14 September 2023
EMA/435968/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Hepcludex

bulevirtide

Procedure no: EMEA/H/C/004854/P46/005

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	17 July 2023	17 July 2023
☐	CHMP Rapporteur Assessment Report	21 Aug 2023	16 Aug 2023
☐	CHMP members comments	4 Sept 2023	4 Sept 2023
☐	Updated CHMP Rapporteur Assessment Report	7 Sept 2023	n/a
☒	CHMP adoption of conclusions:	14 Sept 2023	14 Sept 2023

Table of contents

1. Introduction

On June 27, 2023 the MAH submitted a completed paediatric M&S study (*CTRA-2022-1070 BLV Peds PopPK and PK/PD Sim*) for Hepcludex, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that *study CTRA-2022-1070 BLV Peds PopPK and PK/PD Sim - 2022 Population Pharmacokinetic and Pharmacodynamic Analysis of Bulevirtide in Pediatric Patients Infected With Hepatitis* is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study<ies>

Powder for solution for injection

Simulations in paediatric patients was conducted using SC administration (same formulation as in adults).

2.3. Clinical aspects

2.3.1. Introduction

Bulevirtide (Hepcludex®) was conditionally approved in adults by the European Medicines Agency (EMA) in 2020. A conversion of the conditional marketing authorization to a full marketing authorization was granted on 18-JUL-2023 (EMEA/H/C/004854/II/0019).

In general, HDV is a highly pathogenic virus causing acute and chronic liver disease. 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).

The initial agreed paediatric investigation plan (PIP), submitted by MYR, included 3 agreed measures, including a clinical study, a modeling 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.

This submission consists of the provision of the M&S/extrapolation study report for BLV for the pediatric population (3 to less than 18 years of age).

The MAH submitted the final report for:

• ***CTRA-2022-1070 BLV Peds PopPK and PK/PD Sim - Population Pharmacokinetic and Pharmacodynamic Analysis of Bulevirtide in Pediatric Patients Infected With Hepatitis D***

2.3.2. Clinical M&S study

CTRA-2022-1070 BLV Peds PopPK and PK/PD Sim - Population Pharmacokinetic and Pharmacodynamic Analysis of Bulevirtide in Pediatric Patients Infected With Hepatitis D

Overview of the provided M&S study for this P46 procedure is depicted in table 1.

Table 1. Overview of Key Studies Included in Submission

Type of Study	Description of Study	CSR Cross-reference	m2 Cross-reference
Modelling and Simulation/Extrapolation Study			
Population Pharmacokinetic and Pharmacodynamic Analysis of Bulevirtide in Pediatric Patients Infected with Hepatitis D.	PopPK and PK/PD model that characterizes adult patient data to extrapolate PK and bile acid levels (mechanistic marker of action) to the pediatric population. This PopPK and PK/PD extrapolation study evaluates pediatric dosing options that result in exposures and bile acid levels within the therapeutic window for adults.	5.3.5.3 Population PK Study reports and related information	Module 5, Section 5.3.5.3

PopPK = population PK; PK = pharmacokinetic; PD = pharmacodynamic

Methods

An empirical PopPK model was initially developed to characterize BLV PK in adults following intravenous (IV) and SC administration using data from 6 studies.

The adult PopPK model was updated in order to extrapolate to the paediatric population. Additionally, the PopPK dataset was simplified to facilitate extrapolation of the model to the paediatric population.

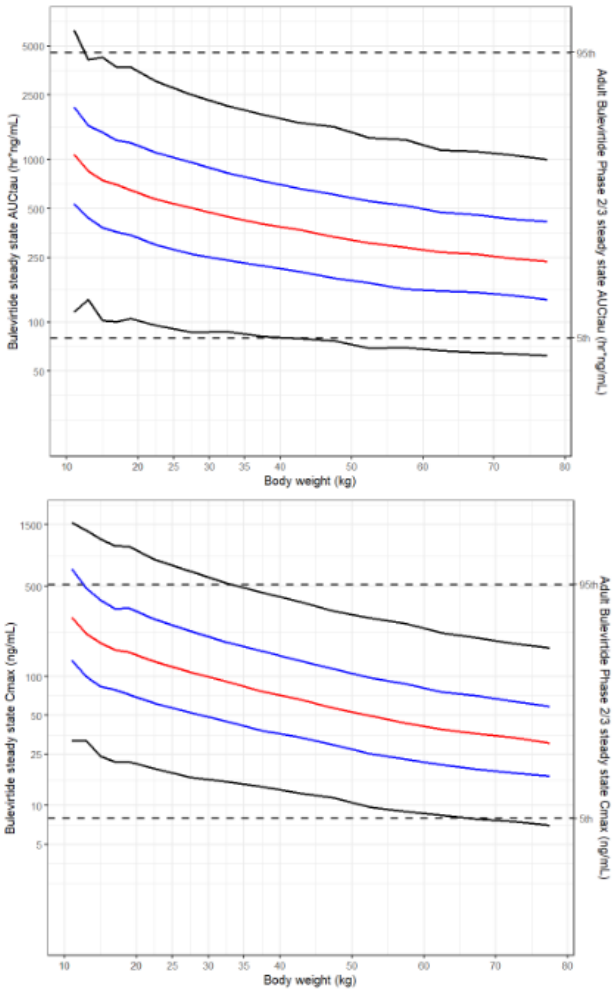
The updated model incorporates a one-compartment model with a parallel nonlinear and linear clearance, time-varying apparent volume, fixed allometric scaling on clearance and volume based on baseline body weight (BWT), body mass index (BMI) dependence on absorption rate, and an effect of the population (patient versus healthy) on bioavailability, absorption, and volume. Nonlinear clearance,

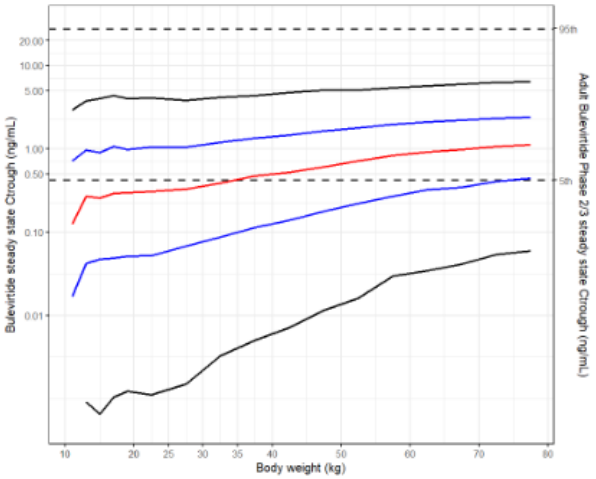
likely attributed to saturation of NTCP receptors with increasing BLV exposures, was characterized with a Michaelis-Menten model.

Results

The updated adult PopPK and PK/PD models were used to estimate the steady-state exposures and corresponding bile acid levels in paediatric patients infected with HDV.

Figure 8. **Simulated Pediatric Steady-state AUC_{tau}, C_{max}, and C_{trough} Versus Body Weight Following 2 mg BLV QD SC, based on Updated BLV Population PK Model**





BLV = bulevirtide (GS-4438), formerly known as Myrcludex B; max = maximum; min = minimum; PK = pharmacokinetic(s); PopPK = population pharmacokinetic; QD = once daily; SC = subcutaneous
Solid lines represent the 5th (black), 25th (blue), 50th (red), 75th (blue), and 95th (black) percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; Adult exposures are the PopPK predicted exposures from the current analysis based on updated BLV population PK model. 5th (based on 2-mg dose) and 95th (based on 10-mg dose) percentiles are shown. From top to bottom, panels show, respectively, AUC_{tau}, C_{max}, and C_{trough}.
Source: blv-sim-pediatric-pk-monolix-v12-20221129-plots.R; blv-sim-pediatric-pkpd-run28-20221129-2mg-plots.R

The extrapolated paediatric PK and bile acid results suggest that BLV 2 mg SC is the optimal or appropriate dose for paediatric patients aged ≥ 3 to < 18 years and weighing ≥ 9 kg, as it ensures that BLV AUCtau and bile acid levels are comparable with safe and efficacious levels established in adult patients.

2.3.3. Discussion on clinical aspects

The applicant has submitted the final popPK report for paediatric patients 3-17 years old and propose that 2 mg SC dose appropriate for patients ≥ 3 to < 18 years and weighing ≥ 9 kg.

The applicant is planning to submit an application for BLV 2 mg SC for the treatment of chronic HDV infection in paediatric patients aged ≥ 3 to < 18 years of age. This is endorsed.

The applicant will have to discuss and justify that the high exposure (figure 8) for the lowest body weight patients is safe in a future application. In addition, the simulated Ctrough levels are lower than in adults and this also needs to be justified with regards to efficacy in the future application.

3. Rapporteur's overall conclusion and recommendation

The company is planning to submit an application for BLV 2 mg SC for the treatment of chronic HDV infection in paediatric patients aged ≥ 3 to < 18 years of age. This is endorsed.

The B/R in children ≥ 3 to < 18 years of age will be assessed in the future application.

☒ **Fulfilled:**