Preliminary pharmacodynamics and safety of repeat dosing of imdusiran (AB-729) followed by VTP-300 or placebo in virally-suppressed, non-cirrhotic subjects with chronic hepatitis B (CHB)

Man-Fung Yuen[1], Kosh Agarwal[2], Stuart K. Roberts[3], Gin-Ho Lo[4], Chao-Wei Hsu[5], Wan-Long Chuang[6], Chi-Yi Chen[7], Pei-yuan Su[8], Sam Galhenage[9], Sheng-Shun Yang[10], Deana Antoniello[11], Emily Thi[12], Susanne O'Brien[13], Louise Bussey[13], Elina Medvedeva[11], Timothy Eley[11], Deepa Patel[11], Tilly Varughese[11], Christine Espiritu[12], Sharie Ganchua[12], Christina Iott[12], Mark Anderson[14], Tiffany Fortney[14], Gavin Cloherty[14], Tom Evans[13], Karen Sims[11]

[1]The University of Hong Kong, Hong Kong, China, [2]Institute of Liver Studies, King's College Hospital, London, England, [3]Alfred Health, Melbourne, Victoria, Australia, [4]E-Da Hospital, Kaohsiung City, Taiwan, [5]Chang Gung Memorial Hospital and University College of Medicine, Taoyuan, Taiwan, [6]Kaohsiung Medical University Hospital, Kaohsiung City, Taiwan, [7]Ditmanson Medical Foundation, Chia-Yi Christian Hospital, Chiayi City, Taiwan, [8]Changhua Christian Hospital, Changhua City, Taiwan, [9]Fiona Stanley Hospital, Murdoch, Western Australia, [10]Taichung Veterans General Hospital, Taichung City, Taiwan, [11]Arbutus Biopharma Clinical Development, Warminster, PA, USA, [12]Arbutus Biopharma Research, Warminster, PA, USA, [13]Barinthus Biotherapeutics, Harwell Oxford, England, [14]Abbott Diagnostics, Infectious Disease Research, Abbott Park, IL, USA

AASLD The Liver Meeting® Nov. 10-14, 2023

LB#5036-C

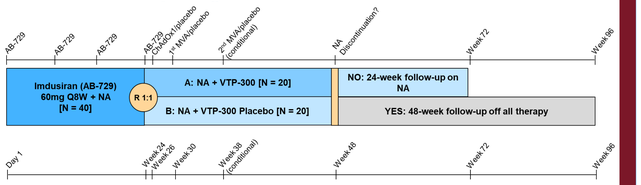
Arbutus BIOPHARMA *Curing Chronic Hepatitis B*

BACKGROUND

- Current approved therapies for chronic hepatitis B (CHB) slow or prevent the development of HBV-related liver complications, but do not typically lead to functional cure.[1,2,3]
- Excess production of HBsAg is believed to contribute to host immune exhaustion, resulting in inadequate T-cell and B-cell responses to CHB infection and failure to suppress the virus.[4] Suppression of HBsAg and other viral antigen production and induction of HBV-specific T cell responses to HBV is likely required to achieve functional cure.
- Imdusiran (AB-729) is a subcutaneously administered *N*-Acetylgalactosamine (GalNAc)-conjugated single trigger, pan-genotypic siRNA therapeutic that blocks all HBV RNA transcripts (including HBx) resulting in suppression of viral replication and production of all viral antigens. Imdusiran leads to mean HBsAg declines of 1.8 to 2.6 $\log_{10}$ from baseline after 48 weeks of treatment[5], and preliminary data suggests that HBV-specific T cell responses may be enhanced following repeat dosing of imdusiran.[6]
- VTP-300 is Barinthus Biotherapeutic's HBV investigational immunotherapeutic composed of 2 components used in sequential combination: a chimpanzee adenoviral vector (ChAdOx1-HBV) and a Modified Vaccinia Ankara (MVA-HBV), both encoding the inactivated polymerase, core, and the entire S region from a consensus genotype C virus. VTP-300 generates robust T cell responses and can induce sustained HBsAg declines in a subset of subjects.[7] Clinical responses were also observed in patients with genotype D and in vitro across all genotypes A-E.
- Study AB-729-202 is a randomized, placebo-controlled, multicenter Phase 2a study assessing the safety, tolerability, immunologic and antiviral activity of 24 weeks of imdusiran (to reduce HBsAg to low levels), followed by VTP-300 (to further enhance HBV-specific T cell responses) or placebo in virally suppressed, non-cirrhotic CHB subjects. Preliminary results of this ongoing study are presented here.

MATERIALS AND METHODS

AB-729-202 Study Design



- Study AB-729-202 enrolled 40 non-cirrhotic, virally suppressed CHB subjects on stable NA therapy for at least 12 months prior to Day 1
- Key inclusion/exclusion criteria included:
  - HBsAg between 100 and 5,000 IU/mL at Screening
  - HBeAg positive or negative
  - Fibroscan® ≤ 8.5 kPa within 6 months of Day 1
  - ALT ≤2 × ULN
- All subjects received 24 weeks (4 doses) of imdusiran 60 mg every 8 weeks (Q8W) and were randomized at Week 24 into Group A or B (stratified by HBsAg level at Week 16 ≤500 or >500 IU/mL):
  - Group A: VTP-300 (ChAdOx1-HBV + MVA-HBV, intramuscular injection) + ongoing NA
  - Group B: placebo (saline, intramuscular injection) + ongoing NA
- Subjects could receive a second dose of MVA-HBV/placebo at Week 38 if they experienced a >0.5 $\log_{10}$ decline in HBsAg between Weeks 26 and 34
- At Week 48, subjects were assessed for NA discontinuation via the following criteria: ALT <2× ULN, HBV DNA <LLOQ, HBeAg negative and HBsAg <100 IU/mL
- Study assay methods/cutoffs:
  - ALT upper limit of normal (ULN) = 44 U/L for males, 41 U/L for females

Parameter	Assay Method	LLOQ
HBsAg	Diasorin Liaison XL	0.05 IU/mL
HBV pgRNA	Abbott HBV pgRNA V2.0 (RUO)	0.49 log U/mL
HBcrAg	Fujirebio Lumipulse G	3 log U/mL
HBeAg (quantitative)	Diasorin Liaison XL	0.11 PEI U/mL
HBV DNA	Abbott RealTime HBV	10 IU/mL

- HBV-specific T cell responses were assessed with IFN-γ ELISpot
- Plasma immune biomarkers were assessed by Luminex
- Ultrasensitive HBsAg was assessed with Abbott Architect HBsAg NEXT assay
- HBsAg immune complex was assessed with Abbott RUO assay

RESULTS

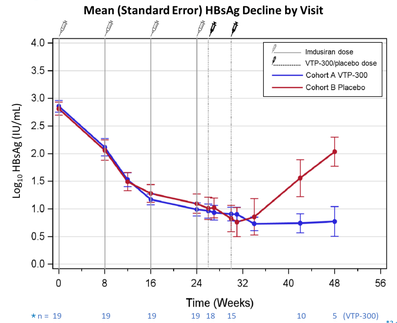
Table 1: Demographics and Baseline Characteristics

Parameter	Imdusiran Lead-in (N=3)	Group A VTP-300 (N=19)	Group B Placebo (N=18)	Total (N=40)
Age, mean (SD)	39.3 (9.29)	52.4 (6.51)	45.2 (7.92)	48.2 (8.37)
Males, n (%)	2 (66.7)	13 (68.4)	13 (72.2)	28 (70.0)
Race				
Asian	2 (66.7)	17 (89.5)	18 (100.0)	37 (92.5)
White	1 (33.3)	1 (5.3)	0	2 (5.0)
Black/African American	0	1 (5.3)	0	1 (2.5)
Genotype, n (%)*				
B	0	5 (28.6)	7 (38.9)	12 (30.8)
C	2 (66.7)	6 (31.6)	6 (33.3)	14 (35.9)
D	0	1 (5.3)	0	1 (2.6)
HBeAg				
Positive, n (%)	1 (33.3)	4 (21.1)	9 (50.0)	14 (35.0)
Mean (SD) (PEI U/mL)	3.11	22.44 (22.29)	10.63 (10.31)	13.47 (8.81)
HBsAg mean (SD), IU/mL	1193.3 (294.47)	1146.6 (252.83)	1100.0 (246.29)	1129.1 (162.07)
ALT mean (SD), U/L	14.7 (4.73)	21.3 (9.68)	23.2 (11.18)	21.7 (10.20)

*Genotype success rate 69.2% (27/39), not typable in 1, 7, and 5 subjects respectively; N = subject number; SD = standard deviation

- More HBeAg+ subjects were randomized to Group B/placebo (not stratified)
- Baseline HBsAg and other characteristics were similar across groups

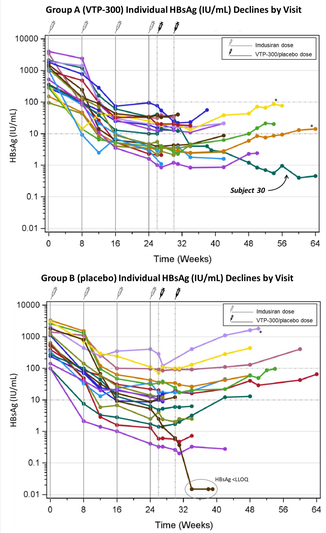
Figure 1: Mean HBsAg Change from Baseline by Treatment Group

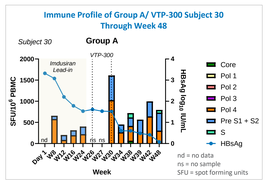


*3 subjects have not yet reached VTP-300 dosing period and are excluded from plot

- Robust HBsAg declines observed after 4 doses of imdusiran (60 mg Q8W)
- After Week 36, the group means begin to diverge
- VTP-300 appears to contribute to maintaining low HBsAg levels in the early post-treatment period
- Additional follow-up is needed to assess ongoing changes in HBV parameters

Figure 2: Individual Subject HBsAg Declines by Treatment Group





- Most subjects in Group A (VTP-300) appear to maintain nadir HBsAg levels after receipt of VTP-300, although follow-up data is limited
- Although the immunology data for this ongoing study is still limited, the HBsAg decline and enhanced IFN-γ production (via ELISpot) after VTP-300 for Group A Subject 30 through Week 48 data is shown below:
- All subjects who have reached Week 48 in Group A/VTP-300 (N=5) have qualified to stop NA therapy and remain off-treatment
- One Group B/placebo HBeAg+ subject reached HBsAg <LLOQ after imdusiran treatment and has remained <LLOQ

* Subjects noted to have high levels of HBsAg immune complex that interferes with accurate HBsAg quantitation

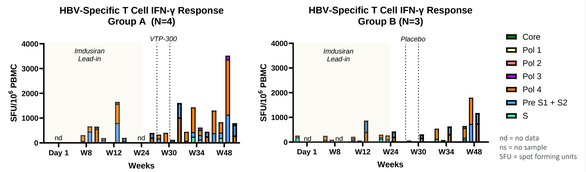
Table 2: Mean HBsAg Change from Baseline and Key Milestones

Study Week	Mean (SE) Change from Baseline N, $\log_{10}$ IU/mL (SE)				HBsAg <100 IU/mL N, (%)		HBsAg <10 IU/mL N, (%)	
	imdusiran 60 mg Q8W x 4 doses							
Baseline	40	2.85 (0.07)			NA		NA	
12	39	-1.31 (0.07)			32/39 (82.1)		7/39 (17.9)	
26	34	-1.86 (0.09)			33/34 (97.1)		15/34 (44.1)	
	N	VTP-300	N	PBO	VTP-300	PBO	VTP-300	PBO
34	13	-2.12 (0.13)	13	-2.01 (0.31)	13/13 (100)	11/13 (84.6)	8/13 (61.5)	6/13 (46.2)
48	5	-1.87 (0.41)	7	-1.03 (0.21)	5/5 (100)	4/7 (57.1)	3/5 (60.0)	0/7 (0)

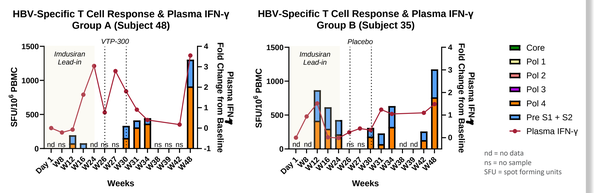
SE = standard error; N = subject number; Week 26 = ChAdOx1-HBV/placebo dose; Week 34 = Eligibility assessed for 2nd MVA-HBV/placebo dose (>0.5 $\log_{10}$ decline in HBsAg between Week 26 and 34)

- Robust reductions of HBsAg were seen during the imdusiran treatment period, with 33/34 (97%) of subjects <100 IU/mL at the time of VTP-300/placebo administration
- VTP-300 appears to maintain low HBsAg levels in the early post-treatment period, as the mean HBsAg levels in the placebo group begin to rebound starting ~12 weeks after the last dose of imdusiran
- All VTP-300 treated subjects have maintained HBsAg <100 IU/mL through Week 48, 60% have maintained HBsAg <10 IU/mL, and all have qualified to stop NA therapy

Figure 3: HBV-Specific T Cell Responses and Soluble Immune Biomarkers



- Elevations in HBV-specific T cell IFN-γ production observed during imdusiran lead-in and after vaccination for N=7 subjects profiled thus far
- HBV-specific T cell responses were observed against HBsAg, PreS1/S2 peptides



- Elevations in HBV-specific T cell responses were associated with increases in plasma IFN-γ in certain subjects (Subjects 48 & 35 shown)
- Transient increases in other plasma immune biomarkers also observed during imdusiran lead-in and vaccination period (BTLA, CD28, GITR, LAG-3, TLR-2, GITRL, PD-1, CTLA-4, CD80, CD86, PD-L1, ICOS, IL-1β, IL-2, IL-3, IL-6, IL-8, sCD40L, EGF, GROα, IL-7, IL-10, IL-12(p70), IL-13, IL-15, IP-10, PDGF-AA/BB, RANTES, TGF-α, VEGF-A)

Table 4: Exploratory HBV Parameters During Imdusiran Treatment

Study Week	HBcrAg (log U/mL) Change from Baseline N	Mean (SE)	HBV pgRNA (log U/mL) Change from Baseline N	Mean (SE)	HBeAg (PEI U/mL) Change from Baseline N	Mean (SE)
Baseline	39	4.05 (0.23)	38	1.98 (0.19)	14	13.47 (8.81)
8	36	-0.18 (0.07)	34	-0.63 (0.08)		N/A
12	37	-0.39 (0.08)	31	-0.79 (0.10)		N/A
16	31	-0.47 (0.09)	27	-0.70 (0.11)		N/A
24	24	-0.48 (0.11)		N/A	13	-12.70 (8.55)

N/A = not available; SE = standard error. HBcrAg <LLOQ was assigned a value of 2.9 log U/mL and target not detected (TND) assigned 1.45 log U/mL; HBV pgRNA <LLOQ assigned 0.48 log U/mL and TND assigned 0.24 log U/mL; HBeAg <LLOQ assigned 0.055 PEI U/mL.

- Imdusiran treatment led to declines in all HBV parameters assessed, including HBcrAg, pgRNA and HBeAg
- Sample collection and analysis is ongoing for the VTP-300/placebo treatment period

RESULTS

Table 5: On-Treatment Safety

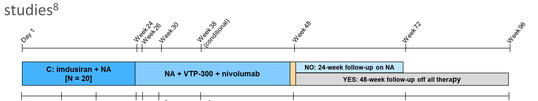
Subjects, N (%) [Events]	Imdusiran Lead-in (N=40)	Group A VTP-300 (N=19)	Group B Placebo (N=18)	Study Total (N=40)
Any TEAE	21 (52.5%) [42]	10 (52.6%) [20]	6 (33.3%) [14]	28 (70.0%) [76]
Grade 1	19 (47.5%) [40]	7 (36.8%) [16]	5 (27.8%) [12]	22 (55.0%) [68]
Grade 2	2 (5.0%) [2]	3 (15.8%) [4]	1 (5.6%) [2]	6 (15.0%) [8]
Grade 3 or 4	0	0	0	0
Treatment-related TEAEs				
Imdusiran	4 (10.0%) [8]	1 (5.3%) [1]	0	5 (12.5%) [9]
VTP-300	N/A	4 (21.1%) [6]	N/A	4 (10%) [6]
SAEs	0	0	0	0
Treatment discontinuation	0	0	0	0

N = subject number; SAE = serious adverse event; TEAE = treatment-emergent adverse event. Subjects were only counted once in the "Total" column, Events were cumulative.

- Imdusiran and VTP-300 were both well-tolerated; there were no Grade 3 or 4 adverse events, no treatment discontinuations, and few treatment-related TEAEs (Grade 1/mild injection site redness, bruising, and/or pain and Grade 1/mild ALT elevations)
- The most common TEAE was COVID-19 infection (N=7 subjects), all other TEAEs occurred in 3 or fewer subjects
- There was one isolated Grade 4 CK elevation in Group B (placebo), otherwise all laboratory abnormalities were Grade 1 or 2 (1 Grade 2 ALT elevation was noted in each treatment group, not assessed as TEAEs)

CONCLUSIONS

- Imdusiran treatment for 24 weeks led to HBsAg declines of -1.86 $\log_{10}$ from baseline and HBsAg <100 in 33/34 subjects at the time of the first VTP-300/placebo dose
- VTP-300 treatment appears to contribute to maintaining low HBsAg levels in the early post-treatment period, although meaningful clinical changes are not expected until at least 6-8 weeks post-MVA-HBV dosing
- Preliminary immunology data suggests HBV-specific T cell IFN-γ production is enhanced in subjects receiving VTP-300 vs placebo
- This early data is promising and additional VTP-300/placebo dosing and follow-up is ongoing; further follow up of these subjects will provide insight into the possibility of functional cure with this regimen
- An amendment to this study is also enrolling to examine addition of low dose nivolumab to the MVA-HBV dose based on data from the HBV002[7] and HBV003 studies[8]



REFERENCES

[1]European Association for the Study of the Liver. J Hepatol, 2017. 67(2):370-398.
[2]Sarin SK, et al. Hepatol Int, 2016. 10(1):1-98.
[3]Terrault N, et al. Hepatol, 2018. 67(4):1560-1599.
[4]Yuen MF, et al. Nature Reviews Disease Primers, 2018. 4:18035.
[5]Yuen MF, et al. Presented at the Global Hepatitis Summit April 25-28, 2023; Oral LB/099.
[6]Thi E, et al. Presented at European Association for the Study of the Liver (EASL) International Liver Congress June 22-26, 2022; Poster SAT397.
[7]Evans T, et al. Presented at EASL Congress June 21-24, 2023; Poster SAT198.
[8]Tait, D. Presented at The Liver Meeting November 10 – 14, 2023; Oral #50, Nov 12th 9:15AM.

CONTACT INFORMATION AND DISCLOSURES

Karen Sims, MD, PhD
Chief Medical Officer
Arbutus Biopharma Inc., 701 Veterans Circle, Warminster, PA 18974
Email: ksims@arbutusbio.com

Authors affiliated with Arbutus Biopharma and Barinthus Biotherapeutics are employees and may own company stock.

Arbutus BIOPHARMA www.arbutusbio.com

BARINTHUS BIOTHERAPEUTICS www.barinthusbio.com