17 October 2024
EMA/542920/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Hepcludex

International non-proprietary name: bulevirtide

Procedure No.: EMEA/H/C/004854/II/0031

Marketing authorisation holder (MAH): Gilead Sciences Ireland Unlimited Company

Note

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

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List of abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BLV	bulevirtide (GS-4438), Hepcludex®
CL/F	apparent oral clearance
C_{max}	maximum observed concentration of drug
C_{trough}	concentration at the end of dosing interval
DDI	drug-drug interaction
EU	European Union
HBV	hepatitis B virus
HDV	hepatitis delta virus
IFN	Interferon
k_a	first order absorption rate constant
NTCP	sodium taurocholate cotransporting polypeptide
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic
QD	once daily
RNA	ribonucleic acid
SC	Subcutaneous
$t_{1/2}$	terminal elimination half-life
T_{max}	time (observed timepoint) at C_{max}
V_c/F	apparent central volume of distribution
V_{max}	maximum rate of nonlinear elimination

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland Unlimited Company submitted to the European Medicines Agency on 7 November 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of chronic hepatitis delta virus (HDV) infection in paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease for Hepcludex, based on a modelling and simulation study and an extrapolation study to evaluate the use of Bulevirtide for the treatment of chronic hepatitis D infection in children from 3 to less than 18 years of age. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet has been updated accordingly. Version 4.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Hepcludex was designated as an orphan medicinal product EU/3/15/1500 on 19 June 2015. Hepcludex was designated as an orphan medicinal product in the following indication:

Treatment of hepatitis delta virus infection

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0270/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0270/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0270/2022.

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 MAH 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.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

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: N/A

Timetable	Actual dates
Submission date	7 November 2023
Start of procedure	25 November 2023
CHMP Rapporteur Assessment Report	19 January 2024
PRAC Rapporteur Assessment Report	24 January 2024
PRAC members comments	31 January 2024
PRAC Outcome	8 February 2024
CHMP members comments	12 February 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 February 2024
Request for supplementary information (RSI)	22 February 2024
CHMP Rapporteur Assessment Report	28 May 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur Assessment Report	20 June 2024
Request for supplementary information (RSI)	27 June 2024
CHMP Rapporteur Assessment Report	17 September 2024
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	03 October 2024
CHMP members comments	07 October 2024
Updated CHMP Rapporteur Assessment Report	10 October 2024
Opinion	17 October 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis, affecting at least 12 million people globally. Delta hepatitis is caused by the HDV, a defective RNA virus that requires the presence of the hepatitis B surface antigen (HBsAg) for its complete replication and transmission, and, as such, this form of hepatitis only occurs in individuals also infected with the hepatitis B virus (HBV). In the European Union (EU), HDV infection is considered an orphan disease, with an estimated prevalence of 130,000 patients. Hepatitis delta virus infections are mostly concentrated in low and middle-income countries.

Hepatitis delta virus can cause acute or fulminant hepatitis, and occurs either as a coinfection with HBV, which can be self-limiting, or as a superinfection in patients with chronic HBV infection, which leads to chronicity in 70% to 90% of cases. Most patients with chronic HDV infection show a more progressive and severe course of disease than chronic HBV infection, with development of cirrhosis within 2 years in 10% to 15% of patients.

State the claimed the therapeutic indication

The current application concerns an extension of indication:

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult and paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease.

Epidemiology and risk factors, screening tools/prevention

Literature on the prevalence, presentation, and treatment of HDV infection in the paediatric population is scarce and available reports suggest that the prevalence of infection in the younger subsets of the paediatric population is extremely low. The prevalence of HDV infection was reported to be 2.9% (6/206) in a study of children chronically infected with HBV in Western Turkey and 12.6% (34/270) in a study of children with chronic liver disease in Italy (Farci 1985, Yuce 1996). In the Hepatitis Delta International Network registry, 9% (n = 1576) of patients with past or ongoing HDV infection were younger than 20 years. Infection rates are low because perinatal transmission of HDV infection is rare due to the global introduction of HBV vaccination of infants and neonates. In addition, the majority of paediatric HDV cases remain undetected because chronic HDV infection in paediatric patients is largely asymptomatic.

Clinical presentation, diagnosis

Paediatric case studies and individual reports provide evidence of disease presentation and progression. Two reports of HDV infection in children demonstrated that similar to adult patients, coinfection of HBV and HDV can lead to high levels of alanine aminotransferase (ALT), rapid

progression of fibrosis, and advanced liver disease. A cross-sectional analysis conducted in Western Turkey reported an HDV infection rate of 1.76% (3/170) in children coinfected with HBV and that the 3 children (aged 6, 12, and 17 years, respectively) chronically infected with HBV and HDV had cirrhosis (Ozgenc 2013). In a second report from Turkey, 2.9% (6/206) of children with HBV were coinfected with HDV (age range between 8 and 13 years). Of these, 3 children had already progressed to cirrhosis, 2 had chronic active hepatitis which is often associated with rapid progression to cirrhosis, and 1 had persistent hepatitis with portal inflammation (Yuce 1996).

Management

There are no approved treatments for chronic HDV infection in paediatric patients, and off-label interferon-alpha (IFN-α) (pegylated and non-pegylated) have been used to delay the rapid progression of disease (European Association for the Study of the Liver 2023). The response observed in paediatric patients with chronic HDV infection treated with IFN is similar to that observed in adults with chronic HDV infection, sustained virological response in 25%-30% of patients, with late relapse in > 50% patients. Based on limited reports, chronic HDV infection is considered similar in adults and in paediatric patients both in disease characteristics, pathogenesis, and in response to treatment. As such, there remains an unmet need for treatment in this paediatric population with chronic HDV as there are currently no approved treatments.

2.1.2. About the product

Bulevirtide is a myristoylated N-terminal and amidated C-terminal 47-amino acid lipopeptide, administered by a subcutaneous (SC) injection, which blocks the entry of HDV into hepatocytes by binding to an essential HDV entry receptor known as sodium-taurocholate co-transporting polypeptide (NTCP).

Hepcludex was conditionally approved in adults by the European Medicines Agency (EMA) in 2020. A conversion of the conditional marketing authorisation to a full marketing authorisation was granted in 2023 (EMEA/H/C/004854/II/0019).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The initial agreed paediatric investigation plan (PIP), submitted by MYR, included 3 agreed measures, including a clinical study, a modelling and simulation (M&S) study, and an extrapolation study (EMEA-002399-PIP01-18).

The Paediatric Committee (PDCO) agreed to a PIP modification (EMA/183400/2022) to remove the requirements for the clinical study, PIP Study 1: open-label, single arm, uncontrolled trial to evaluate safety, tolerability, acceptability, pharmacokinetics, and pharmacodynamics of bulevirtide in children from 3 to less than 18 years of age with chronic hepatitis D infection.

The currently agreed measures in the BLV PIP includes an M&S study (Study 2) and an extrapolation study (Study 3) to evaluate the use of BLV in the treatment of chronic hepatitis D infection in children from 3 to less than 18 years of age. The PDCO agreed to a full extrapolation approach based on:

- disease progression and exposure similarity between adult and pediatric populations
- feasibility issues associated with obtaining pharmacokinetic (PK) and clinical data from pediatric patients (low prevalence of the disease in pediatric population; orphan drug)

- available adult clinical data with BLV
- substantial available safety data
- well characterized mechanism of action.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) was previously submitted for Hepcludex as part of the EU initial marketing authorisation application (MAA) on 10 October 2019. This ERA considered all available data relating to bulevirtide in accordance with the Committee for Medicinal Products for Human Use (CHMP) guideline on the Environmental Risk Assessment of Medicinal Products for Human Use that was adopted by the CHMP on 01 June 2006 (EMEA/CHMP/SWP/4447/00), and 26 May 2016 (Q&A on 'Guideline on the environmental risk assessment of medicinal products for human use').

As included in the original application, bulevirtide contains only naturally occurring amino acids, and no modifications were introduced to increase its stability. Bulevirtide can therefore be regarded as naturally occurring in the environment with a biostability equivalent to that of naturally occurring peptides. In addition, bulevirtide is intended for the orphan indication chronic hepatitis D, such that environmental entry can be expected to remain very low. Therefore, 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. The extended indication to include paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease would not impact this conclusion.

2.2.2. Conclusion on the non-clinical aspects

The extended indication does not lead to an increase in environmental exposure further to the use of bulevirtide. Bulevirtide is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

No clinical data have been submitted in this type II variation. The MAH has provided a new popPK/PD analysis to support that the bulervirtide exposure in paediatric patients from 3 years of age weighing at least 10 kg match the adult reference range.

2.3.2. Extrapolation

The progression of HDV disease is comparable between adult and paediatric patients and thus, it is considered that BLV efficacy and safety can be extrapolated from adults to paediatric patients based on similar plasma PK exposures between adults and children.

It has also been reported that NTCP expression and glycosylation is completed by approximately 1-year post birth. Thus, no difference in NTCP function and viral response or bile salt response to BLV therapy was expected in the proposed indication and as such changes in age-related NTCP receptor expression/maturation were not included in the PD model.

GCP

Not applicable.

2.3.3. Pharmacokinetics

The MAH has submitted a new PopPK/PD. The simultaneous PopPK/PD model consisting of a PK model for BLV and a PD model for bile salts.

It has been reported that NTCP expression and glycosylation is completed by approximately 1-year post birth. Thus, no difference in NTCP function and viral response or bile salt response to BLV therapy was expected in the proposed indication and as such changes in age-related NTCP receptor expression/maturation were not included in the PD model.

Table 1 presents an overview of clinical studies that have contributed to the characterization of the clinical pharmacology of BLV in adults. Thus, there are no data available in paediatric subjects. Pharmacokinetic data of BLV were collected in a total of 7 clinical studies, out of which intensive PK sample collection was collected in 3 studies (MYR101, MYR102, and the PK substudy of MYR201 [HBV]) and sparse PK sample collection in 2 studies (MYR204 and MYR301).

Table 1: Overview of Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of BLV

Study Number	Study Description (Countries That Randomized[a] Participants)	Test Treatment(s)		Reference Treatment(s) Dose and Formulation	PK Sampling (Intensive or Sparse)
		Dose and Formulation	N[b]		
MYR101	Phase 1a, open-label, single-center, single-dose, first-in-human, ascending dose to assess safety, tolerability, PK, and immunogenicity (Germany)	BLV 300 ng, 3 µg, 10 µg, 100 µg, 800 µg, 3 mg, 5 mg, 10 mg, 20 mg IV infusion over 2 hours Formulation: lyophilized powder for injection	27	—	Intensive
		BLV 800 µg, 5 mg, 10 mg SC bolus Formulation: lyophilized powder for injection	9		Intensive
MYR102	Phase 1, open-label, single-center, to assess potential DDI between BLV and TDF (Germany)	BLV 10 mg QD SC for 6 days Formulation: lyophilized powder for injection	12	TDF[c] 300 mg QD PO Formulation: film-coated tablet	Intensive
MYR201 (HBV)	Phase 1b/2a, randomized, open-label, active-controlled, multicenter, parallel-group, exploratory, clinical study to assess efficacy in participants with HBeAg− CHB, PK profile, immunogenicity, safety, and tolerability (Russia)	BLV 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg QD SC for 12-24 weeks Formulation: lyophilized powder for injection	16	Entecavir: 0.5 mg QD PO Formulation: film-coated tablets	Intensive
MYR202	Phase 2, randomized, open-label, multicenter clinical study to assess efficacy, safety, PK, and immunogenicity in participants with CHD (Germany, Russia)	BLV SC 2 mg, 5 mg or 10 mg QD SC + TDF[d] 300 mg QD PO for 24 weeks Formulation: lyophilized powder for solution for SC injection	25[d]	TDF[c,e] 300 mg QD PO Formulation: film-coated tablet	Intensive and sparse
MYR203	Phase 2, randomized, open-label, multicenter, parallel-group, comparative clinical study to assess efficacy, safety, PK, and immunogenicity in combination with Peg-IFNα in participants with CHD (Russia)	BLV 2 mg, 5 mg or 10 mg QD SC + Peg-IFNα 180 µg QW SC or BLV 2 mg QD SC or BLV 5 mg BID SC + TDF[d] 300 mg QD PO for 48 weeks Formulation: lyophilized powder for solution for SC injection	30[d]	Peg-IFNα 180 µg Formulation: solution for SC administration	Intensive and sparse

Study Number	Study Description (Countries That Randomized[a] Participants)	Test Treatment(s)		Reference Treatment(s) Dose and Formulation	PK Sampling (Intensive or Sparse)
		Dose and Formulation	N[b]		
MYR204	Phase 2b, randomized, open-label, multicenter, active-controlled, parallel-group clinical study to assess efficacy and safety of BLV in combination with Peg-IFNα in participants with CHD (France, Moldova, Romania, and Russia)	BLV 2 mg or 5 mg QD SC + Peg-IFNα 180 µg QW SC or BLV 10 mg QD SC for 96 weeks (data up to 48 weeks) Formulation: lyophilized powder for solution for SC injection	150[d]	Peg-IFNα 180 µg Formulation: solution for SC administration	Sparse
MYR301	Phase 3, randomized, open-label, multicenter, parallel-group clinical study to assess efficacy and safety of BLV in participants with CHD (Germany, Italy, Russia, and Sweden)	BLV 2 mg or 10 mg QD SC for 96 to 144 weeks (data up to 48 weeks) Formulation: lyophilized powder for solution for SC injection	99[d]	—	Sparse

BID = twice daily; BLV = bulevirtide (GS-4438), Hepcludex®; CHB = chronic hepatitis B infection; CHD = chronic hepatitis delta infection; DDI = drug-drug interaction; IV = intravenous; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; N = number of participants in a population; Peg-IFNα = pegylated interferon alfa; PK = pharmacokinetic(s); PO = orally; PopPK = population pharmacokinetic; QD = once daily; QW = once weekly; SC = subcutaneous; TDF = tenofovir disoproxil fumarate

a For Studies MYR101 and MYR102, which were not randomized clinical studies, "N" is the number of participants that were enrolled.
b Number of participants who were administered any dose of BLV therapy, underwent PK sampling, and had PK parameters were reported.
c TDF 300 mg equivalent to tenofovir disoproxil fumarate 245 mg.
d Where sparse PK sampling occurred, single plasma samples were collected at 1 hour (± 15 minutes) postdose on various days from all study participants. These samples contributed to the PopPK modeling dataset.
e Participants received TDF in addition to BLV in the study or study group.

2.3.4. Target exposure

The MAH has defined the target exposure/reference range as the exposure from adult Phase 2/3 adult studies for 2 mg and 10 mg dose levels, i.e. 5th percentile following 2-mg once-daily SC BLV and 95th percentile following 10-mg once-daily SC BLV, see Table 2 below.

Table 2: Target exposure

Age Category	AUC_{tau} (ng·h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	$t_{1/2}$ (h)	T_{max} (h)
Adult reference range	[65.2-7007]	[5.8-712.7]	[0.2-49.3]	[3.5-9.8]	[0.8-4.6]
Adult maximum values	16,032	1331.4	NA	NA	NA

2.3.5. PK/PD modelling

Population PK model analysis (Updated popPK analysis (REP-1f-GIL-FTE2-BLV-PMX-1))

The MAH has provided an updated popPK analysis, starting with the popPK model used in the PIP. The dosing of Hepcludex in children is based on this analysis.

The selection of observation records used to update the population PK model previously presented in PIP, EMEA-002399-PIP01-18-M01, is referred to as the updated popPK analysis data set. Counts of the observation records and subjects in the updated popPK analysis data set are presented in Table 3.

Table 3: Number of subjects with observation and number of observations in the updated popPK analysis data set, presented by study and treatment group

Study / Dose	nID[a]	nObs[b]	nObs/nID[c]
MYR101			
3 mg QD	3	60	20.0
5 mg QD	6	108	18.0
10 mg QD	6	108	18.0
20 mg	3	60	20.0
All	18	336	18.7
MYR102			
10 mg QD	12	316	26.3
MYR202			
2 mg QD	29	437	15.1
5 mg QD	33	396	12.0
10 mg QD	31	413	13.3
All	90	1 246	13.8
MYR203			
2 mg QD	30	566	18.9
5 mg QD	30	851	28.4
10 mg QD	15	164	10.9
All	75	1 581	21.1
MYR204			
2 mg QD	50	614	12.3
10 mg QD	100	1 311	13.1
All	150	1 925	12.8
MYR301			
2 mg QD	49	882	18.0
10 mg QD	100	1 448	14.5
All	149	2 330	15.6
All			
All	494	7 734	15.7

See Glossary for explanation of abbreviations.
[a]Number of subjects
[b]Number of observations
[c]Average number of observations per subject

The final previous legacy model (CTRA-2021-1057 BLV PopPK) was a 2-compartment model with sequential zero- first-order absorption and first-order elimination. A dose effect on CL addressed the non-linearity observed in PK. Moreover, effects of WT on CL, Vc, Vp, and Q were included and supported by the data using fixed allometric exponents of 0.75 and 1 for clearances and volume of distributions, respectively. Finally, cirrhosis was found to affect CL and sex was found to affect Vc.

The legacy model was re-run with the updated dataset and further developed/simplified to a 1 compartment model.

The final updated model (Table 4) has the following characteristics.
Absorption model: first-order absorption
Disposition model: one-compartment model with first-order elimination
Covariate model: WT and dose on CL; WT on V; time after first dose larger than 100 hours on F (fixed)
IIV model: exponential IIV on ka, V, and CL
RUV model: proportional RUV model (implemented as additive on the log-scale)

Table 4: Parameter estimates of the final updated popPK model

	Final updated popPK model			
Run	11			
OFV	3506.88			
Condition number	222702			
	Unit	**Value**	**RSE (%)**	**SHR (%)**
V	(L)	3.92	6.29	
CL	(L/h)	4.96	6.64	
Day 1 absolute SC F relative to day 1 intravenous (IV)[a,c]	-	0.135	(FIX)	
k_a	h^{-1}	0.125	4.72	
Dose on CL relative to 2 mg	-	-0.179	19.3	
Time-varying apparent SC F relative to day 1 IV[b,c]		20.6	(FIX)	
IIV V	(CV)	0.881	3.92	39.1
IIV CL	(CV)	0.833	3.42	18.1
IIV k_a	(CV)	0.628	5.45	38.4
RUV	(CV)	0.667	0.266	4.85

[a] Parameter is reported on the logit-scale and translates into an absolute SC bioavailability relative to day 1 IV of 53.4%.
[b] Parameter is reported on the logit-scale and translates into an apparent SC bioavailability relative to day 1 IV of 94.8% after 100 hours.
[c] Parameters were fixed to the values reported in CTRA-2021-1057[1].
IIV parameters are reported on the standard deviation (SD) scale, i.e. the square root of the IIV estimate from NONMEM. In case the IIV is modeled in an exponential fashion, this corresponds to the approximate coefficient of variation (CV)[4].
The RSE for IIV and RUV parameters are reported on the approximate SD scale.

Simulated steady state exposures for the paediatric population assuming either a 2 mg QD flat dose or a body weight-based dosing regimen, using 1 mg QD for children weighting 10 kg to < 25 kg, 1.5 mg QD for children weighting 25 kg to < 35 kg, and 2 mg QD for children weighting 35 kg and above are presented in Figure 1 and Figure 2 respectively.

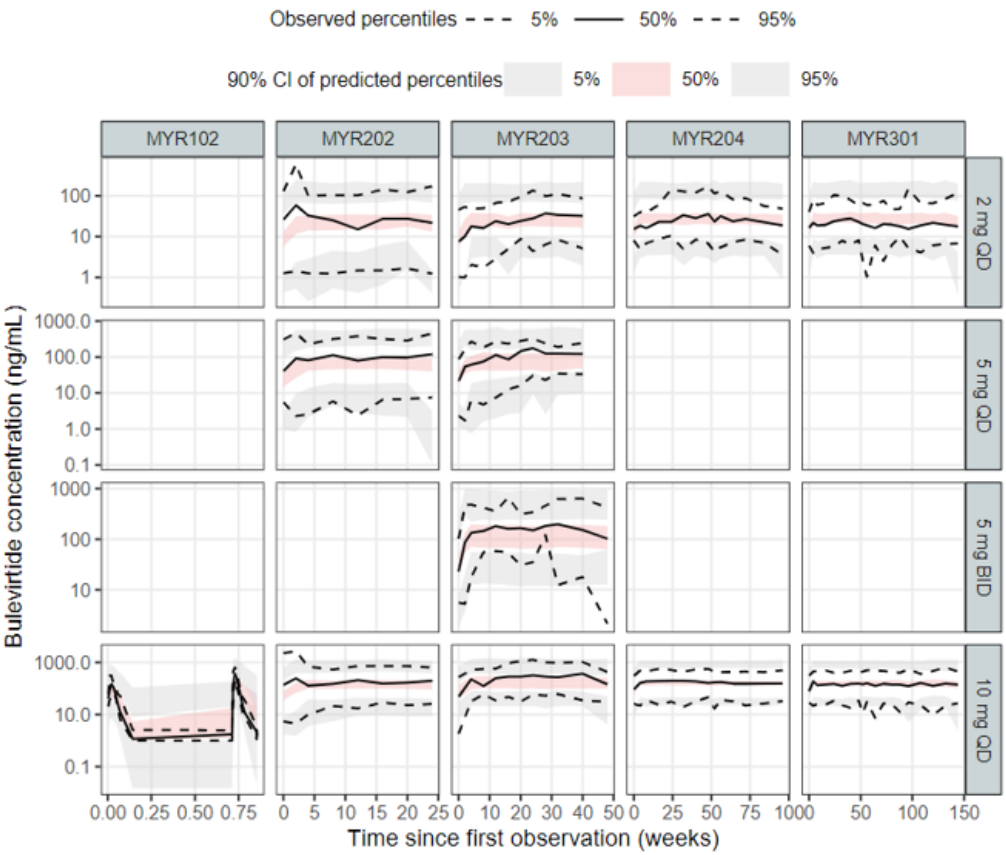


Figure 1: Visual predictive check of bulevirtide plasma concentrations versus time since first observation (weeks) for studies MYR102, MYR202, MYR203, MYR204, and MYR301 in the updated analysis data set, using the final updated popPK model. Data are stratified by nominal dose group and study and presented on a semi-logarithmic scale. Time pints associated with BLQ observations were included in the VPC and observed BLQ values were censored.

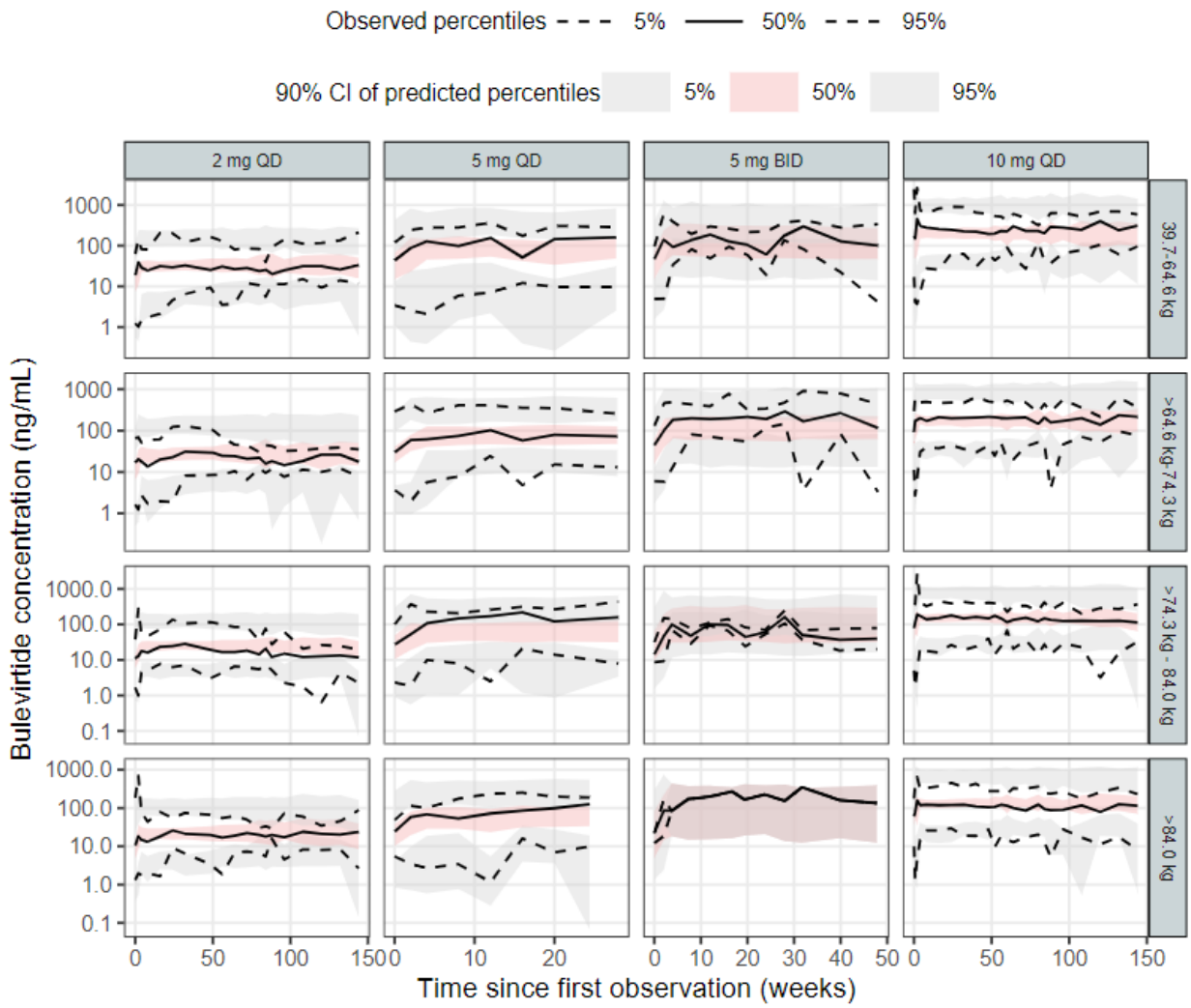


Figure 2: Visual predictive check of bulevirtide plasma concentrations versus time since first observation (weeks) for studies MYR102, MYR202, MYR203, MYR204, and MYR301 in the updated analysis data set, using the final updated popPK model. Data are stratified by nominal dose group and body weight group and presented on a semi-logarithmic scale. Time points associated with BLR observations were included in the VPC and observed BLQ values were censored. Subjects included in study MYR101 are not shown.

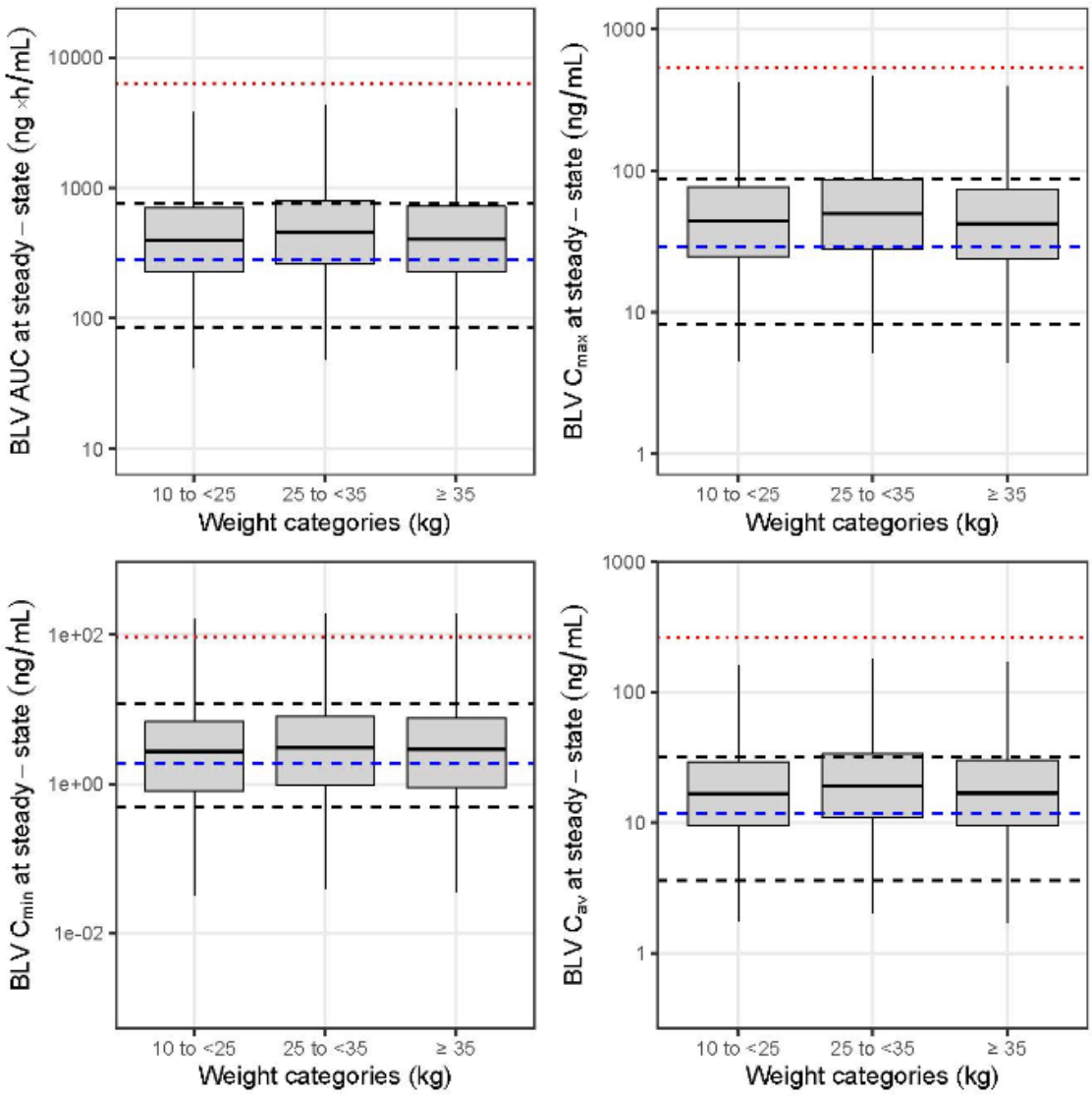
Simulation and dose justification

Based on the updated simulations presented below (Figure 3 and Table 5), the weight-based dosing in paediatric population match steady state metrics AUC, Cmax, Ctrough, and Cavg to the requested adult BLV 2 mg exposure reference reasonably well. Notably, the interquartile range of the paediatric profiles is fully contained within the 5th to 95th percentile of the 2 mg adult reference range for the 10 kg to < 25 kg and ≥ 35 kg weight groups, and for the 25 kg to < 35 kg weight group, the IQR is nearly fully contained within the 5th to 95th percentile of the BLV 2 mg adult range. While some values do fall slightly above the 95th percentile of the 2 mg range, they are still far below the 10 mg adult exposure.

Therefore, the MAH proposes weight-based BLV dosing in paediatrics as follows:

- 1 mg once-daily for children weighing ≥ 10 kg to < 25 kg
- 1.5 mg once-daily for children weighing ≥ 25 kg to < 35 kg

- 2 mg once-daily for children weighing ≥ 35 kg



Simulated steady-state bulevirtide AUC, C_{max}, C_{min}, and C_{avg} within a dosing interval, stratified by age group, following body weight-based dosing (1 mg once daily for children weighting 10 kg to < 25 kg, 1.5 mg once daily for children weighting 25 kg to < 35 kg, and 2 mg once daily for children weighting 35 kg and above) in a virtual pediatric population using the updated bulevirtide population pharmacokinetic model. The lower black dashed horizontal lines represent the 5th percentiles in adults receiving a 2 mg once daily dose and the upper black dashed horizontal lines represent the 95th percentiles in adults receiving a 2 mg once daily dose. The blue horizontal dashed lines represent the median adult exposure based on a 2 mg once daily dose. The red horizontal dotted lines represent the 95th percentile of adult exposures based on a 10 mg once daily dose. The horizontal lines in a box indicate the median value; the box edges represent the 25th and 75th percentiles; and the whiskers extend to the furthest data point that is no greater than 1.5 times the inter-quartile range. Data beyond the end of the whiskers are not shown.

Figure 3: Simulated Steady-state Bulevirtide AUC, C_{max}, C_{min}, and C_{avg} Withing a Dosing Interval Stratified by Age Group Following Body Weight-Based Dosing in a Virtual Pediatric Population

Table 5: Summary of simulated steady-state exposures in paediatric patients following a body weight-based QD dose of SC bulevirtide and reference adult exposures following 2 and 10 mg QD doses of SC bulevirtide.

Weight category (kg)	AUC (ng · h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	Elimination half-life (h)	T_{max} (h)
10 to <25	399 (101) [100-1570]	43.2 (101) [10.6-166]	1.79 (992) [0.0375-23.0]	5.71 (69.2) [2.05-16.0]	1.34 (99.7) [0.320-4.88]
25 to <35	459 (101) [117-1810]	48.6 (99.8) [12.0-184]	2.12 (929) [0.0483-27.6]	5.73 (69.6) [2.06-16.2]	1.51 (96.7) [0.374-5.32]
≥35	405 (104) [99.3-1640]	41.3 (99.5) [10.3-156]	1.99 (975) [0.0438-26.7]	5.83 (69.9) [2.08-16.6]	1.73 (95.4) [0.425-5.90]
Adults, 2 mg	[85.9-763]	[8.22-87.8]	[0.494-11.8]	[3.73-10.2]	[0.753-4.18]
Adults, 10 mg	[556-6280]	[47.2-531]	[1.69-92.4]	[2.90-9.44]	[1.10-5.43]

See **Glossary** for explanation of abbreviations.
Notes: Body weight-based dosing used 1 mg QD for children weighting 10 kg to <25 kg, 1.5 mg QD for children weighting 25 kg to <35 kg, and 2 mg QD for children weighting 35 kg and above. Pediatric data are presented as geometric mean with (Geometric CV%) and [5^{th}-95^{th} percentiles]. Adult reference exposures are presented as [5^{th}- 95^{th}] percentiles following 2 and 10 mg QD SC bulevirtide using EBEs from the final updated PK model.

2.3.6. Discussion on clinical pharmacology

Introduction

No new clinical efficacy or safety data have been submitted in this application. A full extrapolation from adult efficacy and safety data is proposed, this is considered acceptable.

The MAH has provided an updated popPk analysis, starting with the popPK model used in the PIP. The dosing of Hepcludex in children is based on this analysis.

The MAH also provided a popPK/PD model analysis. The model is a simultaneous PopPK/PD model consisting of a PK model for BLV and a PD model for bile salts. The PK sub-model is a 1-compartment model with first-order absorption and parallel linear and non-linear clearance. The model was found to adequately predict adult PK and PD data, but it was unclear if the model could scale well to children with lower body weight than adults since the bile salt affected the elimination of BLV and the simulated Cmin in children appeared not plausible.

Discussion

In the PIP, the MAH had a weight based dosing. In the current application, the MAH initially proposed a flat dose of 2 mg once daily for all subjects above 3 year and older weighing at least 10 kg, which is the same dose as approved in adults. With questions regarding if the popPK/PD model scaled well to children as well as simulated higher exposure in children compared to adults with the 2 mg flat dose, the dosing was questioned and the company provided an updated popPK analysis similar to the model previously provided in the PIP but using the updated PK dataset. Based on the simulations with this model, the MAH proposed to update the dosing to weight based dosing:

· 1 mg once-daily for children weighing ≥ 10 kg to < 25 kg

· 1.5 mg once-daily for children weighing ≥ 25 kg to < 35 kg

· 2 mg once-daily for children weighing ≥ 35 kg

From the provided tables and box plots, the simulated exposure in children using 2 mg flat dose regardless of body weight show high exposure levels compared to adults, especially in the lower body weight children. For the new proposed dosing, the simulated exposure in children match the adult exposure well. However, the simulated steady state median and the 95th percentile exposure are slightly above the adult reference level for all metrics (Cmax, AUC, Cmin and Cavg). The MAH's argument that a slight over exposure compared to exposure level from 2 mg dose in adults could be acceptable in children, based on the 10 mg safety data in adults (not an approved dose but no new safety signals), was agreed by the CHMP. It was considered better to have a slight over exposure in children compared to slight under exposure to avoid a potential lack of efficacy.

2.3.7. Conclusions on clinical pharmacology

Extrapolation from adults to paediatric patients is considered appropriate. The proposed weight-based dosing, based on the latest provided popPK analysis is considered justified and is accepted.

2.4. Clinical efficacy

No new clinical efficacy data were submitted with this application.

A full extrapolation from adult efficacy data was proposed by the MAH and considered acceptable by the CHMP. The data supporting the extension of indication consists of a modelling and simulation study and an extrapolation study (see Clinical Pharmacology section above).

2.5. Clinical safety

No new clinical safety data were initially submitted with this application.

In response to the request for supplementary information the MAH has provided TEAEs occurring in ≥10% of participants and bile salt levels up to week 144 in the MYR301 study (see Table 6 below).

A full extrapolation from adult safety data was proposed by the MAH and considered acceptable by the CHMP.

Safety aspects

BLV is considered to be well tolerated in adults. Asymptomatic bile acid increase was observed at higher frequency in the 10 mg BLV group (27.7%) compared to the 2 mg BLV group (18.8%) in the pooled safety data set from the Phase 2 and Phase 3 studies (MYR203, MYR301) at week 48. Injection site reactions were also common, with 30.0% in the 10 mg BLV group and 16.3% in the 2 mg BLV group.

Other frequently occurring AEs in the Phase 2 and 3 studies included headache, pruritus, eosinophilia, nausea, fatigue, arthralgia. These AEs were in general observed at similar frequencies in the 2 mg and 10 mg treated groups. The current safety database in adults is overall considered small, which precludes certain conclusions regarding rare AEs.

Safety data up to 96 weeks from the Phase 3 study, MYR301, was presented at the European Association for the Study of the Liver (EASL) Congress 2023 (press release from the MAH dated June

23, 2023). According to the MAH the safety profile at Week 96 is consistent with what was observed at Week 48, with no resistance observed and no serious adverse events attributed to bulevirtide treatment. Increases in bile acids without a correlation to pruritus or other symptoms were noted with bulevirtide treatment. Injection site reactions occurred in a higher proportion of study participants receiving 10 mg of bulevirtide.

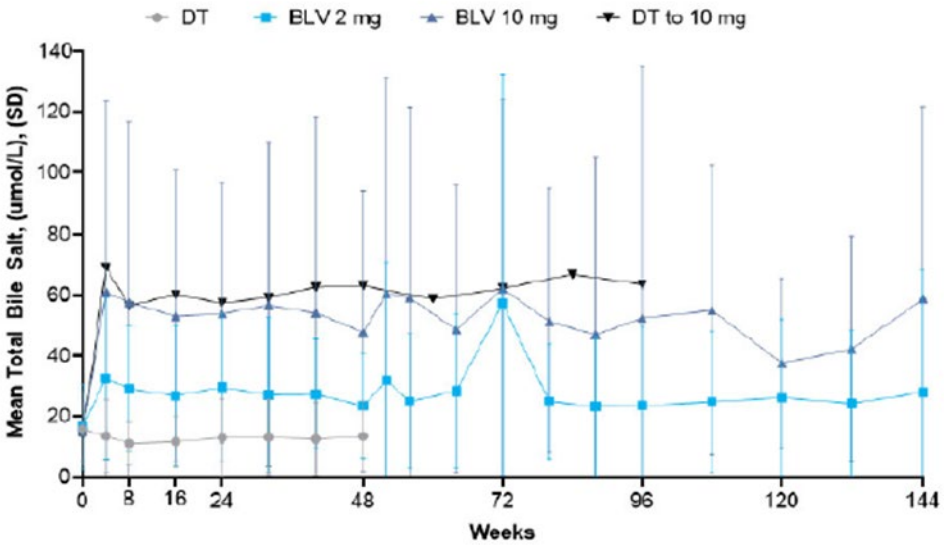
At week 144 frequencies of TEAEs were similar between the BLV 2 mg and BLV 10 mg treatment groups. Few participants had treatment-emergent serious adverse event (TE SAEs) and none of the TE SAEs were considered related to BLV. No participant discontinued BLV due to a TEAE and 1 death due to plasma cell myeloma was reported in the delayed treatment (DT) to BLV 10 mg group, which was not considered related to BLV.

Table 6: MYR301: Treatment-emergent Adverse Events Occurring in ≥10% of Participants of Any Treatment Group by PT

	Baseline to Week 48			Baseline to Week 144		Week 48 to Week 144
PT, n(%)	DT (N=51)	BLV 2 mg (N=49)	BLV 10 mg (N=50)	BLV 2 mg (N=49)	BLV 10 mg (N=50)	DT to BLV 10 mg (N=50)
Vitamin D deficiency	13 (25.5%)	7 (14.3%)	7 (14.0%)	22 (44.9%)	19 (38.0%)	14 (28.0%)
Headache	0	9 (18.4%)	10 (20.0%)	10 (20.4%)	12 (24.0%)	7 (14.0%)
Leukopenia	10 (19.6%)	7 (14.3%)	5 (10.0%)	10 (20.4%)	9 (18.0%)	7 (14.0%)
Thrombocytopenia	8 (15.7%)	5 (10.2%)	5 (10.2%)	10 (20.4%)	8 (16.0%)	7 (14.0%)
Lymphopenia	4 (7.8%)	4 (8.2%)	4 (8.0%)	8 (16.3%)	6 (12.0%)	6 (12.0%)
Neutropenia	3 (5.9%)	2 (4.1%)	5 (10.0%)	8 (16.3%)	10 (20.0%)	3 (6.0%)
Arthralgia	0	3 (6.1%)	4 (8.0%)	7 (14.3%)	8 (16.0%)	1 (2.0%)
Fatigue	1 (2.0%)	5 (10.2%)	7 (14.0%)	7 (14.3%)	9 (18.0%)	3 (6.0%)
Pruritus	0	6 (12.2%)	7 (14.0%)	6 (12.2%)	8 (16.0%)	0
ALT increased	4 (7.8%)	2 (4.1%)	3 (6.0%)	5 (10.2%)	4 (8.0%)	0
Anaemia	3 (5.9%)	3 (6.1%)	2 (4.0%)	5 (10.2%)	3 (6.0%)	3 (6.0%)
COVID-19	2 (3.9%)	1 (2.0%)	0	5 (10.2%)	8 (16.0%)	6 (12.0%)
Eosinophilia	0	5 (10.2%)	5 (10.0%)	5 (10.2%)	5 (10.0%)	1 (2.0%)
Nasopharyngitis	2 (3.9%)	4 (8.2%)	0	5 (10.2%)	2 (4.0%)	3 (6.0%)
Injection site erythema	0	2 (4.1%)	5 (10.0%)	3 (6.1%)	5 (10.0%)	2 (4.0%)
Injection site reaction	0	3 (6.1%)	5 (10.0%)	3 (6.1%)	6 (12.0%)	3 (6.0%)
Nausea	2 (3.9%)	3 (6.1%)	4 (8.0%)	3 (6.1%)	6 (12.0%)	1 (2.0%)
Abdominal pain upper	1 (2.0%)	0	5 (10.0%)	2 (4.1%)	5 (10.0%)	2 (4.0%)
Urinary tract infection	1 (2.0%)	1 (2.0%)	2 (4.0%)	2 (4.1%)	6 (12.0%)	3 (6.0%)

Bile salt elevations were dose-dependent and more pronounced with BLV 10 mg compared with BLV 2 mg (Figure 4). No accumulation of bile salts was seen over the treatment period.

According to the MAH an analysis was performed comparing bile salt levels with the presence or absence of clinical symptoms that could potentially be associated with higher bile salt levels (including pruritus, cardiac disorders, vitamin D deficiency, bone events, lipid metabolism disorders, hypersensitivity, and eosinophilia) and no association was found.



BLV = bulevirtide (GS-4438), Hepcludex®; DT = delayed treatment; ET = early termination; SD = standard deviation;
DT: baseline at randomization to prior to BLV first dose at Week 48 visit or to ET before the Week 48 visit of DT group.
DT to BLV 10 mg: first dose of BLV at the Week 48 visit to the Week 144 visit of DT group. The baseline was reset at the Week 48 visit (ie, rebaseline).
Baseline value was the last available value collected on or prior to first dose of BLV for the BLV 2 mg, BLV 10 mg, and DT to BLV 10 mg treatment groups, and the last available value collected prior to or at randomization for the DT group.

Figure 4: MYR301: Total Serum Bile Salt Levels Over Time (Safety Analysis Set)

2.5.1. Conclusion on clinical safety

There are no new safety issues identified that are associated with long-term bulevirtide treatment up to 144 weeks. The safety profile of bulevirtide remains consistent with the safety profile of bulevirtide 2 mg described in the Summary of Product Characteristics and is anticipated to be similar in the paediatric population.

2.5.2. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

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

Pharmacovigilance plan

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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
GS-US-589-6206 – A Registry Study of Treatment with Bulevirtide in Participants with Chronic Hepatitis D Infection Planned	Primary objective: • To evaluate the long-term effects of bulevirtide treatment on clinical progression of liver disease through the incidence of liver-related events in participants treated with bulevirtide Secondary objectives: • To evaluate the development of cirrhosis in participants treated with bulevirtide who were previously noncirrhotic • To evaluate the safety of participants treated with bulevirtide	Long term safety of bile acid elevation	Estimated study completion date (submission of clinical study report)	August 2027
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 Chronic Hepatitis Delta	Primary objectives: • 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 objectives: • To assess the safety of bulevirtide	Long term safety of bile acid elevation Hepatitis exacerbation after drug discontinuation	Estimated study completion date (submission of clinical study report)	Q2 2024

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Ongoing	Exploratory objectives: • To investigate the immunogenicity of bulevirtide • To investigate the influence of bulevirtide on quality of life • HBV/HDV genotyping • Resistance testing			
MYR301 – A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta Ongoing	Primary objectives: • The primary objective of this study is to evaluate the efficacy of bulevirtide administered subcutaneously for 48 weeks at a dose of 2 mg or 10 mg once daily for treatment of chronic hepatitis delta in comparison to delayed treatment. Secondary objectives: • To evaluate optimal treatment duration • To assess the safety of bulevirtide Exploratory objectives: • To investigate the immunogenicity of bulevirtide • To investigate the influence of bulevirtide on quality of life • HBV/HDV genotyping • Resistance testing	Long term safety of bile acid elevation Hepatitis exacerbation after drug discontinuation	Estimated study completion date (submission of clinical study report)	28 February 2025

Risk minimisation measures

Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
Hepatitis exacerbation after drug discontinuation	Routine risk minimization measures: SmPC section 4.4. where advice is given on monitoring of HBV DNA, HDV RNA, and transaminase levels after the cessation of bulevirtide. SmPC section 4.8 PL sections 2 and 3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: 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 Chronic Hepatitis Delta MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		Safety of Bulevirtide in Patients with Chronic Hepatitis Delta
Missing information		
Long term safety of bile acid elevation	Routine risk minimization measures: SmPC section 4.8 PL section 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: GS-US-589-6206 - A Registry Study of Treatment with Bulevirtide in Participants with Chronic Hepatitis D Infection MYR301 - A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta 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 Chronic Hepatitis Delta
Use in patients with moderate or severe renal impairment	Routine risk minimization measures: SmPC sections 4.8 and 5.2 SmPC section 4.2 and PL section 2, where advice is given on the monitoring of renal function. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with decompensated liver disease	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 5.2 PL section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 5.1,5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reason:

The changes are presented in a simple manner with lay terminology and do not affect the overall structure of the package leaflet. Therefore, they do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis, affecting at least 12 million people globally. Delta hepatitis is caused by the HDV, a defective RNA virus that requires the presence of the hepatitis B surface antigen (HBsAg) for its complete replication and transmission, and, as such, this form of hepatitis only occurs in individuals also infected with the hepatitis B virus (HBV). In the European Union (EU), HDV infection is considered an orphan disease, with an estimated prevalence of 130,000 patients. Most patients with chronic HDV infection show a more progressive and severe course of disease than chronic HBV infection, with development of cirrhosis within 2 years in 10% to 15% of patients.

Based on limited reports, chronic HDV infection is considered similar in adults and in paediatric patients both in disease characteristics, pathogenesis, and in response to treatment. Similar to adult patients, coinfection of HBV and HDV in paediatric patients can lead to high levels of alanine aminotransferase (ALT), rapid progression of fibrosis, and advanced liver disease.

The claimed extension of indication (bold):

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult ***and paediatric patients 3 years of age and older weighing at least 10 kg*** *with compensated liver disease.*

3.1.2. Available therapies and unmet medical need

There are no approved treatments for chronic HDV infection in paediatric patients, and off-label interferon-alpha (IFN-α) have been used to delay the rapid progression of disease. The response observed in paediatric patients with chronic HDV infection treated with IFN-α is similar to that observed in adults with chronic HDV infection, sustained virological response in 25%-30% of patients, with late relapse in > 50% patients. Bulevirtide (Hepcludex) is the only approved therapy specific for HDV in adult patients. As such, there remains an unmet need for treatment in the paediatric population with chronic HDV as there are currently no approved treatments.

3.1.3. Main clinical studies

The are no clinical studies in paediatric patients and there are no PK data in children. The extension of indication is based on a modelling and simulation study and an extrapolation study.

3.2. Favourable effects

The favourable effects of bulevirtide in terms of virological suppression and reduced transaminitis are known from the adult pivotal trial. In this paediatric application, the efficacy is established by extrapolation of efficacy and safety from adults based on similar plasma exposure. There are no clinical efficacy, safety or PK data in paediatric patients.

With similar exposure as in adults, bulevirtide is expected to be effective in the treatment of hepatitis D in paediatric patients from 3 years of age and weighing at least 10 kg.

Based on the simulations with the latest provided popPK model, the dosing was updated to weight-based dosing:

· 1 mg once-daily for children weighing ≥ 10 kg to < 25 kg

· 1.5 mg once-daily for children weighing ≥ 25 kg to < 35 kg

· 2 mg once-daily for children weighing ≥ 35 kg

The simulated exposure in children match the adult exposure well.

3.3. Uncertainties and limitations about favourable effects

No clinical data are available in children. The proposed dosing is based on simulations. The simulated exposure in children match the adult exposure well. However, the simulated steady state median and the 95th percentile exposure are slightly above the adult reference level for all metrics (Cmax, AUC, Cmin and Cavg). The MAH´s argument that a slight over exposure compared to exposure level from 2 mg dose in adults could be acceptable in children, based on the 10 mg safety data in adults, is agreed with. It is considered better to have a slight over exposure in children compared to slight under exposure to avoid a potential lack of efficacy.

3.4. Unfavourable effects

No clinical safety data in paediatric patients are available. Bulevirtide is in general considered to be well tolerated in adults. Asymptomatic bile acid increase was observed at higher frequency in the 10 mg bulevirtide group (27.7%) compared to the 2 mg bulevirtide group (18.8%) in the pooled safety data set from the Phase 2 and Phase 3 studies (MYR203, MYR301). Injection site reactions were also common, with 30.0% in the 10 mg bulevirtide group and 16.3% in the 2 mg bulevirtide group.

Other frequently occurring AEs in the Phase 2 and 3 studies included headache, pruritus, eosinophilia, nausea, fatigue, arthralgia. These AEs were in general observed at similar frequencies in the 2 mg and 10 mg treated groups.

The MAH has also provided TEAEs and presented bile salt levels up to week 144 in the MYR301 study. No new safety concerns were identified with long-term bulevirtide treatment.

3.5. Uncertainties and limitations about unfavourable effects

There does not seem to be an accumulation of bile salts over the treatment period of 144 weeks in the MYR301 study. Safety beyond 144 weeks is unknown and long term safety of bile acid elevation is listed as Missing Information in the Summary of Safety Concerns. The current safety database in adults is overall considered small, which precludes certain conclusions regarding rare AEs.

While the safety profile in adults for 2 mg and 10 mg doses are fairly similar, matching the exposure of the approved 2 mg dose in adults is considered the appropriate approach, especially considering the lack of data in children. A slightly higher exposure in paediatric patients is acceptable.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Hepatitis D is a rare disease and the incidence of hepatitis D in children has decreased with the implementation of hepatitis B vaccination programmes. Limited data indicates that the prevalence in children is expected to be very low. The only treatment option for these patients is off-label interferon-alpha to delay the rapid progression of disease with sustained virological response in 25%-30% of patients. As no specific treatment for hepatitis D is available for paediatric patients there is an unmet medical need.

Efficacy and safety have been established in adults. Based on similar plasma exposure of bulevirtide in paediatric patients, similar favourable outcomes are expected as in adults. The MAH has adequately justified the dosing in children aged 3 years of age and older and weighing at least 10 kg.

3.6.2. Balance of benefits and risks

The overall benefit-risk of Hepcludex for paediatric patients aged 3 years of age and older and weighing at least 10 kg is positive.

3.7. Conclusions

The overall benefit-risk of Hepcludex is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of chronic hepatitis delta virus (HDV) infection in paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease for Hepcludex, based on a modelling and simulation study and an extrapolation study to evaluate the use of bulevirtide for the treatment of chronic hepatitis D infection in children from 3 to less than 18 years of age. As a consequence, sections 4.1, 4.2, 5.1,5.2 and 6.6 of the SmPC are updated. The Package Leaflet has been updated accordingly. Version 4.1 of the RMP has also been adopted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

In addition, 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0270/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.