SAT352

Integrated Safety Analysis of 24-Week Data From Three Phase 2 and One Phase 3 Clinical Trial of Bulevirtide Monotherapy Given at 2- or 10-mg Dose Level for Treatment of Chronic Hepatitis Delta

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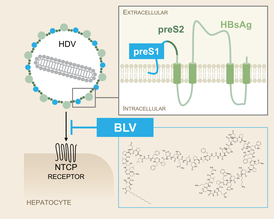
Introduction

Hepatitis Delta Virus (HDV)

- HDV is a satellite virus of hepatitis B virus (HBV) and requires HBV envelope proteins to infect hepatocytes and propagate[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 mono-infection[4,5]
- Pegylated interferon-alfa (Peg-IFNα) is recommended by treatment guidelines; however, Peg-IFNα therapy is estimated to provide a lasting benefit for ~10% of patients[6]

Bulevirtide (BLV)



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

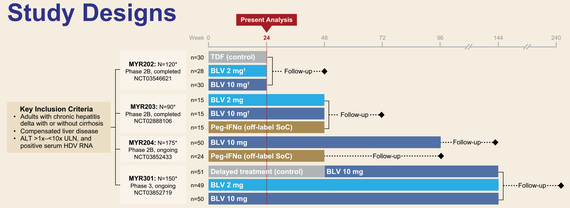
- BLV is a first-in-class entry inhibitor for treatment of chronic hepatitis delta infection
- Linear 47-amino acid chemically synthesized lipopeptide
- Specifically binds to NTCP at the basolateral membrane of hepatocytes; NTCP is used by HBV and HDV to enter hepatocytes[7]
- BLV monotherapy was shown to be generally safe and well tolerated in individual trials[8-12]
- BLV 2 mg given once daily (qd) subcutaneously (sc) is conditionally approved in Europe for treatment of chronic hepatitis delta

Objective

- To evaluate the safety of BLV monotherapy at 2 and 10 mg once-daily subcutaneously for treatment of chronic hepatitis delta based on integrated 24-wk data from three phase 2 (MYR202, MYR203, MYR204) and one phase 3 (MYR301) trial

Methods

Study Designs



*Total n of study patients; only arms pooled for 24-wk integrated analysis are shown; groups treated with combination of BLV and Peg-IFNα are not included in this analysis; 24-wk treatment-free follow-up period data from MYR202 and MYR203 were included in analysis; †in combination with tenofovir disoproxil fumarate (TDF). ALT, alanine aminotransferase; SoC, standard of care; ULN, upper limit of normal.

- 24-wk data were pooled from 355 patients participating in 4 multicenter, open-label, randomized, clinical trials conducted in 7 countries (France, Germany, Italy, Moldova, Romania, Russian Federation, and Sweden)
  - Patients pooled in 4 groups: control (TDF-only group from MYR202 and delayed treatment group from MYR301), BLV 2 mg, BLV 10 mg, and Peg-IFNα
- Safety parameters assessed included graded (Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0, US Dept of Health and Human Services, Washington, DC, USA) treatment-emergent adverse events (AEs) and laboratory abnormalities
- Subgroup analysis of safety by cirrhosis status was performed for the BLV 2- and 10-mg dose groups

Results

Demographics and Disease Characteristics

	Control n=79	BLV 2 mg n=92	BLV 10 mg n=145	Peg-IFNα n=39
Mean age, y (SD)	40 (8.0)	42 (9.0)	40 (9.2)	38 (8.4)
Men, n (%)	46 (58)	56 (61)	102 (70)	23 (59)
White, n (%)	63 (80)	77 (84)	129 (89)	34 (87)
Mean BMI, kg/m² (SD)	25.7 (4.15)	24.9 (3.50)	25.2 (3.72)	25.5 (4.21)
Cirrhosis, n (%)	37 (47)	41 (45)	57 (39)	12 (31)
Mean HDV RNA, $\log_{10}$ IU/mL (SD)	5.2 (1.36)	5.3 (1.27)	5.3 (1.33)	5.1 (1.07)
Mean ALT, U/L (SD)	108 (71.9)	107 (70.7)	116 (88.7)	110 (79.9)
Median HBsAg, $\log_{10}$ IU/mL (Q1, Q3)	3.9 (3.6, 4.1)	4.0 (3.7, 4.3)	3.9 (3.6, 4.1)	3.9 (3.6, 4.1)
HBeAg negative, n (%)	74 (94)	79 (86)	128 (88)	37 (95)
Median HBV DNA, $\log_{10}$ IU/mL (Q1, Q3)	1.0 (0.0, 1.6)	1.3 (0.0, 1.7)	1.2 (0.0, 1.8)	1.3 (0.0, 1.9)
Median creatinine clearance, mL/min (Q1, Q3)	113.0 (98.0, 139.0)	111.8 (97.7, 130.1)	117.0 (98.5, 132.5)	128.1 (105.2, 137.4)
Baseline creatinine clearance 60–<90 mL/min, n (%)	14 (18)	18 (20)	20 (14)	4 (10)
Previous IFN therapy, n (%)	47 (59)	47 (51)	64 (44)	16 (41)

BMI, body mass index; HBeAg, hepatitis B e antigen; Q, quartile; SD, standard deviation.

- Overall, demographic and baseline characteristics were similar across groups

Overall Summary of Adverse Events

Preferred Term, n (%)	Control n=79	BLV 2 mg n=92	BLV 10 mg n=145	Peg-IFNα n=39
AE	39 (49)	62 (67)	107 (74)	34 (87)
Grade ≥3 AE	3 (4)	4 (4)	10 (7)	17 (44)
AE related to BLV	0	45 (49)	87 (60)	0
Grade ≥3 AE related to BLV	0	2 (2)	5 (3)	0
AE related to Peg-IFNα	0	0	0	34 (87)
Grade ≥3 AE related to Peg-IFNα	0	0	0	16 (41)
Serious AE	2 (3)	0	1 (1)	2 (5)
AE leading to premature D/C of BLV	0	0	0	0
All deaths*	0	0	0	0

*1 death occurred after Week 24 visit and was, therefore, not included in integrated safety analysis. D/C, discontinuation.

- Most AEs were mild or moderate in severity
- There were no serious AEs related to BLV or AEs leading to D/C of BLV observed

Grade 3–4 Adverse Events
Observed in >1 Patient

Preferred Term, n (%)	Control n=79	BLV 2 mg n=92	BLV 10 mg n=145	Peg-IFNα n=39
Any Grade ≥3 AE	3 (4)	4 (4)	10 (7)	17 (44)
Neutropenia	1 (1)	0	2 (1)	9 (23)
Leukopenia	1 (1)	0	2 (1)	6 (15)
Thrombocytopenia	2 (3)	1 (1)	1 (1)	4 (10)
Neutrophil count decreased	0	1 (1)	0	2 (5)
ALT increased	0	0	0	3 (8)
AST increased	0	0	0	3 (8)
GGT increased	0	0	0	3 (8)
Total bile acids increased	0	0	2 (1)	0
Amylase increased	0	0	2 (1)	0
Lipase increased	0	0	2 (1)	0
Lymphopenia	0	1 (1)	0	1 (3)

AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.

- Rates of Grade 3–4 AEs were low, and comparable between the BLV 2- and 10-mg, and control groups
- As expected in the Peg-IFNα group, the rates of Grade 3 or 4 AEs were notably higher

Serious Adverse Events

Preferred Term, n (%)	Control n=79	BLV 2 mg n=92	BLV 10 mg n=145	Peg-IFNα n=39
Any serious AE	2 (3)	0	1 (1)	2 (5)
Pyrexia	0	0	0	1 (3)
Cholelithiasis	1 (1)	0	0	0
Hepatic cirrhosis*	1 (1)	0	0	0
Appendicitis	0	0	0	1 (3)
Urinary tract infection	0	0	1 (1)	0

*Reported as decompensation of hepatic cirrhosis.

- No serious AEs related to BLV were observed
- No liver-related serious AEs were observed in the BLV groups

Most Common Adverse Events*

Patients, n (%)	Control n=79	BLV 2 mg n=92	BLV 10 mg n=145	Peg-IFNα n=39
Total bile acids increased	5 (6)	20 (22)	30 (21)	3 (8)
Headache	0	12 (13)	22 (15)	5 (13)
Injection-site reactions	0	7 (8)	22 (15)	1 (3)
Leukopenia	6 (8)	8 (9)	11 (8)	20 (51)
Pruritus	1 (1)	6 (7)	11 (8)	2 (5)
Fatigue	2 (3)	5 (5)	13 (9)	2 (5)
Thrombocytopenia	8 (10)	7 (8)	9 (6)	22 (56)
Dizziness	0	5 (5)	10 (7)	1 (3)
Nausea	1 (1)	4 (4)	11 (8)	6 (15)
ALT increased	6 (8)	4 (4)	8 (6)	12 (31)

*10 most common AEs in BLV groups.

Grade 3 or 4 Laboratory Abnormalities
Observed in >1 Patient in BLV Groups

Laboratory Abnormalities, n (%)	Control n=79	BLV 2 mg n=92	BLV 10 mg n=145	Peg-IFNα n=39*
Any Grade ≥3	6 (8)	6 (7)	11 (8)	16 (43)
Leukocytes decreased	1 (1)	1 (1)	3 (2)	7 (19)
Platelet decreased	2 (3)	1 (1)	3 (2)	5 (14)
ALT increased	3 (4)	4 (4)	2 (1)	6 (16)
Amylase increased	0	0	2 (1)	0

*Postbaseline value only available for 37 patients; denominator: n=37.

- Rates of Grade 3 or 4 laboratory abnormalities with BLV were similar to those in the control group and lower than in the Peg-IFNα group
- No case of Grade 3 or 4 elevation in bile acids or eosinophilia was observed in any group

Overview of Adverse Events: Cirrhosis vs No Cirrhosis

Patients, n (%)	BLV 2 mg		BLV 10 mg	
	Cirrhosis n=41	No Cirrhosis n=51	Cirrhosis n=41	No Cirrhosis n=73
Any AE	25 (61)	37 (73)	44 (77)	48 (66)
Serious AE	0	0	0	1 (1)
Reported serious AE	—	—	—	Urinary tract infection
Related to study drug	16 (39)	29 (57)	36 (63)	36 (49)
Leading to premature drug D/C	0	0	0	0

Injection-Site Reactions
Observed in >1 Patient

Patients, n (%)	BLV 2 mg n=92	BLV 10 mg n=145
Any AE of injection-site reaction	7 (8)	22 (15)
Reaction*	1 (1)	6 (4)
Erythema	4 (4)	11 (8)
Pruritus	0	4 (3)
Hematoma	0	2 (1)
Pain	1 (1)	1 (1)

*Not otherwise specified.

- All injection-site reactions were mild–moderate in severity
- No serious injection-site reactions or injection-site reactions leading to D/C of BLV were observed
- Fewer injection-site reactions were observed in the BLV 2- vs 10-mg group, likely due to increased injection burden with 10 mg (2x 5-mg doses qd)

Median Total Bile Acids by Visit

- Dose-dependent elevations in serum total bile acids were observed, which were expected based on BLV mode of action (NTCP inhibition)
- Elevations were asymptomatic, without clinical sequelae, and reversible upon treatment cessation

Conclusions

- In this integrated safety analysis of 24-wk data from 355 patients:
  - Among patients treated with BLV 2 mg, there were few Grade 3 or serious AEs, with no discontinuations related to study drug
    - The safety profile of BLV was similar between patients with and without compensated cirrhosis
    - Asymptomatic bile acid elevations and injection-site reactions were less frequently observed with BLV 2 mg qd
  - Overall, treatment with BLV was safe and well tolerated, with a more favorable safety profile compared with Peg-IFNα, the current off-label SoC

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.** Heidrich B, et al. Hepatology 2014;60:87-97; **7.** Ni Y, et al. Gastroenterology 2014;146:1070-83; **8.** Asselah T, et al. EASL 2021, abstr 2717; **9.** Wedemeyer H, et al. EASL 2018, abstr GS-005; **10.** Wedemeyer H, et al. EASL 2021, abstr LBP-2730; **11.** Wedemeyer H, et al. J Hepatol 2020;73(suppl 1):S52 (abstr AS072); **12.** Wedemeyer H, et al. EASL 2021, abstr LBP-2730.

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Viral hepatitis
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