Off-treatment antiviral efficacy and safety of repeat dosing of imdusiran followed by VTP-300 with or without nivolumab in virally-suppressed, non-cirrhotic subjects with chronic hepatitis B (CHB)

Grace Lai Hung Wong[1], Man-Fung Yuen[2], Patrick Kennedy[3], Ashley Brown[4], Chi-Yi Chen[5], Gin-Ho Lo[6], Pei-Yuan Su[7], Sheng-Shun Yang[8], I-Ta Lu[8], Kosh Agarwal[9], Stuart Roberts[10], Chao-Wei Hsu[11], Wan-Long Chuang[12], Sam Galhenage[13], Deana Antoniello[14], Elina Medvedeva[14], Emily P. Thi[14], Christine Espiritu[14], Timothy Eley[14], Leon Hooftman[15], Bethan Jones[15], Vicky Wheeler[15], Mark Anderson[16], Tiffany Fortney[16], Gavin Cloherty[16], Gaston Picchio[14], Karen Sims[14], Tilly Varughese[14]

[1]Medical Data Analytics Centre, State Key Laboratory of Disease, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China, [2]The University of Hong Kong, Queen Mary Hospital, Hong Kong, China, [3]Liver Centre, Blizard Institute, Barts and The London SMD, London, United Kingdom, [4]Imperial College Healthcare NHS Trust, London, United Kingdom,[5]Chia-Yi Christian Hospital, Chia-Yi City, Taiwan ,[6]E-Da Hospital, Kaohsiung, Taiwan, [7]Changhua Christian Hospital, Changhua, Taiwan, [8]Taichung Veterans General Hospital, Taichung, Taiwan, [9]King's College Hospital, London, United Kingdom,[10]Alfred Health, Monash University, Melbourne, Australia, [11]Chang Gung Memorial Hospital – Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan, [12]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan,[13]Fiona Stanley hospital, Murdoch, Australia, [14]Arbutus Biopharma, Warminster, PA, United States, [15]Barinthus Biotherapeutics, Harwell, United Kingdom, [16]Abbott Laboratories, Abbott Diagnostics, Infectious Disease Research, Abbott Park, IL, United States

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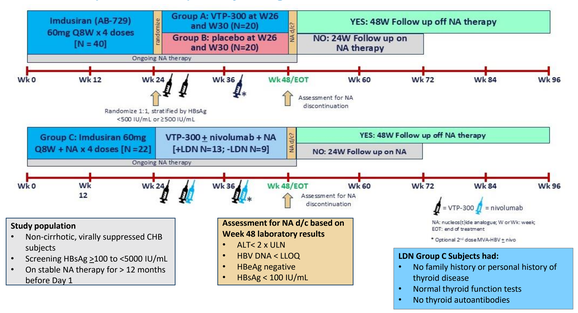
BACKGROUND

- 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 Barinthus 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.[7,8] Preliminary results in Group C up to Week 48 from IM-PROVE II also demonstrated that 1-2 doses of LDN was well tolerated and did not result in any immune related adverse events (irAEs) in a low-risk population.[9]
- 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. End of treatment results have been previously reported. [9, 10]
  - End of study (EOS) data from Groups A and B and data through Week 84 (FC timepoint) from Group C are reported here.

MATERIALS AND METHODS

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



- All subjects received 24 weeks (4 doses) of imdusiran 60 mg every 8 weeks (Q8W) in every group
  - For Groups A and B, subjects were randomized at Week 24 into Group A or B (stratified by HBsAg level at Week 16 <500 or >500 IU/mL). Group A received VTP-300 + ongoing NA (n=20) and Group B received placebo + ongoing NA (n=20) at Weeks 26 and 30.
  - Group C was an open label arm where all subjects received imdusiran followed by VTP-300 at Week 26 and 30 ± LDN at Week 30 (VTP-300+LDN n=13 ; VTP-300 alone n=9)
  - Subjects could receive a second dose of MVA-HBV (±LDN in Group C) at Week 38 if:
    - Group A and B: ≥0.5 $\log_{10}$ decline in HBsAg between Weeks 26 and 34
    - Group C: HBsAg ≥10 IU/mL at Week 34
- At Week 48, subjects were assessed for NA discontinuation. If NA therapy was discontinued, subjects were followed for 48 weeks post discontinuation for virological and clinical HBV relapse

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 quantification; ULN, upper limit of normal

RESULTS

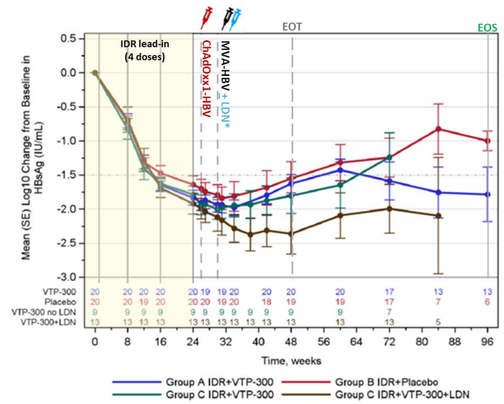
Table 1: Demographics and Baseline Characteristics

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 (69.2)	6 (66.7)	43 (69.4)
Race, n (%)					
Asian	18 (90)	19 (95)	12 (92.3)	8 (88.9)	57 (91.9)
Black/ African American	1 (5)	0	1 (7.7)	1 (11.1)	3 (4.8)
White	1 (5)	1 (5)	0	0	2 (3.2)
Genotype, n (%)*					
A	0	0	0	1 (11.1)	1 (1.6)
B	8 (40)	10 (50)	9 (69.2)	4 (44.4)	31 (50)
C	9 (45)	9 (45)	3 (23.1)	4 (44.4)	25 (40.3)
D	3 (15)	1 (5)	1 (7.7)	0	5 (8.1)
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. *HBV Genotype was determined by Next Generation Sequencing (NGS). Samples which failed PCR amplification were genotyped using the IMMUNIS HBV Genotype EIA

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

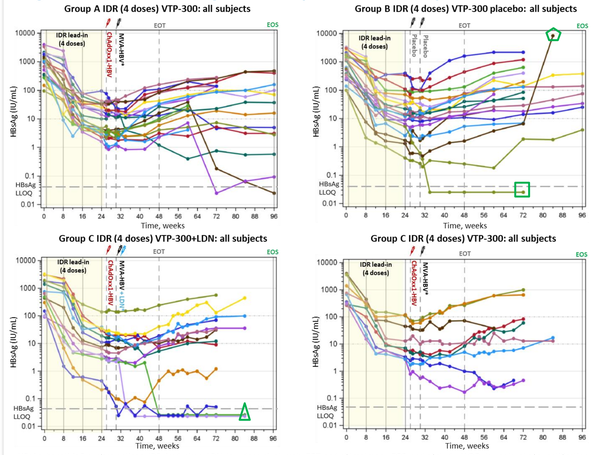
Figure 1: Mean HBsAg Change from Baseline by Treatment Group



HBsAg, hepatitis B surface antigen; IDR, imdusiran; LDN, low-dose nivolumab; EOT, end of treatment; EOS, end of study; *Optional second dose of MVA-HBV ± LDN at Week 38

- IDR treatment for 24 weeks (4 doses) led to a mean HBsAg $\log_{10}$ decline of -1.86 by Week 26 in all groups
- There was no statistical difference in mean HBsAg decline between Group C1 (IDR+VTP-300+LDN) and other groups at Week 84 (-0.6119 [95% CI -1.3670; 0.1432] p=0.110) compared to IDR alone.

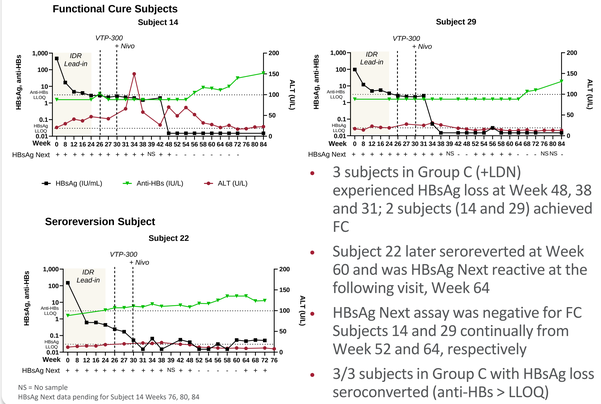
Figure 2: Individual HBsAg Declines by Treatment Group



HBsAg, hepatitis B surface antigen; IDR, imdusiran; LDN, low-dose nivolumab; EOT, end of treatment; EOS, end of study; LLOQ, lower level of quantification; ❑ Subject HBsAg <LLOQ at W48, but did not d/c NA due to HBeAg+; ☐ Subject withdrew from the study once restarting NA therapy; Δ 2 subjects reached functional cure (FC). FC defined as sustained HBsAg loss (< LLOQ) and HBV DNA < LLOQ for ≥24 weeks off NA therapy in an HBeAg- individual.

- Three subjects in Group C receiving IDR+VTP-300+LDN (N=13) had HBsAg < LLOQ at W48
- 2 of 3 of these subjects reached functional cure (FC), resulting in a FC rate of 15.3% (2/13 subjects)
- Both subjects had HBsAg < 1000 IU/mL at baseline (BL, 480 and 98 IU/mL), thus 25% of subjects with BL HBsAg <1000 (2/8) reached FC

Figure 3: HBV Biomarkers in Functional Cure Subjects



NS = No sample
HBsAg Next data pending for Subject 14 Weeks 76, 80, 84

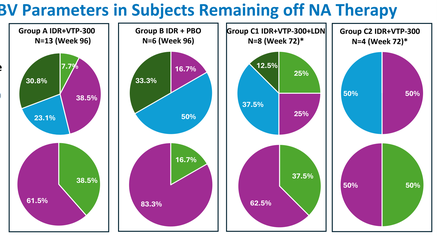
- 3 subjects in Group C (+LDN) experienced HBsAg loss at Week 48, 38 and 31; 2 subjects (14 and 29) achieved FC
- Subject 22 later seroreverted at Week 60 and was HBsAg Next reactive at the following visit, Week 64
- HBsAg Next assay was negative for FC Subjects 14 and 29 continually from Week 52 and 64, respectively
- 3/3 subjects in Group C with HBsAg loss seroconverted (anti-HBs > LLOQ)

Table 2: Treatment Administration and NA Discontinuation Summary

n/N (%)	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
Optional treatment administration at Week 38: MVA-HBV/placebo ± LDN	2/20 (10)[a]	1/20 (5)[a]	5/13 (38)[b]	4/9 (44)[b]	12/62 (19)
NA discontinuation after Week 48**	16/20 (80)	10/19 (53)	9/13 (69)	6/9 (67)	41/62 (66)
Did not meet NA stopping criteria	4/20 (20)	9/19 (47)	4/13 (31)	3/9 (29)	20/62 (32)
HBeAg positive	2/4 (50)	9/9† (100)	3/4 (75)	1/3 (33)	15/20 (75)
HBsAg >100	2/4 (50)	3/9† (33)	0/4	2/3 (100)	7/20 (35)
HBV DNA > LLOQ	0	0	1/4 (25)	0	1/20 (5)
Met NA restart criteria‡	3/16 (13)	4/10 (40)	1/9 (11)	1/6 (17)	9/41 (22)

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. *1 subject lost to follow-up in Group B at W48; **NA discontinuation criteria: HBV DNA ≤LLOQ, HBeAg negative, ALT <2x upper limit of normal (ULN), HBsAg <100 IU/mL; ‡3 subjects were both HBeAg+ and HBsAg<100 IU/mL; ‡ All NA restarts were due to confirmed HBV DNA > 20,000 IU/mL without ALT >2x ULN †Received if >0.5 log10 decline in HBsAg between Weeks 26 and 34; [a]Received if HBsAg ≥10 IU/mL at Week 34; | Data obtained at subject's most recent visits, either Week 72 or 84.

Figure 4: HBV Parameters in Subjects Remaining off NA Therapy



*1 subject each d/c NA therapy but has not reached Week 72

Table 3: Adverse Events in Treatment Groups

Number (%) [Events] of Subjects	Lead In Treatment	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
TEAE	31 (50.0) [80]	12 (60.0) [41]	15 (75.0) [39]	6 (46.2) [28]	5 (55.6) [11]
TEAE Severity					
Grade 1	27 (43.5) [76]	7 (35.0) [32]	11 (55.0) [34]	4 (30.8) [25]	3 (33.3) [9]
Grade 2	4 (6.5) [4]	3 (15.0) [7]	4 (20.0) [5]	2 (15.4) [3]	2 (22.2) [2]
Grade 3	0	2 (10.0) [2]	0	0	0
Grade 4	0	0	0	0	0
Related TEAE to Imdusiran	8 (12.9) [16]	1 (5.0) [1]	0	0	0
Related TEAE to VTP-300	0	3 (15.0) [6]	0	5 (38.5) [14]	0
Related TEAE to Nivolumab	0	0	0	2 (15.4) [8]	0

- No SAEs, deaths, or early treatment discontinuations occurred in any group
- Most common treatment-related TEAEs in 2 or more subjects (all Grade 1 or 2):
  - Imdusiran: ALT increased in 3 subjects and injection site pain in 2 subjects
  - VTP-300: Injection site pain/reaction in 5 subjects; fatigue and pruritus in 2 subjects
  - Nivolumab: Only 2 subjects had related TEAEs (post-vaccination symptoms, injection site pain, pruritus and headache in 1 subject; rhinorrhea in another subject)
- Isolated Grade 3 or 4 laboratory abnormalities were observed, but none were assessed as TEAEs or related to treatment: Isolated Grade 3 ALT, AST, INR and Grade 4 CK elevations in 5 different subjects
- There were no immune related adverse events, including thyroid abnormalities, noted in the Group C LDN group

CONCLUSIONS

- Two subjects who received IDR+VTP-300+LDN (Group C) reached functional cure (FC) with detectable anti-HBs levels.
- IDR+VTP-300±LDN was well tolerated, and the regimen demonstrated the safety of 1-2 doses of LDN in a selected population at lower risk for thyroid immune related events.
- Most subjects treated with IDR maintained quantitative HBsAg levels that were consistently lower than pre-treatment HBsAg levels during the post-treatment follow-up period.
- While only 2 subjects achieved FC, 2 subjects at Week 96 in Group A and 1 subject at Week 84 in Group C IDR+VTP-300+LDN have HBsAg levels at or close to LLOQ.
- Compared to IDR+placebo (Group B), more subjects receiving IDR+VTP-300 (Group A) were able to remain off NA therapy even without achieving FC. Additional follow-up is continuing for subjects in Group C.

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CONTACT AND DISCLOSURES

Corresponding Author: Tilly Varughese, MD
Medical Director, Clinical Development
Arbutus Biopharma Inc., 701 Veterans Circle, Warminster, PA 18974
Email: tvarughese@arbutusbio.com

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