBV would constitute a patient population in urgent need for treatment with Hepcludex.

The experts could however not provide a reasonable figure on the size of this patient population, taken account the uncertainties in numbers due to differences of patient characteristics between countries.

2. **Considering the use of surrogate endpoints, to what extent do you consider that bulevirtide 2 mg addresses the unmet medical need of chronic HDV treatment and that the efficacy data will translate into clinical benefit?**

The experts agreed that, taking account the use of surrogate endpoints, the proposed 2 mg dose addresses the unmet medical need for a treatment for chronic HDV and that the available data supports a clinical benefit as an initial treatment dose. However, the experts suggest that the availability of the 10 mg dose is desirable for individual patients who do not or partially respond to the initial 2 mg dose therapy (non-responders or partial responders) to be able to escalate the dose to achieve an undetectable HDV-RNA, which is considered to be the desired endpoint in infinite treatment.

3. **Does the SAG think that bulevirtide 2 mg would be the appropriate dose for registration, given the efficacy data of 2 mg and 10 mg as well as the limited exposure to doses higher than 2 mg? To what extent does the SAG find virological breakthroughs and viral resistance development a matter of concern?**

The experts considered that a 2mg dose would constitute an appropriate initial dose allowing approval (see also above). However, based on medical need, a dose escalation to 10 mg is suitable in non-responders and partial responders. The experts believe that such a dosage is defensible on the limited available data.

Viral resistance has not been recognised as an issue so far; however it was noted that some patients do not respond, only partially respond, or slowly respond to treatment and the Applicant is encouraged to examine the mechanism as to why some individuals are non-responders, partial responders or slow responders to therapy.

4. **How do you evaluate the potential long-term consequences of dose-dependent bulevirtide-induced bile acid elevations? Does the SAG have any suggestions for post-approval investigations that could be relevant to further characterise the safety concerns?**

The group did not consider the observed bile acid elevations to be of concern. The increases seem small and although the long-term effects in humans are not fully established, they do not seem to constitute a considerate safe safety issue. Nevertheless, in this respect, a negative effect of high bile acid levels in pregnancy cannot be excluded. It was noted that the proposed SmPC includes a precautionary statement in section 4.6 "*As a precautious measure, it is preferable to avoid the use of bulevirtide during pregnancy and in women of child-bearing age who do not use contraception*", which would adequately address the issue and minimise the risk.

5. **One cirrhotic patient in the -202 study (01018-R049) presented with pancytopenia at the study week 2 visit and was lost to follow up at week 16. What is your evaluation of this case, and the possibility of a causal relation with bulevirtide exposure?**

The experts considered as plausible the Applicant's explanation that the pancytopenia finding observed in this case is entirely compatible with manifestation of cirrhotic decompensation and agreed that the subsequent haemorrhage was unlikely attributable to the use of bulevirtide.

2.5.3. Conclusions on the clinical efficacy

The assessment of bulevirtide efficacy is based on two small, open-label phase 2 studies with a less than satisfactory statistical design. Notwithstanding this, it can be concluded that the 2 mg dose of bulevirtide provides meaningful antiviral activity. There is also an impact on rates of ALT normalisation, which is an accepted surrogate for clinical benefit in chronic viral hepatitis, as it indicates reduction or cessation of necro-inflammation, which is the cause of fibrosis progression. The 2 mg dose is not optimal from an efficacy perspective but could be acceptable if this does not convey an increased risk of resistance development. The overall risk of resistance development appears low.

There are currently not sufficient data to support a sustained off-treatment effect of bulevirtide in combination with PEG-IFN.

2.6. Clinical safety

Patient exposure

Six finalised trials investigating the safety of bulevirtide are available. In these trials, a total of 239 individuals have been exposed to various doses of bulevirtide.

Except for the first-in-man trial MYR101, where 27 individuals received bulevirtide via the i.v. route, all patients received bulevirtide s.c..

Thirty-six subjects received single doses only, while 191 were treated for at least 12 weeks. The proposed dose of 2 mg or higher was administered to 205 subjects, of which 175 patients were treated for at least 12 weeks.

38 patients received bulevirtide in combination with PEG-IFNα, and 102 subjects in combination with tenofovir.

In addition to the described finalised trials, two investigator-sponsored trials are ongoing, and preliminary safety information is available from the corresponding DSUR. In the first trial (K510), administering 5 mg bulevirtide/day for 12 weeks, 13 patients were enrolled and had received at least one dose at the time of the data lock point (i.e. 14 August 2019). In the second (K621), administering 10 mg bulevirtide/day (BID) for 1 week in combination with 40 mg pravastatin, 20 patients were enrolled and 19 had received at least one dose of bulevirtide (DSUR No1 for K510 and K621).

Furthermore, at the data lock point 14 August 2019, a total of 21 patients with HDV infection were part of bulevirtide compassionate use programs.

Table 38. Study subject drug exposure by mean daily dose and duration of exposure in completed clinical trials. Intravenous formulation N=27. Subcutaneous formulation N=212. Cut-off Date: 14 August 2019

Duration (Weeks)	0 < Dose <2 mg	2 mg	3 mg	5 mg	10 mg	10 < Dose ≤20 mg	Total (Any Dose)
1 day > 12 weeks	18	1	3	6	18	3	49
12 weeks	16	8		8			32
>12 <24 weeks				2	1		3
24 weeks		44		30	37		111
48 weeks		29		15			44
Total (any duration)	34	82	3	61	56	3	239

Source: MYR101, MYR102, MYR201 (HBV), MYR201 (HDV), MYR202, MYR203

MYR201(HDV): 1 patient receiving 2 mg dose discontinued after 8 weeks of treatment

MYR202: 1 patient receiving 5 mg dose discontinued after 16 weeks of treatment; 1 patient receiving 5 mg dose discontinued after 20 weeks of treatment; 1 patient receiving 10 mg dose discontinued after 20 weeks of treatment

MYR203: 1 patient receiving 2 mg dose discontinued after 24 weeks of treatment

Table 39. Subject drug exposure in ongoing clinical trials and compassionate use programs

Trial	Planned daily dose	Planned duration	# patients at data lock point	Comments
MYR203 extension / Phase 2	10 mg	48 weeks	30	15 patients received BLV 10 mg once daily, 15 patients received BLV 5 mg BID
K621 / Phase 1	10 mg BID	7 days	19	BLV 10 mg BID, in combination with pravastatin
K510 / Phase 1	5 mg	12 weeks	13	
MYR301 / Phase 3	2 mg and 10 mg	144 weeks	41	
MYR204 / Phase 2	2 mg and 10 mg	96 weeks	27	
CUP	2 mg and 10 mg	N/A	21	

Source: DSUR. Limited information is available. It is assumed that all patients enrolled at the data lock point were exposed with the full dose planned in the trial
Abbreviation: BID = twice daily (bis in diem); BLV = bulevirtide; CUP = compassionate use program; N/A = not applicable

From the MYR202 data distribution parameters (interquartile range and range) it is clear that most patients received bulevirtide for 24 weeks, in line with the study protocol. However, a limited number of subjects in the bulevirtide arms seem to have received study drug for up to 36.7 weeks.

In MYR202, the tenofovir exposure varies between 4.1 and 61.6 weeks. It is assumed that the median 60 weeks is an indication that the protocol-defined 12-week minimum NUC lead-in phase has been included in the exposure data if TDF was used for the lead-in.

The majority of patients were male, Caucasian and with a mean age of about 38 years in BLV 2 mg groups and the mean BMI was <30 Kg/m^2. No patients older than 65 years have been included in these studies. Moreover, races other than Caucasian (such as Black or Asian) are underrepresented.

Justification to omit QT study

The Applicant has provided justification for the omission of a QT study, which is accepted.

Bulevirtide is a highly targeted peptide that binds exclusively to NTCP and is thus highly localised in its distribution. NTCP is localised exclusively at the basolateral membrane of differentiated hepatocytes and its expression is hepatocyte specific.

In the non-clinical program conducted, bulevirtide was found to be exclusively distributed to the liver in all tested animals except for the cynomolgus monkey (which exhibits a mutated binding site for bulevirtide). Pharmacokinetic studies performed with radiolabelled peptides have shown a rapid accumulation already 10 min after injection of radioactivity in the liver of all tested species including mice, rats and dogs. Neither in mice, rats nor dogs, radioactivity was detected in the heart.

In line with ICH S6 (R1), safety pharmacology studies were incorporated into the toxicology program. Briefly, no bulevirtide-related influence on pulmonary, neuropharmacological, cardiovascular, renal, hepatic, ophthalmologic, or auditory parameters were observed.

The cardiovascular function was assessed in a 13-week repeated dose toxicity study in beagle dogs (24196) neither demonstrating any drug-related abnormalities of the electrical complexes including the QT interval and QTc value nor any changes in the heart rate in dogs treated with 0.25, 1, and 2.5mg bulevirtide/day subcutaneously for 91 days. This result was confirmed in the chimpanzee study (TBRI-101) where ECGs after treatment with bulevirtide were considered normal for the seduction conditions.

In the frame of the phase I clinical trial MYR101 investigating the safety, pharmacokinetics, and tolerability of single doses of bulevirtide (300 ng – 20 mg) continuous ECG monitoring during the first 12 hours after administration and 12-lead ECG was one of the outcome measures. After administration of Bulevirtide either intravenously or subcutaneously in all cohorts of the MYR101 there were no relevant changes in the 12-lead ECG observed.

Taken together no effects of bulevirtide were observed within the non-clinical program nor in the phase I study that warrant the conduct of a thorough QT/QTc clinical trial. Within the phase II clinical trials conducted, 12-lead ECGs were performed as an additional safety measure. In general, results from these ECGs showed only few clinically significant changes and no trends were observed.

Adverse events

Due to the differences in drug combinations, dose and comparators, safety data from the pivotal studies MYR202 and MYR203 are presented separately below, followed by an integrated analysis of aggregable safety data.

MYR202

There were two study discontinuations due to AEs. All events were assessed as unrelated to the study treatment.

Table 40. Overview of adverse events (safety analysis set)

	MXB 2 mg (N=28)		MXB 5 mg (N=32)		MXB 10 mg (N=30)		Tenofovir (N=28)		MXB total (N=90)		Total (N=118)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Any adverse event	18 (64.3%)	74	21 (65.6%)	131	23 (76.7%)	146	14 (50.0%)	55	62 (68.9%)	351	76 (64.4%)	406
Any serious adverse event	0	0	3 (9.4%)	3	2 (6.7%)	2	1 (3.6%)	1	5 (5.6%)	5	6 (5.1%)	6
Any adverse event leading to withdrawal of the study treatment	0	0	1 (3.1%)	1	0	0	1 (3.6%)	1	1 (1.1%)	1	2 (1.7%)	2
Any adverse event leading to death	0	0	0	0	0	0	0	0	0	0	0	0
Adverse events by severity												
Mild	16 (57.1%)	58	19 (59.4%)	86	22 (73.3%)	108	13 (46.4%)	40	57 (63.3%)	252	70 (59.3%)	292
Moderate	5 (17.9%)	13	14 (43.8%)	33	10 (33.3%)	31	6 (21.4%)	14	29 (32.2%)	77	35 (29.7%)	91
Severe	3 (10.7%)	3	4 (12.5%)	12	3 (10.0%)	7	1 (3.6%)	1	10 (11.1%)	22	11 (9.3%)	23
Adverse events by causality												
Not related	12 (42.9%)	33	16 (50.0%)	75	15 (50.0%)	57	14 (50.0%)	55	43 (47.8%)	165	57 (48.3%)	220
Related	12 (42.9%)	41	17 (53.1%)	56	22 (73.3%)	89	0	0	51 (56.7%)	186	51 (43.2%)	186

n = number of subjects, m = number of events.
Percentages are based on the number of subjects within each treatment group.
Program: \Subprogs\Tables\AE.sas
Date and time program was run: 2019-05-23T08:40. Date and time analysis database was run: 2019-05-20T14:24

Table 41. Adverse events in MYR202 – most common PTs (safety set)

	Arm A BLV 2 mg (N=28)	**Arm B BLV 5 mg (N=32)**	**Arm C BLV 10 mg (N=30)**	**Arm D TDF (N=28)**	**BLV total (N=90)**	**Total (N=118)**
Preferred term	**n (%)/c**					
Any adverse event	18 (64.3%)/ 74	21 (65.6%)/ 131	23 (76.7%)/ 146	14 (50.0%)/ 55	62 (68.9%)/ 351	76 (64.4%)/ 406
Total bile acids increased	8 (28.6%)/ 12	12 (37.5%)/ 20	15 (50.0%)/ 24	6 (21.4%)/ 8	35 (38.9%)/ 56	41 (34.7%)/ 64
Alanine aminotransferase increased	4 (14.3%)/ 4	7 (21.9%)/ 11	9 (30.0%)/ 12	4 (14.3%)/ 10	20 (22.2%)/ 27	24 (20.3%)/ 37
Aspartate aminotransferase increased	3 (10.7%)/ 3	7 (21.9%)/ 10	8 (26.7%)/ 12	3 (10.7%)/ 4	18 (20.0%)/ 25	21 (17.8%)/ 29
Thrombocytopenia	3 (10.7%)/ 3	5 (15.6%)/ 10	2 (6.7%)/ 5	3 (10.7%)/ 4	10 (11.1%)/ 18	13 (11.0%)/ 22

Fatigue	1 (3.6%)/ 1	2 (6.3%)/ 2	5 (16.7%)/ 6	2 (7.1%)/ 2	8 (8.9%)/ 9	10 (8.5%)/ 11
Nausea	1 (3.6%)/ 1	4 (12.5%)/ 4	3 (10.0%)/ 11	0	8 (8.9%)/ 16	8 (6.8%)/ 16
Neutropenia	1 (3.6%)/ 1	4 (12.5%)/ 8	0	3 (10.7%)/ 4	5 (5.6%)/ 9	8 (6.8%)/ 13
Dizziness	2 (7.1%)/ 2	2 (6.3%)/ 2	3 (10.0%)/ 4	0	7 (7.8%)/ 8	7 (5.9%)/ 8
Headache	2 (7.1%)/ 3	2 (6.3%)/ 2	3 (10.0%)/ 3	0	7 (7.8%)/ 8	7 (5.9%)/ 8
Leukopenia	4 (14.3%)/ 4	2 (6.3%)/ 4	0	1 (3.6%)/ 1	6 (6.7%)/ 8	7 (5.9%)/ 9
Gamma-glutamyltransferase increased	0	1 (3.1%)/ 1	2 (6.7%)/ 2	3 (10.7%)/ 3	3 (3.3%)/ 3	6 (5.1%)/ 6
Lymphopenia	3 (10.7%)/ 3	0	0	0	3 (3.3%)/ 3	3 (2.5%)/ 3

BLV: bulevirtide, c: number of events, n: number of patients, TDF: tenofovir, SOC: system organ class

The most common PTs reported by ≥10% patients in any group are listed

Source: Table 14.4.2.29 in MYR202

The overall frequency of AEs increased with increasing doses of bulevirtide. PTs overall more common in the bulevirtide groups include bile acid increase, nausea, dizziness, headache and lymphopenia, all predominantly presenting in the on-treatment phase of the study. In the follow-up phase, ALT and AST increases were more common in the bulevirtide groups.

A dose-dependent asymptomatic increase in total bile acids from baseline to week 24 was observed in all three bulevirtide groups but not in the tenofovir only group. At week 48, total bile acid levels returned to baseline levels and were similar between the all the treatment groups. The bile acid increase was less pronounced in the 2 mg group then in the 5 mg and 10 mg group.

From the full on-treatment AE dataset in the CSR annex (data not shown) it can be concluded that AEs more common in the bulevirtide groups include bile acid elevations (38.9% vs 17.9%), GI-related symptoms (17.8% vs 3.6% of patients), dizziness (7.8% vs 0%), headache (6.7% vs 0%) and injection site reactions (5.6% vs 0%) while elevated levels of ALT and GT (likely related to underlying disease) are more common on the TDF only group. Injections site reactions were reported to be mostly mild in intensity with very few moderate reactions; the onset was in the beginning of treatment and resolved still on treatment without intervention.

Given the mode of bulevirtide administration, it may be that GI symptoms arise from changes in bile secretion or composition. However, there was no clear relation between bile acid elevations and GI symptoms.

The on-treatment severe AEs were lymphopenia (n=1), thrombocytopenia (n=1), anemia (n=1), lipase elevation (n=2) and amylase elevation (n=2). All cases of lipase and amylase elevation were in the 10 mg bulevirtide group. There were no cases of pancreatitis.

In the follow-up phase ALT elevations (21.6% vs 12.0% of subjects), AST elevation (19.3% vs 8%), lipase elevations (3.4% vs 0%) and amylase elevations (3.4% vs 0) were more common in the bulevirtide groups, likely related to virologic HDV flares after cessation of therapy. HBV flares are considered less likely as TDF therapy was ongoing in all groups. A wording in 4.4 advises that "In the clinical study of bulevirtide MYR202, only patients with signs of active hepatitis despite nucleoside/nucleotide analogue treatment were included" providing prescribers with the setting that clinical benefit has been shown.

The severe AEs in the follow-up phase were almost exclusively ALT/AST elevations. The events were asymptomatic. Except in one case, there was no bilirubin increase. HDV RNA exhibited diverse patterns among the patients, in several cases the flair was associated with subsequent HDV RNA decline.

Four cases of ALT elevations during treatment occurred. All four patients started with elevated ALT levels at baseline, during the further course of bulevirtide treatment ALT levels declined continuously and even normalised in three of these patients.

MYR203

In total, 60 patients (groups A to D) received at least one dose of bulevirtide monotherapy, bulevirtide in combination with PEG-IFNα or PEG-IFNα monotherapy in the study; 15 patients in each group received PEG-IFNα (group A), bulevirtide 2 mg + PEG-IFNα (group B), bulevirtide 5 mg + PEG-IFNα (group C) or bulevirtide 2 mg (group D).

Table 42. Overview of adverse events. Safety analysis set.

	PEG-IFN (N=15)		MXB 2mg + PEG-IFN (N=15)		MXB 5mg + PEG-IFN (N=15)		MXB 2mg (N=15)		Total (N=60)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Any adverse event	13 (86.7%)	282	15 (100.0%)	163	14 (93.3%)	181	15 (100.0%)	121	57 (95.0%)	747
Any serious adverse event	0	0	1 (6.7%)	2	0	0	0	0	1 (1.7%)	2
Any adverse event leading to withdrawal of PEG-IFN	2	6	1	1	3	4	0	0	6	11
Any adverse event leading to withdrawal of MXB	0	0	0	0	0	0	0	0	0	0
Any adverse event leading to death	0	0	0	0	0	0	0	0	0	0
Adverse events by severity										
Mild	13 (86.7%)	191	15 (100.0%)	71	13 (86.7%)	96	15 (100.0%)	97	56 (93.3%)	455
Moderate	10 (66.7%)	68	11 (73.3%)	57	12 (80.0%)	58	9 (60.0%)	18	42 (70.0%)	201
Severe	7 (46.7%)	23	11 (73.3%)	33	10 (66.7%)	27	3 (20.0%)	6	31 (51.7%)	89
Life-threatening/ disabling	0	0	1 (6.7%)	2	0	0	0	0	1 (1.7%)	2
Adverse events by causality to PEG-IFN										
Not Related	5	12	12	31	9	38			26	81
Unassessable	0	0	0	0	0	0			0	0
Unlikely	4	5	2	6	0	0			6	11
Possible	6	23	4	27	2	4			12	54
Probable	2	3	6	26	4	25			12	54
Certain	13	239	10	73	12	114			35	426

Adverse events by causality to MXB								
Not Related	15	132	14	135	7	24	36	291
Unassessable	0	0	0	0	0	0	0	0
Unlikely	2	2	2	5	6	15	10	22
Possible	3	7	3	6	13	60	19	73
Probable	5	6	3	8	5	13	13	27
Certain	5	16	8	27	4	9	17	52

n = number of subjects, m = number of events.
Percentages are based on the number of subjects within each treatment group.
For the safety analysis set, subjects are analysed as treated (i.e. actual treatment).
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Date and time program was run: 2019-06-06T10:58. Date and time analysis database was run: 2019-06-03T14:32

Table 43. Adverse events in MYR203 – most common PTs (safety set)

	Arm A PEG-IFNα (N=15)	Arm B BLV 2 mg + PEG-IFNα (N=15)	Arm C BLV 5 mg + PEG-IFNα (N=15)	Arm D BLV 2 mg (N=15)	Total (N=60)
Preferred term	n (%)/c				
Any adverse event	13 (86.7%)/282	15 (100.0%)/ 163	14 (93.3%)/ 181	15 (100.0%)/ 121	57 (95.0%)/ 747
Total bile acids increased	5 (33.3%)/18	10 (66.7%)/21	9 (60.0%)/31	12 (80.0%)/22	36 (60.0%)/92
Neutropenia	8 (53.3%)/32	10 (66.7%)/28	9 (60.0%)/28	3 (20.0%)/6	30 (50.0%)/94
Thrombocytopenia	8 (53.3%)/16	11 (73.3%)/23	7 (46.7%)/18	3 (20.0%)/7	29 (48.3%)/64
Leukopenia	9 (60.0%)/25	8 (53.3%)/21	7 (46.7%)/19	4 (26.7%)/8	28 (46.7%)/73
Alanine aminotransferase increased	5 (33.3%)/11	5 (33.3%)/9	6 (40.0%)/11	8 (53.3%)/8	24 (40.0%)/39
Aspartate aminotransferase increased	5 (33.3%)/11	4 (26.7%)/8	4 (26.7%)/6	8 (53.3%)/8	21 (35.0%)/33
Influenza like illness	1 (6.7%)/1	9 (60.0%)/11	8 (53.3%)/8	0	18 (30.0%)/20
Gamma-glutamyltransferase increased	4 (26.7%)/9	4 (26.7%)/7	3 (20.0%)/5	4 (26.7%)/5	15 (25.0%)/26
Asthenia	3 (20.0%)/3	3 (20.0%)/3	5 (33.3%)/5	0	11 (18.3%)/11

Hyperthermia	7 (46.7%)/26	0	1 (6.7%)/5	1 (6.7%)/1	9 (15.0%)/32
Lymphopenia	5 (33.3%)/12	1 (6.7%)/1	1 (6.7%)/2	1 (6.7%)/1	8 (13.3%)/16
Reticulocytopeina	5 (33.3%)/12	0	1 (6.7%)/2	2 (13.3%)/2	8 (13.3%)/16
Headache	3 (20.0%)/8	1 (6.7%)/2	2 (13.3%)/3	1 (6.7%)/1	7 (11.7%)/14
Haemoglobin decreased	4 (26.7%)/5	0	2 (13.3%)/2	1 (6.7%)/2	7 (11.7%)/9
Anaemia	3 (20.0%)/6	2 (13.3%)/4	1 (6.7%)/1	0	6 (10.0%)/11
Erythropenia	4 (26.7%)/7	0	1 (6.7%)/1	0	5 (8.3%)/8
Alopecia	4 (26.7%)/4	0	1 (6.7%)/1	0	5 (8.3%)/5
Pyrexia	1 (6.7%)/1	1 (6.7%)/1	3 (20.0%)/3	0	5 (8.3%)/5
Platelet count decreased	1 (6.7%)/1	0	3 (20.0%)/6	0	4 (6.7%)/7
Nausea	4 (26.7%)/6	0	0	0	4 (6.7%)/6
Insomnia	2 (13.3%)/2	0	1 (6.7%)/1	1 (6.7%)/1	4 (6.7%)/4
Rash	3 (20.0%)/3	1 (6.7%)/1	0	0	4 (6.7%)/4
Neutrophil count decreased	0	0	3 (20.0%)/6	0	3 (5.0%)/6
Monocytopenia	3 (20.0%)/5	0	0	0	3 (5.0%)/5
White blood cell count decreased	1 (6.7%)/2	0	2 (13.3%)/2	0	3 (5.0%)/4
Pruritus	2 (13.3%)/2	0	0	1 (6.7%)/1	3 (5.0%)/3
Respiratory tract infection	1 (6.7%)/1	2 (13.3%)/2	0	0	3 (5.0%)/3
Myalgia	2 (13.3%)/6	0	0	0	2 (3.3%)/6
Irritability	2 (13.3%)/3	0	0	0	2 (3.3%)/3
Somnolence	2 (13.3%)/3	0	0	0	2 (3.3%)/3
Decreased appetite	2 (13.3%)/2	0	0	0	2 (3.3%)/2
Menstrual disorder	2 (13.3%)/2	0	0	0	2 (3.3%)/2
Respiratory tract infection viral	0	0	0	2 (13.3%)	2 (3.3%)/2

BLV: bulevirtide, c: number of events, n: number of patients, PEG-IFNα: Peginterferon alpha-2a, SOC: system organ class. The most common PTs reported by ≥10% patients in any group are listed

There were no deaths in the study, but two serious adverse events (SAEs) (anal fistula and proctitis; both assessed as severe, not related to bulevirtide and possibly related to PEG-IFNα) occurred in one patient in the bulevirtide 2 mg + PEG-IFNα group (group B), none of these were considered as a suspected unexpected serious adverse reaction (SUSAR).

There were no consistent changes in the mean vital signs values during the study related to any particular treatment group and no obvious differences between treatment groups in the physical examination or ECG findings. Occasional clinically significant findings were made in these assessments in all treatment groups and were reported as AEs.

The AE profile, except for bile acid elevation, is apparently driven by PEG-IFN in the combination arms. However, given the limited size of the study and substantial discontinuation rate, a detailed safety profile for the bulevirtide+PEG-IFN combination cannot be established.

Integrated safety analysis

In the course of the integrated safety analysis, safety data collected from 135 patients with chronic HDV infection exposed to bulevirtide in course of the pivotal phase II studies MYR202 and MYR203, were pooled for analysis and are presented below.

Table 44. Overview on patient cohort included into the integrated safety analysis

Clinical study code/ Phase	Population	Number of patients with bulevirtide exposure	Duration of exposure
MYR202 / Phase II	HDV infection	90 patients	24 weeks
MYR203 / Phase II	HDV infection	45 patients	48 weeks

Overall, 106 of 135 patients (78.5%) experienced 816 treatment emergent adverse events (TEAEs) during ≥24 weeks of treatment. Bulevirtide monotherapy was administered to 105 of 135 patients included into the integrated analysis, of these 77 patients (73.3%) experienced 472 TEAEs. Combination therapy of bulevirtide and PEG-IFNα was administered to 30 out of 135 patients, of those 29 (96.7%) patients reported 344 TEAEs. Thus, the frequency of TEAEs under combination therapy is higher compared to monotherapy treatment regimen.

The majority of bulevirtide-related TEAEs under monotherapy were mild (n=215) and moderate (n=44). Five patients experienced 9 severe AEs. Same profile was observed for combination therapy regimen, bulevirtide-related TEAEs were mostly mild (n=47) and moderate (n=21), with two severe TEAEs (ALT increase and total bile acid increase). Within the bulevirtide-related TEAEs, the increase in total bile acid levels was reported as the most frequent bulevirtide related TEAEs with 123 events out of total 338 TEAEs.

The most frequently reported TEAEs with an overall incidence ≥5% by preferred term and by decreasing incidence are listed below.

Table 45. TEAE with an overall incidence ⩾5% by Preferred Term by decreasing overall incidence

Preferred Term	Overall		Overall
	BLV* (N=105) n (%) #E	BLV + PEG-IFNα (N=30) n (%) #E	(N=135) n (%) #E
Any TEAE	75 (71.4) 274	28 (93.3) 274	103 (76.3) 548
Total Bile Acids Increased	47 (44.8) 78	19 (63.3) 52	66 (48.9) 130
Alanine Aminotransferase Increased	28 (26.7) 35	11 (36.7) 20	39 (28.9) 55
Aspartate Aminotransferase Increased	26 (24.8) 33	8 (26.7) 14	34 (25.2) 47
Thrombocytopenia	13 (12.4) 25	18 (60.0) 41	31 (23.0) 66
Neutropenia	8 (7.6) 15	19 (63.3) 56	27 (20.0) 71
Leukopenia	10 (9.5) 16	15 (50.0) 40	25 (18.5) 56
Influenza Like Illness	3 (2.9) 5	17 (56.7) 19	20 (14.8) 24
Gamma-Glutamyltransferase Increased	7 (6.7) 8	7 (23.3) 12	14 (10.4) 20
Headache	8 (7.6) 9	3 (10.0) 5	11 (8.1) 14
Asthenia	1 (1.0) 1	8 (26.7) 8	9 (6.7) 9
Fatigue	9 (8.6) 10	-	9 (6.7) 10
Dizziness	8 (7.6) 9	-	8 (5.9) 9
Injection Site Erythema	6 (5.7) 7	2 (6.7) 2	8 (5.9) 9
Nausea	8 (7.6) 16	-	8 (5.9) 16
Anaemia	4 (3.8) 7	3 (10.0) 5	7 (5.2) 12

*BLV treatment on top of tenofovir (TDF); BLV = bulevirtide

Full description of TEAE with an overall incidence ≥5% by different bulevirtide dosage regimes is given in supplementary Table 27 in M2.7.4.

Total bile acid increase was the most frequent TEAE, followed by liver enzyme elevations (ALT and AST increase), and haematological laboratory abnormalities (thrombocytopenia, neutropenia, leucopenia. The frequency of haematological events was higher in the combination treatment group.

The majority of ALT elevations recorded in clinical trials with bulevirtide occurred post treatment and were possibly related to viral rebound and hepatitis exacerbation after cessation of bulevirtide. On treatment, rather a decrease of ALT was observed in the majority of patients. Notably, 55 AEs "ALT increased" were recorded in 39 patients exposed to bulevirtide in the MYR202 and MYR203 studies. However, only 4 reactions (3 mild, one moderate) in 3 patients were reported during bulevirtide treatment in the MYR202 study, and

only one of those (moderate) was considered related to bulevirtide. In the MYR203 study, the overall number of on-treatment ALT increases was higher (16 AEs in 12 patients), however, this is linked to the co-administration of peginterferon. Two reactions (mild and moderate) were noted in the bulevirtide monotherapy arm of the MYR203 study.

Serious adverse event and deaths

Deaths

No deaths occurred in any of the conducted or ongoing trials.

Serious adverse events

No SAEs were reported in the two Phase 1 trials MYR101 and MYR102. No SAE was reported in MYR201 (HDV).

MYR201 (HBV)

A total of 2 SAEs were reported in the study. Two patients experienced one SAE each during the trial. Both SAEs were assessed as drug related and are summarised below.

Table 46. Summary of treatment emergent serious adverse events in MYR201 (HBV) (safety set)

Patient ID	Arm	Age [years]	Sex	SAE (Verbatim term/ preferred term	Severity	Drug relatedness
55513	Arm C BLV 2 mg	33	Male	Reaction to the abolition of the antiviral drug/ Drug withdrawal syndrome	Mild	Certain
55520	Arm B BLV 1 mg	25	Male	Reactivation of replication HBV-DNA after stop therapy/ Drug withdrawal syndrome	Mild	Certain

1. BLV: bulevirtide, SAE: serious adverse event

2. Source: MYR201 (HBV), Table 12.11

The events occurred 12 weeks after discontinuation of study drug and, notably, did not meet a standardised definition of hepatitis flare (ALT >10 x ULN and more than twice the baseline value). Both patients had ALT normalisation during the main course of study treatment, which might be related with the mechanism of action of bulevirtide, i.e. the protection of the healthy cells from new infections.

In both events, the ALT elevations were considered to be of mild severity; no abnormal bilirubin values or any sign of hepatic decompensation were reported; clinical picture and laboratory investigations did not provide any evidence of hepatotoxicity or involvement of other organ system. Both events were readily resolved upon initiation of the antiviral therapy with nucleoside analogues.

MYR202

SAEs were reported by six patients during the study period. Two patients reported two SAEs before initiation of study treatment (post biopsy bleeding, rectal bleeding). Treatment-emergent SAEs are summarised below.

Table 47. Summary of treatment emergent serious adverse events in MYR202 (safety set)

	Arm	Age [years]	Sex	SAE (Verbatim term/ preferred term	Severity	Drug relatedness	Outcome
SAEs reported during the 24-week treatment period							
	Arm B BLV 5 mg/day	57	Male	Anaemia/ Anaemia	Life-threatening	Not related	Not resolved
	Arm D Tenofovir	44	Female	Decompensated cirrhosis/ Hepatic cirrhosis	Severe	Not related	Resolved
SAEs reported during the follow-up period (week 24-48)							
	Arm B BLV 5 mg/day	34	Male	Elevated ALT / ALT increased	Severe	Not related, reassessed as related#	Resolved
	Arm C BLV 10 mg/day	44	Male	Renal colic	Moderate	Not related	Resolved
	Arm C BLV 10 mg/day	55	Male	Cholecystitis	Severe	Not related	Resolved
	Arm B BLV 5 mg/day	45	Female	ALT elevation/ ALT increased	Severe	Related#	Resolved

+ Patient discontinued trial due to SAE # Reported as a SUSAR, see MYR202, Section 12.3.2 for narrative

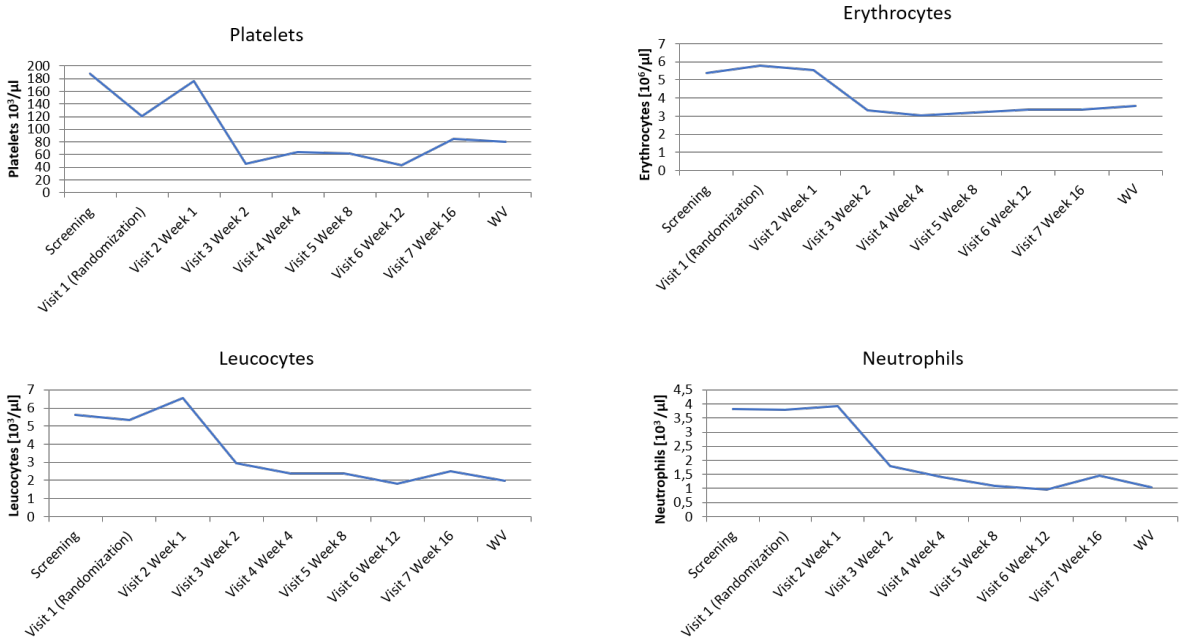
BLV: bulevirtide, SAE: serious adverse event

Source: MYR202, Section 12.3.1.3 and 12.3.2

During the treatment period from first dose of study treatment until week 24, two patients reported two SAEs; One cirrhotic patient in group B (Myrcludex B 5 mg/day) discontinued from the study due to anaemia. Anaemia was diagnosed at the week 2 visit of the study and was initially seen as a symptom of underlying

disease. However, curiously, anaemia was associated with a precipitous fall in both platelets and neutrophils, thus exhibiting the clinical picture of pancytopenia.

Figure 22. Patient withdrawn from study



When haemoglobin continued to decrease, further investigations were done to investigate the cause (blood test for tumour markers, faecal occult blood test, gastroscopy, colonoscopy), but no signs of bleeding was identified. In January 2017 the haemoglobin level was 70.3 g/L. The investigator decided to withdraw the patient from treatment and the study at week 16. The patient was hospitalised to investigate the cause of anaemia. 1.5 years later the patient was still alive, but the diagnosis was unclear.

The applicant proposes that this represents a case of hepatic decompensation. No similar cases were seen in other patients treated with bulevirtide in monotherapy. Overall, it does not seem possible to exclude that this is a case of drug-induced pancytopenia, although this is also not possible to confirm. While it appears that only a larger safety database can provide more conclusive insights into the matter, the case was discussed with external experts at an *Ad Hoc* Expert Group meeting (see benefit-risk section). Here the experts concurred that the applicant's interpretation of the case as related to advanced liver disease was plausible, and that the level of suspicion of drug-induced haematological abnormalities, was low. One patient in group D (Tenofovir only) reported hepatic cirrhosis which was assessed as severe in intensity and not related to Tenofovir, but due to progression of the underlying disease. The SAE was resolved.

During the follow-up period from week 24 to week 48, four patients reported four SAEs;

One patient in group B (Myrcludex B 5 mg/day) reported elevated ALT levels. The event was severe in intensity and was assessed as not related to Myrcludex B by the investigator. During SAE data reconciliation the event was reassessed as related to Myrcludex B and unexpected. The event was reported as a SUSAR. Information regarding HBV and HDV replication in the narrative of this patient was not provided and is requested from the Applicant, if available.

One patient in group C (Myrcludex B 10 mg/day) reported renal colic. The event was assessed as moderate in intensity, not related to Myrcludex B and was resolved.

One patient in group C (Myrcludex B 10 mg/day) reported cholecystitis. The event was assessed as severe in intensity, not related to Myrcludex B and was resolved.

One patient in group B (Myrcludex B 5 mg/day) reported elevated ALT levels five weeks after end of Myrcludex B treatment. The event was judged as medically important, severe in intensity and related to Myrcludex B. The event was reported as a SUSAR.

The patient in the bulevirtide 5 mg group MYR202 with emergent life-threatening anaemia is of particular interest. Rapidly progressing anaemia to a level of 70 g/L is not expected in an HBV/HDV-coinfected population with compensated liver disease (see above).

MYR203

Two SAEs were reported by one patient in the bulevirtide 2 mg + PEG-IFNα group (group B). The patient received first treatment with bulevirtide 2 mg and PEG-IFNα. The SAEs, reported after the patient had completed the treatment period, were:

Proctitis (reported term acute ischiorectal para proctitis), assessed as severe, not related to treatment with bulevirtide and possibly related to treatment with PEG-IFNα. The SAE was recovered/resolved after five days, and the patient continued in the follow-up period of the study.

Anal fistula (reported term front trans sphincteric rectum fistula), assessed as severe and possibly related to treatment with PEG-IFNα and not related to treatment with bulevirtide. The SAE was recovered/resolved after eleven days. The patient was prematurely discontinued from the study (reason withdrawal by subject).

Laboratory findings

MYR202

The MYR202 study brings the most important contribution to the bulevirtide safety database, given the (comparatively) large number of patients, absence of PEG-IFN in the bulevirtide arms and presence of a comparator arm (TDF) with a well-established and favourable short- to medium term safety profile.

Haematology

Adverse events with the following PTs were reported: Haemoglobin decreased (5 events reported by 4 patients), neutrophil count decreased (reported by 3 patients), white blood cell count decreased (reported by 2 patients), reticulocyte count decrease (3 events reported by 1 patient), lymphocyte count decreased (reported by 1 patient), aPTT prolonged (reported by 1 patient) and platelet count decreased (reported by 1 patient).

Clinical chemistry

There was an on-treatment decrease of transaminases and subsequent return to the elevated levels observed at baseline (or above) is in line with the observations presented in the efficacy section.

Total blood bile acids

A summary of mean values at baseline, week 24 and week 48 can be found below. Clinically significant abnormalities in total bile acids were reported as AEs by 41 patients.

Table 48. Mean (SD) total bile acids (µmol/L) over the 24-week treatment period in MYR202 (safety set)

Visit	Arm A BLV 2 mg (N=28)	Arm B BLV 5 mg (N=32)	Arm C BLV 10 mg (N=30)	Arm D TDF (N=28)
Baseline	8.07 (7.12)	13.88 (27.07)	8.00 (6.33)	10.76 (14.09)
Week 24	25.19 (22.51)	43.68 (46.05)	63.97 (49.87)	11.16 (14.71)
Week 48	13.24 (8.83)	16.24 (19.90)	17.49 (27.43)	16.54 (13.11)

BLV: bulevirtide, SD: standard deviation, TDF: Tenofovir
Source: MYR202 Section 14, Table 14.4.3.75

In line with the virologic response, a dose of 2 mg qd of bulevirtide does not completely block the NTCP-mediated absorption of bile acids. Instead a positive dose-response is seen up to 10 mg and could possibly extend further as no higher doses have been explored. The long-term effects of bulevirtide-induced bile acid elevations are currently unknown, but the approximately three-fold increase in the 2 mg group at 24 weeks is substantially lower than what has been observed in patients with genetic NTCP deficiencies.

Whereas the increase bile salt increase was asymptomatic during the studies, there is no data available on the long-term impact (> 48 weeks) of this effect induced by bulevirtide. A recent publication on a cohort of subjects with NTCP mutation provided data on long term effects of genetically determined hypercholemia (Liu et al. 2017). Eight subjects were identified who were carrying the p.Ser267Phe mutation in the SLC10A1 gene associated with the complete loss of NTCP function. The authors concluded that this mutation was associated with low levels of vitamin D and 3 of 6 patients that were subjected to bone mineral density analysis presented with osteoporosis/osteopenia. Also, sex hormones and blood lipids were deviated in all subjects.

In the MYR301/204 studies, vitamin D levels and blood lipids will be investigated. Clinical presentations of osteopenia/osteoporosis (e.g. fractures, and, if available, DXA scans) will be captured in the MYR-HDV registry.

MYR203

Laboratory findings are dominated by the presence of peg-IFN in all arms except that of 2 mg bulevirtide monotherapy.

Haematology

Most haematology parameters decreased between baseline and week 48 in the groups receiving bulevirtide and PEG-IFNα combined or PEG-IFNα alone (groups A to C) and increased again during follow-up. However, this trend was not observed in the bulevirtide 2 mg group.

Erythrocyte sedimentation rate followed a different pattern from the other parameters, by increasing during the treatment period and decreasing during follow-up in all groups receiving PEG-IFNα (groups A to C).

Haematology related AEs occurred in all the groups but tended to be more frequently reported in the groups that received treatment with PEG-IFNα (groups A to C).

The most common types of AEs related to haematology laboratory assessments were neutropenia, thrombocytopenia, and leukopenia, which were each reported by >47% of patients in all three groups receiving PEG-IFNα with or without bulevirtide (groups A to C) and by 20-27% of patients receiving bulevirtide 2 mg only (group D). Lymphopenia, reticulocytopenia, decreased haemoglobin and erythropenia

were each reported in 27-33% of patients in the group receiving PEG-IFNα as monotherapy (group A) while occurring in 0-13% of patients in the other groups. Monocytopenia and anaemia were each reported by 20% of patients in the PEG-IFNα group vs. 0-13% in the other groups (groups B to D) and decreased neutrophils and decreased platelets were each reported by 20% of patients in the bulevirtide 5 mg + PEG-IFNα group (group C) vs. 0-13% in the other groups. Other AEs related to haematology parameters occurred in up to two patients (13%) per group.

Clinical chemistry

Between baseline and week 48, there were mean decreases in ALT and AST levels in the bulevirtide 5 mg + PEG-IFNα group (group C) and bulevirtide 2 mg group (group D) but no clear pattern in the other two groups. The GGT mean values increased from baseline after start of treatment and decreased toward the end of the treatment period in both groups receiving bulevirtide and PEG-IFNα (groups B and C), while GGT values in the bulevirtide 2 mg group (group D) decreased after start of treatment and increased during the follow-up period. In the PEG-IFNα group (group A), the GGT values changed slightly over the study, following the same pattern as the groups receiving the combination treatments (groups B and C) but with smaller changes.

Clinically significant increases in ALT, AST and GGT (reported as AEs) occurred in all the groups, with no obvious relationship to either bulevirtide or PEG-IFNα.

Alkaline phosphatase mean values increased from baseline during the first 8 to 12 weeks of treatment with PEG-IFNα (groups A to C) and then returned to approximately baseline values to week 16 (within the normal range for most patients). This was followed by a decrease in values in the groups treated with bulevirtide monotherapy (group D) or bulevirtide in combination with PEG-IFNα (groups B to D) which was most noticeable in the groups that received the combination therapy with bulevirtide and PEG-IFNα (groups B and C). After EOT (week 48), all groups again returned to the baseline values.

Calcium levels decreased in all groups treated with PEG-IFNα (groups A to C) immediately following start of treatment and gradually returned to baseline levels towards the EOT, continuing also during the follow-up period. In the group treated with bulevirtide 2 mg only (group D), there were some fluctuations in the mean calcium values during the study but no obvious patterns over time as in the other groups.

For all other clinical chemistry parameters, coagulogram parameters, and thyroid hormones, there were no clinically important changes over time in any treatment group.

Total bile acids

At baseline, the mean total blood bile acids levels were 9.01±10.98 µmol/L, 15.51±39.63 µmol/L, 8.27±5.87 µmol/L and 5.53±3.90 µmol/L in groups A, B, C and D, respectively.

During treatment, the total bile acids increased in all groups, with the greatest increase in the bulevirtide 5 mg + PEG-IFNα group (group C), 32.21±31.11 µmol/L. In the other groups (A, B and D), the mean changes from baseline to week 24 were 4.89±18.07 µmol/L, 9.61±30.64 µmol/L and 13.96±13.77 µmol/L, respectively.

At week 48, the levels were still elevated in all groups, the greatest increase compared to baseline was still in group C, 46.91±37.24 µmol/L. In the other groups (A, B and D), the mean change from baseline to week 48 were 7.89±19.58 µmol/L, 2.22±47.03 µmol/L and 24.25±32.88 µmol/L, respectively.

At week 72, the mean values of total bile acids returned to values more or less similar to the baseline values in all four groups. The means were 17.01±17.09 µmol/L, 8.25±3.54 µmol/L, 8.66±3.90 µmol/L and 6.98±4.33 µmol/L in groups A, B, C and D, respectively.

Clinically significant increases in total bile acids occurred in ≥60% of patients in patients that received treatment with bulevirtide (groups B, C and D) compared to 33% of patients in the PEG-IFNα group.
Summary

Given the limited size of the MYR203 study, the safety conclusions that can be drawn regarding the safety of the bulevirtide+PEG-IFN are limited. However, the observed changes in haematologic parameters, and most clinical chemistry parameters, appear related to PEG-IFN treatment. Bile acid increases are in line with the findings in the MYR202 study and as expected related to bulevirtide dose.

Safety in special populations

Intrinsic factors

Clinical testing of bulevirtide was performed in predominantly Caucasian, male and female non-elderly adults (age range 19 to 64 years) of normal or slightly elevated body mass index (BMI). Due to the relative homogeneity of the tested population, no formal evaluation of safety relating to age, gender or BMI was performed. The number of non-Caucasians in the conducted trials was too low to conclude on any potential effects of race.

Safety information in children will be generated in a planned separate PK/PD trial in accordance with the approved PIP and are not available yet.

Safety in patients with compensated cirrhosis

Patients with compensated liver cirrhosis were recruited into both MYR202 and MYR203 studies. In total, 56 patients with compensated liver cirrhosis received treatment with bulevirtide as monotherapy or combination therapy. There were no cases of hepatic decompensation within the studies.

The incidence of TEAEs in cirrhotic patients is comparable to the reported TEAEs in the overall patient population, and there was no apparent impact of compensated cirrhosis on the safety of bulevirtide.

There are no safety data in patients with decompensated liver disease. A study in patients with hepatic decompensation is recommended.

Safety in patients with renal impairment

Patients with creatinine clearance <60 mL/min (MYR202) or serum creatinine >1.5 ULN (MYR203) were excluded from clinical studies, due to the risk of further increased bile acid levels when the renal escape route is affected. Hence, the safety in patients with moderate and severe impairment is considered Missing information. A study in patients with renal impairment, with the purpose of assessing bile acid levels, is recommended.

Safety in elderly

No studies were performed with patients aged 65 years old and above. The safety table as described in the D60 assessment report for this special population cannot be provided now. A warning about the lack of data in the elderly population is added in the SmPC.

Immunological events

Development of anti-drug antibodies against bulevirtide was analysed in the clinical trials MYR101, MYR201 HBV, MYR201 HDV, MYR202 and MYR203. Antibody determination was performed by validated RIA or ELISA methods.

For MYR101 and MYR201 studies, a patient was considered to be positive if the baseline anti-bulevirtide antibody values were increased by >2 fold during treatment.

For MYR202 and MYR203, guidance from FDA (2016) "Assay Development and validation for Immunogenicity Testing of therapeutic protein products" and EMA (2015) "Guideline on Immunogenicity assessment of therapeutic proteins" were taken into consideration to determine positive immunogenicity signals.

Table 49. Development of anti-drug antibodies

Clinical trial	Time after first administration	n positive subjects/n subjects with measurement (%)				
		0.5 mg	2 mg	5 mg	10 mg	Total
MYR101	up to 6 months	-	-	-	-	0#/36
MYR201 HBV	up to 12 weeks	4/8 (50.0%)	-	5/8 (62.5%)	5/8 (62.5%)	14/24 (58.3%)
MYR202	12 weeks	-	1/28 (3.6%)	5/32 (15.6%)	5/30 (16.7%)	11/90 (12.2%)
	24 weeks	-	5/28 (17.9%)	6/30 (20.0%)	7/28 (25.0%)	18/86 (20.9%)
	36 weeks	-	2/28 (7.1%)	1/29 (3.4%)	1/29 (3.4%)	4/86 (4.7%)
	48 weeks	-	1/28 (3.6%)	1/29 (3.4%)	0/29 (0%)	2/86 (2.3%)
		2 mg	2 mg + PEG-IFNα	5 mg + PEG-IFNα		Total
MYR201 HDV	12 weeks	2/8 (25%)	6/7 (85.7%)	-		8/15b (53.3%)
	24 weeks	3/8 (37.5%)	7/7 (100%)	-		10/15 (66.7%)
	48 weeks	1/7 (24.3%)	n/a	-		1/7 (24.3%)
	72 weeks	n/a	0/6 (0%)	-		0/6 (0%)
	96 weeks	0/7 (0%)	n/a	-		0/7 (0%)
MYR203	12 weeks	1/15 (6.7%)	14/15 (93.3%)	13/15 (86.7%)		28/45 (62.2%)

	24 weeks	2/14 (14.3%)	14/15 (93.3%)	12/15 (80.0%)		28/44 (63.6%)
	48 weeks	0/15	13/15 (86.7%)	13/15 (86.7%)		26/45 (57.8%)
	72 weeks	0/13	5/13 (38.5%)	7/15 (46.7%)		12/41 (29.3%)

Source: study reports MYR101, MYR201 HBV, MYR201 HDV, MYR202, MYR203

[#] dose range from 3 µg i.v. to 10 mg s.c.

[*] Treatment arm A (therapy with 2 mg/day bulevirtide for 24 weeks followed by therapy with PEG-IFNα for 48 weeks): 4/8 (50.0%); treatment arm B (combination therapy with 2 mg/day bulevirtide plus PEG-IFNα for 24 weeks followed by therapy with PEG-IFNα for another 24 weeks): 7/7 (100%)

ADAs appear in approximately 20-60% of patients after 24 weeks of treatment, depending on whether PEG-IFN is co-administered.

The Applicant provided tables with listings of AEs in ADA positive and ADA negative subjects. In the BLV 2 mg arm of MYR202 study, no clinically significant differences in AEs were noted between ADA negative and positive subjects. The rate of any AE during the treatment was 55.6% vs 57.9% in ADA positive and ADA negative subjects, respectively. General disorder and administration site conditions were reported in 11.1% and 21.1%, respectively with an apparent higher incidence of injections site erythema and hyperthermia (1 subject [11.1%] each) in ADA positive, compared to 5.3% and 0% in ADA negative subjects, which, however, in the first case, occurred only in one patient. In Study MYR203, taking into consideration only BLV 2 mg monotherapy arm, AEs occurred in 100% of ADA positive and 85.7% of ADA negative subjects. General disorders and administration site conditions were higher in ADA positive (3 subjects, 37.5%: injection site erythema, haematoma and injection site induration) compared to ADA negative (1 subject, 14.3%: chest pain and hyperthermia). No AEs of hypersensitivity were reported. Therefore, even if some differences were noted in the occurrence of some AEs (referring in particular to the SOC of general disorders and administration site conditions) between ADA positive and negative subjects mainly in MYR203 study, the limited sample size (MYR202 2 mg arm: 9 subjects in ADA positive and 19 in ADA negative group; MYR203 2 mg arm: 8 and 7 in ADA positive and negative groups) and the paucity of events, do not allow to draw firm conclusions on the impact of ADA on safety.

However, the Applicant is expected to provide data on ADAs in the phase 3 programme, both in relation to efficacy and safety.

With regards to the potential impact of ADA on PK, see section on clinical pharmacology.

Safety related to drug-drug interactions and other interactions

No safety issues have been identified in relation to PK or PD interactions. See separate PK report for details.

Discontinuation due to adverse events

In MYR202 there were two treatment discontinuations due to AEs. One patient randomised to bulevirtide 5 mg/day discontinued treatment as well as study due to an SAE (anaemia). In addition, one patient

randomised to tenofovir only discontinued from study treatment due to the AEs "pruritus generalised" and "fatigue". All events were assessed as unrelated to the study treatment.

In MYR203, two patients in the PEG-IFNα group (group A) were discontinued from the study due to AEs (anaemia, erythropenia and decreased haematocrit in one patient and increased levels of aspartate aminotransferase (AST), ALT and gamma-glutamyl transferase (GGT) in the other patient).

Four patients discontinued treatment with PEG-IFN due to AEs, without changing the BLV dosing. However, no HDV or HBV DNA rebound was reported in the four patients who discontinued PEG-IFNα treatment.

Post-marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The size of the safety dataset of bulevirtide is limited, allowing only characterisation of relatively common safety issues. Moreover, there are no long-term safety data from patients with drug-induced bile acid elevations, which is the most common side effect, due to the primary mechanism of action of bulevirtide, blocking the NTCP channel, which is both a bile acid transporter as well as the cellular receptor for HDV through an interaction via HBsAg.

The MYR202 study brings the most important contribution to the bulevirtide safety database, given the number of patients, absence of PEG-IFN in the bulevirtide arms and presence of a comparator arm (TDF) with a well-established and a, in the time span of the study, favourable safety profile.

A particular concern is a cirrhotic patient in the MYR202 study receiving 5 mg bulevirtide/day, who presents with pancytopenia at week 2 on treatment. This patient discontinued therapy and the study at week 16. The ultimate diagnosis is unclear. This case was discussed at an *Ad Hoc* Expert Group meeting, where the experts considered it plausible that this was a manifestation of advanced liver disease rather than a case of drug induced pancytopenia.

In the MYR202 study, a higher frequency AEs were reported in the bulevirtide treatment groups compared to the tenofovir group during both the on-treatment. The overall frequency of AEs increased with increasing doses of bulevirtide. PTs more common in the bulevirtide groups include bile acid increase, nausea, dizziness, headache and lymphopenia.

AEs more common in the bulevirtide groups include bile acid elevations (38.9% vs 17.9%), GI-related symptoms (17.8% vs 3.6% of patients), dizziness (7.8% vs 0%), headache (6.7% vs 0%) and injection site reactions (5.6% vs 0%) while elevated levels of ALT and GT (likely related to underlying disease) are more common on the TDF only group.

Given the mode of bulevirtide administration, it may be that GI symptoms arise from changes in bile secretion or composition. However, it is not clear whether the on-treatment equilibrium with elevated steady-state levels of circulating bile acids implies that the secretion is restored through the natural pathways or whether bile acid escape routes are available.

The on-treatment severe AEs were lymphopenia (n=1), thrombocytopenia (n=1), anaemia (n=1), lipase elevation (n=2) and amylase elevation (n=2). All cases of lipase and amylase elevation were in the 10 mg bulevirtide group.

In the follow-up phase ALT elevations (21.6% vs 12.0% of subjects), AST elevation (19.3% vs 8%), lipase elevations (3.4% vs 0%) and amylase elevations (3.4% vs 0) were more common the in the bulevirtide groups, likely related to virologic HDV flares after cessation of therapy. HBV flares are considered less likely as TDF therapy was ongoing in all groups. The severe AEs in the follow-up phase were almost exclusively ALT/AST elevations.

The observed on-treatment decrease of transaminases and subsequent return to the elevated levels observed at baseline (or above) is in line with the observations presented in the efficacy section.

ADAs appear in approximately 20-60% of patients after 24 weeks of treatment, depending on whether PEG-IFN is co-administered. Even if some differences were noted in the occurrence of some AEs (referring in particular to the SOC of general disorders and administration site conditions) between ADA positive and negative subjects mainly in MYR203 study, the limited sample size (MYR202 2 mg arm: 9 subjects in ADA positive and 19 in ADA negative group; MYR203 2 mg arm: 8 and 7 in ADA positive and negative groups) and the paucity of events, do not allow to draw firm conclusions on the impact of ADA on safety.

However, the Applicant is expected to provide data on ADAs in the phase 3 programme, both in relation to efficacy and safety".

Dose response and concerns with respect to dose selection

The proposed dose of 2 mg or higher was administered to 205 subjects, of which 175 patients were treated for at least 12 weeks. With regards to the 10 mg dose, 56 patients received this, at any duration.

In line with the virologic response, a dose of 2 mg qd of bulevirtide does not completely block the NTCP-mediated absorption of bile acids. A positive dose-response is seen up to 10 mg and could possibly extend further as no higher doses have been explored. The long-term effects of bulevirtide-induced bile acid elevations are currently unknown, but the approximately three-fold increase in the 2 mg group at 24 weeks is substantially lower than what has been observed in patients with NTCP deficiencies.

Altogether, the size of the safety database for the 2 mg dose or higher, although limited, might be acceptable in the context of apparently favourable findings, an unmet medical need and established efficacy. There is, however, residual uncertainty as to the long-term impact of bile acid elevations. With regards to the 10 mg dose, which seems optimal from an antiviral activity point of view, the impact on bile acids is considerably higher, and safety database of 56 patients is not considered sufficient to provide similar confidence.

Safety in combination with pegIFN

Given the limited size of the MYR203 study, the safety conclusions that can be drawn regarding the safety of the bulevirtide+PEG-IFN combination are limited. The AE profile, except for bile acid elevation, is apparently driven by PEG-IFN in the combination arms.

The observed changes in haematologic parameters, and most clinical chemistry parameters, appear related to PEG-IFN treatment. Bile acid increases are in line with the findings in the MYR202 study and as expected related to bulevirtide dose.

Additional safety data needed in the context of a conditional MA

To comprehensively establish the safety of bulevirtide, in particular with respect to the relation of dose and response and what would ultimately be the most appropriate dose, data from the MYR301 study (150 subjects, monotherapy approach) are needed.

2.6.2. Conclusions on the clinical safety

Altogether, the total safety database is small. the general safety profile of bulevirtide at 2 mg appears favourable, with bile acid elevation being the most common adverse effect, based on the primary mechanism of action. This effect is more pronounced at 10 mg; given only 56 patients treated with this dose, more data are needed to support a higher dose than 2 mg.

Given the poor prognosis of RNA positive HDV patients with ALT elevation in spite of NUC treatment for HBV, the overall safety and tolerability appear acceptable for a conditional approval awaiting safety data from the ongoing phase 3 trial and long-term follow-up of patients.

The limited safety database contributes to the non-comprehensiveness of data in the sense of the CMA legislation.

Studies in patients with hepatic decompensation and in patients with renal impairment, respectively, are recommended.

2.7. Risk Management Plan

Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hepatitis exacerbation after drug withdrawal
Important potential risks	None
Missing information	Use in patients with moderate to severe renal impairment Use in patients with decompensate liver disease Long term safety of bile acid elevation

Discussion on safety specification

It is agreed that cholestasis is not an appropriate word to describe inhibition of the NTCP-mediated bile acid transport. It is also agreed that the possible long-term adverse effects of bile acid elevation are hypothetical at this time. As requested, the Applicant has listed "Long term safety of bile acid elevation" as missing information.

Conclusions on the safety specification

Having considered the data in the safety specification, the summary of safety concerns is endorsed.

Pharmacovigilance plan

Summary of planned additional pharmacovigilance activities from RMP

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study *(study short name, and title)* **Status** *(planned/on-going)*	**Summary of objectives**	**Safety concerns addressed**	Milestones (required by regulators)	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation				
MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta Ongoing	Primary: The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta in comparison to delayed treatment. Secondary: • To evaluate optimal treatment duration • To assess the safety of bulevirtide. Exploratory: • To investigate the immunogenicity of bulevirtide • To investigate influence of bulevirtide on quality of life	Long term safety data: bile acid increase Hepatitis exacerbation after treatment cessation	Regular updates.	Study start date: 17 April 2019. Estimated study completion date: 2025.

	• HBV/HDV genotyping • Resistance testing			
Category 3 - Required additional pharmacovigilance activities				
Data collection from participation in the MYR-HDV registry	1) To evaluate incidence of all-cause mortality and adverse events of special interest: treatment-related serious adverse events, hepatic decompensation, liver transplantation, hepatic carcinoma and liver-related death 2) To bridge surrogate endpoints investigated in the pivotal clinical trials with real-life clinical event rate under bulevirtide treatment.	Long term safety data: bile acid increase	Regular updates	Registry will start in Q3 2020. Data will be reviewed on an on-going basis as a part of signal detection and reported within PSURs, when available. An interim data report will be provided upon 200 patient/years included.
MYR204 - A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with	Primary: The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously at a dose of 2 mg or 10 mg in combination with pegylated interferon alfa-2a once weekly relative to 10 mg bulevirtide monotherapy in subjects with chronic hepatitis delta (CHD). Secondary:	Long term safety data: bile acid increase Hepatitis exacerbation after treatment cessation	Regular updates	Study start date: 31 May 2019. Estimated study completion date: 28 February 2023.

Chronic Hepatitis Delta Ongoing	• To assess the safety of bulevirtide. Exploratory: • To investigate the immunogenicity of bulevirtide. • To investigate influence of bulevirtide on quality of life. • HBV/HDV genotyping. • Resistance testing.			

All on-going and planned categories 1-3 safety studies were included in the Pharmacovigilance Plan are presented above.

There is one study, currently ongoing, listed as specific obligations (category 2) that will provide additional efficacy as well as safety data. This study will address clinical consequences of long-term bile acid increase and hepatitis exacerbation after bulevirtide treatment cessation.

Additionally, one category 3 study MYR HDV Registry is planned. There is also one ongoing study that assess efficacy and safety of bulevirtide in combination with pegylated interferon alfa-2a in patients with chronic hepatitis Delta.

Overall conclusions on the Pharmacovigilance Plan

The PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Hepatitis exacerbation after drug withdrawal	Routine risk communication: SmPC section 4.4. PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk:

	Recommendation for routine monitoring of HBV DNA, HDV RNA, and ALT levels after the cessation of bulevirtide Other routine risk minimisation measures beyond the Product Information: none
Long term safety of bile acid elevation	Routine risk communication: SmPC section 4.4. PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for routine monitoring of serum bile acid levels during and after cessation of treatment* Other routine risk minimisation measures beyond the Product Information: none
Use in patients with moderate or severe renal impairment	Routine risk communication: SmPC section 4.4. PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other routine risk minimisation measures beyond the Product Information: none
Use in patients with decompensated liver disease	Routine risk communication: SmPC section 4.4. PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other routine risk minimisation measures beyond the Product Information: none

Additional risk minimisation measures

No additional risk minimisation measures are proposed.

Overall conclusions on risk minimisation measures

The PRAC, having considered the data submitted, is of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. New Active Substance

The applicant compared the structure of bulevirtide with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers bulevirtide to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Hepcludex (bulevirtide) is included in the additional monitoring list because

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU
- it is approved under a conditional marketing authorisation according to Article 14-a of Regulation (EC) No 726/2004
- it has an obligation to conduct post-authorisation efficacy studies according to Articles 9(4)(cc) and 10a(1)(b) of Regulation (EC) No 726/2004, and Articles 21a(f) and 22a(1)(b) of Directive 2001/83/EC

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HDV is a satellite virus of HBV which requires the presence of HBV for its replication and dissemination Chronic hepatitis D (CHD) on top of hepatitis B virus (HBV) infection is associated with a worse prognosis. Chronic HBV/HDV infection is associated with an increased risk of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma.

Since HDV is an incomplete virus requiring the presence of HBsAg for its lifecycle, the epidemiology of HDV is necessarily linked to HBV epidemiology. In 2015, the HBV prevalence in the European Union (EU) is estimated to be 0.9% corresponding to 4.7 million chronic HBV cases. The assumption of an HDV co-infection prevalence of 1-2% in the European Hepatitis B patient population results in an estimated range of minimum 6.909 to 20.492 patients with HDV infection.

The liver disease associated with HDV runs a more progressive course than chronic hepatitis B (CHB. Chronic HDV infection is associated with faster progression to fibrosis and cirrhosis, earlier onset of hepatic complications and likelihood of liver transplantation.

3.1.2. Available therapies and unmet medical need

Worldwide, no therapeutic regimen or drug is currently approved for the treatment of CHD. PEG-IFNα is used however, based on limited data, and remains the only available therapeutic option recommended by treatment guidelines (EASL 2017).

In CHD patients with ongoing HBV DNA replication therapy with nucleos(t)ide analogue (NA) should be considered (EASL 2017, AASLD 2018). NAs approved for treatment of HBV infection show negligible antiviral effects on HDV since they neither affect HDV replication nor suppress HBsAg production.

The efficacy of PEG-IFN is altogether relatively low and supported by limited documentation. Furthermore, only ~50% of patients are eligible for PEG-IFNα therapy e.g. due to contraindications, intolerabilities or advanced liver disease. For such patients there are no available treatment options.

There is an unmet medical need in patients with CHD.

3.1.3. Main clinical studies

Bulevirtide is a peptide blocking the NCPT bile acid transporter, which is also the entry receptor for HDV, through an interaction with HBsAg, encoded by HBV, but present at the surface of HDV virions.

The clinical efficacy of bulevirtide in chronic HDV infection has been studied in two phase 2 studies: MYR202 (completed) and MYR203 (ongoing). In the MYR203 study, the evaluation of the first 4 cohorts is completed, these cohort are referenced as MYR203 study in the application. For the MYR203 study, two additional cohorts are ongoing (MYR203 extension); however, only information on deaths, SAEs and pregnancies are included into this application.

The MYR202 study compared three doses of bulevirtide versus observation. Patients of the observation group received nucleotide analogue tenofovir (TDF) for control of underlying HBV infection.

In the MYR203 study, patients of the control group received pegylated interferon alpha 2a (PEG-IFNα), which is used in HDV patients per recommendation of the current treatment guidelines (EASL 2017).

The design of the MYR202 and MYR203 studies suggest two fundamentally different treatment strategies; one using bulevirtide as continuous monotherapy for an indefinite treatment duration (along with NUC therapy for HBV control) in analogy with the treatment of HBV using nukes, or the treatment of HUV, and the other using bulevirtide in combination with PEG-IFN for finite duration therapy, in analogy with PEG-IFN use in HBV, as well as the treatment paradigm for Hepatitis C.

In the case of treatment with indefinite duration, on-treatment responses are relevant to capture clinical benefit. In the case of treatment with a finite duration, off-treatment sustained virological and biochemical response is relevant for the same purpose.

With regards to endpoints, the surrogacy of plasma HDV-RNA decreases for clinical benefit has not been established. However, ALT normalisation, which represents decreased necro-inflammation, has been recognised as a surrogate for a decrease in fibrosis progression in chronic hepatitis B as well as C since decades. This mechanism is considered relevant also for CHD. Therefore, a combination of HDV-RNA reduction and ALT normalisation is considered evidence of a favourable drug effect.

3.2. Favourable effects

The MYR202 study, including 90 patients treated with bulevirtide (with background TDF) for 24 weeks in comparison with 30 patients treated with TDF only, provides ground for the following conclusions regarding the clinical efficacy of bulevirtide:

- Bulevirtide is effective in reducing HDV RNA with 53.6% of patients treated reaching the primary endpoint of a 2 log10 HDV RNA reduction or becoming negative at week 24 of therapy, when treated with the 2 mg daily dose proposed by the Applicant, significantly superior to TDF only.
- There is an apparent dose-response up to at least 10 mg, which was the highest dose group, where 76.7% of patients reached the primary endpoint.
- Along with virologic response, a superior biochemical response is seen in the bulevirtide groups compared to TDF only, with 40-50% of patients in the bulevirtide group normalising their ALT levels after 24 weeks of therapy compared to 7% of TDF patients, suggesting a reduction of hepatic necroinflammation in the bulevirtide groups.
- On discontinuation of bulevirtide at week 24, patients rapidly revert to their pre-treatment status with respect to HDV-RNA and ALT levels, indicating that viral clearance is not reached and a consequent need for indefinite continuation of therapy to retain clinical benefit.
- The table below summarises the efficacy results in mITT population at week 24:

Table 50. Efficacy results in mITT population at week 24

HDV RNA response	**Arm A:** **(n=28)** **2mg bulevirtide + TDF**	**Arm B:** **(n=32)** **5mg bulevirtide + TDF**	**Arm C:** **(n=30)** **10mg bulevirtide +** **TDF**	**Arm D:** **(n=28)** **TDF**
Patients with undetectable HDV RNA or decrease by ≥2log$_{10}$ from baseline to week 24,	53.6 %*	50.0% *	76.7%*	3.6%
Patients with undetectable HDV RNA or decline by >2log$_{10}$ and normal ALT at week 24	21.4%*	28.1% *	36.7% *	0.0%
Patients with ALT normalisation	42.9%*	50.0%*	40.0%*	7.1%

The MYR203 study included 30 patients treated for 48 weeks with bulevirtide in combination with PEF-IFN, 15 patients treated with bulevirtide only and 15 patients treated with PEG-IFN only. The primary outcome measure (HDV-RNA negative at week 72 (24 weeks post discontinuation of therapy, was as follows:

Table 51. Primary efficacy variable: HDV RNA response at week 72. Statistical analysis on the difference in proportions, using Fisher's exact test. Full analysis set

HDV RNA response	PEG-IFN (N=15)	MXB 2mg + PEG-IFN (N=15)	MXB 5mg + PEG-IFN (N=15)	MXB 2mg (N=15)
Week 72				
Number of subjects in analysis	15	15	15	15
Number of responders	0	8	4	1
Proportion Responders (95% CI)	0 (0.0%, 21.8%)	53.3% (26.6%, 78.7%)	26.7% (7.8%, 55.1%)	6.7% (0.2%, 31.9%)
Difference in proportions (95% CI)		53.3 (25.1, 78.7)	26.7 (0.9, 55.1)	6.7 (-16.0, 31.9)
p-value		0.0022	0.0996	1.0000

HDV RNA response is defined as HDV RNA value below lower level of detection (LLoD), where LLoD=10.
Proportions in percent are based on the number of subjects in analysis within each treatment group.
CI = Confidence interval, calculated using Clopper-Pearson (exact) for within group proportions and exact unconditional for difference in proportions.
Fisher's exact test was used for the comparison of respective MXB group and PEG-IFN alfa-2 only group.
For the full analysis set, subjects are analysed as randomised (i.e. planned treatment).
Program: \Subprogs\Tables\EFF1 HDV RNA Response.sas
Date and time program was run: 2019-06-27T12:39. Date and time analysis database was run: 2019-06-03T14:32

- In comparison to the reference PEG-IFN arm, the bulevirtide monotherapy arm shows a statistically significant difference in the proportion of subjects with on-treatment ALT normalisation. This is not seen in the bulevirtide+PEG-IFN combination arms, likely due to the proinflammatory interferon effect. At 24 weeks post therapy (week 72), there is a numerically higher but non-significant proportion of responders in the 2 mg bulevirtide + PEF-IFN arm but in line with the virologic response the 5 mg combination arm performs less well.
- 9/15 patients treated with 2 mg bulevirtide alone showed normalised ALT at week 24, and 11/15 patients at week 48 (end of therapy).
- The applicant is not making a labelling claim for co-treatment with PEG-IFN.

3.3. Uncertainties and limitations about favourable effects

The MYR202 study provides the main support of bulevirtide efficacy. The size of this study is limited, but statistically significant beneficial effects of bulevirtide were shown in all dose groups (2/5/10 mg). Still there are uncertainties on the magnitude of the effect and its generalisability to a larger, less selected patient population.

In the MYR202 study, patients consenting to participate in the PK sub-study were not eligible for randomisation to the control arm. This is a fundamental methodological flaw which creates uncertainty about effect sizes. An analysis excluding these patients provide directionally similar results as the whole dataset, although the statistical significance of the effect of bulevirtide 2mg on combined response is lost.

Due to the smallness of the 202 study it is clear that randomisation does not fully do its trick, since baseline ALT is conspicuously lower in the 2 mg dose suggested for registration. This creates uncertainty on the relative efficacy of this dose, proposed for registration, compared to the higher doses.

An uncertainty is the relation between on treatment effects on plasma HDV-RNA and reduction in ALT, which are presumed to lie on a causal pathway. While both effects are evident, there appears the overall quantitative relation between on-treatment effects on these two parameters appears weak.

In MYR203 the small sample size (n=60) is explained by the clearly stated exploratory nature of the study. Due to a substantial number of withdrawals and protocol violations, only 43 patients in total and 8/15 in the PEF-IFN arm are available for per protocol-analyses. This, together with inconsistent results between the 2 mg and 5 mg combination therapy arm, introduces a level of uncertainty that makes the estimation of efficacy and clinically relevant activity (which would be dependent on durable off-treatment effects) highly uncertain.

Virologic response increases with dose. Hence the proposed 2 mg dose is not optimal from the perspective of antiviral activity. However, there is presently no indication that the lower dose would be associated with loss of viral suppression due to the selection of resistant viral variants.

As virological rebound to pre-treatment values is observed after discontinuation, durability of treatment response is not achieved. Although virological breakthrough was observed in 3 bulevirtide-treated subjects (2 under monotherapy and 1 under combination therapy), resistance development seems unlikely.

Antiviral effects and ALT normalisation have been demonstrated in cirrhotic and non-cirrhotic subjects, but not in patients with decompensated liver disease; these are not proposed to be included in the indication.

3.4. Unfavourable effects

The bulevirtide safety database contain 239 patients treated with bulevirtide. Of these, 111 have been treated for at least 24 weeks and 44 patients for 48 weeks. Fifty percent of the patients in MYR202 and 23.3% in MYR203 had cirrhosis at baseline, but patients with decompensated liver disease were not included.

The MYR202 study brings the most important contribution to the bulevirtide safety database, and shows, within in the time span of the study, an overall favourable safety profile. However, one patient discontinued therapy due to pancytopenia at week 2 after initiation of 5 mg bulevirtide (no PEG-IFN).

The major side effect of bulevirtide is consequent to its mechanism of action, i.e. blocking the NTCP bile acid transporter. In line with the virologic response, a dose of 2 mg qd of bulevirtide does not completely block the NTCP-mediated absorption of bile acids. Instead a positive dose-response is seen up to 10 mg and could possibly extend further as no higher doses have been explored.

The most common AEs in the bulevirtide groups is bile acid elevations (38.9% vs 17.9%). Other AE's include GI-related symptoms (17.8% vs 3.6% of patients), dizziness (7.8% vs 0%), headache (6.7% vs 0%) and injection site reactions (5.6% vs 0%) while elevated levels of ALT and GT (likely related to underlying disease) are more common on the TDF only group.

The on-treatment severe AEs were lymphopenia (n=1), thrombocytopenia (n=1), anaemia (n=1), lipase elevation (n=2) and amylase elevation (n=2). All cases of lipase and amylase elevation were in the 10 mg bulevirtide group.

In the follow-up phase ALT elevations (21.6% vs 12.0% of subjects), AST elevation (19.3% vs 8%), lipase elevations (3.4% vs 0%) and amylase elevations (3.4% vs 0) were more common the in the bulevirtide groups, likely related to virologic HDV flares after cessation of therapy. HBV flares are considered less likely as TDF therapy was ongoing in all groups. The severe AEs in the follow-up phase were almost exclusively ALT/AST elevations.

The observed on-treatment decrease of transaminases and subsequent return to the elevated levels observed at baseline (or above) is in line with the observations presented in the efficacy section.

Given the size of the MYR203 study, the safety conclusions that can be drawn regarding the safety of the bulevirtide+PEG-IFN combination are limited. The AE profile, except for bile acid elevation, is apparently driven by PEG-IFN in the combination arms.

The observed changes in haematologic parameters, and most clinical chemistry parameters, appear related to PEG-IFN treatment. Bile acid increases are in line with the findings in the MYR202 study and as expected related to bulevirtide dose.

ADAs appear in approximately 20-60% of patients after 24 weeks of treatment, depending on whether PEG-IFN is co-administered. Even if some differences were noted in the occurrence of some AEs (referring in particular to the SOC of general disorders and administration site conditions) between ADA positive and negative subjects mainly in MYR203 study, the limited sample size and the paucity of events, do not allow to draw firm conclusions on the impact of ADA on safety. However, the Applicant is expected to provide data on ADAs in the phase 3 programme, both in relation to efficacy and safety.

The safety profile did not seem to differ between cirrhotic and non-cirrhotic patients.

3.5. Uncertainties and limitations about unfavourable effects

The proposed dose of 2 mg or higher was administered to 205 subjects, of which 175 patients were treated for at least 12 weeks. With regards to the 10 mg dose, 56 patients received this, at any duration. Thus, the safety database is non-comprehensive.

One patient in the -202 study, randomised to 5 mg bulevirtide, presented with anaemia, thrombocytopenia and neutropenia at week 2 post baseline. This patient discontinued therapy and subsequently the study at week 16. The patient was then formally lost to follow up but has been confirmed to be alive 1.5 years post treatment. This case was discussed at an *Ad Hoc* Expert Group meeting preceding the approval; the experts believed this adverse event were likely related to advanced liver disease, and that the index of suspicion of a causal link to bulevirtide was low.

No patients older than 65 years old have been included in pivotal studies, races other than Caucasian (such as Black or Asian) are underrepresented and genotypes other than 1 are lacking, not allowing for an evaluation of safety profile in these patients.

The size of the safety dataset of bulevirtide is limited, allowing only characterisation of relatively common safety issues. Moreover, there are no long-term safety data from patients with drug-induced bile acid elevations. The long-term effects of bulevirtide-induced bile acid elevations are currently unknown, but the

approximately three-fold increase in the 2 mg group at 24 weeks is substantially lower than what has been observed in patients with inborn NTCP deficiencies. Whereas the bile salt increase was asymptomatic during the studies, there is no data available on the long-term impact (> 48 weeks) of this effect induced by bulevirtide.

A recent publication on a cohort of subjects with NTCP mutation provided data on long term effects of genetically determined hypercholemia (Liu et al. 2017). Eight subjects were identified who were carrying the p.Ser267Phe mutation in the SLC10A1 gene associated with the complete loss of NTCP function. The authors concluded that this mutation was associated with low levels of vitamin D and 3 of 6 patients that were subjected to bone mineral density analysis presented with osteoporosis/osteopenia. Also, sex hormones and blood lipids were deviated in all subjects.

In line with the virologic response, a dose of 2 mg qd of bulevirtide does not completely block the NTCP-mediated absorption of bile acids. A positive dose-response is seen up to 10 mg and could possibly extend further as no higher doses have been explored. The long-term effects of bulevirtide-induced bile acid elevations are currently unknown, but the approximately three-fold increase in the 2 mg group at 24 weeks is substantially lower than what has been observed in patients with NTCP deficiencies.

The safety database for 5 mg or 10 mg is not considered sufficient to presently evaluate whether the safety profile substantially differ from that of 2 mg. Therefore, 2mg is the proposed dose presently, whereas the relative efficacy of 2 mg and 10 mg are further evaluated in the -301 study.

3.6. Effects Table

Table 52. Effects Table for MYR202 – week 24 (on treatment).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects (for proposed 2 mg dose of bulevirtide)						
HDV RNA response	Virologic response (2 log10 decline)	%	53.6	3.6	Single study, limited size	
ALT normalisation	Biochemical response (normalisation)	%	42.9	7.1	Single study, limited size	
Combined response		%	21.4	0	Single study, limited size	
Unfavourable Effects						
ALT elevation	Flare due to virologic relapse at cessation of therapy	%	21.6	12.0	Single study, limited size	
Bile acid increase	Due to NTCP inhibition	%	28.6	21.4	Single study, limited size	
GI AEs	Gastrointestinal adverse events	%	17.8	3.6	Open-label study, limited size	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Chronic HDV infection with active hepatitis, as indicated by a positive HDV RNA and ALT elevation, is in many cases a severe disease with rapid progression to clinical liver disease. Currently there is no effective therapy approved in the EU. Despite the uncertainties connected to study size, design and conduct, the MYR202 provides evidence of both durable antiviral effects and decreased ALT which would generally be understood to imply reduced necroinflammation. The latter, if sustained during treatment, is assumed to incur clinical benefit through decreased progression of hepatic fibrosis.

The MYR202 study investigated bulevirtide as monotherapy for 24 weeks at 2, 5 and 10 mg q.d., whereupon patients ceased therapy. There was general relapse and return towards baseline status with respect to HDV-RNA and ALT, on discontinuation. Therefore, this study support monotherapy of indefinite duration to suppress viral replication and decrease necro-inflammation. Results in the bulevirtide 2 mg monotherapy arm in study MYR203 provides some corroboration of the results seen for the 2 mg dose in MYR202.

The MYR203 study investigated treatment of a finite duration, with bulevirtide alone or in combination with PEG-IFN. In such a setting, sustained off-treatment responses are the key index of efficacy. Data from this very small study do not allow an evaluation of the efficacy of combination therapy with regards to the frequency of clinically meaningful off-treatment response. Therefore, this treatment strategy is presently not

supported by data, as the B/R cannot be ascertained. The main mechanistic side effect is asymptomatic bile acid elevations, presently not understood to be hazardous. However, safety data are not comprehensive, and more information is needed. Available safety data indicate good tolerability in non-cirrhotic as well as cirrhotic patients with compensated liver disease. There are no efficacy and safety data to support use in decompensated liver disease.

While the proposed 2 mg dose is not optimal from an antiviral perspective, it is associated with plasma HDV-RNA decreases and ALT normalisations, and response appears durable during treatment (no selection for resistant variants). The safety database for the higher doses tested is presently not sufficient for a benefit-risk evaluation; however, more data will be generated in the MYR301 study. Once the safety of the 10 mg dose is sufficiently documented, a change in posology is anticipated.

3.7.2. Balance of benefits and risks

There are numerous uncertainties regarding efficacy and safety. Efficacy estimates (plasma HDV-RNA decrease, ALT normalisation, and the combined virological/biochemical endpoint) are imprecise, and not statistically compelling in the usual sense. The optimal dose is uncertain, and the safety database presently only supports a dose that has sub-maximal antiviral efficacy. Further, there is unclarity on the relation between antiviral effect and impact on necroinflammation. There is uncertainty about when to cease therapy in case of limited or absent virological or biochemical response,

Further, there is uncertainty due to a novel mechanism of action, with regard to a small safety database, short follow up, and the long-term safety of bulevirtide-induced bile acid elevations; and there uncertainty about the causal relation to bulevirtide, ultimate diagnosis and outcome of the patient presenting with treatment emergent pancytopenia at the week 2 visit in the MYR202 study.

Notwithstanding these uncertainties, the benefits shown indicate that Hepcludex will provide clinical benefit and has a reasonable safety profile despite the absence of comprehensive data, in a disease for which there are no approved treatments and there is a clear unmet medical need.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the efficacy and safety of bulevirtide are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease and is designated as an orphan medicinal product.

The product fulfils the requirements for a conditional marketing authorisation provided that the benefit-risk balance can be shown to be positive, as discussed above.

- There are presently no approved products for the treatment of HDV, which is associated with a higher rate of disease progression and end-stage liver disease compared to HBV mono-infection. Thus, an unmet need would be addressed.

- It is likely that the applicant will be able to provide comprehensive data on safety and efficacy through the MYR301 study. Furthermore, the proposed MYR-HDV registry study is expected to characterise the frequency of hepatic decompensation, hepatocellular cancer, liver transplantation, liver related- and overall mortality in patients treated with bulevirtide and bridge the surrogate endpoints used in clinical trials to long-term clinical benefit.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall benefit-risk of Hepcludex is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Hepcludex is favourable in the following indication:

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
Data collection from participation in the MYR-HDV registry	-
MYR204 - A Multicentre, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta	28 February 2023
MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta.	28 February 2025

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that bulevirtide is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.