Preliminary Off-Treatment Responses Following 48 Weeks of Vebicorvir, Nucleos(t)ide Reverse Transcriptase Inhibitor, and AB-729 Combination in Virologically Suppressed Patients With Hepatitis B e Antigen Negative Chronic Hepatitis B: Analysis From an Open-Label Phase 2 Study

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- His current research interests include
  - Treatment of hepatitis B and C
  - Viral hepatitis and steatotic liver disease
  - Management of antiviral-resistant hepatitis B

Presenter Disclosures

- Scott Fung reports speaking and teaching for AbbVie, Gilead Sciences, Inc., and Lupin; serving as an advisor for AbbVie, Gilead Sciences, Inc., Novo Nordisk, and Pfizer; and receiving grant/research support from Gilead Sciences, Inc.

Background

- Combination regimens with agents of complementary mechanisms are likely required for finite duration therapy
- HBV capsid assembly modulators (CAM) and small interfering RNAs (siRNA) are such potential agents

Vebicorvir (VBR)

- 1st-generation CAM
- Deeper reductions in HBV DNA and RNA with more rapid normalization of ALT when added to NrtIs compared with NrtIs alone[1,2]

Imdusiran (AB-729)

- Single-trigger GalNAc–conjugated siRNA targeting all HBV RNA transcripts
- Reduced HBsAg in HBV DNA positive and virologically-suppressed participants[3-5]

Nucleos(t)ide reverse transcriptase inhibitors (NrtIs)

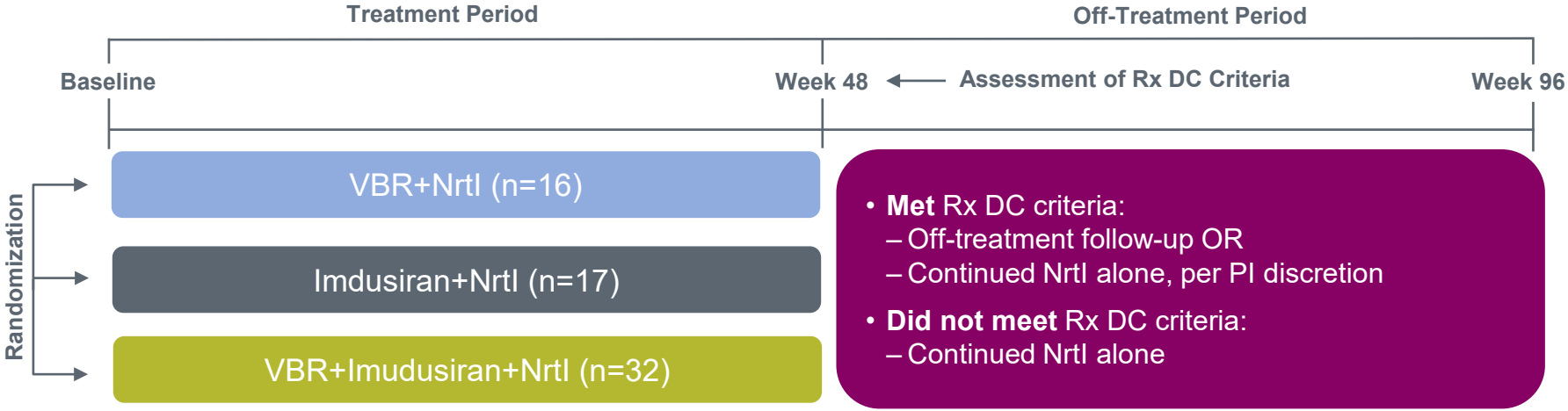
- Suppress HBV DNA to <LLOQ in most participants
- Durable off-treatment virologic responses are rare[6]

- Here, we report final on-treatment and off-treatment responses from an open-label study evaluating VBR+NrtI, imdusiran+NrtI, and VBR+imdusiran+NrtI in virologically-suppressed participants with HBeAg-negative cHBV

GalNAc, N-acetylgalactosamine; LLOQ, lower limit of quantification.

1) Yuen MF, et al. *J Hepatol*. 2022;77(3):642-52. **2)** Sulkowski MS, et al. *J Hepatol*. 2022;77(5):1265-75. **3)** Yuen MF, et al. Oral presentation at AASLD: Nov 13-16, 2020, #83. **4)** Yuen MF, et al. Poster at EASL: June 22-26, 2022, #SAT443. **5)** George J, et al. Poster at AASLD Nov 4-8, 2022, #5064. **6)** Seto WT, et al. *Lancet*. 2018;392(10161):2313-24.

Study Design and Objectives



Key eligibility criteria:

- Male or female
- Aged 18 to 50 years
- VS on NrtI ≥6 months
- HBeAg negative
- HBsAg ≥100 IU/mL

Treatments:

- VBR 300 mg PO, QD
- Imdusiran 60 mg SC, Q8 weeks
  - Last dose at Week 40
- NrtI

Participants stratified by:

- HBsAg ≤1000 IU/mL vs >1000 IU/mL

Rx DC criteria:

- ALT <2× ULN AND
- HBV DNA <LLOQ AND
- HBsAg <100 IU/mL

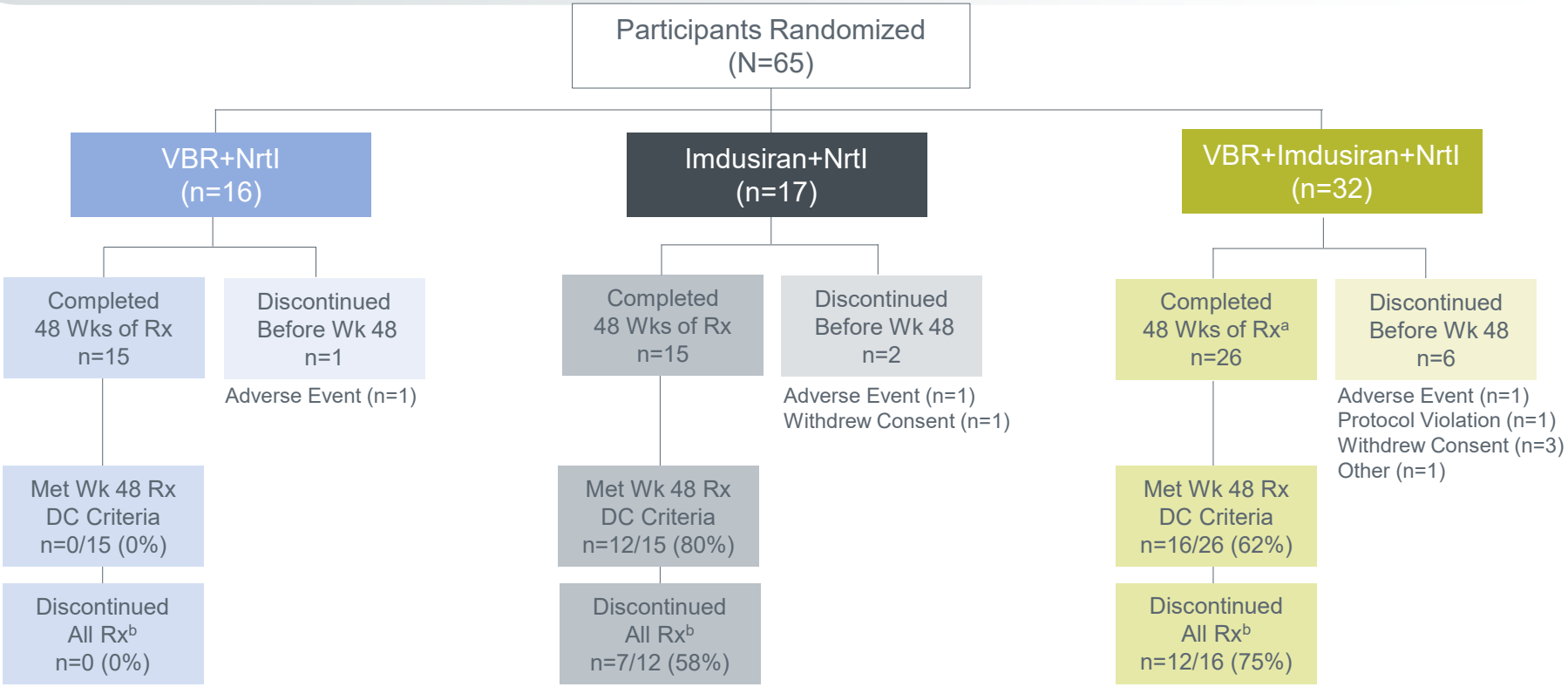
DC, discontinuation; PO, by mouth; Rx, treatment; SC, subcutaneous; ULN, upper limit of normal; VS, virologically suppressed.

Baseline Demographics and Disease Characteristics

Baseline	VBR+Nrtl (n=16)	Imdusiran+Nrtl (n=17)	VBR+Imdusiran+Nrtl (n=32)
Age, Years; Median (Min, Max)	42 (23, 49)	43 (29, 51)	41 (22, 51)
Sex, Male; n (%)	13 (81.3)	10 (58.8)	20 (62.5)
Race, Asian; n (%)	10 (62.5)	10 (58.8)	17 (53.1)
Years on Current Nrtl; Median (Min, Max)	4.3 (1.8, 10.1)	5.4 (1.5, 13.5)	6.6 (1.2, 14.8)
HBV DNA <LLOQ; n (%)[a]	16 (100)	17 (100)	32 (100)
HBV DNA <LOD; n (%)[b]	12 (75.0)	13 (76.5)	25 (78.1)
HBV RNA, $\log_{10}$ U/mL; Mean (SD)[c]	1.1 (0.7)	1.4 (0.9)	1.2 (0.9)
HBsAg, $\log_{10}$ IU/mL; Mean (SD)[d]	3.3 (0.6)	3.3 (0.6)	3.4 (0.6)
HBsAg ≤1000 IU/mL; n (%)[d]	5 (31.3)	6 (35.3)	9 (28.1)
HBcrAg, $\log_{10}$ U/mL; Mean (SD)[e]	3.7 (1.0)	3.4 (0.5)	3.6 (0.7)
ALT, U/L; Mean (SD)	27 (12.8)	28 (17.3)	29 (19.8)

[a]HBV DNA: Roche COBAS TaqMan (LLOQ=10 IU/mL). [b]HBV DNA: Assembly Assay (LOD=5 IU/mL). [c]HBV RNA: Abbott RUO Assay version 2.0 (LLOQ=0.49 $\log_{10}$ U/mL).
[d]HBsAg: Abbott Architect i2000SR (LLOQ=0.05 IU/mL). [e]HBcrAg: Fujirebio Lumipulse G (LLOQ=3 $\log_{10}$ U/mL).
LLOQ, lower limit of quantification; LOD, limit of detection.

Disposition



[a]Completed 48 wks of imdusiran; n=23 completed 48 wks of VBR. [b]This study was terminated early.
DC, discontinuation; Rx, treatment.

End-of-Treatment Virologic Response (Week 48)

	VBR+Nrtl (n=16)	Imdusiran+Nrtl (n=17)	VBR+Imdusiran+Nrtl (n=32)
HBV DNA <LLOQ; n/N (%)[a]	14/15 (93.3)	9/10 (90.0)	26/27 (96.3)
HBV DNA <LOD; n/N (%)[b]	13/15 (86.7)	8/10 (80.0)	23/26 (88.5)
HBV RNA, CFB $\log_{10}$ U/mL; Mean (SD)[c]	−0.1 (0.6)	−0.7 (0.5)	−0.8 (1.1)
HBV RNA <LLOQ; n/N (%)[c]	4/15 (26.7)	5/10 (50.0)	18/26 (69.2)
HBsAg, CFB $\log_{10}$ IU/mL; Mean (SD)[d]	0.0 (0.1)	−1.9 (0.5)	−1.9 (0.5)
HBcrAg, CFB $\log_{10}$ U/mL; Mean (SD)[e]	0.0 (0.2)	−0.2 (0.2)	−0.2 (0.4)
HBcrAg <LLOQ; n/N (%)[e]	5/15 (33.3)	3/10 (30.0)	11/27 (40.7)
ALT, U/L; Mean (SD)	30 (22.4)	59 (50.0)	46 (25.3)
Met Wk 48 Rx DC Criteria; n/N (%)	0/15	12/15 (80.0)	16/26 (61.5)
Stopped Rx After 48 Wks; n/N (%)	0	7/12 (58.3)	12/16 (75.0)

Treatment discontinuation criteria: ALT <2× ULN + HBV DNA <LLOQ + HBsAg <100 IU/mL

[a]HBV DNA: Roche COBAS TaqMan (LLOQ=10 IU/mL). [b]HBV DNA: Assembly Assay (LOD=5 IU/mL). [c]HBV RNA: Abbott RUO Assay version 2.0 (LLOQ=0.49 $\log_{10}$ U/mL; values below LLOQ or not detected are imputed as 0.19 $\log_{10}$ U/mL for analysis purposes). [d]HBsAg: Abbott Architect i2000SR (LLOQ=0.05 IU/mL; values below LLOQ are imputed as 0.025 IU/mL or −1.60 $\log_{10}$ IU/mL for analysis purposes). [e]HBcrAg: Fujirebio Lumipulse G (LLOQ=3 $\log_{10}$ U/mL; values below LLOQ are imputed as 2.7 $\log_{10}$ U/mL).
CFB, change from baseline; DC, discontinuation; LLOQ, lower limit of quantification; LOD, lower limit of detection; Rx, treatment.

On-Treatment Safety

n (%)	VBR+Nrtl (n=16)	Imdusiran+Nrtl (n=17)	VBR+Imdusiran+Nrtl (n=32)
TEAE	12 (75.0)	12 (70.6)	26 (81.3)
Grade 1	9 (56.3)	8 (47.1)	13 (40.6)
Grade 2	2 (12.5)	4 (23.5)	12 (37.5)
Grade 3	1 (6.3)	0	1 (3.1)
TE SAE	0	0	1 (3.1)[a]
TEAE Leading to Study Discontinuation	1 (6.3)	0	0
Death	0	0	0
Increased ALT	1 (6.3)	7 (41.2)	13 (40.6)
Grade 1	1 (6.3)	5 (29.4)	7 (21.9)
Grade 2	0	0	5 (15.6)
Grade 3	0	2 (11.8)	1 (3.1)
Grade 4	0	0	0

[a]COVID-19 pneumonia unrelated to treatment.
ALT, alanine aminotransferase; COVID-19, coronavirus disease 2019; SAE, serious adverse event; TE, treatment emergent; TEAE, TE adverse event.

Off-Treatment Safety (Rx DC Participants Only)

n (%)	Imdusiran+Nrtl (n=7)	VBR+Imdusiran+Nrtl (n=12)
TEAE	1 (14.3)	6 (50.0)
Grade 1	1 (14.3)	4 (33.3)
Grade 2	0	2 (16.7)
Grade 3/4	0	0
TE SAE	0	0
TEAE Leading to Study Discontinuation	0	0
Death	0	0
Increased ALT	0	2 (16.7)
Grade 1	0	2 (16.7)
Grade 2/3/4	0	0

- TEAEs occurring in >1 participant: COVID-19 (n=2) in the triple-combination group

Data for participants discontinuing all treatments. All AEs that occurred during the off-treatment phase were considered TEAEs.
ALT, alanine aminotransferase; DC, discontinuation; Rx, treatment; SAE, serious adverse event; TE, treatment emergent; TEAE, TE adverse event.

Off-Treatment Virologic Response

- No participants met the protocol-mandated NrtI restart criteria or had ALT ≥2× ULN during follow-up
- Participants who maintained HBV DNA <LLOQ and/or HBsAg <100 IU/mL are shown below

n/N[a] (%)		Off-Treatment Week									
		4	8	12	16	20	24	28	32	36	40
HBV DNA <LLOQ	Imdusiran+NrtI	7/7	5/6	5/6	3/5	0/3	0/3	0/2	0/1	0/1	0/1
	VBR+Imdusiran+NrtI	8/12	6/10	3/6	1/5	1/3	1/3	1/2	2/2	1/2	NA
HBsAg <100 IU/mL	Imdusiran+NrtI	6/7	5/6	5/6	4/5	1/2	2/3	1/2	1/1	0/1	0/1
	VBR+Imdusiran+NrtI	12/12	8/9	5/6	4/4	3/3	3/3	2/2	2/2	2/2	NA

[a]N=number of participants with data available at each timepoint.
NA, not applicable.

Key Take-Aways

- All regimens tested in this study were generally well tolerated
- The HBsAg reductions of −1.9 $\log_{10}$ IU/mL from baseline at Week 48 were comparable in both the imdusiran+NrtI and VBR+imdusiran+NrtI groups, suggesting no antagonism between the siRNA and CAM in this trial
- No participants receiving VBR+NrtI met treatment discontinuation criteria. A greater percentage of participants receiving imdusiran+NrtI met treatment discontinuation criteria than participants receiving VBR+imdusiran+NrtI
- Although the number of participants remaining at off-treatment visits beyond Week 16 was small, some participants maintained HBV DNA <LLOQ and/or HBsAg <100 IU/mL at these later timepoints
  - No participants had ALT ≥2× ULN, even at late off-treatment timepoints
- The triple combination did not result in significantly greater on- or post-treatment improvements in markers of active HBV infection vs the dual combination without VBR
  - This trial was terminated early and clinical development of VBR was discontinued
  - Imdusiran is currently in two ongoing Phase 2a clinical trials in combination with other agents for the treatment of cHBV (see Late Breaker Poster #5036-C)

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