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Bulevirtide Monotherapy at Low and High Doses in Patients With Chronic Hepatitis Delta: 24-Week Interim Data of the Phase 3 MYR301 Study

Heiner Wedemeyer,[1] Soo Aleman,[2] Pietro Andreone,[3] Antje Blank,[4] Maurizia Brunetto,[5] Pavel Bogomolov,[6] Vladimir Chulanov,[7] Natalia Geyvandova,[8] Gudrun Hilgard,[9] Nina Mamonova,[10] Uta Merle,[4] Morozov Viacheslav,[11] Olga Sagalova,[12] Tatyana Stepanova,[13] Julian Schulze zur Wiesch,[14] Sergey Zotov,[15] Stefan Zeuzem,[16] Pietro Lampertico[17]

[1]Medizinische Hochschule Hannover, Germany; [2]Karolinska Universitetssjukhuset, Karolinska Institutet, Stockholm, Sweden; [3]Università degli studi di Modena e Reggio Emilia, Italy; [4]Universitätsklinikum Heidelberg, Germany; [5]UO Epatologia, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; [6]M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russian Federation; [7]Central Research Institute of Epidemiology, Moscow; [8]Stavropol Regional Clinical Hospital, Stavropol, Russian Federation; [9]Universitätsklinikum Essen, Germany; [10]National Research Medical Center for Phthisiopulmonology and Infectious Diseases, Moscow; [11]Hepatolog, LLC, Samara, Russian Federation; [12]Southern Ural State Medical University, Chelyabinsk, Russian Federation; [13]Clinic of Modern Medicine, Moscow; [14]Universitätsklinikum Hamburg-Eppendorf, Medizinische Klinik Studienambulanz Hepatologie, Hamburg, Germany; [15]Specialized Clinical Infectious Diseases Hospital, Krasnodar, Russian Federation; [16]Universitätsklinikum Frankfurt, Germany; [17]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, CRC "A.M. and A. Migliavacca" Center for Liver Disease, Università degli Studi di Milano, Italy

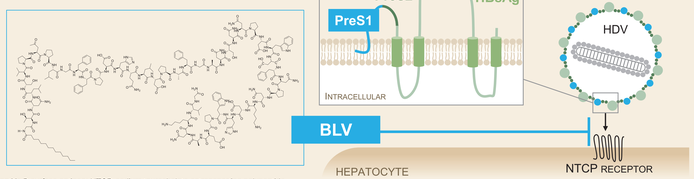
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, California, USA 94404
800-445-3235

Introduction

Hepatitis Delta Virus (HDV)

- HDV is a satellite virus of hepatitis B virus (HBV) and requires HBV envelope proteins to infect hepatocytes[1]
- ~12 million people are infected with HDV worldwide[2]
- HDV is the most severe form of chronic viral hepatitis,[3] with 2–3-fold increased risk of mortality compared with HBV monoinfection[4,5]
- U.S. Food & Drug Administration draft guidance for development of HDV treatment states that undetectable HDV RNA or a 2-log_{10} decline with alanine aminotransferase (ALT) normalization is an acceptable chronic on-therapy surrogate endpoint[6]

Bulevirtide (BLV)



HBsAg, hepatitis B surface antigen; NTCP, sodium taurocholate cotransporting polypeptide.

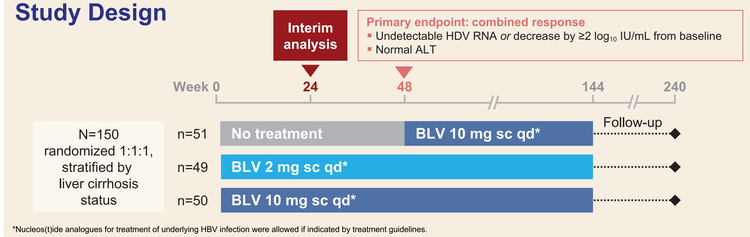
- First-in-class entry inhibitor for treatment of chronic HDV infection
- Linear 47-amino acid chemically synthesized lipopeptide bearing an N-terminal myristoyl moiety and a C-terminal carboxamide
- Specifically binds to NTCP at the basolateral membrane of differentiated hepatocytes; this transporter is also used by HBV and HDV to enter hepatocytes[7]
- Shows very low off-target toxicity, and excellent safety and tolerability
- Conditionally approved in Europe for treatment of chronic HDV[8]

Objectives

- To evaluate the safety and efficacy of BLV administered subcutaneously at a dose of 2 or 10 mg qd for treatment of chronic HDV compared with no treatment at interim Week 24

Methods

Study Design



*Nucleos(t)ide analogues for treatment of underlying HBV infection were allowed if indicated by treatment guidelines.

- Multicenter, open-label, randomized, Phase 3 study (ClinicalTrials.gov NCT03852719) conducted in 5 countries (Germany, Italy, Russian Federation, Sweden, and USA)
- Patient population: adults with chronic HDV with or without cirrhosis; 1x < ALT < 10x upper limit of normal; and Child-Pugh-Turcotte (CPT) ≤7 (controlled HIV coinfection was allowed)
- Undetectable HDV RNA defined as below lower limit of detection (6 IU/mL)
- Secondary endpoints: undetectable HDV RNA and ALT normalization (Week 48); sustained virologic responses at Weeks 24 and 48; and change from baseline in liver stiffness (measured by elastography; Weeks 48, 96, 144, 192, and 240)
- Statistical analyses: difference in response rates between treatment groups was calculated using Fisher exact test

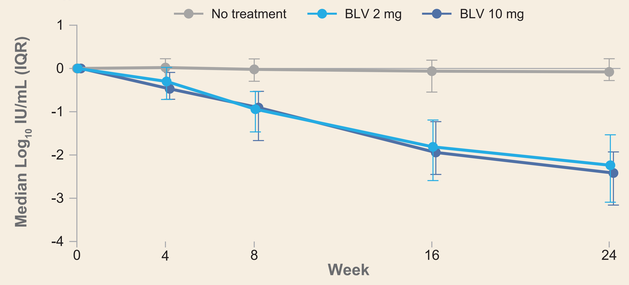
Results

Baseline Characteristics

	No Treatment n=51	BLV 2 mg n=49	BLV 10 mg n=50
Mean age, y (SD)	40.5 (7.5)	43.6 (9.0)	41.3 (8.5)
Men, n (%)	26 (51)	30 (61)	30 (60)
Race, n (%)			
White	40 (78)	41 (84)	43 (86)
Asian	11 (22)	8 (16)	6 (12)
Black	0	0	1 (2)
Cirrhosis, n (%)	25 (49)	23 (47)	23 (46)
Mean liver stiffness, kPa (SD)	15.26 (8.95)	13.99 (8.19)	14.81 (9.26)
>20 kPa, n (%)	10 (20)	9 (18)	10 (20)
Mean ALT, U/L (SD)	101.6 (61.9)	107.9 (62.5)	123.4 (80.6)
Median HDV RNA, log_{10} IU/mL (IQR)	5.38 (1.84)	5.23 (1.30)	5.03 (1.85)
HBV genotype, n (%)			
A	0	2 (4)	2 (4)
D	10 (20)	16 (33)	12 (24)
Missing	41 (80)	32 (65)	37 (74)
HDV genotype, n (%)			
1	51 (100)	49 (100)	49 (98)
5	0	0	1 (2)
Mean HBsAg, log_{10} IU/mL (SD)	3.676 (0.465)	3.667 (0.511)	3.615 (0.575)
Mean HBV DNA, log_{10} IU/mL (SD)	0.885 (0.989)	1.311 (1.300)	1.110 (1.263)
Positive, n (%)	13 (25)	15 (31)	11 (22)
HBeAg positive, n (%)	4 (8)	4 (8)	7 (14)

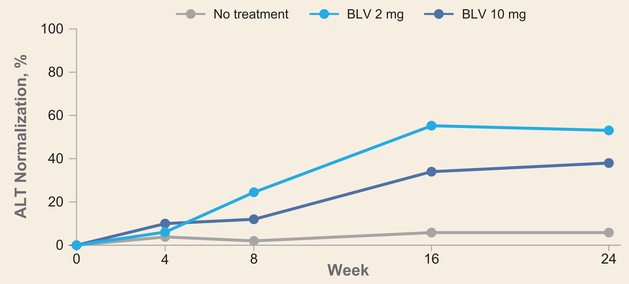
HBeAg, hepatitis B e antigen; IQR, interquartile range; SD, standard deviation.

Changes in HDV RNA Over Time



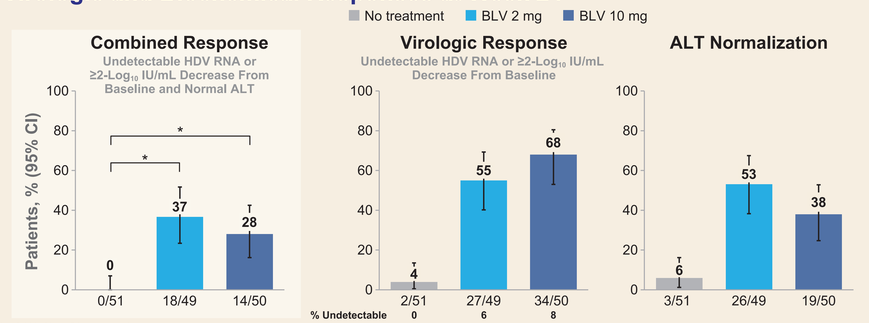
- Compared with no treatment, BLV led to a decline in HDV RNA, with similar rates of HDV RNA decline with BLV 2 and 10 mg over 24 wk of treatment

ALT Normalization Over Time



- After 24 wk of treatment, rapid ALT reduction and normalization were observed in >50% of patients in the BLV 2-mg arm

Virologic and Biochemical Responses at Week 24



*p <0.001. CI, confidence interval.

- 24 wk of treatment with BLV 2 mg led to a higher combined viral and biochemical response compared with no treatment or BLV 10 mg

Other Efficacy Endpoints at Week 24

	No Treatment n=51	BLV 2 mg n=49	BLV 10 mg n=50
HBsAg decrease >1 log_{10} IU/mL from baseline, n (%)	0	1 (2)	0
HBsAg loss/seroconversion, n	0	0	0
Mean HBV DNA change from baseline, log_{10} IU/mL (SD)	0.025 (0.792)	-0.510 (0.869)	-0.641 (1.006)

- Treatment with BLV for 24 wk led to modest declines in HBV DNA compared with no treatment

Safety

	Patient, n (%)	No Treatment n=51	BLV 2 mg n=49	BLV 10 mg n=50
Adverse Events*	Any AE	26 (51)	32 (65)	36 (72)
	Grade 3–4 AE	2 (4)†	2 (4)‡	1 (2)§
	Any serious AE	1 (2)	0	0
	D/C due to AE	0	0	0
	Death	0	0	0
Adverse Events of Special Interest	Injection-site reactions	0	3 (6)	13 (26)
	Liver-related AEs	0	0	0
Grade 3–4 Lab Abnormalities	Thrombocytopenia	2 (4)	0	0
	Leukopenia	1 (2)	0	1 (2)
	Neutropenia	1 (2)	0	0

*All adverse events (AEs) reported in table considered treatment emergent; only symptomatic and clinically significant total bile salt elevations were collected; †Cholelithiasis (n=1) and COVID-19 infection (n=1); ‡Foot fracture (n=1), and headache, asthenia, and depression (n=1); §Pneumonia due to COVID-19 infection (n=1). D/C, discontinuation.

- There were no serious AEs related to BLV or AEs leading to D/C of study drug
- Injection-site reactions were rare and mostly mild in grade
- No symptomatic elevations in total bile salts were observed across the BLV 2- and 10-mg arms

Conclusions

- BLV monotherapy was safe and well tolerated in cirrhotic or noncirrhotic patients with compensated chronic HDV, with most AEs being mild–moderate and no BLV-related serious AEs
- 24 wk of treatment with BLV was associated with significant HDV RNA declines and improvements in biochemical disease activity
  - BLV 2 and 10 mg had significantly superior responses to the no treatment arm
  - BLV 2 mg for 24 wk had a numerically higher combined response rate than BLV 10 mg
- These findings further support the conditional approval of BLV 2 mg in the EU

References: **1.** Rizzetto M, et al. J Infect Dis 1980;141:590-602; **2.** Stockdale AJ, et al. J Hepatol 2020;73:523-32. **3.** Wedemeyer H, et al. Nat Rev Gastroenterol Hepatol 2010;7:31-40; **4.** Fattovich G, et al. Gut 2000;46:420-6; **5.** Romeo R, et al. Gastroenterology 2009;136:1629-38; **6.** U.S. Food & Drug Administration. Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry; 11/19. **7.** Ni Y, et al. Gastroenterology 2014;146:1070-83; **8.** Hepcludex [SmPC]. Bad Homburg, Germany: Myr GmbH; 7/20.

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