Development of Antidrug Antibodies on Bulevirtide Monotherapy in Chronic Hepatitis Delta Does Not Impact Bulevirtide Efficacy, Safety, or Pharmacokinetics

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Key Findings

- Incidence of ADA development over 48 weeks of BLV treatment was 23% among the 2-mg group and 22% among the 10-mg group
- No clinically meaningful differences were observed in the combined virologic and biochemical responses at both doses based on ADA status
- BLV was safe and well tolerated regardless of ADA status

Conclusions

Development of ADAs in response to BLV monotherapy did not impact efficacy, safety, or PK throughout 48 weeks of treatment

References: 1. Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. **2.** European Medicines Agency. Hepcludex (bulevirtide). Accessed August 28, 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex. **3.** Bogomolov P, et al. *J Hepatol*. 2016;65:490-8.

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Introduction

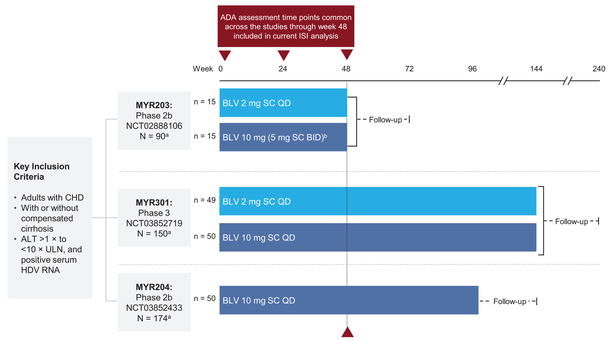
- Hepatitis delta virus (HDV) represents the most severe form of chronic viral hepatitis and is estimated to affect between 10 and 20 million people worldwide[1]
- Bulevirtide (BLV), a novel entry inhibitor of HDV, is approved in the European Union at 2 mg/day for the treatment of adults with chronic hepatitis delta (CHD) and compensated liver disease[2]
- BLV is a linear 47–amino acid chemically synthesized lipopeptide
- Early results from a Phase 1/2 study (MYR201) reported no correlation between antidrug antibody (ADA) development and the efficacy, safety, or pharmacokinetic (PK) profile of BLV after 24 weeks[3]

Objective

- To evaluate the impact of ADA development on the efficacy, safety, and PK of 48-week BLV monotherapy during treatment for CHD

Methods

Figure 1. Study Design



[a]Total number of treated study patients; only arms pooled for integrated analyses are shown; groups treated with the combination of BLV and pegylated interferon are not included in this analysis. [b]In combination with TDF.
ADA, antidrug antibody; ALT, alanine aminotransferase; BID, twice daily; BLV, bulevirtide; CHD, chronic hepatitis delta; HDV, hepatitis delta virus; ISI, integrated summary of immunogenicity; QD, once daily; SC, subcutaneous; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

- Completed and ongoing Phase 2 and 3 studies that include BLV monotherapy up to week 48 are included in this integrated summary of immunogenicity analysis
  - The efficacy analysis included studies MYR203 and MYR301. Efficacy parameters assessed included virologic and biochemical response rates
  - Safety and PK analysis included studies MYR203, MYR301, and MYR204. Safety parameters assessed included graded treatment-emergent adverse events (TEAEs) and hypersensitivity or immune-mediated TEAEs. TEAEs were coded according to MedDRA version 24.0
  - ADA assessment time points that were evaluated across the 3 studies through week 48 are baseline, week 24, and week 48
- ADA detection was performed via an enzyme-linked immunosorbent assay and was developed and validated at Prolytic GmbH (Frankfurt, Germany), with a calibrated range of 500 to 10,000 ng/mL and a sensitivity of 250 ng/mL
- The incidence of ADA development (ADA+) was defined as ADA negativity or missing at baseline with subsequent ADA positivity at any postbaseline visit through week 48. Patients with at least one available ADA measurement postbaseline were included
- ADA assessments through week 48 were done at the following time points:
  - MYR203: day 1, week 12, week 24, and week 48
  - MYR204 and MYR301: day 1, week 16, week 24, and week 48

Results

Table 1. Baseline Characteristics by Dose and ADA Incidence by Week 48

	BLV 2 mg		BLV 10 mg	
	ADA+ (n = 15)	ADA− (n = 49)	ADA+ (n = 25)	ADA− (n = 88)
Age, years, mean (SD)	41 (7)	44 (10)	40 (9)	40 (8)
Male sex, n (%)	11 (73)	30 (61)	16 (64)	63 (72)
White race, n (%)	13 (87)	43 (88)	23 (92)	77 (88)
Cirrhosis, n (%)	6 (40)	20 (41)	8 (32)	32 (36)
Concomitant HBV NUC treatment, n (%)	7 (47)	24 (49)	9 (36)	40 (45)
ALT, U/L, mean (SD)	121.7 (97.5)	107.7 (64.7)	107.0 (65.2)	116.9 (96.8)
Platelet count, 10^9/L, mean (SD)	164.2 (57.3)	158.0 (53.2)	193.6 (46.3)	168.8 (51.1)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	4.8 (1.5)	5.4 (1.2)	5.5 (1.7)	5.2 (1.3)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.7 (0.5)	3.8 (0.5)	3.8 (0.7)	3.7 (0.7)
LSM, kPa, mean (SD)	14.9 (10.9)	13.7 (6.7)	12.5 (5.5)	13.5 (8.4)
Total bile acid, µmol/L, mean (SD)	16.1 (17.5)	13.3 (11.8)	10.6 (6.5)	14.1 (11.6)

Demographics of total cohort include MYR203, MYR301, MYR204.
ADA, antidrug antibody; ALT, alanine aminotransferase; BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; LSM, liver stiffness measurement; NUC, nucleos(t)ide analogue.

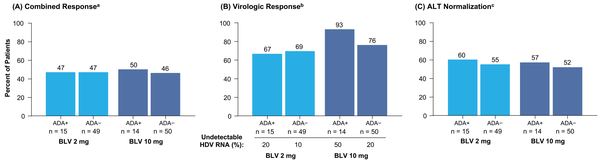
Table 2. Onset and Duration of On-Treatment ADA Incidence by Week 48

	BLV 2 mg	BLV 10 mg	Total
ADA onset, weeks, mean (SD)	26 (14.1) n = 15	21 (11.3) n = 25	23 (12.5) n = 40
ADA duration, weeks, mean (SD)	11 (12.5) n = 11	7 (8.3) n = 22	9 (9.9) n = 33

ADA, antidrug antibody; BLV, bulevirtide.

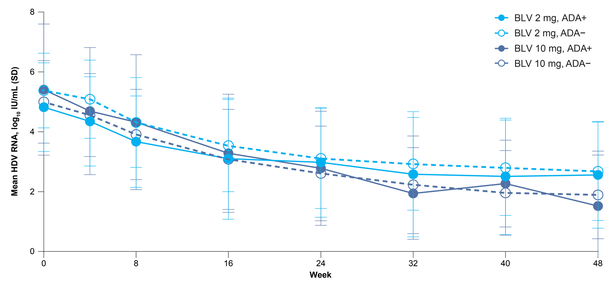
- Incidence rates for ADA development were similar with BLV 2 and 10 mg (23% and 22%, respectively). For this analysis, only patients who were evaluable for ADA incidence were included
- At baseline, 3 patients were ADA+ in the BLV 2- and 10-mg groups each

Figure 2. Efficacy by Week 48 of BLV Monotherapy by ADA Incidence



[a]Combined response determined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decrease from baseline and ALT normalization. [b]Virologic response determined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decrease from baseline; [c]ALT normalization was 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. Efficacy ISI analysis includes MYR203 and MYR301.
ADA, antidrug antibody; ALT, alanine aminotransferase; BLV, bulevirtide; HDV, hepatitis delta virus; ISI, integrated summary of immunogenicity.

Figure 3. HDV RNA Decline Over 48 Weeks of BLV Monotherapy



ADA, antidrug antibody; BLV, bulevirtide; HDV, hepatitis delta virus.

- ADA status did not have a clinically meaningful impact on HDV RNA decline with either BLV treatment group
- Combined, virologic, and biochemical response rates were similar regardless of ADA status in both BLV treatment groups

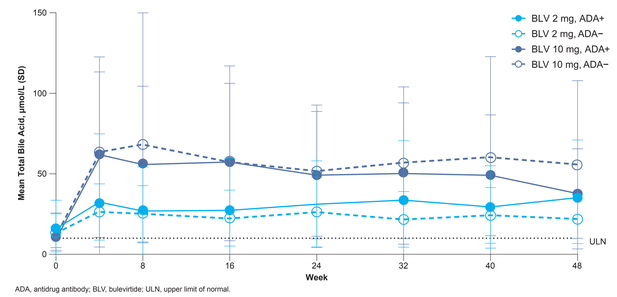
Table 3. Safety Outcomes by Dose and ADA Incidence by Week 48

Preferred Term, n (%)	BLV 2 mg		BLV 10 mg	
	ADA+ (n = 15)	ADA− (n = 49)	ADA+ (n = 25)	ADA− (n = 88)
TEAEs	15 (100)	40 (82)	22 (88)	76 (86)
TEAEs related to BLV	11 (73)	27 (55)	16 (64)	55 (63)
TEAEs of Grade ≥3	0	7 (14)	0	13 (15)
TE SAEs	0	2 (4)	1 (4)	1 (1)
TEAEs leading to premature BLV discontinuation	0	0	0	0
All deaths	0	0	0	0
TEAEs, ISR[a]	6 (40)	4 (8)	5 (20)	18 (20)
TEAEs, hypersensitivity[b]	0	2 (4)	0	5 (6)
TEAEs, immune-mediated/autoimmune[c]	1 (7)	0	0	1 (1)

[a]ISR terms included erythema, reaction, pruritus, pain, hematoma, swelling, dermatitis, induration, rash, coldness, and irritation. [b]Hypersensitivity terms included rash, injection-site dermatitis, injection-site rash, angioedema, rash macular, and toxic skin eruption. [c]Immune-mediated/autoimmune terms included chronic gastritis and psoriasis.
ADA, antidrug antibody; BLV, bulevirtide; ISR, injection-site reaction; SAE, serious adverse event; TE, treatment-emergent; TEAE, treatment-emergent adverse event.

- Rates of TEAEs, including those of Grade ≥3 and serious AEs, were comparable between subgroups
- No correlation was observed between ADA development and hypersensitivity or immune-mediated TEAEs

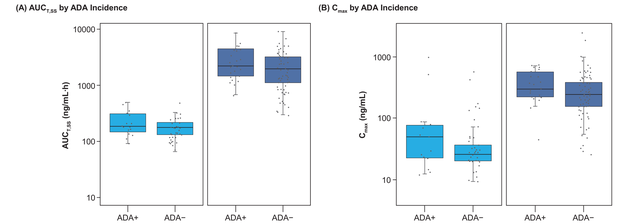
Figure 4. Total Bile Acid Levels Over 48 Weeks of BLV Monotherapy



ADA, antidrug antibody; BLV, bulevirtide; ULN, upper limit of normal.

- Dose-dependent asymptomatic elevations in total bile acids were not impacted by ADA incidence

Figure 5. BLV PK by ADA Incidence



	2 mg		10 mg	
	ADA+ (n = 15)	ADA− (n = 49)	ADA+ (n = 25)	ADA− (n = 88)
AUC_{0-24}, ng/mL·h, geometric mean	202	165	2330	1760
GMR ADA+/ADA− (90% CI)	1.22 (1.0–1.6)		1.32 (1.0–1.7)	
C_{max}, ng/mL, geometric mean	51.9	31.5	329	237
GMR ADA+/ADA− (90% CI)	1.65 (0.9–3.0)		1.39 (1.1–1.8)	

Boxplots depict the median, 25th percentile, and 75th percentile of AUC_{0-24} and C_{max} for patients receiving 2 or 10 mg bulevirtide from population PK modeling; gray dots represent individual patient data points.
ADA, antidrug antibody; AUC_{0-24}, area under the plasma concentration-time curve over a dosing interval at steady state; BLV, bulevirtide; C_{max}, maximum observed concentration of drug; GMR, geometric mean ratio; PK, pharmacokinetic.

- Development of ADAs did not meaningfully influence BLV PK exposure