Title: A circular PK/PD/PK model explains the exposure of bulevirtide and bile salts in adult patients with chronic hepatitis D

Author: Nieves Velez de Mendizabal [*](1), Anna M. Mc Laughlin* (2) Parag Kumar (1)

*These authors contributed equally

Institution: (1) Gilead Sciences, (2) Pharmetheus AB

Characters: 4,459/4,500 (including spaces and in-text citations, excluding references)

Objectives: Chronic hepatitis D (CHD) is a rare inflammatory liver disease caused by hepatitis delta virus (HDV). It is the most severe form of hepatitis, with 10-15% of patients developing cirrhosis within 2 years [1]. Bulevirtide (BLV, Hepcludex®) is a novel virus protein-derived lipopeptide and the first EU-approved treatment option for adults with CHD infection with compensated liver disease. Its mechanism of action (MoA) involves binding to the sodium-taurocholate co-transporting polypeptide (NTCP) receptor, which is the point of entry of HDV into hepatocytes [2]. Through binding to NTCP, it also inhibits the uptake of bile salts into hepatocytes, which is NTCP's physiological function. Consequently, treatment with BLV results in significant but asymptomatic increases of bile salts in plasma [3].

In studies with intensive pharmacokinetic (iPK) sampling on day 1 and day 14, an increase (~2-fold) of BLV concentrations after multiple once-daily dosing was observed. This increase was unexpected given BLV's short half-life (3-7 h) after a single dose. Considering that BLV and bile salts bind to the same target, we aimed to investigate a potential interaction between BLV and bile salts, resulting in increased BLV concentrations following repeat dosing.

Methods: Data from 414 patients with CHD from four clinical studies (MYR202, MYR203, MYR204, and MYR301), were included in the analysis. Patients received subcutaneous injections of BLV 2, 5, and 10 mg once daily, or 5 mg twice daily, for up to 48 weeks. PK samples were collected 1h post-dose every 4 or 8 weeks. Studies MYR202 and MYR203 additionally performed iPK sampling on days 1 and 14. Total bile salts were measured in plasma in all studies at baseline and every 4 or 8 weeks thereafter.

A positive correlation was observed between the fold change in the BLV C_{max} from day 1 to day 14 and the fold change from baseline in bile salts after the first dose, suggesting an effect of bile salts on the BLV PK. Since the bile salt increases in plasma were in turn explained by BLV's MoA, a simultaneous circular PK/PD/PK model of BLV and bile salts was developed. The model consisted of a one-compartment model with first-order absorption and parallel linear (unspecific) and non-linear (NTCP-mediated) clearance (CL) for BLV, and an indirect response model for bile salts. Two inhibitory E_{max} models were implemented to characterize the circular interaction: (1) BLV inhibiting the k_{out} of the bile salts, and (2) bile salts inhibiting the V_{max} of BLV. Exploratory covariate testing was performed based on graphical exploration and IIV vs. covariate plots.

Results: The developed model allowed the characterization of the bi-directional interaction between BLV and bile salts. The estimate for the linear BLV CL was low (0.905 L/h), indicating the non-linear CL as the main route of elimination. Several significant covariate relationships were identified: baseline body weight (WT) had an effect on the BLV volume of distribution and CLs and was implemented using allometric scaling. In addition, a negative effect of baseline WT on k_a was identified. Baseline aspartate aminotransferase (AST) levels were positively correlated with baseline bile salt levels. The influence of antidrug antibodies on CL/F was additionally tested and found nonsignificant.

The bile salt baseline levels was 8.72 µmol/L and the E_{max} for the inhibition of the BLV V_{max} by bile salts was estimated as 85.3%, with an EC_{50} of 25.8 µmol/L. The E_{max} for the inhibition of the bile salt k_{out} by BLV was estimated as 88.1%, with an EC_{50} of 2.02 ng/mL (0.374 nmol/L). Consequently, the maximum inhibition of the bile salt k_{out} was reached at much lower concentrations than the maximum inhibition of the BLV V_{max}.

While other explanations are possible, the most likely hypothesis for the observed increase in BLV exposure following repeat dosing is competition between BLV and bile salts for binding to the NTCP receptor [4], [5] resulting in an inhibition of the bile salt transport at high BLV concentrations and an inhibition of the NTCP-mediated BLV CL at high bile salt concentrations.

Conclusion: A circular population PK/PD/PK model of BLV and bile salts successfully explained the increase in exposures of both BLV and bile salts after repeat dosing of BLV. The developed model can now be leveraged in drug-disease models to evaluate the impact of BLV plasma concentrations on disease-related biomarkers.

References:

[1] C. Yurdaydın, R. Idilman, H. Bozkaya, and A. M. Bozdayi, "Natural history and treatment of chronic delta hepatitis," *Journal of Viral Hepatitis*, vol. 17, no. 11, pp. 749–756, Nov. 2010, doi: 10.1111/j.1365-2893.2010.01353.x.

[2] Y. Ni *et al.*, "Hepatitis B and D Viruses Exploit Sodium Taurocholate Co-transporting Polypeptide for Species-Specific Entry into Hepatocytes," *Gastroenterology*, vol. 146, no. 4, pp. 1070-1083.e6, Apr. 2014, doi: 10.1053/j.gastro.2013.12.024.

[3] A. Blank *et al.*, "The NTCP-inhibitor Myrcludex B: Effects on Bile Acid Disposition and Tenofovir Pharmacokinetics," *Clinical Pharmacology and Therapeutics*, vol. 103, no. 2, pp. 341–348, Feb. 2018, doi: 10.1002/cpt.744.

[4] J. Asami *et al.*, "Structure of the bile acid transporter and HBV receptor NTCP," *Nature*, vol. 606, no. 7916, pp. 1021–1026, Jun. 2022, doi: 10.1038/s41586-022-04845-4.

[5] A. König, B. Döring, C. Mohr, A. Geipel, J. Geyer, and D. Glebe, "Kinetics of the bile acid transporter and hepatitis B virus receptor Na + /taurocholate cotransporting polypeptide (NTCP) in hepatocytes."