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Hepcludex® (bulevirtide-gmod) Resistance Data

This document is in response to your request for information regarding the use of Hepcludex® (bulevirtide-gmod [BLV]) for the treatment of chronic HDV infection and resistance data from the phase 2 MYR202 and phase 3 MYR301 clinical studies.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hdv/hepcludex/hepcludex_pi.

Summary

Product Labeling[1]

BLV is indicated for the treatment of chronic HDV infection in adults without cirrhosis or with compensated cirrhosis.

This indication is approved under accelerated approval based on a decrease in HDV RNA and ALT normalization. An improvement in disease-related clinical outcomes has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

The recommended dosage in adults is BLV 8.5 mg once daily administered by SUBQ injection.

The efficacy of BLV once daily in the treatment of adults with chronic HDV infection without cirrhosis or with compensated cirrhosis is based on data through Week 144 from a multicenter, randomized, open-label, parallel-arm phase 3 trial, Trial MYR301 (NCT03852719), in which 100 participants received BLV 8.5 mg once daily. The MYR301 protocol specified the BLV dose as 10 mg; however, a dose recovery study later showed that the delivered dose was 8.5 mg.

HBV or HDV viruses resistant to BLV in cell culture have not been identified to date.

In Trials MYR301 and MYR204, resistance analysis was performed for 13/150 participants at Week 48, 20/150 participants at Week 96, and 5/50 participants at Week 144 on BLV treatment (n=24 unique participants).

No baseline polymorphisms identified in the BLV region of HBsAg or in HDAg were associated with virologic non-response or breakthrough. Similarly, no post-baseline substitutions in the BLV region or in HDAg showed an association with virologic breakthrough. All identified baseline and post-baseline variants retained susceptibility to BLV in cell culture assays. A positive control for resistance was not available for these experiments.

BLV Resistance Data

A resistance analysis was conducted using the Week 24 data of 21 adult participants with HBV/HDV who participated in the phase 2 MYR202 or phase 3 MYR301 studies, and another resistance analysis was performed using Week 96 data among 19 adult participants with chronic HDV in the MYR301 study.[2,3]

- In both analyses, the observed amino acid substitutions in HBV preS1, HDAg, and NTCP were not associated with reduced sensitivity to BLV.
- There was no resistance associated with BLV after 24 or 96 weeks of treatment in participants with chronic HDV.

Product Labeling[1]

Clinical Pharmacology

Microbiology: antiviral resistance

In cell culture

HBV or HDV viruses resistant to BLV in cell culture have not been identified to date. It is not possible to select for HBV or HDV resistance to antivirals using current cell culture systems. As described above, BLV maintained activity against lab-generated HDV carrying envelopes from HBV GTs A to H, lab-generated HDV carrying 24 different envelope variants from HBV GTs A to D, and HDV clinical isolates in primary human hepatocytes. In addition, NTCP polymorphisms that disrupt BLV activity while permitting HDV infection have not been identified to date.

In clinical trials

The antiviral activity of BLV 8.5 mg against different HBV and HDV GTs was evaluated in trials MYR301 and MYR204. HBV GT D was the most prevalent in these trials, in 129/150 (86%) participants, followed by GT A in 12/150 (8%) participants. For participants treated with BLV 8.5 mg for 96 weeks, a virologic response (HDV RNA declining ≥2 $\log_{10}$ IU/mL or becoming undetectable) was achieved by 6/12 (50%) participants with GT A and 112/129 (87%) participants with GT D, which included 1/12 (8.3%) participants with GT A who achieved undetectable HDV RNA compared with 52/129 (40%) participants with GT D.

Resistance analysis was performed for participants who had virologic non-response (HDV RNA decline <1 $\log_{10}$ IU/mL from baseline) or who experienced virologic breakthrough (2 consecutive increases in HDV RNA of ≥1 $\log_{10}$ IU/mL from nadir or 2 consecutive HDV RNA values ≥LLoQ if previously <LLoQ during treatment with BLV).

In Trials MYR301 and MYR204, resistance analysis was performed for 13/150 participants at Week 48, 20/150 participants at Week 96, and 5/50 participants at Week 144 on BLV treatment (n=24 unique participants). Amino acid sequences for the BLV region of HBsAg were determined at baseline for 17/24 participants with virologic non-response or breakthrough at any time point, and paired baseline and post-baseline sequence data were determined for 10/24 participants. For HDV, baseline sequence data for the HDAg region were determined for 23/24 participants, and paired baseline and post-baseline sequence data were determined for 21/24 participants.

No baseline polymorphisms identified in the BLV region of HBsAg or in HDAg were associated with virologic non-response or breakthrough. Similarly, no post-baseline substitutions in the BLV region or in HDAg showed an association with virologic breakthrough. All identified baseline and post-baseline variants retained susceptibility to BLV in cell culture assays. A positive control for resistance was not available for these experiments.

Cross-resistance

Cross-resistance is not expected between BLV and nucleos(t)ide analog reverse transcriptase inhibitors approved for the treatment of chronic HBV infection given their different mechanisms of action.

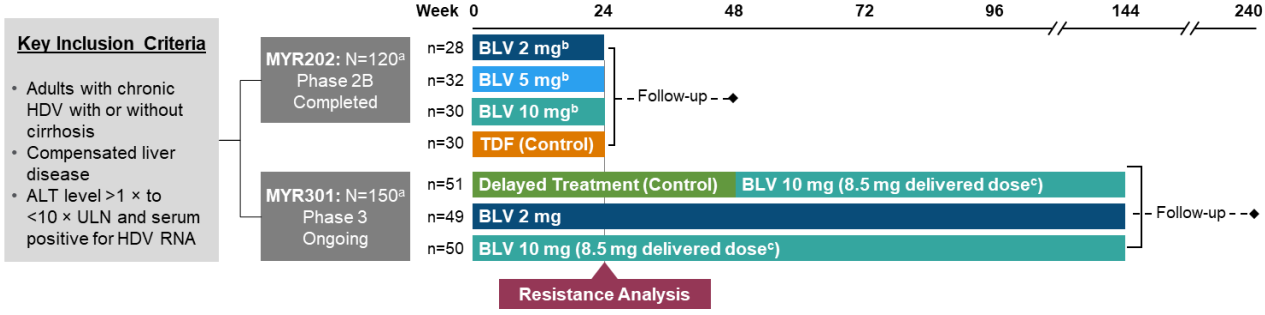
BLV Resistance Data

MYR202 and MYR301 Studies: Resistance Analysis of Week 24 Data

Study design[2,4]

A resistance analysis was conducted with a participant sample at Week 24 from the phase 2 MYR202 and phase 3 MYR301 studies of BLV for the treatment of participants with chronic HDV co-infected with HBV (Figure 1). The resistance analysis was conducted for nonresponders (defined as participants with a decrease in HDV RNA by <1-$\log_{10}$ IU/mL from baseline at Week 24) and in participants with virologic breakthrough (defined as participants with two consecutive HDV RNA values ≥LLoD if HDV RNA was <LLoD at ≥2 consecutive time points or with confirmed HDV RNA increases of ≥1-$\log_{10}$ IU/mL on two consecutive visits during treatment and/or until end of treatment, assuming the nadir was previously ≥1-$\log_{10}$ IU/mL below the HDV RNA baseline value at two consecutive visits).

Figure 1. Resistance Analysis of MYR202 and MYR301: Study Designs[2,4]



Abbreviation: ULN=upper limit of normal.
[a]Total N of participants. [b]Administered with TDF 300 mg.
[c]The MYR301 protocol specified the dose as 10 mg per vial; the delivered dose was 8.5 mg.

Results[2]

A total of 21 participants who were considered to be nonresponders (BLV 2 mg, n=10; BLV 5 mg, n=8; BLV 10 mg, n=2) or had a virologic breakthrough (BLV 2 mg, n=1) were included in this analysis. None of the amino acid substitutions observed in HBV preS1, HDAg, or NTCP were associated with reduced sensitivity to BLV. At Week 24, there were

2 participants in the BLV 2 mg group with new HDV polymorphic substitutions (Table 1). Viruses with amino acid substitutions in HBV preS1 or HDAg remained sensitive to BLV.

Table 1. Resistance Analysis of Nonresponders in MYR202 and MYR301: Amino Acid Substitutions in HBV preS1, HDV HDAg, and NTCP Sequencing Through Week 24[2]

Participants	Timepoint	Available Data for Sequence Analysis, n	Amino Acid Substitution
HBV[a] n=21	Baseline	6	G35K
	Week 24	5	No sequence changes from baseline
HDV[b] n=21	Baseline	19	S2G, R13K, K25R, I54V, D62E, K72R, D77N, E125D, E126D, L133S, E184D, L186I, L186I/M
	Week24	8	Participant 1: N121N/Y and S170S/N Participant 2: S210S/G
NTCP n=21	Baseline	6	G225A (T75T)
	Week 24	Not reported	Not reported

[a]Participants with data available at both baseline and Week 24, n=1.
[b]Participants with data available at both baseline and Week 24, n=7.
[c]Participants with data available at both baseline and Week 24, n=1.

In an analysis of treatment outcome groups (nonresponders, n=7; partial responders, n=19; responders, n=50; no treatment, n=39), no differences in sensitivity to BLV were observed across groups. Among the 4 nonresponders with HBV GT D or A who had both baseline and Week 24 EC_{50} data, there were no changes in BLV sensitivity.

There was no resistance associated with BLV after 24 weeks of treatment.

MYR301 Study: Resistance Analysis of Week 96 Data[3]

Study design

A resistance analysis was conducted among participants with chronic HDV infection in the phase 3 MYR301 study who received BLV 2 or 10 mg for 96 weeks to determine whether BLV resistance occurred. A Week 96 resistance analysis was conducted for all nonresponders (HDV RNA decline <1 $\log_{10}$ IU/mL from baseline) and participants with virologic breakthrough (two consecutive HDV RNA values ≥LLoQ of 50 IU/mL or a confirmed increase in HDV RNA ≥1 $\log_{10}$ IU/mL from the nadir at ≥2 consecutive visits under treatment).

Results

At Week 96, 19/99 participants qualified for resistance testing (BLV 2 mg, n/N=14/49; BLV 10 mg, n/N=5/50); 2 participants were nonresponders, and 17 participants had virologic breakthroughs. At Week 96, 13 participants had polymorphic site changes (Table 2). None of the amino acid substitutions observed in HBV preS1, HDAg, or NTCP were associated with reduced sensitivity to BLV through Week 96.

Table 2. MYR301: Resistance Analysis of Nonresponders or Participants With Virologic Breakthrough Through Week 96[3]

Participants	Timepoint	Available Data for Sequence Analysis, n	Amino Acid Substitution
HBV[a] n=19	Baseline	8	None
	Week 96	3	No sequence changes from baseline
HDV[b] n=19	Baseline	18	R13K, I54V,[c] D64E,[c] P85S/T, P85P.G, S123G
	Week 96	18	13 participants had polymorphic site changes; only R132K and G/K139R were observed in >1 tested participant
NTCP n=19	Baseline	17	G225A (T75T)[c]
	Week 96	Not conducted	Not conducted

[a]Participants with data available at both baseline and Week 96, n=3. All had no sequence change from baseline.
[b]Participants with data available at both baseline and Week 96, n=17. All had >99% conservation from baseline.
[c]Substitutions were also observed in virologic responders (undetectable HDV RNA at Week 96 or ≥2 $\log_{10}$ IU/mL decline from baseline).

Among participants with available data at baseline and Week 96, no differences in sensitivity to BLV were observed across outcome groups (nonresponders, n=2; participants with virologic breakthrough, n=14; partial responder, n=1; virologic responders, n=63).

There was no resistance associated with BLV after 96 weeks of treatment.

References

1. Enclosed. Gilead Sciences Inc. HEPCLUDEX® (bulevirtide) injection, for subcutaneous use. US Prescribing Information. Foster City, CA.
2. Hollnberger J, Liu Y, Xu S, et al. No virologic resistance to bulevirtide monotherapy detected in patients through 24 weeks treatment in phase II and III clinical trials for chronic hepatitis delta. *J Hepatol.* 2023;79(3):657-665.
3. Aleman S, Liu Y, Xu S, et al. No Detectable Resistance to Bulevirtide Monotherapy Through 96 Weeks Treatment inPatients With Chronic Hepatitis Delta. [Poster 1237-C]. Paper presented at: AASLD - The Liver Meeting; November 10-14, 2023; Boston, MA.
4. Wedemeyer H, Aleman S, Brunetto MR, et al. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. *N Engl J Med.* 2023;389(1):22-32.

Abbreviations

BLV=bulevirtide-gmod
EC_{50}=half-maximal effective concentration
GT=genotype
HBsAg=hepatitis B surface antigen
HDAg=hepatitis D antigen
LLoD=lower limit of detection
LLoQ=lower limit of quantitation
NTCP=sodium taurocholate co-transporting polypeptide
TDF=tenofovir disoproxil fumarate

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Hepcludex US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hdv/hepcludex/hepcludex_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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