Paediatric Pharmacokinetic-Pharmacodynamic Extrapolation to Identify Suitable Bulevirtide Doses for Children and Adolescents With Chronic Hepatitis Delta

WED-311

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Conclusions

- Simulated age-based and body weight–based bulevirtide (BLV) dosing in children and adolescents predicted exposures similar to those in adults with chronic hepatitis delta (CHD) who received the BLV 2 mg once-daily (QD) dose, which is established as safe and efficacious in adults
- BLV exposures comparable to those observed with up to BLV 10 mg QD in adults with CHD may be achieved in children and adolescents with a 2 mg QD flat dose
- Based on the results herein, BLV was recently approved in the European Union (EU) to treat paediatric patients with CHD infection and compensated liver disease

Plain Language Summary

- In this study, researchers developed a model to predict which doses of bulevirtide may be effective and safe in children and adolescents with chronic hepatitis delta
- The doses identified in the simulated population of children and adolescents support the use of bulevirtide treatment in this population

References: **1.** Hepcludex. Summary of product characteristics. European Medicines Agency. Gilead Sciences, Inc.; 2024. **2.** European Association for the Study of the Liver. *J Hepatol*. 2023;79:433-60. **3.** Hepcludex (bulevirtide acetate). Australian Register of Therapeutic Goods. Gilead Sciences, Inc.; 2024. **4.** Wedemeyer H, et al. *N Engl J Med*. 2023;389(1):22-32. **5.** Lampertico P, et al. Poster presented at: EASL 2024. Poster LBP-029. **6.** Xue MM, et al. *J Pediatr Gastroenterol Nutr*. 2015;61(3):271-81. **7.** Stockdale A, et al. *J Hepatol*. 2020;73:523-32.

Acknowledgements: Editorial support was provided by Molly Yeager, PhD, of Red Nucleus, and funded by Gilead Sciences, Inc. This study was funded by Gilead Sciences, Inc. Pharmetheus AB was funded by Gilead Sciences, Inc., to perform pharmacometric analyses for bulevirtide.

Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Introduction

- BLV 2 mg QD is approved in the EU and in non-EU countries for treatment of CHD in adults with compensated liver disease[1-3]
- Ongoing investigations are evaluating the efficacy and safety of BLV 10 mg QD in adults[4,5]
- The low prevalence of CHD in children hinders the potential for clinical trials in this population,[6,7] which limits the development of treatments for this population

Objective

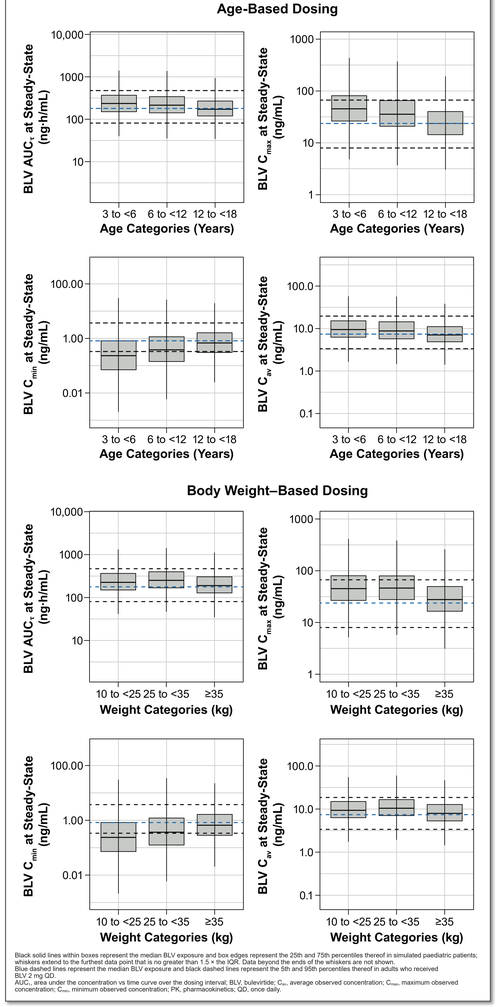
- To apply paediatric pharmacokinetic (PK)-pharmacodynamic (PD) extrapolation and exposure matching to identify BLV doses that would achieve similar exposure levels in children and adolescents as those seen in adults treated with BLV 2 or 10 mg QD

Methods

- In the paediatric population PK-PD model of BLV, the dosing regimens investigated were as follows:
  - Age-based dosing: 3 to 6 years of age (y), 1 mg QD; 6 to 12 y, 1.5 mg QD; 12 to 18 y, 2 mg QD
  - Body weight–based dosing: 10 to 25 kg, 1 mg QD; 25 to 35 kg, 1.5 mg QD; ≥35 kg, 2 mg QD
  - Flat subcutaneous (SC) dosing: 1 mg QD, 1.5 mg QD, 2 mg QD
- Simulated PK profiles and steady-state exposures were compared with exposures in adults who received SC BLV 2 or 10 mg QD in Phase 2 and 3 studies (MYR202, MYR203, MYR204, and MYR301)
- A BLV trough concentration at 50% of the maximum effect ($EC_{50,CTR}$) in adults with CHD treated with BLV was previously estimated via a longitudinal hepatitis delta virus viral load model (see Poster WED-310 for more details)
- In this study, the adult BLV $EC_{50,CTR}$ was compared with the simulated paediatric exposures

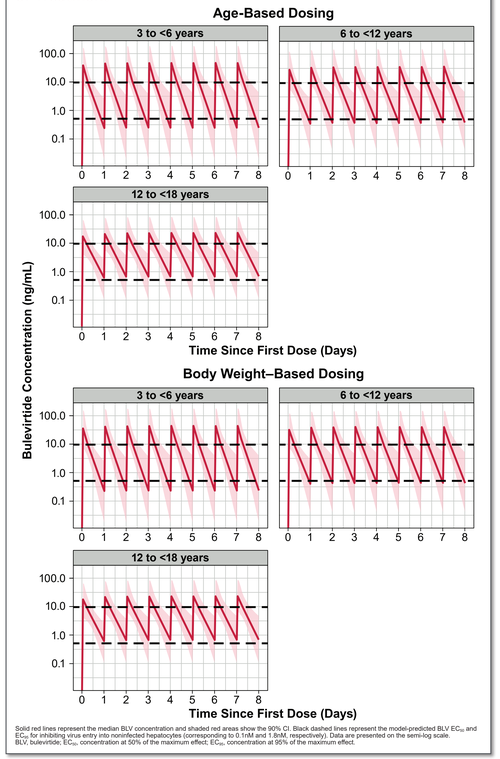
Results

Simulated Paediatric Steady-State BLV PK Parameters



Black solid lines within boxes represent the median BLV exposure and box edges represent the 25th and 75th percentiles thereof in simulated paediatric patients; whiskers extend to the furthest data point that is no greater than 1.5 × the IQR. Data beyond the ends of the whiskers are not shown.
Blue dashed lines represent the median BLV exposure and black dashed lines represent the 5th and 95th percentiles thereof in adults who received BLV 2 mg QD.
AUC$_{τ}$, area under the concentration vs time curve over the dosing interval; BLV, bulevirtide; C$_{av}$, average observed concentration; C$_{max}$, maximum observed concentration; C$_{min}$, minimum observed concentration; PK, pharmacokinetics; QD, once daily.

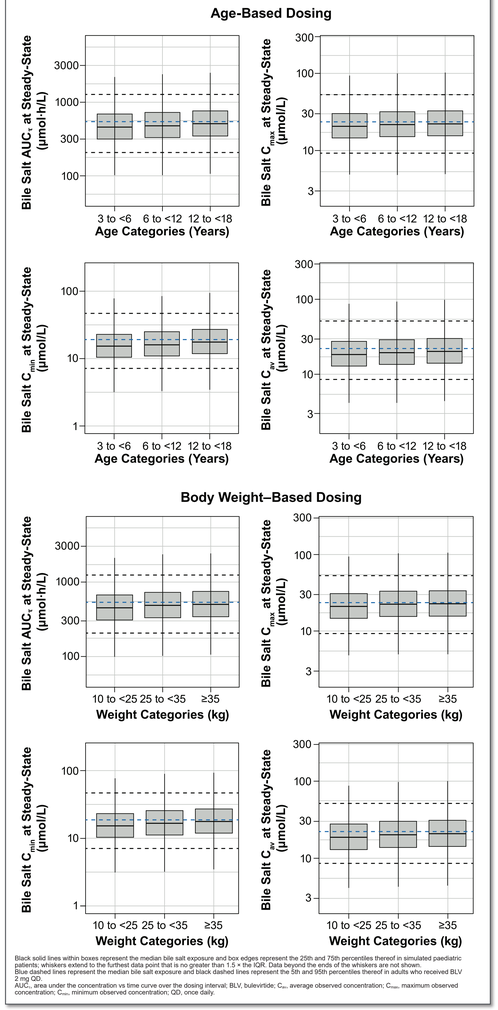
Simulated Paediatric BLV Concentrations Over the First 8 Days of Treatment



Solid red lines represent the median BLV concentration and shaded red areas show the 90% CI. Black dashed lines represent the model-predicted BLV EC_{50} and EC_{50} for inhibiting virus entry into noninfected hepatocytes (corresponding to 0.1nM and 1.8nM, respectively). Data are presented on the semi-log scale.
BLV, bulevirtide; EC_{50}, concentration at 50% of the maximum effect; EC_{90}, concentration at 95% of the maximum effect.

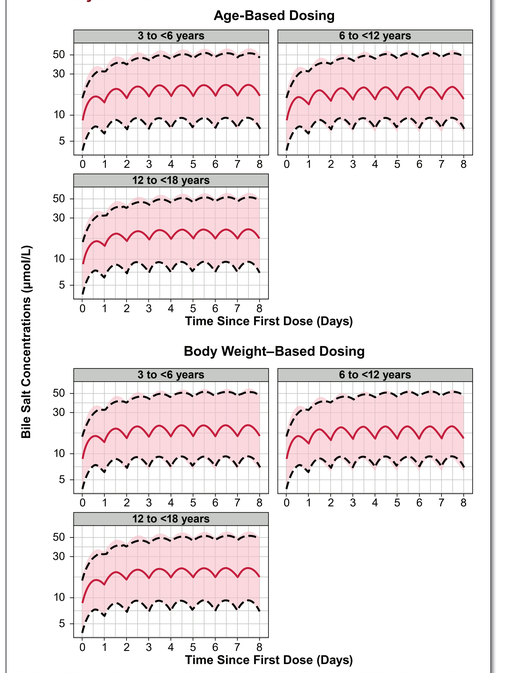
- The simulated age-based and body weight–based dosing approaches produced similar BLV exposures across all paediatric age ranges
- Flat dosing resulted in the following:
  - For the 12 to 18 y range, flat 1 mg dosing yielded IQRs of BLV exposure that extended below the 5th percentile of that in adults who received BLV 2 mg QD (data not shown)
  - For the 3 to 6 y and 6 to 12 y ranges, flat 1.5 mg and 2 mg doses generally yielded IQRs of BLV exposures exceeding the 95th percentile of exposure in adults who received BLV 2 mg QD, but the IQRs of exposures were generally contained within the 5th to 95th percentiles for adults who received BLV 10 mg QD (data not shown)
- For all paediatric age-based or weight-based BLV doses, IQRs of BLV exposure were generally within the 5th to 95th percentiles for adults who received BLV 2 mg QD, except for the median C$_{min}$ for younger age and lower weight categories that were below the 5th percentile for adults
- With all dosing strategies, the simulated median paediatric concentration at the end of the dosing interval (C_{trough}) in each age group exceeded the adult BLV $EC_{50,CTR}$ in >70% of patients (data not shown)

Simulated Paediatric Steady-State Parameters of Bile Salts



Black solid lines within boxes represent the median bile salt exposure and box edges represent the 25th and 75th percentiles thereof in simulated paediatric patients; whiskers extend to the furthest data point that is no greater than 1.5 × the IQR. Data beyond the ends of the whiskers are not shown.
Blue dashed lines represent the median bile salt exposure and black dashed lines represent the 5th and 95th percentiles thereof in adults who received BLV 2 mg QD.
AUC$_{τ}$, area under the concentration vs time curve over the dosing interval; BLV, bulevirtide; C$_{av}$, average observed concentration; C$_{max}$, maximum observed concentration; C$_{min}$, minimum observed concentration; QD, once daily.

Simulated Paediatric Concentrations of Bile Salts Over the First 8 Days of Treatment



Solid red lines represent the median bile salt concentration and shaded red areas show the 90% CI. Black dashed lines represent the model-predicted 5th and 95th percentiles of the simulated bile salt concentration of adults who received BLV 2 mg QD. Data are presented on the semi-log scale.
BLV, bulevirtide; QD, once daily.

- For all paediatric age-based or weight-based BLV doses, IQRs of bile salt exposure were within the 5th to 95th percentiles for adults who received BLV 2 mg QD and did not exceed the median bile salt exposure in adults who received BLV 10 mg QD (data from BLV 10 mg dosing is not shown)

European Medicines Agency–Approved BLV Dosing for Paediatric Patients[a]

Body Weight (kg)	Dosing of Reconstituted BLV 2 mg Powder for Solution for Injection	BLV Daily Dose
10 kg to <25 kg	0.5 mL	1 mg
25 kg to <35 kg	0.75 mL	1.5 mg
≥35 kg	1 mL	2 mg

[a]Adapted from the Hepcludex summary of product characteristics. Gilead Sciences, Inc.; 2024.[1]
BLV, bulevirtide.

- The results herein supported the European Medicines Agency's approval of BLV for paediatric patients with compensated liver disease who are aged ≥3 years and weigh ≥10 kg[1]
- These results support the use of BLV 2 mg QD flat dosing for children and adolescents with CHD

European Association for the Study of the Liver; 7–10 May 2025; Amsterdam, the Netherlands