SAT385

No Detectable Resistance to Bulevirtide in Participants With Chronic Hepatitis D Through 24 Weeks of Treatment

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Introduction

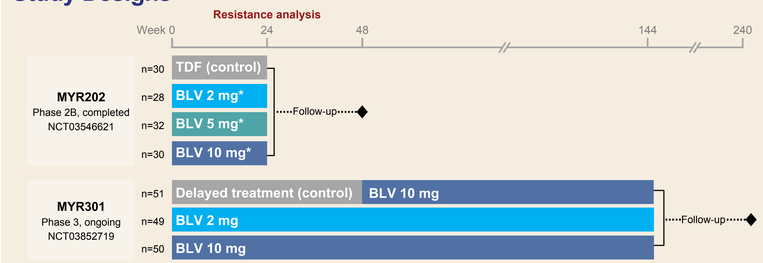
- Bulevirtide (BLV) blocks entry of hepatitis delta virus (HDV) into hepatocytes via competitive inhibition of the interaction between the hepatitis B virus (HBV) preS1 domain and the sodium taurocholate cotransporting polypeptide (NTCP) receptor[1,2]
- Previous studies showed that treatment with BLV alone led to substantial HDV RNA declines in patients with chronic HDV[3,4]

Objective

- To perform a resistance analysis in patients with chronic HDV who received BLV for 24 weeks across 2 studies (MYR202 [phase 2] and MYR301 [phase 3])

Methods

Study Designs

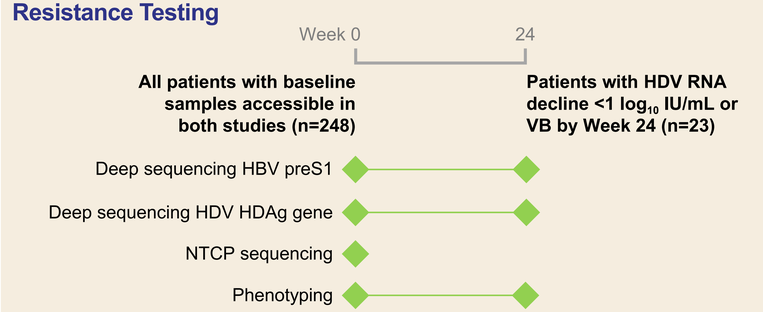


*In combination with tenofovir disoproxil fumarate (TDF).

Virologic Response Definitions and Resistance Analysis Population

- Virologic responder: HDV RNA < lower limit of detection (LLOD) at Week 24 or decline ≥2 $\log_{10}$ IU/mL from baseline at Week 24
- Partial responder: HDV RNA decline ≥1, but <2 $\log_{10}$ IU/mL from baseline at Week 24
- Nonresponder (NR): HDV RNA decline <1 $\log_{10}$ IU/mL from baseline at Week 24
- Virologic breakthrough (VB):
  - 2 consecutive HDV RNA values ≥LLOD if HDV RNA was previously <LLOD at ≥2 consecutive time points; or
  - Confirmed increase in HDV RNA ≥1 $\log_{10}$ IU/mL from the nadir on 2 consecutive visits under treatment and/or until end of treatment, assuming the nadir was previously ≥1 $\log_{10}$ IU/mL below the HDV RNA baseline value at 2 consecutive visits
- Resistance analysis was performed for NRs and patients who experienced a VB

Resistance Testing

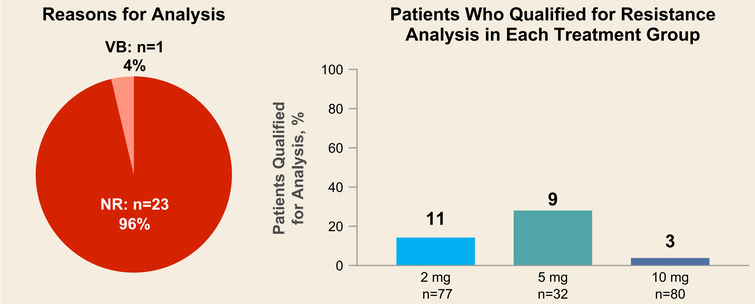


HDAg, hepatitis delta antigen.

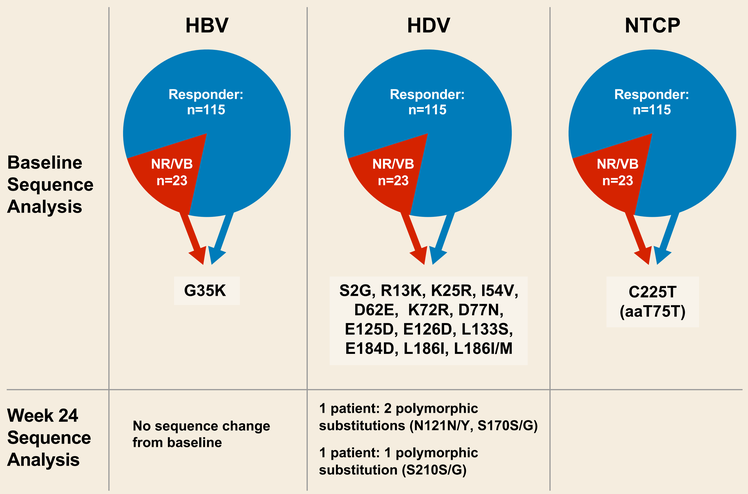
- HBV preS1 deep sequencing: total HBV nucleic acids were extracted from patient plasma followed by cDNA synthesis; polymerase chain reaction was conducted using both DNA and cDNA to increase assay sensitivity
- HDV HDAg deep sequencing: HDV RNA was extracted from patient plasma followed by complementary DNA (cDNA) synthesis and HDV full-genome amplification with 2 overlapping fragments
- NTCP sequencing: whole exome sequencing followed by analysis of single-nucleotide polymorphisms/small insertions and deletions, and variants in NTCP target region
- Phenotyping: primary human hepatocytes were pretreated with BLV and then infected with patient plasma; after 5 days, immunofluorescence staining was performed to determine cells that were positive for HDAg and half-maximal effective concentration (EC_{50}) was obtained

Results

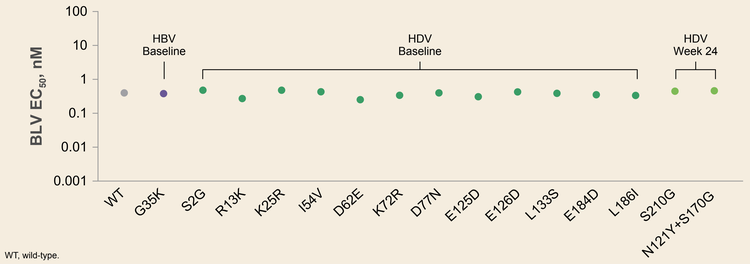
Patients Who Qualified for Resistance Analysis at Week 24



Amino Acid Substitutions Observed in HBV preS1, HDAg, and NTCP

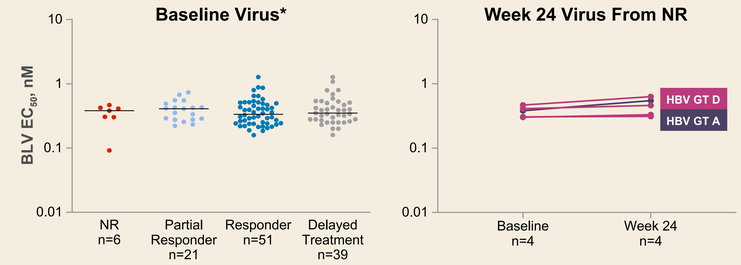


Virus With Amino Acid Substitution in HBV preS1 or HDAg Remained Sensitive to BLV



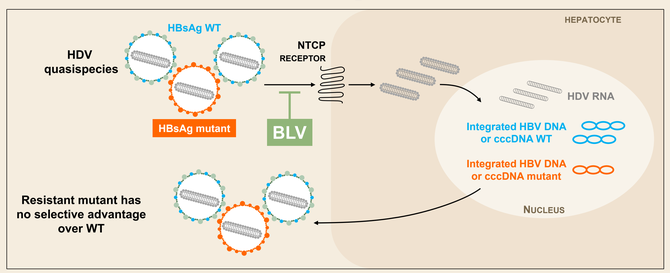
WT, wild-type.

No BLV Sensitivity Difference Across Different Treatment Outcome Groups and Baseline/Week 24 Viruses



*Circles represent individual data; *horizontal lines* represent median. GT, genotype.

Lack of Resistance Selection During BLV Treatment



cccDNA, covalently closed circular DNA; HBsAg, hepatitis B surface antigen.

Conclusions

- No unique amino acid substitutions associated with reduced sensitivity to BLV were observed in HBV preS1, HDV HDAg, and NTCP
- No BLV sensitivity differences were observed across different treatment outcome groups and baseline/Week 24 viruses
- This largest dataset to date demonstrated no resistance associated with BLV after 24 weeks of treatment

References: **1.** Ni Y, et al. Gastroenterology 2014;146:1070-83; **2.** Yan H, et al. Elife 2012;1:e00049; **3.** Wedemeyer H, et al. EASL 2021, abstr LBP-2730; **4.** Wedemeyer H, et al. Hepatology 2017;66(suppl):20A (abstr 37).
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