Preliminary Antiviral Efficacy and Safety of Repeat Dosing of Imdusiran (AB-729) Followed by VTP-300 With or Without Nivolumab in Virally-Suppressed, Non-Cirrhotic Subjects With Chronic Hepatitis B (CHB)

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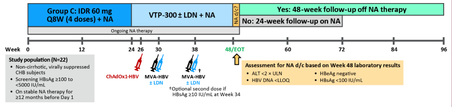
BACKGROUND

- Current approved therapies for chronic hepatitis B (CHB) slow or prevent the development of hepatitis B virus (HBV)–related liver complications but do not typically lead to functional cure (FC)[1-4]
- Suppression of hepatitis B surface antigen (HBsAg) and other viral antigen production and induction of HBV-specific T-cell responses are likely required to achieve FC[1]
- Imdusiran (IDR; AB-729) is a subcutaneously administered *N*-Acetylgalactosamine–conjugated, single trigger, pan-genotypic small interfering RNA therapeutic that blocks all HBV RNA transcripts, including HBV X protein, resulting in suppression of viral replication and production of all viral antigens[5]
- VTP-300 is Bainthus Biotherapeutics' investigational HBV immunotherapeutic with 2 components: a chimpanzee adenoviral vector (ChAdOx1-HBV) and a modified vaccinia Ankara (MVA-HBV), both encoding the inactivated polymerase, core, and the entire surface antigen from a consensus genotype C HBV[6]
- Single and multiple doses of low-dose nivolumab (LDN; 0.3 mg/kg) are being examined to potentiate reduction of HBsAg and are well tolerated with a low risk of immune-mediated events in several CHB clinical trials, including Bainthus Biotherapeutics' HBV003 trial (NCT05343481)[7,8]
- IM-PROVE II (AB-729-202; ACTRN12622000317796) is an ongoing phase 2a study assessing the safety, pharmacodynamics, and immunogenicity of repeat doses of IDR followed by VTP-300 (Group A), placebo (Group B), or VTP-300 ± LDN (Group C) in nucleos(t)ide analogue (NA)–suppressed CHB subjects[9]
  - Data for 20/22 subjects who reached Week 48/end of treatment (EOT) from Group C are reported here

MATERIALS AND METHODS

IM-PROVE II (AB-729-202) Group C Study Design



- Group C was added as an amendment to the study based on data from the HBV002 (NCT04778904) and HBV003 studies that showed addition of LDN to VTP-300 increased both the number of subjects responding and the magnitude of HBsAg decline[7,8,10]
- After the initiation of Group C, the protocol was further amended to exclude subjects at risk of immune-related thyroiditis (family/current history of thyroid disease, presence of thyroid auto-antibodies, or abnormal thyroid function tests) from receiving LDN following reports of mild/moderate thyroid dysfunction in some subjects in the HBV003 trial[7] (eligible to receive LDN, n=13; not eligible, n=9)

Table 1. Study Assay Methods

Parameter	Assay method	Assay cutoff
ALT	—	ULN = 44 U/L for males and 41 U/L for females
Immune biomarkers	Luminex® Assays (MilliporeSigma)	—
HBsAg (quantitative)	Liaison® XL assay (Diasorin)	LLOQ = 0.05 IU/mL
Ultrasensitive HBsAg (qualitative)	ARCHITECT HBsAg Next Qualitative Assay (Abbott Diagnostics)	LLOD = 0.005 IU/mL
Anti-HBs	ADVIA Centaur Anti-HBs2 (Siemens)	LLOQ = 10 IU/L

ALT, alanine aminotransferase; anti-HBs, anti–hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; LLOD, lower limit of detection; LLOQ, lower limit of quantitation; ULN, upper limit of normal.

RESULTS

Table 2. Demographics and Baseline Characteristics

Parameter	Group A IDR + VTP-300 N=20	Group B IDR + Placebo N=20	Group C IDR + VTP-300 + LDN N=13	Group C IDR + VTP-300 N=9	Total N=62
Age, mean (SD), y	52.2 (6.5)	44.3 (8.3)	40.6 (8.2)	47.2 (9.2)	46.5 (8.9)
Males, n (%)	14 (70)	14 (70)	9 (69)	6 (67)	43 (69)
Race, n (%)					
Asian	18 (90)	19 (95)	12 (92)	8 (89)	57 (92)
Black/African American	1 (5)	0	1 (8)	1 (11)	3 (5)
White	1 (5)	1 (5)	0	0	2 (3)
Genotype, n (%)[a]					
A	0	0	0	1 (11)	1 (2)
B	5 (25)	7 (35)	8 (62)	4 (44)	24 (39)
C	7 (35)	7 (35)	3 (23)	4 (44)	21 (34)
D	1 (5)	0	0	0	1 (2)
HBeAg positive, n (%)	4 (20)	10 (50)	3 (23)	1 (11)	18 (29)
HBsAg, IU/mL					
Mean (SD)	1123 (1078)	1135 (998)	1105 (1093)	1296 (1468)	1148 (1092)
<1000 IU/mL, n (%)	11 (55)	10 (50)	8 (62)	6 (67)	35 (56)
Range	95-4000	100-3300	93-3200	270-4000	93-4000
ALT, mean (SD), U/L	20.7 (9.5)	22.1 (11.1)	26.9 (9.5)	25.2 (14.9)	23.1 (10.9)

ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; IDR, imdusiran; LDN, low-dose nivolumab. [a]Genotype could not be determined in 15 subjects (Group A, n=7; Group B, n=6; Group C VTP-300 + LDN, n=2).

- Demographics, such as sex and race, and baseline mean HBsAg and ALT values were similar across all groups in the study

Table 3. Treatment Administration and NA Discontinuation Summary in Group C

n/N (%)	Group C IDR + VTP-300 + LDN N=13	Group C IDR + VTP-300 N=9	Total N=22
Treatment administration			
Week 30: MVA-HBV ± LDN	13/13 (100)	9/9 (100)	22/22 (100)
Week 38: MVA-HBV boost ± LDN[a]	5/13 (38)	4/9 (44)	9/22 (41)
NA discontinuation			
Reached Week 48/EOT	13/13 (100)	7/9 (78)	20/22 (91)
Discontinued NA therapy	9/13 (69)	5/7 (71)	14/20 (70)
Did not meet NA stopping criteria	4/13 (31)	2/7 (29)	6/20 (30)
HBeAg positive	3/4 (75)	0/2 (0)	3/6 (50)
HBsAg >100 IU/mL	0/4 (0)	2/2 (100)	2/6 (33)
HBV DNA >LLOQ	1/4 (25)	0/2 (0)	1/6 (17)

EOT, end of treatment; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IDR, imdusiran; LDN, low-dose nivolumab; LLOQ, lower limit of quantitation; NA, nucleos(t)ide analogue. [a]Received if HBsAg ≥10 IU/mL at Week 34.

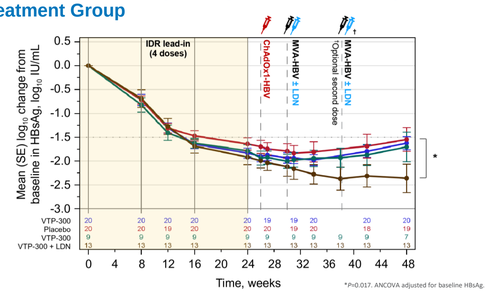
Table 4. Mean HBsAg Change From Baseline and Key Milestones in Group C

Study week	Mean (SE) change from baseline, $\log_{10}$ IU/mL (SE) [n]		HBsAg <100 IU/mL, n/N (%)		HBsAg <10 IU/mL, n/N (%)		HBsAg <LLOQ, n/N (%)	
	IDR 60 mg QBW × 4 doses							
Baseline	2.83 (0.11) [22]		2/22 (9)		0/22 (0)		0/22 (0)	
Week 12	−1.33 (0.12) [22]		15/22 (68)		7/22 (32)		0/22 (0)	
Week 26	−1.97 (0.11) [22]		21/22 (96)		12/22 (55)		0/22 (0)	
	VTP-300 + LDN	VTP-300	VTP-300 + LDN	VTP-300	VTP-300 + LDN	VTP-300	VTP-300 + LDN	VTP-300
Week 34	−2.28 (0.20) [13]	−1.94 (0.17) [9]	12/13 (92)	8/9 (89)	7/13 (54)	5/9 (56)	0/13 (0)	0/9 (0)
Week 48/ EOT	−2.36 (0.30) [13]	−1.70 (0.31) [7]	12/13 (92)	5/7 (71)	7/13 (54)	3/7 (43)	3/13 (23)	0/7 (0)

EOT, end of treatment; HBsAg, hepatitis B surface antigen; IDR, imdusiran; LDN, lose-dose nivolumab; LLOQ, lower limit of quantitation; QBW, every 8 weeks.

- After 4 doses of IDR, 96% (21/22) of subjects achieved HBsAg <100 IU/mL at the time of initial VTP-300 administration at Week 26
- Subjects in Group C who received IDR + VTP-300 + LDN were more likely to reach HBsAg values <100 and <10 IU/mL, and 23% (3/13) reached below the lower limit of quantitation (LLOQ) at Week 48/EOT

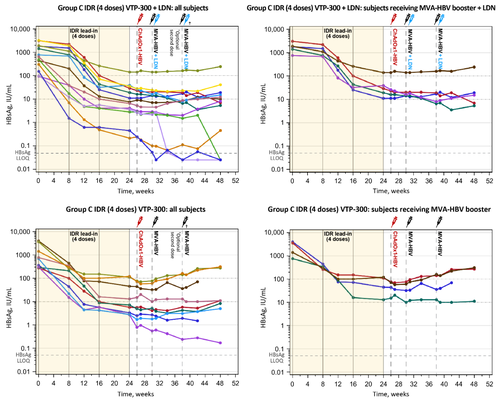
Figure 1. Mean HBsAg Change From Baseline by Treatment Group



*P<0.017. ANCOVA adjusted for baseline HBsAg.

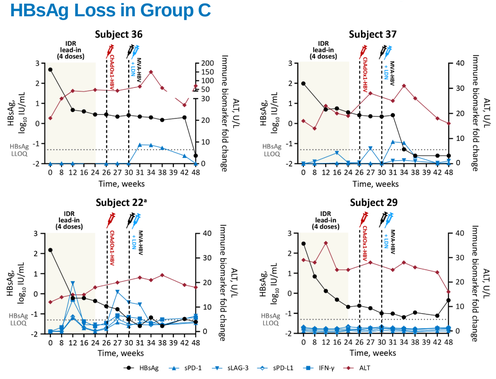
- Subjects in Group C receiving IDR + VTP-300 + LDN (n=13) had a significantly greater mean HBsAg $\log_{10}$ decline at Week 48 compared with all other groups (−0.73 [95% CI: −1.33, −0.10]; *P*=0.017)

Figure 2. Individual Subject HBsAg Declines by Treatment Group in Group C



- By Week 48, 3 subjects in Group C IDR + VTP-300 + LDN reached HBsAg <LLOQ
  - Baseline HBsAg values of the 3 subjects were 480, 98, and 150 IU/mL, which decreased to 2.8, 2.6, and 0.2 IU/mL, respectively, at the initial VTP-300 dose at Week 26
  - All 3 subjects had samples tested by the ultrasensitive Abbott HBsAg Next Qualitative Assay and 1 of the 3 subjects was negative (non-reactive) for HBsAg at Weeks 42 and 48
    - The subject had HBsAg values at baseline and Week 26 of 98.0 and 2.6 IU/mL, respectively
- To date, an additional dose of MVA-HBV ± LDN does not appear to result in further significant HBsAg decline at Week 48 in most subjects, but additional follow-up will evaluate its effect at later time points

Figure 3. Immune Biomarker Evaluation in Subjects With HBsAg Loss in Group C



BTLA, B- and T-lymphocyte attenuator; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; GITR, glucocorticoid-induced tumor necrosis factor–related protein; GITRL, glucocorticoid-induced tumor necrosis factor receptor–related protein ligand; GROα, growth-regulated protein alpha; ICOS, inducible T cell costimulator; IFNg, interferon gamma; PDGF, platelet-derived growth factor; sLAG-3, soluble lymphocyte activation gene 3; sPD-L1, soluble programmed death ligand-1; sPD-1, soluble programmed death protein 1; TLR-2, toll-like receptor 2; VEGF, vascular endothelial growth factor.
[a]Elevations in soluble GROα, PDGF-AA, VEGF, BTLA, CD28, GITR, GITRL, TLR-2, CTLA-4, CD80, CD86, and ICOS also present in Subject 22. Subject 22's immune biomarker profile is similar to those observed in IM-PROVE I subjects (see Poster #1383).[11]

- Increases in soluble immune biomarkers associated with immune checkpoint proteins, inflammation, and T-cell activation were observed in subjects in Group C who had HBsAg <LLOQ at any point through Week 48 (Subjects 36, 37, and 22)
- No marked production of anti–hepatitis B surface antibodies was seen in these subjects through Week 48
- No immune biomarker increases were observed for Subject 29, who had similar HBsAg baseline levels as Subjects 36, 37, and 22 but did not achieve HBsAg loss through Week 48

Table 5. On-Treatment Safety in Group C

Subjects, n (%) [events]	Group C IDR + VTP-300 + LDN N=13	Group C IDR + VTP-300 N=9
Any TEAE[a]	6 (46) [22]	6 (67) [11]
Grade 1	4 (31) [19]	5 (56) [10]
Grade 2	2 (15) [3]	1 (11) [1]
Grade 3 or 4	0	0
Study drug–related TEAEs		
IDR	0	0
VTP-300[b]	3 (23) [12]	0
LDN[b]	2 (15) [9]	0
SAEs	0	0
Treatment discontinuation	0	0

IDR, imdusiran; LDN, low-dose nivolumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event. [a]No individual TEAEs occurred in ≥2 subjects per treatment group. [b]Most TEAEs related to VTP-300 and LDN were Grade 1 and post-procedural; these included injection site pain, injection pruritus, fever, headache, rhinorrhea, and pruritus.

- In Group C, IDR, VTP-300, and LDN were all well tolerated, with no Grade 3 or 4 treatment-emergent adverse events (TEAEs), no treatment discontinuations, and few study drug–related TEAEs
- There were no Grade 3 or 4 laboratory abnormalities in Group C or any laboratory abnormalities deemed related to any study drugs
- In the 13 subjects who received LDN in Group C, no significant thyroid-stimulating hormone or free thyroxine abnormalities were detected, and no thyroid-related symptoms were reported

CONCLUSIONS

- IDR treatment for 24 weeks (4 doses) led to a mean decline from baseline in HBsAg of −1.97 $\log_{10}$ IU/mL by Week 26, consistent with data from Groups A and B[9]
- At Week 48, greater mean $\log_{10}$ declines in HBsAg levels were seen in the group that received IDR + VTP-300 + LDN, which was statistically significant compared with the other groups
- 3 subjects receiving IDR + VTP-300 + LDN had HBsAg values <LLOQ at Week 48, which was not observed in the other treatment groups
- The IDR + VTP-300 + LDN regimen was well tolerated and did not result in any thyroid-related TEAEs
- These early data for the IDR + VTP-300 + LDN combination in virally suppressed CHB subjects is promising; further follow-up is ongoing and will provide insight on the possibility of functional cure with this regimen

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