Sodium Taurocholate Cotransporting Polypeptide Intronic Polymorphism rs17556915 Had No Impact on Hepatitis Delta Virus RNA Levels and Bulevirtide Response in Patients Treated With Bulevirtide

FRI-290

Yang Liu[1], Gabriel Cuellar Partida[1], Simin Xu[1], Thomas Aeschbacher[1], Ross Martin[1], Savrina Manhas[1], Dmitry Manuilov[1], Renee-Claude Mercier[1], Amos Lichtman[1], Evguenia Maiorova[1], Hongmei Mo[1], Pietro Lampertico[2,3]

[1]Gilead Sciences, Inc., Foster City, CA, USA; [2]Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Conclusions

- Sodium taurocholate cotransporting polypeptide (NTCP) polymorphism rs17556915 distribution in the MYR301 and MYR204 studies was consistent with that previously described in the European population and did not lead to a different baseline hepatitis delta virus (HDV) RNA level compared with those without this polymorphism
- NTCP polymorphism rs17556915 had no impact on bulevirtide (BLV) treatment outcomes in patients receiving BLV 2 mg or 10 mg monotherapy or BLV + pegylated interferon alfa-2a (PegIFNα) combination therapy

Plain Language Summary

- Recent data suggest that alternate forms (variants) of sodium taurocholate cotransporting polypeptide (NTCP) may impact how patients with chronic hepatitis delta (CHD) respond to bulevirtide (BLV) 2 mg monotherapy
- This study looked at the potential impact of NTCP rs17556915 variant on outcomes of patients with CHD who were treated with BLV 2 mg or 10 mg monotherapy or BLV + pegylated interferon alfa-2a combination therapy
- The results showed that this variant had no impact on treatment outcomes in patients receiving BLV-containing regimens

References: **1.** Ni Y, et al. *Gastroenterology.* 2014;146:1070-83. **2.** Yan H, et al. *eLife.* 2012;1:e00049. **3.** Hepcludex. Summary of product characteristics. European Medicines Agency. Gilead Sciences, Inc.; 2023. **4.** Hepcludex (bulevirtide acetate). Australian Register of Therapeutic Goods. Gilead Sciences, Inc.; 2024. **5.** Toniutto P, et al. *J Hepatol.* 2024;81(5):819-26.

Acknowledgements: This study was funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Danielle L. Rubin-Shepherd, PhD, CMPP, of Red Nucleus, and were funded by Gilead Sciences, Inc.

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

Introduction

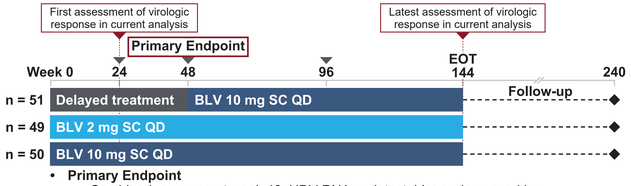
- BLV is an entry inhibitor that binds to the HDV entry receptor, NTCP[1,2]
- BLV has been demonstrated to have potent antiviral efficacy in Phase 2 and 3 studies and has been approved for the treatment of compensated CHD in the European Union (EU) and in non-EU countries[3,4]
- Recently, a retrospective study reported a possible influence of the NTCP intronic polymorphism rs17556915 on baseline HDV RNA levels and early response to BLV in patients with CHD receiving BLV 2 mg monotherapy[5]

Objective

- To evaluate the impact of NTCP intronic polymorphism rs17556915 on baseline HDV RNA levels and BLV treatment outcomes in patients with CHD from the MYR301 (BLV monotherapy) and Phase 2b MYR204 (BLV with or without PegIFNα) studies

Methods

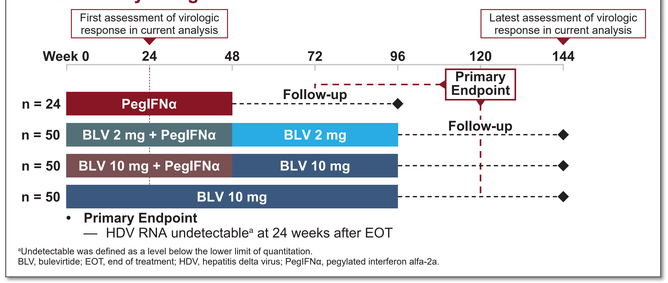
MYR301 Study Design



- **Primary Endpoint**
  - Combined response at week 48: HDV RNA undetectable[a] or decreased by ≥2 log_{10} IU/mL from BL and ALT normalisation[b]

[a]Undetectable HDV RNA was defined as less than the lower limit of quantitation (50 IU/mL; target not detected). [b]ALT normalisation was defined as ≤31 U/L for females and ≤41 U/L for males (Russian sites) and ≤34 U/L for females and ≤49 U/L for males (all other sites).
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; EOT, end of treatment; HDV, hepatitis delta virus; QD, once daily; SC, subcutaneous.

MYR204 Study Design



- **Primary Endpoint**
  - HDV RNA undetectable[a] at 24 weeks after EOT

[a]Undetectable was defined as a level below the lower limit of quantitation.
BLV, bulevirtide; EOT, end of treatment; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa-2a.

- Whole-genome sequencing (WGS) was performed on whole blood samples from a total of 290 patients in MYR301 and MYR204 at baseline
  - 128 of 150 (85%) patients in MYR301
  - 162 of 174 (93%) patients in MYR204
  - All patients were from Europe
- Virologic treatment outcomes at weeks 24, 48, 96, and 144 were defined as follows:
  - Virologic responder (VR): achieved undetectable (below the limit of detection) HDV RNA or ≥2 log_{10} IU/mL HDV RNA decline from baseline
  - Partial responder (PR): achieved ≥1 log_{10} IU/mL but <2 log_{10} IU/mL HDV RNA decline from baseline
  - Nonresponder (NR): achieved <1 log_{10} IU/mL HDV RNA decline from baseline
- Data analysis
  - Statistical analysis was conducted using one-way analysis of variance (ANOVA), Fisher's exact test, or a linear mixed-effect regression model to calculate the *P* value

Results

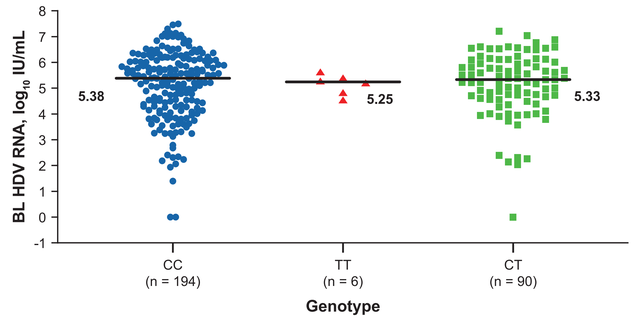
Prevalence of NTCP Polymorphism rs17556915 at Baseline in MYR301 and MYR204

Polymorphism	WT (CC)	Homozygous (TT)	Heterozygous (CT)
Prevalence, n/N (%)	194/290 (67)	6/290 (2)	90/290 (31)
HDV RNA, median, log_{10} IU/mL	5.38	5.25	5.33

Genotypes are provided in parentheses with CC, TT, and CT representing the genotypes for WT, homozygous, and heterozygous, respectively.
HDV, hepatitis delta virus; NTCP, sodium taurocholate cotransporting polypeptide; WT, wild type.

- WGS was performed for all samples (n = 290), and the polymorphism rs17556915 data were obtained from all tested samples
- The genotype distribution was consistent with that previously reported in the European population and met Hardy-Weinberg equilibrium expectations

NTCP Polymorphism rs17556915 Was Not Associated With Differences in Baseline HDV RNA Levels



Numbers represent the median HDV RNA. CC, TT, and CT represent the genotypes for WT, homozygous, and heterozygous, respectively.
BL, baseline; HDV, hepatitis delta virus; NTCP, sodium taurocholate cotransporting polypeptide; WT, wild type.

- Baseline HDV RNA had no significant difference across the 3 genotype groups (*P* = .40; one-way ANOVA)

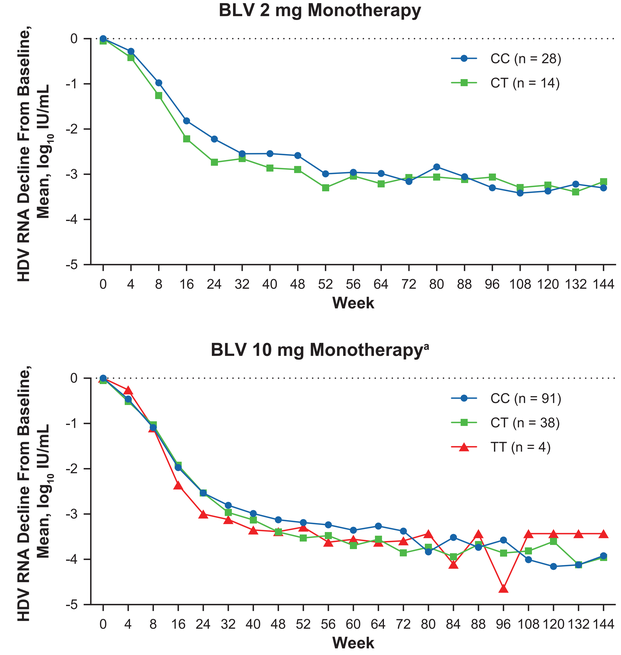
Week 24 Virologic Response for Patients Receiving a BLV-Containing Regimen in MYR301 and MYR204

Response Category n (%)	BLV 2 mg Monotherapy			BLV 10 mg Monotherapy[a]			BLV + PegIFNα Combination Therapy[b]		
	CC (n = 26)	CT (n = 13)	*P* Value	CC (n = 87)	CT (n = 38)	*P* Value	CC (n = 64)	CT (n = 26)	*P* Value
VR	14 (54)	10 (77)	.30	64 (74)	31 (82)	.51	61 (95)	26 (100)	.55
PR	8 (31)	3 (23)	.79	21 (24)	5 (13)	.23	1 (2)	0 (0)	1
NR	4 (15)	0 (0)	.28	2 (2)	2 (5)	.58	2 (3)	0 (0)	1

CC, TT, and CT represent WT, homozygous, and heterozygous genotypes, respectively. [a]Included patients in the MYR301 BLV 10 mg and delayed treatment groups and the MYR204 BLV 10 mg group. Four patients with genotype TT were not included in the analysis due to the small size. [b]Included patients in MYR204 BLV 2 mg + PegIFNα group and BLV 10 mg + PegIFNα group. Two patients with genotype TT were not included in the analysis due to the small size.
BLV, bulevirtide; NR, nonresponder; PegIFNα, pegylated interferon alfa-2a; PR, partial responder; VR, virologic responder; WT, wild type.

- NTCP polymorphism rs17556915 had no impact on virologic response
- Patients with the wild-type genotype (CC) had similar VR, PR, and NR rates compared with the heterozygous genotype (CT) group at week 24 in the BLV 2 mg monotherapy, BLV 10 mg monotherapy, and BLV + PegIFNα combination treatment groups
- Consistent results were observed at weeks 48, 96, and 144

HDV RNA Decline Kinetics



CC, TT, and CT represent WT, homozygous, and heterozygous genotypes, respectively. [a]Included patients in the MYR301 BLV 10 mg and delayed treatment groups (only the BLV 10 mg immediate treatment group had data through week 144) and the MYR204 BLV 10 mg group. [b]Included patients in the MYR204 BLV 2 mg + PegIFNα and BLV 10 mg + PegIFNα groups. Two patients with genotype TT were not included in the analysis due to the small size.
BLV, bulevirtide; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa-2a; WT, wild type.

- Patients with the wild-type genotype (CC) had similar decline rates in HDV RNA at each individual time point during treatment compared with the heterozygous (CT) or the homozygous (TT) groups in the BLV 2 mg monotherapy (*P* = .70), BLV 10 mg monotherapy (*P* = .67), and BLV + PegIFNα combination (*P* = .63) treatment groups