# Antiviral activity and safety of the hepatitis B core inhibitor ABI-H0731 administered with a nucleos(t)ide reverse transcriptase inhibitor in patients with HBeAg negative chronic hepatitis B infection

Scott Fung[1], Mark S. Sulkowski[2], Jacob Lalezari[3], Eugene R. Schiff[4], Douglas Dieterich[5], Tarek Hassanein[6], Paul Kwo[7], Magdy Elkhashab[8], Ronald Nahass[9], Walid Ayoub[10], Steven-Huy Han[11], Maurizio Bonacini[3], Katia Alves[12], Hany Zayed[12], Qi Huang[12], Richard Colonno[12], Steven J Knox[12], Luisa M. Stamm[12], Alnoor Ramji[13], Michael Bennett[14], Edward Gane[15], Natarajan Ravendhran[16], James Park[17], Ira Jacobson[17], Ho Bae[18], Sing Chan[19], Hie-Won Hann[20], Xiaoli Ma[21], Tuan T. Nguyen[22], Man-Fung Yuen[23]

[1]University of Toronto, Toronto, Canada; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Quest Clinical Research, San Francisco, CA, US; [4]Schiff Center for Liver Diseases, University of Miami School of Medicine, Miami, FL, US; [5]Department of Medicine, Division of Liver Diseases, Icahn School of Medicine, Mount Sinai Hospital, New York, NY, US; [6]Southern California Research Center, Coronado, CA, US; [7]Stanford University Medical Center, Stanford, CA, US; [8]Toronto Liver Centre, Toronto, ON, Canada; [9]Infectious Disease Care, Hillsborough, FL, US; [10]Cedars-Sinai Medical Center, Los Angeles, CA, US; [11]Pfleger Liver Institute, University of California, Los Angeles, CA, US; [12]Assembly Biosciences, Inc., South San Francisco, CA, US; [13]Providence Health Care Research Institute, Vancouver, BC, Canada; [14]Medical Associates Research Group, San Diego, CA, US; [15]Auckland Clinical Studies Ltd, Auckland, New Zealand; [16]Digestive Disease Associates, Catonsville, MD, US; [17]New York University Langone Medical Center, New York, NY, US; [18]Asian Pacific Liver Center, Los Angeles, CA, US; [19]Sing Chan MD, New York, NY, US; [20]Thomas Jefferson University Hospital, Philadelphia, PA, US; [21]Office of Xiaoli Ma, Philadelphia, PA, US; [22]T Nguyen Research and Education, Inc., San Diego, CA, US; [23]Department of Medicine, The University of Hong Kong, Hong Kong, Hong Kong

# Disclosures: Scott Fung

- Assembly Biosciences
  - Consulting
- Gilead Sciences
  - Consulting, Teaching & Speaking, Research Support
- Springbank Pharma
  - Consulting

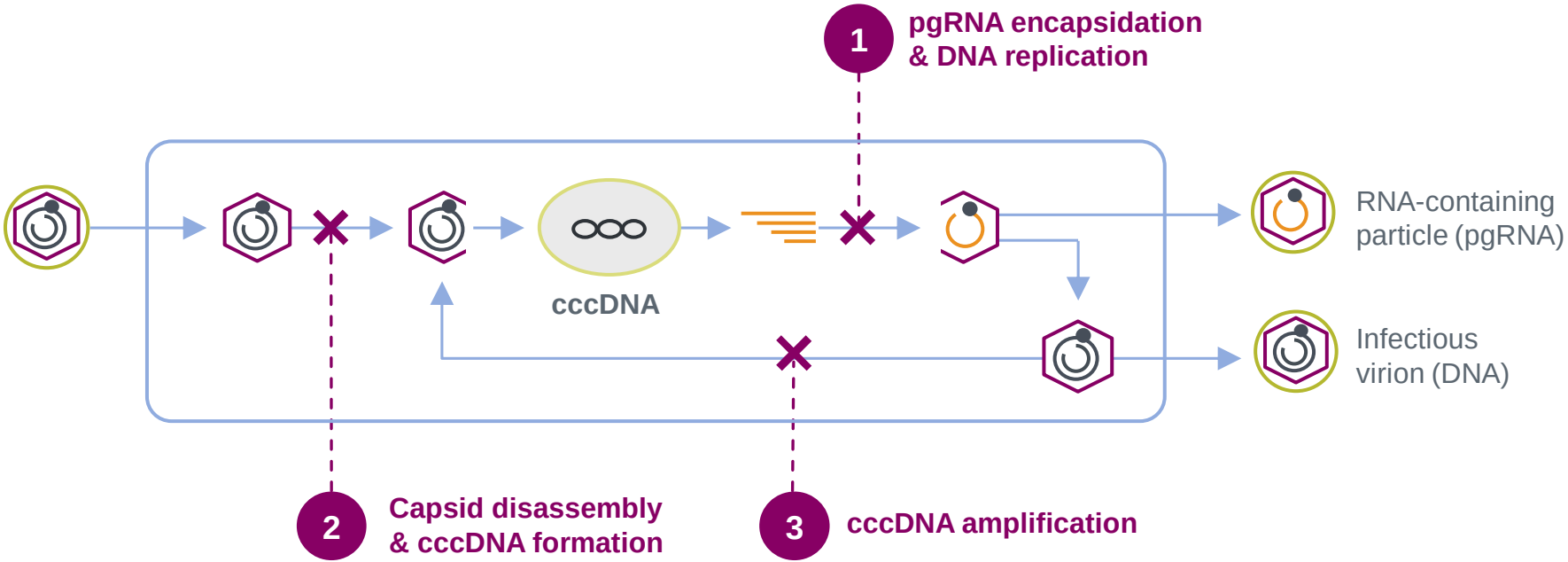
# Background

- Worldwide, an estimated 250 million people are chronically infected with HBV and 600,000–1 million die each year due to cirrhosis and HCC associated with CHB infection[1–4]
  - Based on global prevalence modelling, of the estimated 94 million patients considered to be eligible for treatment, only approximately 4.8 million (5%) actually receive antiviral therapy[5]
- New therapies are needed to provide deeper suppression of HBV replication that may ultimately achieve off-therapy sustained virologic response and allow for finite therapy
- Incorporation of pgRNA quantification in clinical studies will enable a more comprehensive assessment of the level of cccDNA transcriptional activity and HBV replication and should lead to improved treatment options for patients with CHB[6–8]
  - The presence of HBV pgRNA is associated with persistent viral replication and the risk of relapse following cessation of treatment with NrtI[8–12]

cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NrtI, Nucleos(t)ide analogue reverse transcriptase inhibitor; pgRNA, pregenomic RNA.

1) European Association for the Study of the Liver. *J Hepatol*. 2017;67:370–98. 2) World Health Organization. Global Hepatitis Report. 2017. 3) El-Serag HB et al. *Gastroenterology*. 2012;142(6):1264–73. 4) Colvin HM & Mitchell AE. National Academies Press. 2010. 5) The Polaris Observatory Collaborators. *Lancet Gastroenterol*. 2018;3:383–403. 6) Bai F et al. *Int J Hepatol*. 2013;1–9. 7) Cornberg M et al. *J Hepatol*. 2020;72:539–57. 8) Lin N et al. *J Clin Microbiol*. 2020;58:e01275–19. 9) Wang J et al. *J Hepatol*. 2016;65:700–10. 10) Carey I et al. *Hepatology*. 2020;72:42–57. 11) Fan R et al. *Clin Gastroenterol Hepatol*. 2020; 18:719–27. 12) Fan R et al. *J Infect*. 2020;222:611–18.

# Core Inhibitor Mechanisms of Action

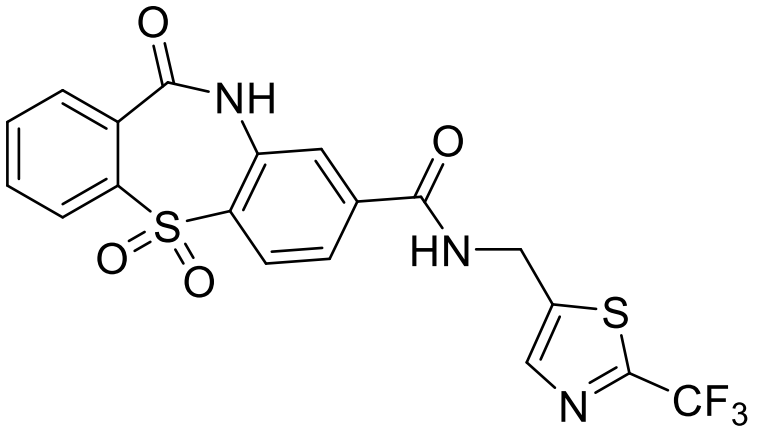



- Core inhibitors target multiple steps of the HBV life cycle to suppress HBV DNA, pgRNA, and cccDNA
- Combination treatment with a core inhibitor and a NrtI, which have distinct mechanisms of action, has the potential to lead to deeper virologic suppression and to improve treatment outcomes of CHB

cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; HBV, hepatitis B virus; NrtI, nucleos(t)ide analogue reverse transcriptase inhibitor; pgRNA, pregenomic RNA.

# Vebicorvir (VBR, ABI-H0731): A Novel Inhibitor of HBV Core Protein

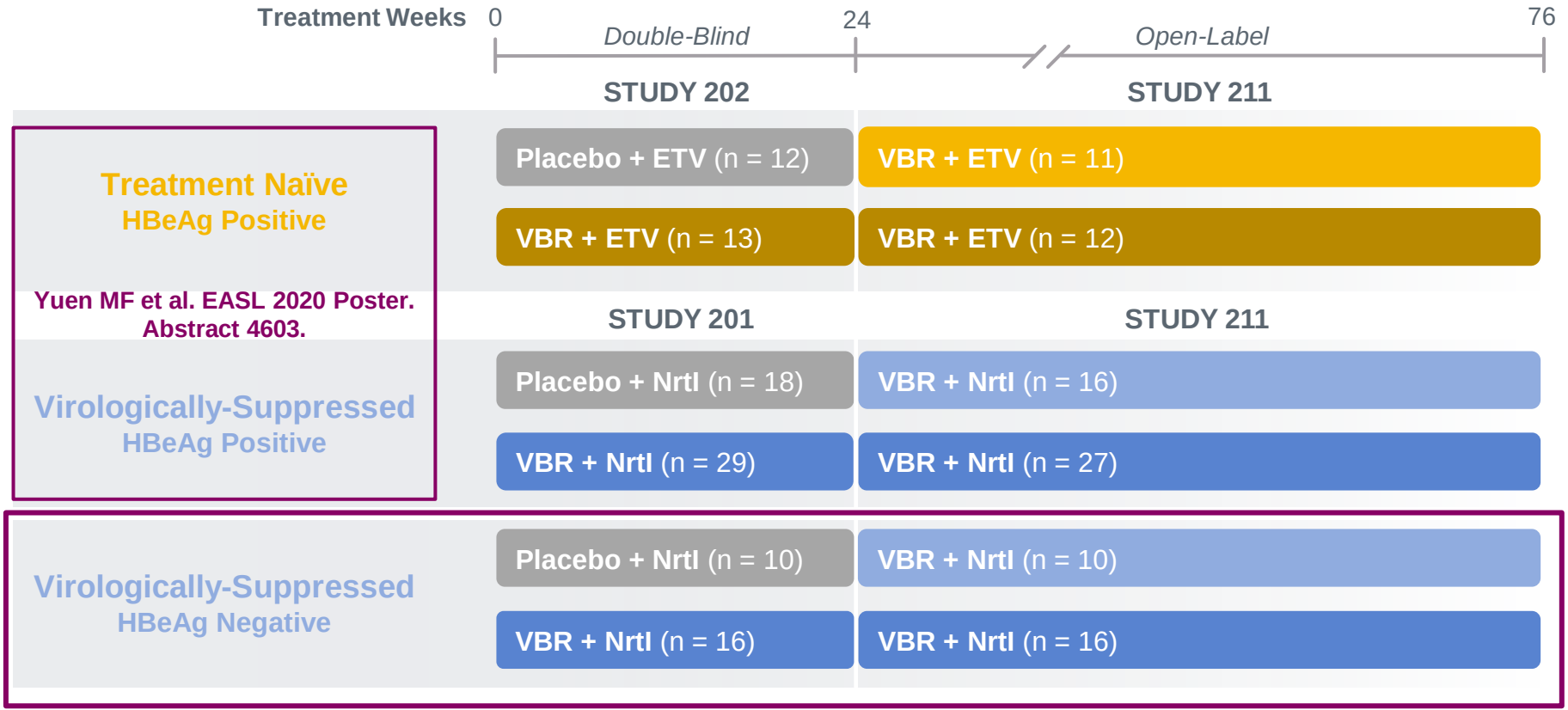
- Disrupts HBV capsid formation by allosteric binding and interference with core protein
- Broad in vitro antiviral activity[1]
  - Inhibits virion and pgRNA particle production ($EC_{50}$= 0.17–0.31 µM; $CC_{50}$ = >20 µM)
  - Inhibits de novo formation of cccDNA and downstream HBeAg and HBsAg production ($EC_{50}$= 2–7 µM)
  - Pangenotypic and fully active against NrtI-resistant HBV
- Orally administered as 300 mg once daily without regard to food
- No drug interaction with NrtIs
- Favorable clinical safety profile
- Superior reduction in HBV DNA and pgRNA in combination with NrtIs compared to NrtI alone in HBeAg positive CHB patients[2]




$CC_{50}$, 50% cytotoxic concentration; $EC_{50}$, concentration of drug that gives half-maximal response; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; VBR, vebicorvir.

1) Huang Q et al. *Antimicrob Agents Chemother*. 2020 (Submitted). 2) Sulkowski MS et al. *Hepatology*. 2019;70(Suppl 1):936A.

# Phase 2 Clinical Trial Overview




ETV, entecavir.

# Objectives and Key Entry Criteria

**The objectives of Study 201 and 211 were to:**

- Evaluate the safety of VBR in patients with HBeAg negative CHB
- Determine the efficacy of VBR in patients with HBeAg negative CHB

**Patients from 21 sites in the United States, Canada, Hong Kong, and New Zealand were enrolled if they met the following key entry criteria:**



Patients 18 to 70 years old with CHB in good general health



Metavir F0-F2 or equivalent (no history of hepatic decompensation)



Study 201: On NrtI with HBV DNA ≤LLOQ by COBAS for at least 6 months, HBsAg >100 IU/mL; ALT ≤5x ULN



Study 211: Completion of Study 201 with compliance to study drug

ALT, alanine aminotransferase; LLOQ, lower limit of quantification; ULN, upper limit of normal.

# Methods

- Safety was assessed by AEs and laboratory parameters
- Efficacy was assessed through monitoring of HBV nucleic acids and HBV antigens

| Assay | Limits |
|---|---|
| Assembly HBV DNA Assay (Study 201/211)[a] | LOD = 5 IU/mL |
| Assembly HBV pgRNA Assay (Study 201/211)[a] | LLOQ = 35 U/mL |
| Assembly HBV Total Nucleic Acids (Composite DNA + pgRNA; Study 211)[a] | LLOQ = 20 IU/mL |
| Hepatitis B e-antigen, Quantitative Abbott ARCHITECT i2000SR | LLOQ = 0.11 IU/mL |
| Hepatitis B surface antigen, Quantitative Abbott ARCHITECT i2000SR | LLOQ = 0.05 IU/mL |
| Hepatitis B core-related antigen, Lumipulse G | LLOQ = 1 kU/mL |

[a]Detailed information regarding Assembly assays is included in Huang Q et al. EASL 2020 Poster Presentation, Abstract 4154.

- Resistance monitored by population sequencing of the HBV core protein and polymerase RT regions (mutant detection limit ≥5%)
- Genotyping was performed with highly sensitive PCR (DNA) and RT-PCR (DNA + pgRNA) assays to detect a single copy of HBV genome

AE, adverse events; LOD, limit of detection; PCR, polymerase chain reaction; RT, reverse transcription.

# Study 201/211: Virologically-Suppressed, HBeAg Negative Patients

## *Baseline Demographics and Disease Characteristics*

| HBeAg Negative | Placebo + NrtI N = 10 | VBR + NrtI N = 16 |
|---|---|---|
| Age, years, mean (SD) | 46.9 (8.3) | 49.3 (7.7) |
| Male, n (%) | 5 (50) | 11 (69) |
| Asian, n (%) | 9 (90) | 11 (69) |
| Genotype A, n (%) | 2 (20) | 4 (25) |
| B, n (%) | 0 | 4 (25) |
| C, n (%) | 1 (10) | 1 (6) |
| D, n (%) | 0 | 1 (6) |
| Not determinable[a], n (%) | 7 (70) | 6 (38) |
| Duration of NrtI at randomization, years, mean (SD) | 6.6 (5.8) | 2.8 (3.6) |
| Tenofovir disoproxil fumarate (TDF), n (%) | 4 (40) | 7 (44) |
| Tenofovir alafenamide fumarate (TAF), n (%) | 4 (40) | 6 (38) |
| Entecavir (ETV), n (%) | 2 (20) | 3 (19) |

[a]Not enough sequence data to confirm genotype.

SD, standard deviation.

# Study 201/211: Virologically-Suppressed, HBeAg Negative Patients

## *Baseline Demographics and Disease Characteristics*

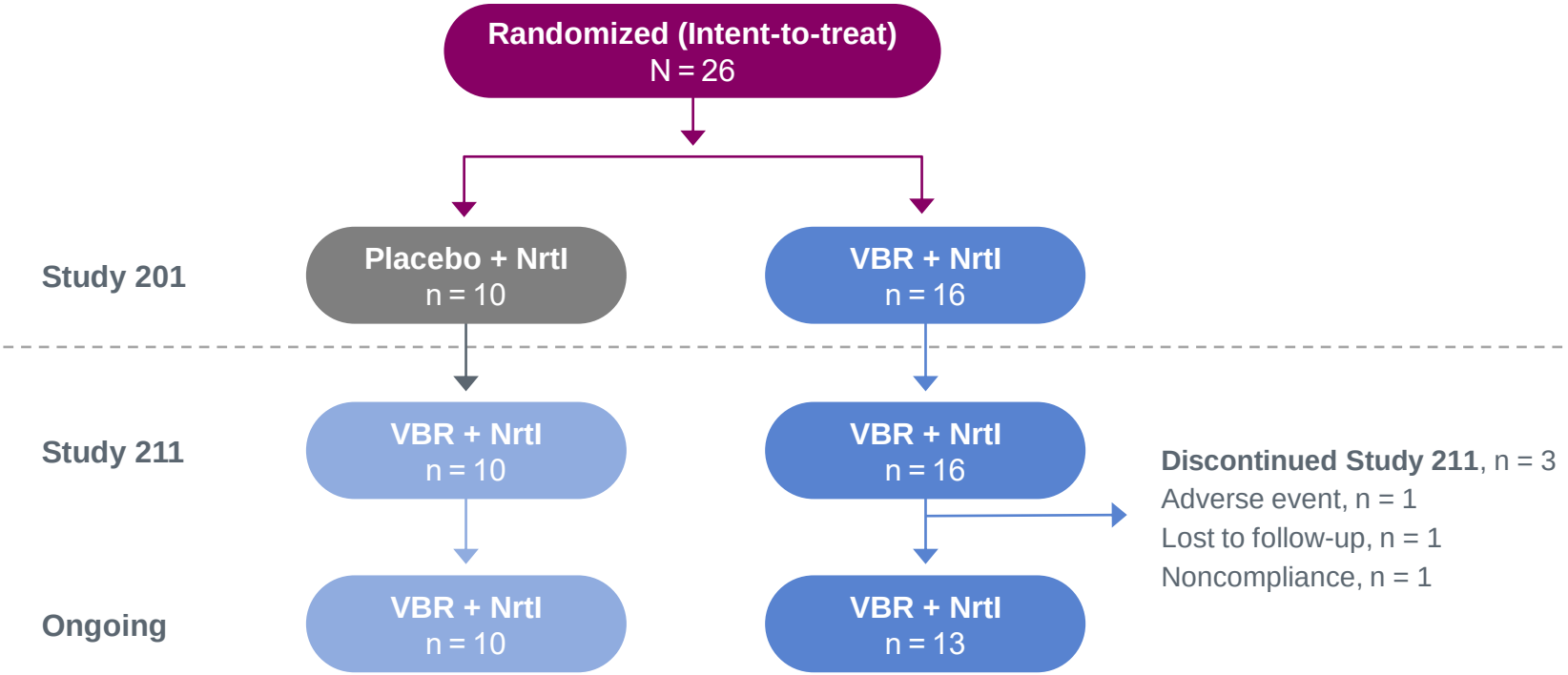
| HBeAg Negative | Placebo + NrtI N = 10 | VBR + NrtI N = 16 |
|---|---|---|
| HBV DNA (COBAS) <LLOQ[a], n (%) | 10 (100) | 16 (100) |
| HBV DNA (Assembly), n (%) | | |
| Target not detected[b] | 8 (80) | 10 (63) |
| HBV pgRNA, $Log_{10}$ U/mL, mean (SD) | 1.6 (0.1) | 1.7 (0.3) |
| <LLOQ[c], n (%) | 9 (90) | 13 (81) |
| HBeAb Positive, n (%) | 9 (90) | 14 (88) |
| HBsAg, $Log_{10}$ IU/mL, mean (SD) | 3.3 (0.7) | 3.0 (0.6) |
| HBcrAg, $Log_{10}$ kU/mL, mean (SD) | 0.6 (0.6) | 0.5 (0.7) |
| ALT, U/L, mean (SD) | 21 (10) | 27 (13) |

[a]LLOQ = 20 IU/mL.
[b]LOD = 5 IU/mL.
[c]LLOQ = 35 U/mL.

HBcrAg, hepatitis B core-related antigen; HBeAb, hepatitis B e-antibodies.

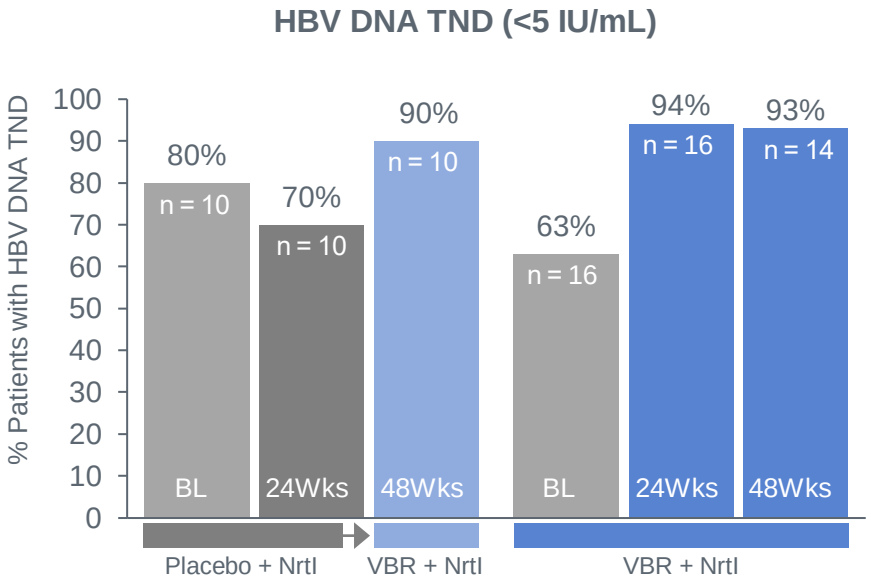
# Study 201/211: Virologically-Suppressed, HBeAg Negative Patients

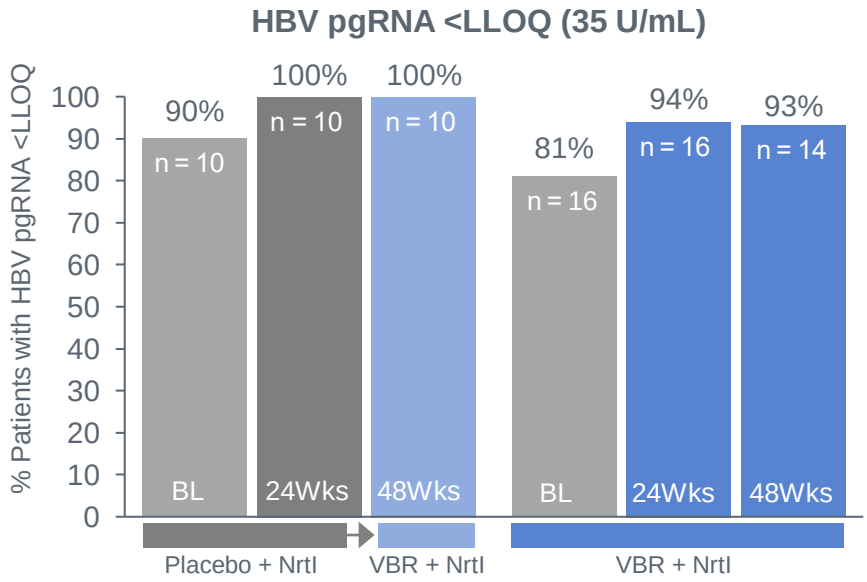
## *Disposition*



# Study 201/211: Virologically-Suppressed, HBeAg Negative Patients

## *Efficacy: HBV DNA and HBV pgRNA*



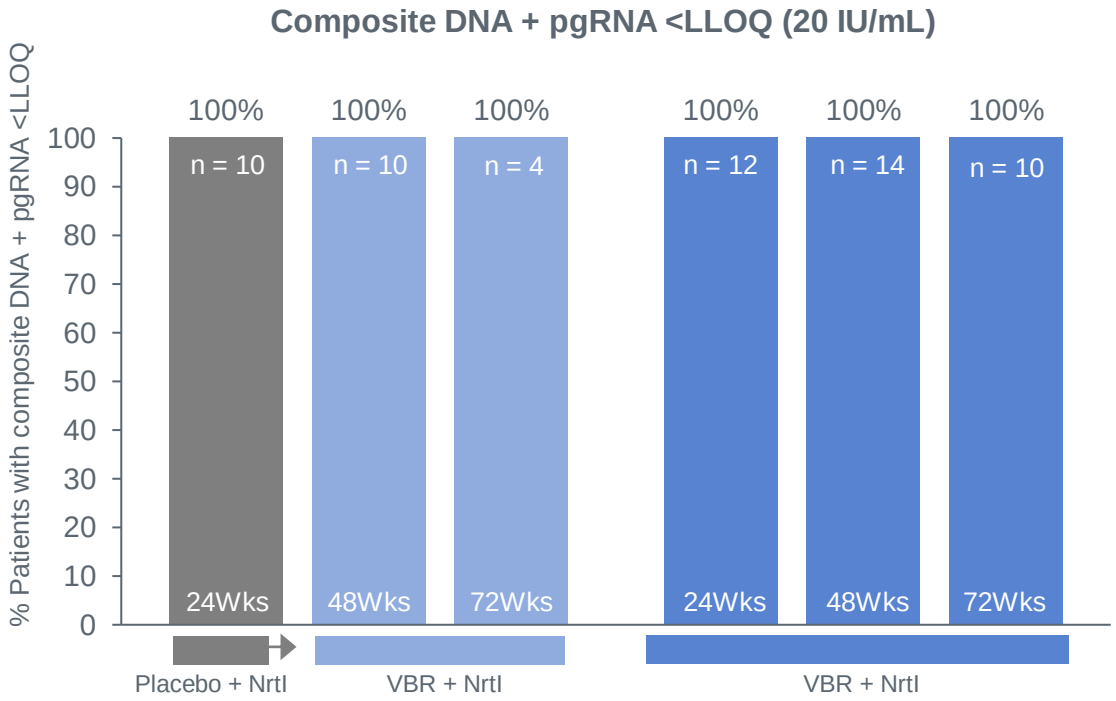




- 31% of patients (8/26) had detectable HBV DNA at baseline when assessed using the more sensitive assay
- One patient experienced HBV DNA rebound (1 $\log_{10}$ increase from nadir) in the setting of noncompliance with both study drugs

BL, baseline; TND, target not detected; Wks, weeks.

# Study 201/211: Virologically-Suppressed, HBeAg Negative Patients

## *Efficacy: Composite DNA + pgRNA Assay*




- The composite DNA + pgRNA assay is being utilized to determine which patients are eligible to stop treatment

# Study 201/211: Virologically-Suppressed Patients

## *Criteria For Stopping Therapy*


- HBV Total Nucleic Acids (Composite DNA + pgRNA Assay) <20 IU/mL

**AND**

- HBeAg Negative or HBeAg ≤5 IU/mL

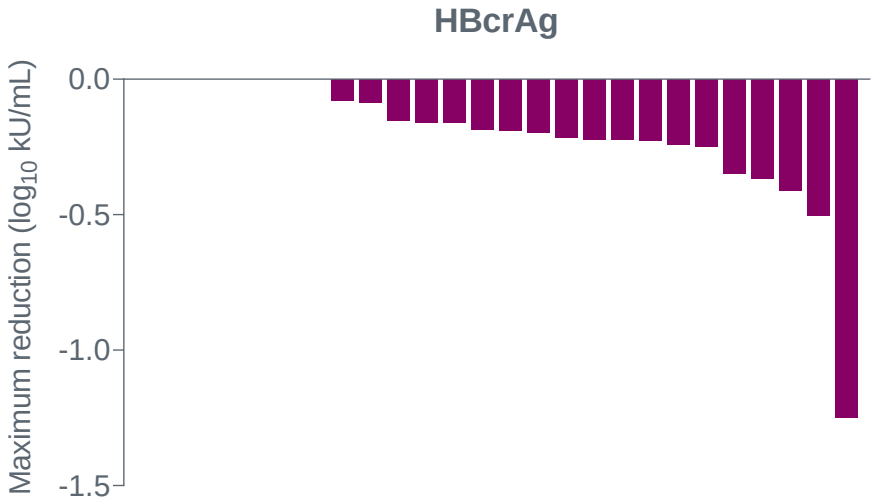
**For at least 6 months prior to Treatment Week 76**

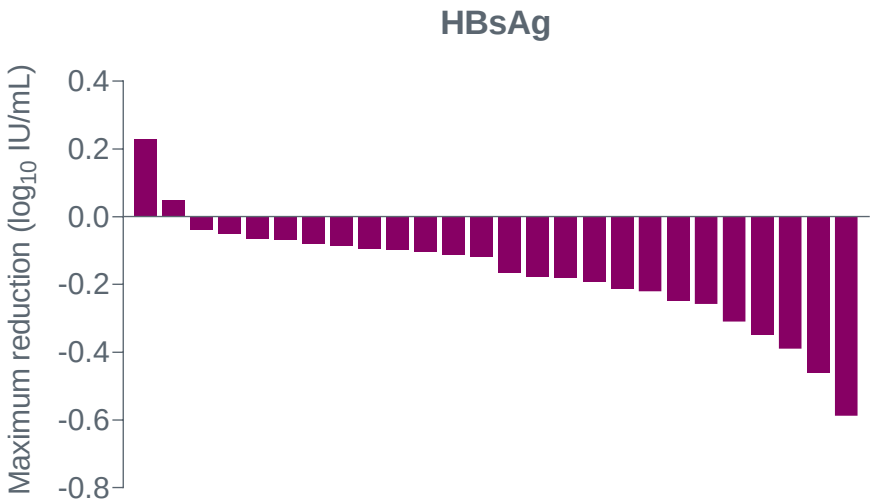
- 88% (23/26)[a] of patients who enrolled in Study 211 are projected to discontinue both VBR + NrtI (12% [3 patients] have discontinued VBR for other reasons)

[a]As of July 9, 2020 data cut.

# Study 201/211: Virologically-Suppressed, HBeAg Negative Patients

## *Efficacy: HBV Antigens*




- Most patients experienced some decrease in HBcrAg and HBsAg on treatment with VBR + NrtI

# Study 201/211: Virologically-Suppressed, HBeAg Negative Patients

## *Safety: Overall Summary*

| Patients, n (%) | Study 201 (24 weeks) | | Study 211 (24 to 72 weeks) | |
|---|---|---|---|---|
| | Placebo + NrtI N = 10 | VBR + NrtI N = 16 | VBR + NrtI[a] N = 10 | VBR + NrtI N = 16 |
| Any TEAE | 3 (30) | 10 (63) | 6 (60) | 8 (50) |
| Grade 1 | 3 (30) | 8 (50) | 3 (30) | 5 (31) |
| Grade 2 | 0 | 2 (13) | 3 (30) | 3 (19) |
| Grade ≥3 | 0 | 0 | 0 | 0 |
| Serious AEs | 0 | 0 | 0 | 0 |
| AEs leading to DC | 0 | 0 | 1[b] | 0 |
| Deaths | 0 | 0 | 0 | 0 |

[a]Patients who received placebo + NrtI in Study 201.
[b]Grade 1 rash, which began in Study 201 led to study drug discontinuation in Study 211.

DC, discontinuation; TEAE, treatment-emergent adverse event.

# Study 201/211: Virologically-Suppressed, HBeAg Negative Patients

## *Safety: Treatment-Emergent Adverse Events*

| Patients, n (%) | Study 201 (24 weeks) | | Study 211 (24 to 72 weeks) | |
|---|---|---|---|---|
| | Placebo + NrtI N = 10 | VBR + NrtI N = 16 | VBR + NrtI[a] N = 10 | VBR + NrtI N = 16 |
| Upper respiratory tract infection | 0 | 2 (13) | 3 (30) | 0 |
| Rash | 0 | 0 | 0 | 4 (25)[b] |
| Nausea | 0 | 2 (13) | 0 | 1 (6) |
| Viral gastroenteritis | 0 | 0 | 0 | 2 (13) |
| Nephrolithiasis | 0 | 0 | 0 | 2 (13) |

Reported for >1 patient in any column by preferred term.
[a]Patients who received placebo + NrtI in Study 201.
[b]All rash events were Grade 1 (1 event led to study drug discontinuation; 2 events resolved on continued treatment; 1 event ongoing, intermittent and not requiring medication).

# Study 201/211: Virologically-Suppressed, HBeAg Negative Patients

## *Safety: Laboratory Abnormalities*

| Patients, n (%) | Study 201 (24 weeks) | | Study 211 (24 to 72 weeks) | |
|---|---|---|---|---|
| | Placebo + NrtI N = 10 | VBR + NrtI N = 16 | VBR + NrtI[a] N = 10 | VBR + NrtI N = 16 |
| Grade 1 | 8 (80) | 4 (25) | 6 (60) | 8 (50) |
| Grade 2 | 2 (20) | 3 (19) | 2 (20) | 3 (19) |
| Grade 3[b] | 0 | 1 (6) | 0 | 1 (6) |

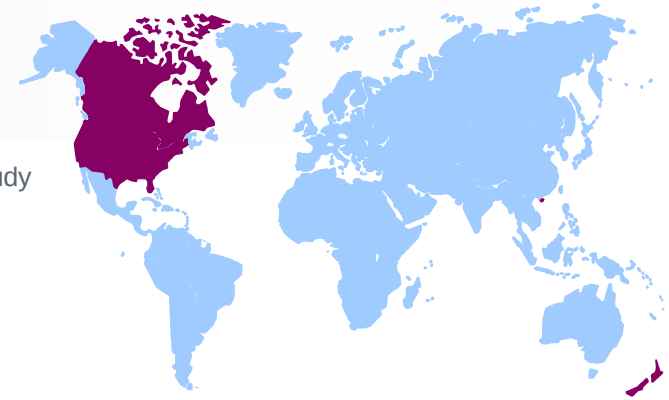
[a]Patients who received placebo + NrtI in Study 201.
[b]Grade 3 abnormalities were elevated AST (1 patient, isolated and in the setting of strenuous exercise) and decreased lymphocytes (1 patient).

AST, aspartate aminotransferase.

# Conclusions

- In virologically-suppressed patients with HBeAg negative CHB, VBR given in combination with NrtI has a favorable safety and tolerability profile with no observed treatment-emergent resistance
- Despite chronic long-term NrtI therapy, evidence of residual viral replication was detectable in one third of patients at baseline when measured using a more sensitive HBV DNA assay
- On treatment with VBR and NrtI, all patients had DNA + pgRNA levels <LLOQ measured by the most sensitive composite assay
- Discontinuation of both VBR and NrtI treatment in the majority of these patients who have achieved the stopping criteria will now assess the durability of the virologic response

# Acknowledgments




- We express our gratitude to all the patients, investigators, and site staff who participated in the study
  - **Canada**
    - Scott Fung (University of Toronto, Toronto)
    - Magdy Elkhashab (Toronto Liver Centre, Toronto)
    - Alnoor Ramji (Providence Health Care Research Institute, Vancouver)
  - **Hong Kong**
    - Man-Fung Yuen (Department of Medicine, The University of Hong Kong, Hong Kong, Hong Kong)
  - **New Zealand**
    - Edward Gane (Auckland Clinical Studies Ltd, Auckland)
  - **USA**
    - Mark S Sulkowski (Johns Hopkins Univ. School of Medicine, Baltimore, MD)
    - Jacob Lalezari· Maurizio Bonacini (Quest Clinical Research, San Francisco, CA)
    - Eugene R Schiff (Schiff Center for Liver Diseases, Univ. of Miami School of Medicine, Miami, FL)
    - Douglas Dieterich (Icahn School of Medicine, Mount Sinai Hospital, New York, NY)
    - Tarek Hassanein (Southern California Research Center, Coronado, CA)
    - Paul Kwo (Stanford University Medical Center, Stanford, CA)
    - Ronald Nahass (Infectious Disease Care, Hillsborough, FL)
    - Walid Ayoub (Cedars-Sinai Medical Center, Los Angeles, CA)
    - Steven-Huy Han (Pfleger Liver Institute, University of California, Los Angeles, CA)
    - Michael Bennett (Medical Associates Research Group, San Diego, CA)
    - Natarajan Ravendhran (Digestive Disease; Associates, Catonsville, MD)
    - James Park, Ira Jacobson (New York University Langone Medical Center, New York, NY)
    - Ho Bae (Asian Pacific Liver Center, Los Angeles, CA)
    - Sing Chan (Sing Chan MD, New York, NY)
    - Hie-Won Hann (Thomas Jefferson University Hospital, Philadelphia, PA)
    - Xiaoli Ma (Office of Xiaoli Ma, Philadelphia, PA)
    - Tuan T Nguyen (T Nguyen Research and Education, Inc., San Diego, CA)
- Writing and editorial support was provided by Lauren Hanlon, PhD, of AlphaBioCom, LLC and funded by Assembly Biosciences
- This study was sponsored by Assembly Biosciences