SAT417

Impact of Patient-Related Factors on the Pharmacokinetics of Bulevirtide

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Introduction

- Bulevirtide (BLV) is a novel, first-in-class, potent, highly selective, hepatocyte entry inhibitor of hepatitis delta virus (HDV) that binds to and inactivates sodium taurocholate cotransporting polypeptide (NTCP), an essential HDV entry receptor
- BLV is a 47-amino acid lipopeptide recommended for treatment of chronic HDV infection in plasma (or serum) HDV RNA-positive adult patients with compensated liver disease at 2 mg qd sc
- BLV demonstrates nonlinear pharmacokinetics (PK), with 11-fold higher exposure for 10 vs 2 mg qd sc. The elimination half-life of BLV is 3–7 h. Despite the short half-life, apparent plasma accumulation of ~2-fold is observed at steady state (based on area under curve [AUC] from time 0 to 24 h and maximal concentration [C_{max}]) with multiple vs a single qd sc dose; this observation is putatively due to target-mediated drug disposition (TMDD), whereby saturation of the target NTCP receptor occurs with the initial dose and more free drug is available in systemic circulation after subsequent doses

Objectives

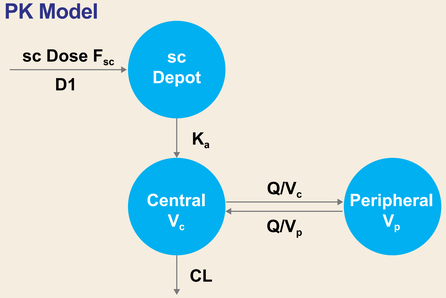
- To characterize the population (Pop)–PK of BLV in patients with or without HDV infection using data collected in 6 studies (MYR101, MYR102, MYR202, MYR203, MYR204, and MYR301)
- To evaluate the effects of demographic and physiologic covariates on BLV PK to better understand intrinsic and extrinsic factors that may affect BLV exposure in individual patients

Methods

- Comprehensive PK data from patients in two phase 1 studies (n=48), three phase 2 studies (n=314), and one phase 3 study (n=99) were analyzed using nonlinear mixed-effects modeling (NONMEM®, ICON plc, Dublin, Ireland) software
- Individual BLV PK parameter estimates were generated and the impact of patient-specific covariates (eg, baseline [BL] body weight [WT], body mass index [BMI], age, sex, race, BLV dose, health status, cirrhosis, route of administration, BL HDV viral load, creatinine clearance (CrCL), presence of antidrug antibodies, liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin], and comedications [oral antivirals and pegylated interferon-α (Peg-IFNα)]) were evaluated
- Covariates that demonstrated a statistically significant (p<0.01) effect were further examined using a forward addition (p<0.01) and backward elimination (p<0.001) methodology; statistically significant covariates were retained in the final Pop-PK model
- The percentage of samples below the limit of quantitation for BLV was 9.9%, with higher percentages at late time points for both iv and sc administration; therefore, the M3 method was used to handle samples below the limit of quantitation in the analysis[1]
- First-order conditional estimation with interaction was the primary method used for PK model parameter estimation
- Sensitivity analyses using all available data were performed to determine the impact of relevant covariates on the following exposure parameters of BLV: steady-state AUC over a dosing interval (AUC_{tau}), C_{max}, and plasma trough concentration (C_{tau})

Results

BLV Structural PK Model



CL, clearance; D1, duration of zero-order absorption; F_{sc}, sc bioavailability; K_a, absorption rate constant; Q, intercompartmental CL; V_c, volume of central compartment; V_p, volume of peripheral compartment.

- The final BLV model was described by a 2-compartment model, with sequential zero–first-order absorption and first-order elimination from the central compartment

Baseline Summary of Covariates Used in Pop-PK Analysis

Continuous Covariates*

Covariate	MYR101 n=18	MYR102 n=12	MYR202 n=90	MYR203 n=75	MYR204 n=149	MYR301 n=99	Total N=443
Age, y	25.5 (21.0–43.0)	32.5 (24.0–48.0)	39.0 (20.0–64.0)	37.0 (18.0–62.0)	40.0 (18.0–65.0)	41.0 (19.0–62.0)	39.0 (18.0–65.0)
WT, kg	70.0 (64.7–88.1)	79.5 (63.0–99.0)	73.1 (51.0–110)	73.5 (49.0–107)	75.0 (39.7–106)	74.9 (48.0–105)	74.2 (39.7–110)
Height, cm	180 (169–195)	181 (168–189)	173 (152–188)	174 (154–194)	173 (146–195)	171 (151–198)	174 (146–198)
BMI, kg/m^2	22.3 (19.9–26.0)	24.3 (21.3–29.0)	24.8 (17.9–34.6)	24.2 (17.0–34.5)	24.8 (16.6–37.0)	24.7 (17.6–35.9)	24.7 (16.6–37.0)
BSA, m^2	1.87 (1.74–2.14)	2.00 (1.71–2.28)	1.85 (1.53–2.36)	1.90 (1.52–2.33)	1.89 (1.27–2.35)	1.87 (1.42–2.32)	1.89 (1.27–2.36)
CrCL, mL/min	136 (109–172)	145 (106–185)	117 (64.6–211)	120 (74.9–176)	119 (50.4–196)	112 (70.7–201)	119 (50.4–211)
HDV RNA, IU/mL	NA	NA	315,000 (50–23,000,000)	1,740,000 (0–67,800,000)	372,000 (0–13,700,000)	155,000 (0–31,100,000)	369,000 (0–67,800,000)
AST–IU/mL	21.0 (12.0–32.0)	22.5 (13.0–28.0)	60.5 (26.0–321)	48.0 (24.0–766)	59.0 (25.0–377)	66.0 (24.0–216)	56.0 (12.0–766)
ALT, IU/mL	19.0 (13.0–43.0)	22.5 (10.0–33.0)	98.5 (32.0–450)	78.0 (27.0–1810)	82.0 (33.0–741)	101 (25.0–335)	81.0 (10.0–1810)

Categorical Covariates

Covariate	Category, n (%)	MYR101 n=18	MYR102 n=12	MYR202 n=90	MYR203 n=75	MYR204 n=149	MYR301 n=99	Total N=443
Sex at birth	Male	18 (100)	11 (92)	59 (66)	52 (69)	105 (70)	60 (61)	305 (69)
	Female	0	1 (8)	31 (34)	23 (31)	44 (30)	39 (39)	138 (31)
Race	White	16 (89)	11 (92)	78 (87)	74 (99)	130 (87)	84 (85)	393 (89)
	Black or African-American	0	0	1 (1)	0	7 (5)	1 (1)	9 (2)
	Asian	1 (6)	1 (8)	11 (12)	1 (1)	11 (7)	14 (14)	39 (9)
	Other	1 (6)	0	0	0	1 (1)	0	2 (<1)
Health status	Healthy	18 (100)	12 (100)	0	0	0	0	30 (7)
	HDV	0	0	90 (100)	75 (100)	149 (100)	99 (100)	413 (93)
Coadministration of Peg-IFNα	No	18 (100)	12 (100)	88 (98)	30 (40)	50 (34)	99 (100)	297 (67)
	Yes	0	0	2 (2)	45 (60)	99 (66)	0	146 (33)
Coadministration of tenofovir	No	18 (100)	0	0	59 (79)	81 (54)	54 (55)	212 (48)
	Yes	0	12 (100)	90 (100)	16 (21)	68 (46)	45 (45)	231 (52)
Cirrhosis	No	18 (100)	12 (100)	44 (49)	35 (47)	98 (66)	52 (53)	259 (58)
	Yes	0	0	46 (51)	10 (13)	51 (34)	47 (47)	154 (35)

*Data presented as median (range). BSA, body surface area; NA, not applicable.

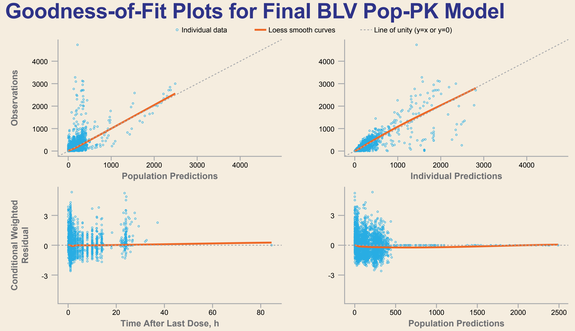
- The Pop-PK analysis dataset included 5122 samples from 461 patients, primarily men (69%) and White (89%), with median (range) age of 39 y (18–65) and WT of 74.2 kg (39.7–110)
- Most patients (93%) were infected with HDV

Summary of Final Model PK Parameters for BLV

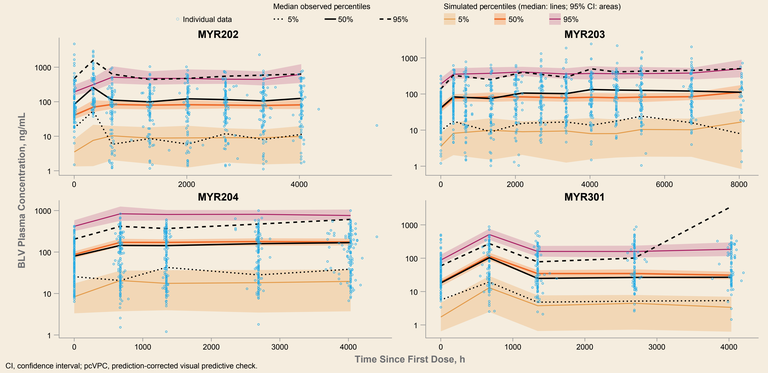
Parameter	Description		Population Estimate	Change From Typical, %	IIV, %
θ_1	V_c, L		4.1	—	88
$\theta_1 \times (\frac{WT}{74.4})^{\theta_7}$	Influence of WT on V_c	5th percentile of WT	2.97	-27.4	—
		95th percentile of WT	5.29	29	—
$\theta_1 \times (1+\theta_{12})$	V_c in females		3.39	-17.3	—
θ_2	BLV 2 mg CL, L/h		11.2	—	88
$\theta_2 \times (\frac{Dose}{2}\theta_{11})$	BLV 5 mg CL, L/h		7.19	-35.8	
$\theta_2 \times (\frac{Dose}{2}\theta_{11})$	BLV 10 mg CL, L/h		5.15	-54.1	
$\theta_2 \times (\frac{WT}{74.4})^{0.75}$	Influence of WT on CL	5th percentile of WT	8.81	-21.4	—
		95th percentile of WT	13.6	21.1	—
$\theta_2 \times (1+\theta_{13})$	CL in patients with cirrhosis		9.63	-14	—
θ_3	Q, L/h		0.000368	—	—
$\theta_3 \times (\frac{WT}{74.4})^{0.75}$	Influence of WT on Q	5th percentile of WT	0.00029	-21.4	—
		95th percentile of WT	0.000446	21.1	—
θ_4	V_p, L		0.194	—	—
$\theta_4 \times (\frac{WT}{74.4})^{\theta_7}$	Influence of WT on V_p	5th percentile of WT	0.141	-27.4	—
		95th percentile of WT	0.25	29	—
θ_5	sc transit K_a, 1/h		0.241 FIXED	—	54
θ_6	Duration of 0-order absorption, h		0.169 FIXED	—	124
$\exp(\theta_7)/(1+\exp(\theta_7))$	Day 1 absolute F_{sc} relative to Day 1 iv		53.4% FIXED	—	—
$\frac{\exp(\theta_7 \times (1+\theta_{10}))}{(1+\exp(\theta_7 \times (1+\theta_{10})))}$	Time-varying apparent F_{sc} relative to Day 1 iv		94.8% FIXED	—	—
θ_8	Proportional error		0.504	—	—
θ_9	Additive error		1.41	—	—

IIV, interindividual variability.

Standard Goodness-of-Fit Plots for Final BLV Pop-PK Model



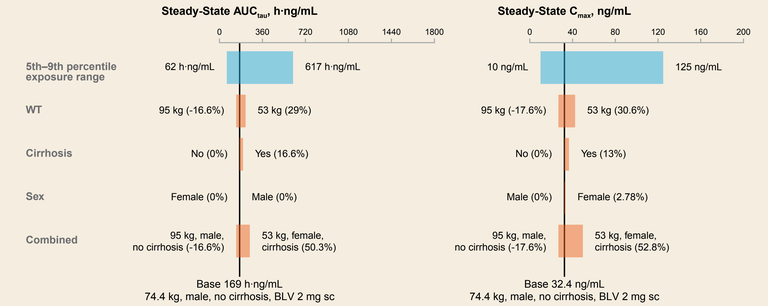
pcVPC of Final BLV Pop-PK Model vs Time Since First Dose Stratified by Study (only 1-h postdose samples)



CI, confidence interval; pcVPC, prediction-corrected visual predictive check.

- The model was able to describe the data adequately, as demonstrated by the diagnostic plots
- An absolute sc bioavailability of 53.4% was quantified on Day 1 compared with reference iv administration on the same day
- Given the available data, an empirical model that would approximate an underlying TMDD process, was selected; a dose effect on CL addressed the nonlinearity observed in PK; in addition, a stepwise, time-varying F_{sc} described the relative increase in exposure between first and subsequent sc administrations that resulted due to TMDD-based saturation of the target
- Interindividual variability was included on CL, V_p, K_a, and D1
- A combined additive and proportional error model was used to characterize residual variability
- Body weight effects were included on CL, Q, V_c, and V_p using fixed allometric exponents of 0.75 and 1 for CL and volume of distribution, respectively

Impact of Various Intrinsic and Extrinsic Factors on BLV AUC_{tau} and C_{max}*



*Observed exposures based only on BLV 2 mg qd sc; base refers to median post hoc BLV AUC_{tau} and C_{max}; *orange shading* represents influence of single or combined covariates on steady-state exposure; upper and lower values for each covariate capture 90% of plausible range in population; %s represent % changes of exposures from base; covariates sorted by descending influence.

- Body weight was the most influential covariate impacting BLV PK, with changes in BLV exposures ranging from -17.6% to +30.6% (relative to exposures at median WT) for patients with extreme covariate values (ie, 5th and 95th WT percentiles)
- The effects of cirrhosis and female sex were minimally influential covariates, with changes <20% for all exposure outcomes considered
- No additional covariates were found to statistically significantly affect BLV exposure

Conclusions

- Across a wide range of patients, BLV exposures were inversely correlated with WT, along with slightly higher exposures in women and patients with cirrhosis; however, these changes in BLV exposures were not considered clinically meaningful
- These data support the use of the recommended BLV 2-mg qd sc dosage across the spectrum of patients with varied patient-related factors

Reference: 1. Ahn JE, et al. J Pharmacokinet Pharmacodyn 2008;35:401-21. Acknowledgments: This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, New York, USA, funded by Gilead.

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