VTP-300 immunotherapeutic, plus low-dose PD-1 inhibitor nivolumab, continues to show meaningful reductions in HBsAg levels

MF. Yuen[1], WL. Chuang[2], CJ. Liu[3], A. Leerapun[4], P.Tangkijvanich[5], L. Bussey[6], R. Kolenovska[6], M. Downs[6], K. Anderson[6], A. Vardeu[6], D. Tait[6]
[1]QUEEN MARY HOSPITAL, The University of Hong Kong, Hong Kong, [2]KAOHSIUNG MEDICAL UNIVERSITY CHUNG-HO MEMORIAL HOSPITAL, Kaohsiung City, Taiwan, [3]NATIONAL TAIWAN UNIVERSITY HOSPITAL, Taipei City, Taiwan, [4]MAHARAJ NAKORN CHIANG MAI HOSPITAL, Chiang Mai , Thailand,
[5]KING CHULALONGKORN MEMORIAL HOSPITAL, Bangkok, Thailand, [6]BARINTHUS BIOTHERAPEUTICS, Didcot, Oxford, United Kingdom.

Contact information
Dr Dereck Tait:
dereck.tait@barinthusbio.com

EASL CONGRESS Milan, Italy 5–8 June 2024

BARINTHUS BIOTHERAPEUTICS

WED-375

Introduction

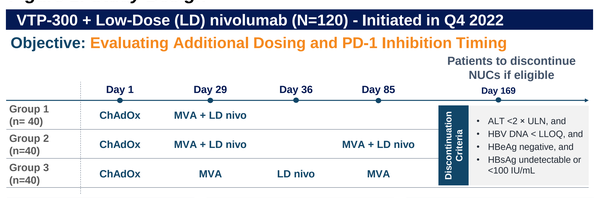
Barinthus Biotherapeutics is developing a novel antigen-specific investigational immunotherapeutic HBV treatment with the aim of achieving functional cure of chronic Hepatitis B (CHB): *HBsAg and HBV DNA undetectable in the blood with or without HBsAb seroconversion, and the immune system maintaining this state for six months off therapy*. VTP-300[1,2,3] is a targeting antigen-specific investigational immunotherapeutic consisting of two viral vectors, ChAdOx1 and MVA, encoding consensus HBV genotype C sequences: full length surface antigen, modified polymerase, and core.

Aim

Study HBV003 (NCT05343481) is an ongoing open-label, randomised, Phase 2b study to assess the safety, immunogenicity, and efficacy of three different regimens of VTP-300 in combination with low-dose (LD) checkpoint inhibitor nivolumab in participants with non-cirrhotic CHB who are on suppressive therapy with nucleos(t)ide analogues (NUC). Here we look at the HBsAg reduction up to Day 169 focusing on reductions of ≥0.5 log and ≥1 log in participants with starting HBsAg ≤200 IU/mL. In addition, eligibility for NUC discontinuation is presented alongside HBV DNA and HBsAg levels.

Method

Figure 1: Study Design



The original study design enrolled CHB patients with HBsAg ≥10 and <4000 IU/mL into three groups. As limited efficacy was observed in participants with HBsAg >200 IU/ml (AASLD 2023 oral #50) the protocol was amended to alter the HBsAg inclusion criteria to ≥10 and ≤200 IU/mL and to exclude participants considered to be at risk of auto-immune thyroiditis. All three groups received ChAdOx1-HBV (2.5×10^{10} viral particles) followed by MVA-HBV (1×10^{8} plaque forming units) and LD nivolumab (0.3 mg/kg IV) as per schematic. NUCs may be discontinued on Day 169 if participants meet criteria in schematic. Safety data, immunology data, and HBV marker data are collected throughout the study to Day 336. Participants who discontinue NUCs are followed up for 48 weeks following discontinuation and must restart NUCs if there is evidence of viral replication (HBV DNA >20 000 IU/mL) or ALT elevations (ALT level >2xULN) and HBV DNA >2000 IU/mL. Study HBV003 has enrolled 91/120 participants, 40 of whom have screening HBsAg ≤200 IU/mL. Interim data cut-off date was 15th April 2024.

Demographics & Safety

Table 1: Baseline (participants with HBsAg ≤200 IU/mL & Day 85 follow-up)

		Group 1 (N=7)	Group 2 (N=8)	Group 3 (N=10)	Total (N=25)
Male, n (%)		6 (86%)	5 (63%)	7 (70%)	18 (72%)
Median age, years		56	56	53	54
Location, n (%)	Hong Kong	1 (14%)	2 (25%)	3 (30%)	6 (24%)
	Taiwan	4 (57%)	4 (50%)	4 (40%)	12 (48%)
	Thailand	2 (29%)	2 (25%)	3 (30%)	7 (28%)
Median years on NUCs		3.8	9.2	8.5	6.5
Median Day 1 HBsAg (IU/mL)		51.3	99.1	79.5	81.5
HBeAg positive, n (%)		1 (14%)	0	4 (40%)	5 (20%)
Detectable HBV DNA, n (%)		2 (29%)	1 (13%)	1 (10%)	4 (16%)

Table 2: Safety (all participants)

	Group 1 (N=29)	Group 2 (N=31)	Group 3 (N=31)	Total (N=91)
Treatment-emergent AE	10 (34%)	13 (42%)	16 (52%)	39 (43%)
Grade 1 max severity	9 (31%)	8 (26%)	11 (35%)	28 (31%)
Grade 2	1 (3%)	3 (10%)	5 (16%)	9 (10%)
Grade 3 or 4	0	2 (6%)	0	2 (2%)
Related AE	2 (7%)	2 (6%)	10 (32%)	14 (15%)
Related to VTP-300	2 (7%)	1 (3%)	4 (13%)	7 (8%)
Related to nivolumab	0	1 (3%)	6 (19%)	7 (8%)
SAE (unrelated)*	0	1 (3%)	0	1 (1%)
AE leading to treatment discontinuation**	0	0	1 (3%)	1 (1%)
AESI - immune-mediated thyroiditis	1 (3%)	0	4 (13%)	5 (5%)
ALT >2xULN through Day 169	4 (14%)	3 (10%)	7 (23%)	14 (15%)
ALT >3xULN through Day 169	0	2 (6%)	3 (10%)	5 (5%)

* Urinary tract infection ** Bell's Palsy (unrelated) diagnosed pre-Day 85 dose.

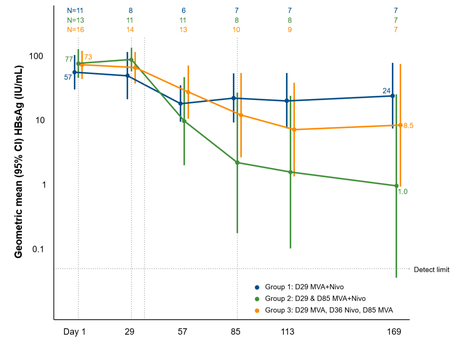
- VTP-300 and LD nivolumab were both generally well tolerated with no treatment related SAEs.
- Thyroid dysfunction was reported in 8 of 91 (9%) participants; normal Thyroid Function Tests reported in 7 of 8 (88%) at last recorded visit.
- ALT elevations >2xULN occurred in 14 participants through Day 169 (2.1-6.7xULN); Most occur soon after first nivolumab and most revert to <2x ULN by Day 85.

Acknowledgements

We thank the patients who participated in the trial, the clinical research units and the health professionals at the trial sites.

Results

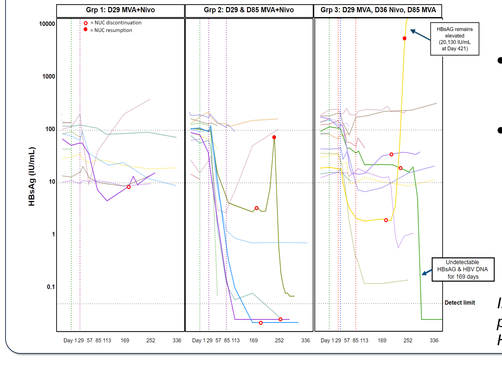
Figure 2: Sustained HBsAg declines observed in all groups



- Robust HBsAg declines occurred soon after Day 29 administration.
- HBsAg declines after Day 85 maintained in all Groups.

HBsAg geometric means (95%CI) to Day 169 in participants with screening HBsAg ≤200 IU/mL are shown. Participants received a Day 85 dose only if HBsAg ≥10 IU/mL; 7 of 18 participants (39%) in Groups 2 and 3 received the Day 85 dose.

Figure 3: Undetectable HBsAg levels observed in 19% of participants



- 19% (4 of 21) with undetectable HBsAg; maintained for ≥16 weeks in 2 cases.
- 67% (14) with HBsAg <10 IU/mL at Day 169 or later.
- 76% (16) eligible for NUC discontinuation; 7 discontinued; 5 remain off NUC therapy and 2 resumed NUC therapy due to elevations in HBV DNA >20,000 IU/mL.

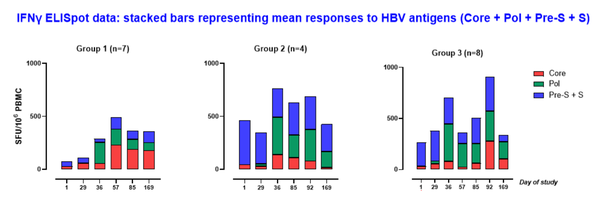
Individual HBsAg declines in participants with screening HBsAg ≤200 IU/mL are shown

Table 3: HBsAg reductions (participants with screening HBsAg ≤200 IU/mL & Day 169 follow-up)

	Group 1 (N=7)	Group 2 (N=7)	Group 3 (N=7)	Total (N=21)
≥0.5 log reduction at Day 169	2 (29%)	5 (71%)	6 (86%)	13 (62%)
≥1 log reduction at Day 169	0	5 (71%)	1 (14%)	6 (29%)
Undetectable at Day 169	0	2 (29%)	0	2 (10%)
Discontinued NUCs	1 (14%)	3 (43%)	3 (43%)	7 (33%)
Undetectable at any time	0	3 (43%)	1 (14%)	4 (19%)
<10 IU/mL at Day 169 or later	4 (57%)	5 (71%)	5 (71%)	14 (67%)

- HBsAg declines were observed in all treatment groups; 62% achieved a ≥0.5 log HBsAg reduction, 29% achieved a ≥1 log HBsAg reduction.
- 76% (16 of 21) of participants became eligible for NUC discontinuation; 7 participants discontinued NUCs (across all groups).

Figure 4: Robust T cell responses observed to all encoded antigens



IFNγ ELISpot assay to measure T cell responses to VTP-300 using peptide pools encompassing HBV antigens Core, Pol and Pre-S/S.

- Post-dose T cell responses were observed across the three HBV antigens.

Conclusions

- VTP-300 and LD nivolumab treatment was generally well tolerated in all three study regimens with no treatment related SAEs.
- 19% of participants across groups with HBsAg baseline <200 IU/mL and Day 169 visit reached undetectable HBsAg.
- 62% of participants across groups with HBsAg baseline <200 IU/mL and Day 169 visit experienced a ≥0.5 log HBsAg reduction.
- HBsAg reductions were greatest following the administration of study drug on Day 29.
- Robust T cell responses were observed to all encoded antigens.
- These preliminary data support the administration of additional doses of VTP-300 to potentially sustain strong T cell responses to enhance rates of HBsAg loss.
- VTP-300 and LD nivolumab regimen is also being studied after a 24-week lead-in of the siRNA, imdusiran, which reduces HBsAg levels prior to administration of VTP-300 with or without nivolumab (AASLD 2023 Poster LB#5036-C).

References

[1] Design and Development of a Multi-HBV Antigen Encoded in Chimpanzee Adenoviral and Modified Vaccinia Ankara Viral Vectors; A Novel Therapeutic Vaccine Strategy against HBV. Chinnakannan et. al. Vaccines. 2020 Apr 14;8(2).
[2] HBV001: Phase I study evaluating the safety and immunogenicity of the therapeutic vaccine ChAdOx1-HBV. Tamsin Cargill et.al. JHEP Reports 2023 vol. 5.
[3] Phase 1b/2a randomized study of heterologous ChAdOx1-HBV/MVA-HBV therapeutic vaccination (VTP-300) as monotherapy and combined with low-dose nivolumab in virally-suppressed patients with chronic hepatitis B. Submitted.