A Mathematical Viral Load Model Characterises the Exposure-Response Relationship Between Bulevirtide and Hepatitis Delta Virus and Identifies the Minimum Duration of On-Treatment Viral Load Monitoring Required for Accurate Prediction of Long-Term Virologic Response

Parag Kumar[1,a], Anna M Mc Laughlin[2,a], Nieves Velez de Mendizabal[1], Luzelena Caro[1], David Damoiseaux[2], Amos Lichtman[1], Dmitry Manuilov[1], Renee-Claude Mercier[1], Liyun Ni[1], Yang Liu[1], Hongmei Mo[1], Ana Ruiz-Garcia[1]

[a]Authors contributed equally

[1]Gilead Sciences, Inc., Foster City, CA, USA; [2]Pharmetheus AB, Uppsala, Sweden

WED-310

Conclusions

- A pharmacokinetic (PK)-pharmacodynamic (PD) model adequately characterised hepatitis delta virus (HDV) viral load in patients with chronic hepatitis delta (CHD) who received bulevirtide (BLV) 2 mg once daily (QD), 5 mg QD, 5 mg twice daily, or 10 mg QD with and without pegylated interferon alfa-2a (PegIFNα) coadministration
- A significant exposure-response relationship was identified between the BLV trough concentration (C_{trough}) and the HDV infectivity rate (β)
  - — Simulations of concentration-time profiles predicted C_{trough} above the estimated C_{trough} at 95% of the maximum effect ($EC_{95,CTR}$) for <50% of patients treated with BLV 2 mg QD vs >90% of patients treated with BLV 10 mg QD
- The PK-PD model also identified a positive influence of PegIFNα coadministration on the elimination of HDV-infected cells, which indicated a synergistic effect between BLV and PegIFNα
- These findings support further investigation of BLV 10 mg QD therapy with and without PegIFNα
- Lastly, the results suggest that HDV viral load monitoring through at least 32 or 40 weeks of treatment is required to accurately predict virologic response at week 96 or week 144

Plain Language Summary

- Researchers developed a model to estimate the amount of hepatitis delta virus within blood samples from patients who received bulevirtide with or without pegylated interferon alfa treatment for chronic hepatitis delta
- The model results predicted less hepatitis delta virus within the blood of patients who received bulevirtide treatment with pegylated interferon alfa than in patients who received bulevirtide only
- Also, the model may help to identify patients who are likely to have controlled virus levels if they continue bulevirtide treatment beyond 32 to 40 weeks

References: **1.** Bogomolov P, et al. *J Hepatol*. 2016;65:490-98. **2.** Hepcludex. Summary of product characteristics. European Medicines Agency. Gilead Sciences, Inc.; 2023. **3.** Wedemeyer H, et al. *N Engl J Med*. 2023;389(1):22-32. **4.** Hepcludex (bulevirtide acetate). Australian Register of Therapeutic Goods. Gilead Sciences, Inc.; 2024. **5.** Lampertico P, et al. Poster presented at: EASL 2024. Poster LBP-029. **6.** Lampertico P, et al. *Liver Int*. 2025;45(2):e70008. **7.** Asselah T, et al. *N Engl J Med*. 2024;391:133-43.

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 is a potent, highly selective inhibitor of HDV entry into hepatocytes[1]
- BLV 2 mg is approved in the European Union (EU) and in non-EU countries as a subcutaneous QD injection for treatment of CHD in patients with compensated liver disease[2-4]
- Ongoing investigations are also evaluating the efficacy and safety of BLV 10 mg QD monotherapy and combined treatment with PegIFNα[3,5-7]
- Previously, a PK-PD model was developed to characterise the plasma BLV concentrations and bile salt levels in patients with CHD
- A similar predictive model is needed to characterise the PK-PD relationship between plasma BLV concentrations and HDV viral load among patients with CHD who receive BLV with or without PegIFNα

Objectives

- To develop a mathematical model to characterise the relationship between BLV exposure and HDV viral load in samples from patients who received BLV with or without PegIFNα during clinical trials
- To explore the potential impact of patient characteristics and PegIFNα co-treatment on the PK-PD relationship
- To explore the minimum duration of on-treatment viral load monitoring needed to accurately predict patient virologic response with long-term BLV treatment

Methods

- Data were included from 464 patients across 4 clinical studies (MYR202, MYR203, MYR204, and MYR301 [interim])
- Patients received subcutaneous injections of BLV 2, 5, or 10 mg QD, or 5 mg twice daily; 35% of the patients received PegIFNα co-treatment
- HDV viral load (HDV RNA) from blood samples was assessed at baseline, week 2, week 4, and every 4 to 12 weeks thereafter up to week 96 or week 144
- A mathematical model of hepatitis C infection was adapted to characterise the HDV viral load data
- A prior PK-PD model was used to derive individual BLV C_{trough} values, which were paired with HDV viral load observations in patients with CHD who received BLV with or without PegIFNα
- The population modelling analyses of the HDV viral load data were performed using nonlinear mixed-effects modelling
- A saturable inhibitory effect of BLV C_{trough} on β and a stimulatory categorical effect for PegIFNα on the elimination rate constant of infected cells were implemented

Covariate-Parameter Relationships Evaluated in the HDV Viral Load Model

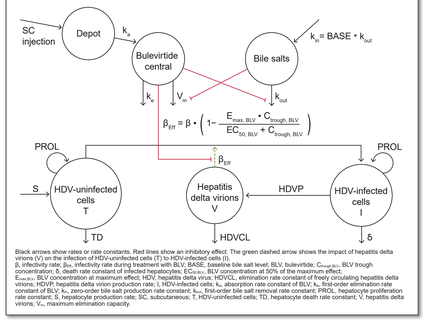
Structural Covariates[a]	
HBsAg	
Parameter	TR_0, HDVP
PegIFNα co-treatment[b]	
Parameter	HDVP, δ
Exploratory Covariates[a]	
WT, age, HBV viral load, total bilirubin, ALT, sex, cirrhosis, race, HBV genotype	
Parameter	TR_0, HDVP, δ
ADA status[b]	
Parameter	β[c]

[a]Structural and exploratory covariates were only considered for parameters associated with IIV. [b]Time-varying covariate. [c]No structural covariates were tested on β.
ADA, antidrug antibody; ALT, alanine aminotransferase; β, infectivity rate; δ, death rate constant of infected hepatocytes; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; HDVP, hepatitis delta virion production rate; IIV, interindividual variability; PegIFNα, pegylated interferon alfa-2a; TR_0, basic reproduction number; WT, wild type.

- Potential covariate-parameter relationships were evaluated using stepwise covariate modelling with adaptive scope reduction
- The impact of covariates on the predicted time to unquantifiable HDV viral load was illustrated using forest plots
- To assess on-treatment response at a given time, virologic response was defined as follows:
  - — **Virologic responder:** unquantifiable HDV RNA (less than the lower limit of quantitation [LLOQ; <50 IU/mL]) or ≥2 $\log_{10}$ IU/mL decline from baseline
  - — **Partial responder:** ≥1 $\log_{10}$ IU/mL but <2 $\log_{10}$ IU/mL HDV RNA decline from baseline
  - — **Nonresponder:** <1 $\log_{10}$ IU/mL HDV RNA decline from baseline
- The final model was refitted with HDV viral load data from the end of treatment (ie, 96 or 144 weeks) and earlier iteratively removed to explore the accuracy of predicted patient virologic responses at the end of treatment with reduced duration of HDV viral load monitoring data

Results

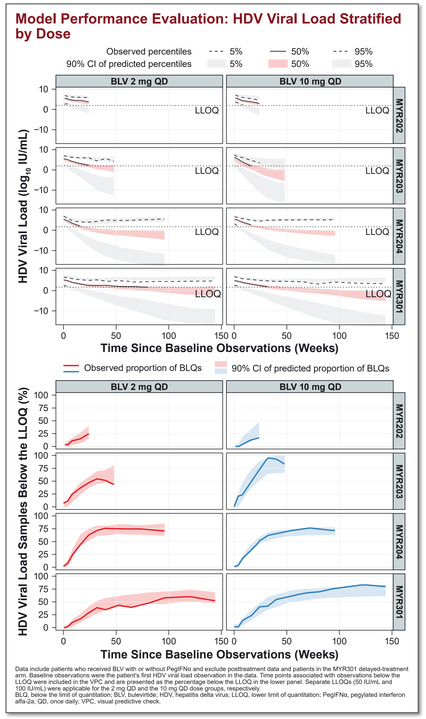
Final HDV Viral Load Model



Black arrows show rates or rate constants. Red lines show an inhibitory effect. The green dashed arrow shows the impact of hepatitis delta virions (V) on the infection of HDV-uninfected cells (T) to HDV-infected cells (I).
β, infectivity rate; β_{ss}, infectivity rate during treatment with BLV; BASE, baseline bile salt level; BLV, bulevirtide; $C_{trough,BLV}$, BLV trough concentration; δ, death rate constant of infected hepatocytes; $EC_{50,BLV}$, BLV concentration at 50% of the maximum effect; $E_{max,BLV}$, BLV concentration at maximum effect; HDV, hepatitis delta virus; HDVCL, elimination rate constant of freely circulating hepatitis delta virions; HDVP, hepatitis delta virion production rate; I, HDV-infected cells; k_a, absorption rate constant of BLV; k_e, first-order elimination rate constant of BLV; k_{in}, zero-order bile salt production rate constant; k_{out}, first-order bile salt removal rate constant; PROL, hepatocyte proliferation rate constant; S, hepatocyte production rate; SC, subcutaneous; T, HDV-uninfected cells; TD, hepatocyte death rate constant; V, hepatitis delta virions; V_m, maximum elimination capacity.

- The final HDV viral load model was a population PK-PD model consisting of compartments for HDV-uninfected hepatocytes, HDV-infected hepatocytes, and hepatitis delta virions
- A BLV concentration at maximum effect ($E_{max,BLV}$) was implemented on β and was driven by the BLV C_{trough}, which was derived from the PK-PD model of BLV and bile salts
- Interindividual variability terms were implemented on the basic reproduction number, the hepatitis delta virion production rate (HDVP), and the death rate constant of infected hepatocytes

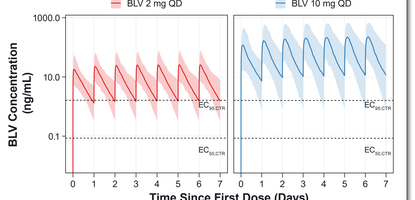
Model Performance Evaluation: HDV Viral Load Stratified by Dose



Data include patients who received BLV with or without PegIFNα and exclude posttreatment data and patients in the MYR301 delayed-treatment arm. Baseline observations were the patient's first HDV viral load observation in the data. Time points associated with observations below the LLOQ were included in the VPC and are presented as the percentage below the LLOQ in the lower panel. Separate LLOQs (50 IU/mL and 100 IU/mL) were applicable for the 2 mg QD and the 10 mg QD dose groups, respectively.
BLQ, below the limit of quantitation; BLV, bulevirtide; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; PegIFNα, pegylated interferon alfa-2a; QD, once daily; VPC, visual predictive check.

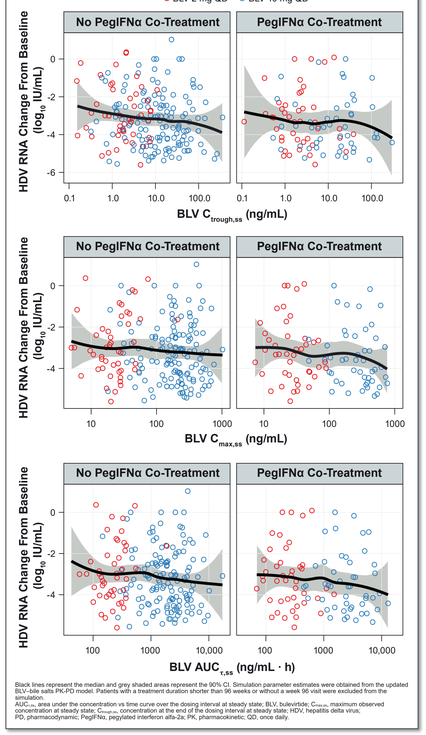
- The visual predictive check plots show acceptable predictive performance of the model for HDV viral load responses over time across all doses
- The E_{max} and BLV concentration at 50% of the maximum effect for the BLV $C_{trough,BLV}$ on β parameter estimates (relative standard error) were 61.2% (9.3%) and 0.0856 ng/mL (17.9%)

Simulations of BLV Concentrations for the First 7 Days of Treatment



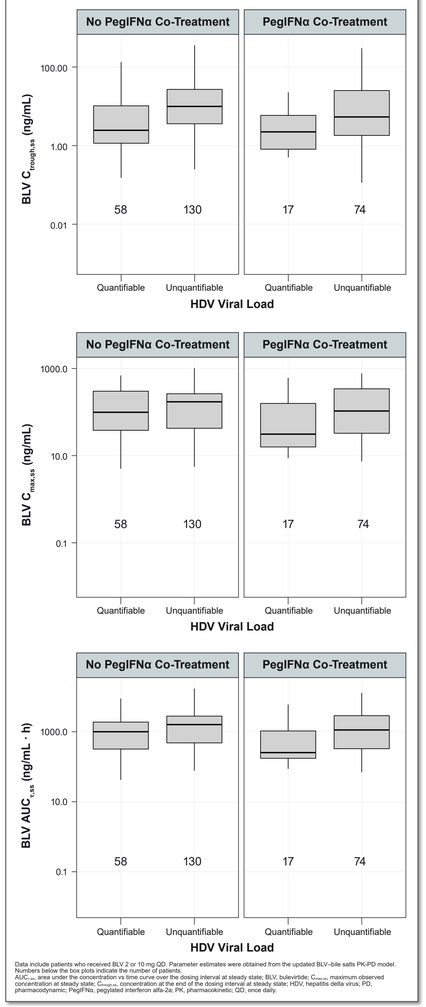
Data are presented on the semi-log scale. Simulations were performed using the updated BLV–bile salts PK-PD model. Solid lines represent the median and the shaded areas show the 90% prediction interval. The $EC_{95,CTR}$ value is based on the final parameter estimate for the $EC_{95,CTR}$ value for BLV on the infectivity rate in the final HDV viral load model.
BLV, bulevirtide; C_{trough}, BLV trough concentration; $EC_{50,CTR}$, C_{trough} at 50% of the maximum effect; $EC_{95,CTR}$, C_{trough} at 95% of the maximum effect; HDV, hepatitis delta virus; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily.

Simulations of BLV Concentration vs HDV Viral Load Change From Baseline to Week 96, Stratified by PegIFNα Co-Treatment



Black lines represent the median and grey shaded areas represent the 90% CI. Simulation parameter estimates were obtained from the updated BLV–bile salts PK-PD model. Patients with a treatment duration shorter than 96 weeks or without a week 96 visit were excluded from the simulation.
$AUC_{\tau,ss}$, area under the concentration vs time curve over the dosing interval at steady state; BLV, bulevirtide; $C_{max,ss}$, maximum observed concentration at steady state; $C_{trough,ss}$, concentration at the end of the dosing interval at steady state; HDV, hepatitis delta virus; PD, pharmacodynamic; PegIFNα, pegylated interferon alfa-2a; PK, pharmacokinetic; QD, once daily.

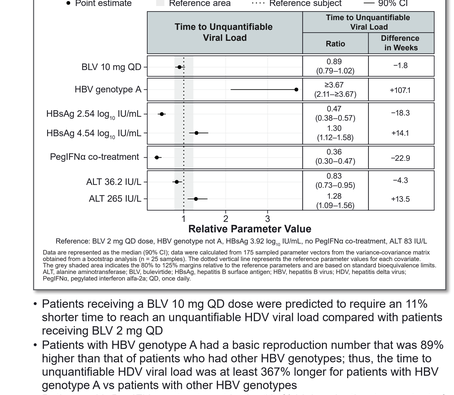
BLV Concentration Parameters for Patients With Quantifiable vs Unquantifiable HDV Viral Load at Week 96, Stratified by PegIFNα Co-Treatment



Data include patients who received BLV 2 or 10 mg QD. Parameter estimates were obtained from the updated BLV–bile salts PK-PD model. Numbers below the box plots indicate the number of patients.
$AUC_{\tau,ss}$, area under the concentration vs time curve over the dosing interval at steady state; BLV, bulevirtide; $C_{max,ss}$, maximum observed concentration at steady state; $C_{trough,ss}$, concentration at the end of the dosing interval at steady state; HDV, hepatitis delta virus; PD, pharmacodynamic; PegIFNα, pegylated interferon alfa-2a; PK, pharmacokinetic; QD, once daily.

- Most (>90%) patients who received BLV 10 mg QD dosing exceeded the $EC_{95,CTR}$, whereas only approximately half (48%) of the patients who received BLV 2 mg QD dosing exceeded the $EC_{95,CTR}$
- The observed reduction in HDV viral load from baseline to week 96 was more pronounced among patients with higher individually predicted BLV exposure, supporting the potential benefit of BLV 10 mg QD vs 2 mg QD dosing
- Similarly, the individually predicted BLV C_{trough} was higher in patients with an unquantifiable vs a quantifiable HDV viral load at week 96, regardless of their PegIFNα co-treatment status

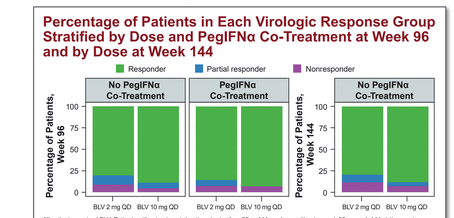
Covariate Effects on Treatment Time to Unquantifiable HDV Viral Load



Reference: BLV 2 mg QD dose, HBV genotype not A, HBsAg 3.92 $\log_{10}$ IU/mL, no PegIFNα co-treatment, ALT 83 IU/L
Data are represented as the median (90% CI); data were calculated from 175 sampled parameter vectors from the variance-covariance matrix obtained from a bootstrap analysis (n = 25 samples). The dotted vertical line represents the reference parameter values for each covariate. The grey shaded area indicates the 80% to 125% margins relative to the reference parameters and are based on standard bioequivalence limits.
ALT, alanine aminotransferase; BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa-2a; QD, once daily.

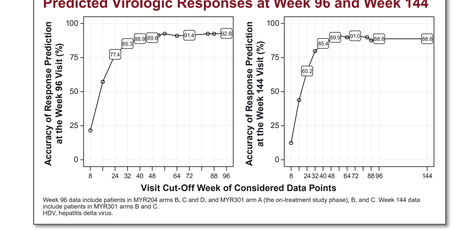
- Patients receiving a BLV 10 mg QD dose were predicted to require an 11% shorter time to reach an unquantifiable HDV viral load compared with patients receiving BLV 2 mg QD
- Patients with HBV genotype A had a basic reproduction number that was 89% higher than that of patients who had other HBV genotypes; thus, the time to unquantifiable HDV viral load was at least 367% longer for patients with HBV genotype A vs patients with other HBV genotypes
- Patients with PegIFNα co-treatment had a 105% higher death rate constant of infected hepatocytes and, consequently, a 64% shorter time to unquantifiable HDV viral load compared with patients without PegIFNα co-treatment
- Baseline HBsAg and ALT levels were positively associated with the hepatitis delta virion production rate
  - — Consequently, a patient with a HBsAg 2.54 $\log_{10}$ IU/mL (5th percentile in the analysis data set) required a 53% shorter time to unquantifiable HDV viral load compared with patients who had median HBsAg (3.92 $\log_{10}$ IU/mL)
  - — Similarly, a patient with an ALT level of 36.2 IU/L (5th percentile in the analysis data set) was predicted to require a 17% shorter time to unquantifiable viral load compared with patients who had median ALT levels (83 IU/L)
- No other covariates had a significant impact on model parameters

Percentage of Patients in Each Virologic Response Group Stratified by Dose and PegIFNα Co-Treatment at Week 96 and by Dose at Week 144



All patients received BLV. Patients with a treatment duration shorter than 96 or 144 weeks or without a week 96 or week 144 visit are not included in the respective figures. Week 96 data include patients in MYR204 arms B, C and D, and MYR301 arm A (the on-treatment study phase); B, and C. Week 144 data include patients in MYR301 arms B and C; patients in MYR301 did not receive PegIFNα co-treatment.
BLV, bulevirtide; PegIFNα, pegylated interferon alfa-2a; QD, once daily.

Modelling of HDV Viral Load Sampling Time and Predicted Virologic Responses at Week 96 and Week 144



Week 96 data include patients in MYR204 arms B, C and D, and MYR301 arm A (the on-treatment study phase), B, and C. Week 144 data include patients in MYR301 arms B and C.
HDV, hepatitis delta virus.

- By iterative modelling, HDV viral load sampling until at least week 32 or week 40 was necessary to achieve >85% accuracy in identifying virologic responder status (complete, partial, or no response) at week 96 or week 144, respectively