SAT351

Integrated Efficacy Analysis of 24-Week Data From Two 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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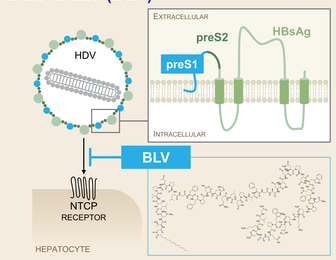
Introduction

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]
- Therapies for HDV control or cure are urgently needed[7]

Bulevirtide (BLV)



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

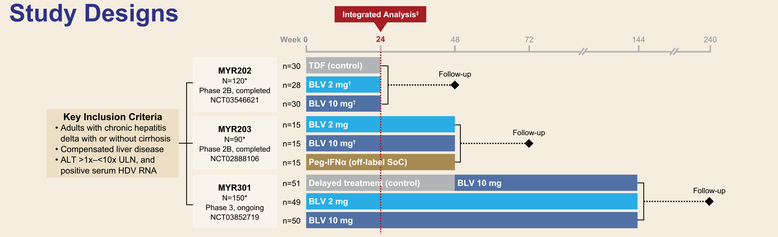
- BLV is a first-in-class entry inhibitor for treatment of chronic hepatitis delta infection
- Linear 47-amino acid chemically synthesized lipopeptide
- Specifically binds to NTCP at the basolateral membrane of hepatocytes; NTCP is used by HBV and HDV to enter hepatocytes[8]
- Patients treated for 24 wk with BLV alone have previously shown pronounced viral and biochemical responses (HDV RNA and alanine aminotransferase [ALT] declines)[9-11]
- BLV 2 mg given once daily (qd) subcutaneously (sc) is conditionally approved in Europe for treatment of chronic hepatitis delta

Objective

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

Methods

Study Designs



*Total n of study patients; only arms pooled for 24-wk integrated analysis are shown; groups treated with the combination of BLV and Peg-IFNα are not included in this analysis; †Administered with tenofovir disoproxil fumarate (TDF) 300 mg; ‡Undetectable HDV RNA defined as below lower limit of detection (14, 10, and 6 IU/mL in Studies MYR202, MYR203, and MYR301, respectively), and ALT normalization defined at Russian sites as ≤31 U/L for women and ≤41 U/L for men, and at all other sites as ≤34 U/L for women and ≤49 U/L for men; 95% confidence intervals (CIs) from Clopper-Pearson exact method. SoC, standard of care; ULN, upper limit of normal.

- 24-wk data pooled from 281 patients participating in 3 multicenter, open-label, randomized clinical trials conducted in 4 countries (Germany, Italy, 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
- Primary analysis: combined response at Week 24
  - Undetectable HDV RNA or decrease ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization (acceptable chronic on-therapy surrogate endpoint [U.S. Food & Drug Administration draft guidance for development of HDV treatment])[12]
- Additional analyses: viral response (undetectable HDV RNA or decline ≥2 $\log_{10}$ IU/mL), ALT normalization, and change in HDV RNA levels at Week 24

Results

Demographics and Disease Characteristics

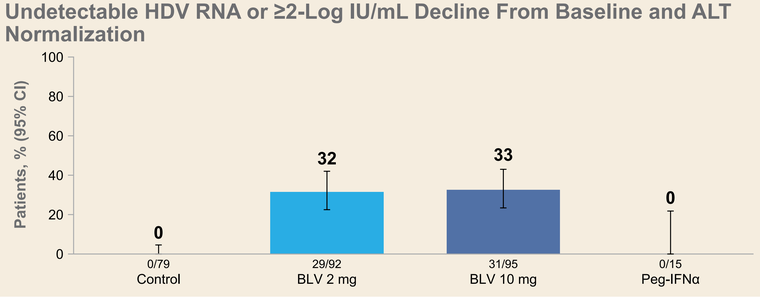
	Control n=79	BLV 2 mg n=92	BLV 10 mg n=95	Peg-IFNα n=15
Mean age, y (SD)	40 (8.0)	42 (9.0)	40 (9.6)	34 (7.0)
Men, n (%)	46 (58)	56 (61)	64 (67)	5 (33)
White, n (%)	63 (80)	77 (84)	85 (89)	14 (93)
Cirrhosis, n (%)	37 (47)	41 (45)	40 (42)	4 (27)
Mean HDV RNA, $\log_{10}$ IU/mL (SD)	5.2 (1.36)	5.3 (1.27)	5.3 (1.44)	5.2 (1.15)
Mean ALT, U/L (SD)	108 (71.9)	107 (70.7)	115 (77.3)	93 (38.4)
HDV genotype, n (%)				
1	78 (99)	89 (97)	84 (88)	14 (93)
2	1 (1)	2 (2)	2 (2)	0
5	0	0	1 (1)	0
Missing	0	1 (1)	8 (8)	1 (7)
HBV genotype, n (%)				
A	9 (11)	3 (3)	5 (5)	0
C	0	1 (1)	0	0
D	61 (77)	72 (78)	72 (76)	2 (13)
E	—	0	1 (1)	0
Missing	9 (11)	16 (17)	17 (18)	13 (87)
Median HBsAg, $\log_{10}$ IU/mL (Q1, Q3)	3.9 (3.6, 4.1)	4.0 (3.7, 4.3)	3.9 (3.6, 4.2)	4.1 (4.0, 4.3)
HBeAg negative, n (%)	74 (94)	79 (86)	85 (89)	14 (93)
Median HBV DNA, $\log_{10}$ IU/mL (Q1, Q3)	1.0 (0.0, 1.6)	1.3 (0.0, 1.7)	1.0 (0.0, 1.5)	0.0 (0.0, 1.7)
Previous Peg-IFNα therapy, n (%)	47 (59)	47 (51)	43 (45)	4 (27)

HBeAg, hepatitis B e antigen; Q, quartile; SD, standard deviation.

- 68% of patients were on concomitant nucleos(t)ide treatment

Combined Response at Week 24

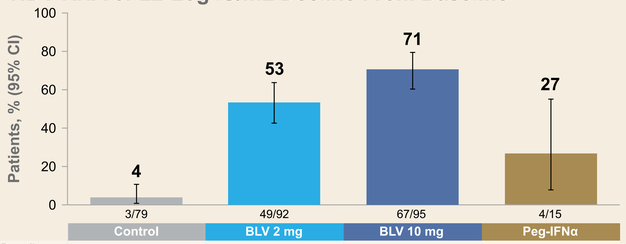
Undetectable HDV RNA or ≥2-Log IU/mL Decline From Baseline and ALT Normalization



- Combined response rates were similar between the BLV 2- and 10-mg groups; no patient in the control or Peg-IFNα groups achieved a combined response

Viral Response at Week 24

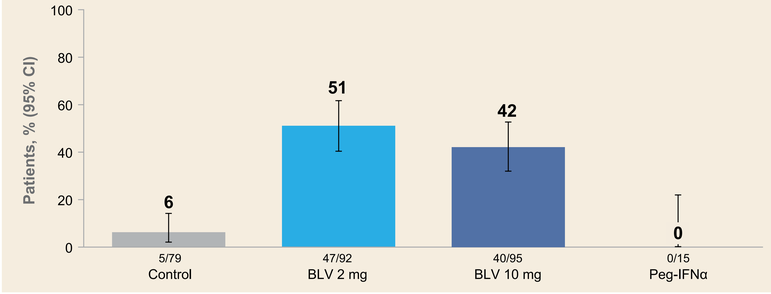
Undetectable HDV RNA or ≥2-Log IU/mL Decline From Baseline



	Control	BLV 2 mg	BLV 10 mg	Peg-IFNα
Mean Change From Baseline in HDV RNA at Week 24, $\log_{10}$ IU/mL (SD)	-0.14 (0.773)	-2.12 (1.228)	-2.49 (1.054)	-1.16 (2.048)

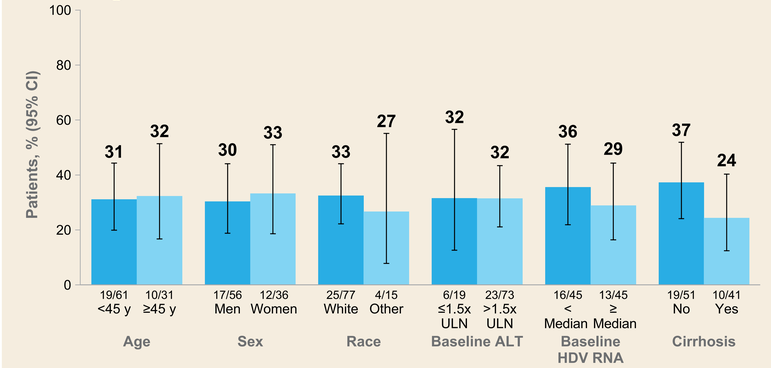
- Viral response rates were higher with BLV vs control and Peg-IFNα arms
- A numerically higher rate was observed with BLV 10 vs 2 mg at Week 24

ALT Normalization at Week 24



- Higher ALT normalization rates were observed with BLV vs control and Peg-IFNα
- At Week 24, the BLV 2-mg group had a numerically higher ALT normalization rate vs the 10-mg group

Combined Response Rates Across Subgroups in Patients Receiving BLV 2 mg



- Treatment benefit was consistent across subgroups, including patients with compensated cirrhosis

Conclusions

- In an integrated efficacy analysis of 24-wk data from 281 patients with chronic hepatitis delta:
  - Combined response rates were ∋2% and 33% in the BLV 2- and 10-mg groups, respectively
  - In comparison, no patients in the control and Peg-IFNα groups achieved a combined response
  - Higher proportions of BLV-treated patients achieved viral response and/or ALT normalization compared with control or Peg-IFNα group
  - Treatment benefit was consistent across subgroups, including patients with cirrhosis
- These results support the use of BLV 2 mg qd as monotherapy for treatment of chronic hepatitis delta

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.** Asselah T, et al. Liver Int 2020;40 S1:54-60; **8.** Ni Y, et al. Gastroenterology 2014;146:1070-83; **9.** Wedemeyer H, et al. EASL 2018, abstr GS-005; **10.** Wedemeyer H, et al. J Hepatol 2020;73(suppl 1):S52 (abstr AS072); **11.** Wedemeyer H, et al. EASL 2021, abstr LBP-2730; **12.** U.S Food & Drug Administration. https://www.fda.gov/media/132137/download, 2019.

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