Phase 1b/2a study of heterologous ChAdOx1-HBV/MVA-HBV therapeutic vaccination (VTP-300) combined with low-dose nivolumab (LDN) in virally-suppressed patients with CHB on nucleos(t)ide analogues

[3]Chen CY, [4]Chuang WL, [5]Lim YS, [6]Lo GH, [7]Tak WY, [8]Tseng KC, [9]K Agarwal, [10]S Ryder, [11]J Heo, [12]B Jang, [13]S Ahn, Bussey L[1], Mehta R[1], Anderson K[1], Vardeu A[1], Brown A[2], Barnes E[2], Evans T[1]

[1]Vaccitech, [2]Oxford University

Abstract

Vaccitech, along with Oxford University, is developing a therapeutic HBV vaccine (VTP-300) using a chimpanzee adenoviral vector (ChAdOx1-HBV) and a heterologous Modified Vaccine Ankara boost (MVA-HBV) that encode the inactivated polymerase, core, and entire large S region from a consensus genotype C virus. A Phase 1b/2a trial (NCT04778904) is currently ongoing but has completed enrolment (n=55) in patients with CHB and on antivirals for a minimum of one year with VL undetectable and HBsAg < 4,000 IU/mL. Group 1 (n=10), MVA-HBV (1 x 10^8 pfu) followed at d28 by homologous MVA-HBV; Group 2 (n=18), ChAdOx1-HBV (2.5 x 10^{10} viral particles) followed at d28 by MVA-HBV; Group 3 (n=18), same as Group 2 with low dose nivolumab (LDN) (0.3 mg/kg IV) at d28; Group 4 (n=9) same as Group 2 with LDN at d0 and d28. HBV-specific T cell responses are being assessed using genotype C and D HBV peptides spanning the HBV immunogen in an IFNɣ ELISpot assay, before and after (days 7, 28, 35, 84, and 168) administration. All 55 patients have been enrolled with no concerning safety signal or vaccine-associated SAE reported. Transaminase flares have been observed, associated with HBsAg decline, in two patients. Groups 1 and 4 had no appreciable change in HBsAg. In Group 2, three patients with starting HBsAg < 50 IU/mL had declines of 0.9, 1.0, and 1.4 $\log_{10}$ by Month 6 that persisted at the final timepoint of 9 months, i.e., 8 months after MVA-HBV administration. In Group 3, the mean $\log_{10}$ reduction was 0.8 (N=18), 0.9 (N=10), and 1.3 (N=7) at Months 3, 6, and 9, respectively.

HBV genotype C T cell responses were assessed in 20 patients to date, targeted HBV core (8/20), HBsAg (17/20) and pol (8/20). After prime vaccination, peak mean magnitude (day 7 or day 28) of total HBV specific T cell responses were 437, 244, 688, 332 SFU/10^6 in Groups 1-4, respectively. After boost vaccination peak (day 35) total HBV specific T cell responses were 344, 689, 689, 277 SFU/10^6 in groups 1-4, respectively. Responses were sustained out to 3-6 months in the majority of patients who received VTP-300 immunotherapy, either alone or combined with nivolumab at the boosting time point. Responses have also been immunogenic and show a reduction in HBsAg in well-controlled CHB patients, while exhibiting a well-tolerated safety profile.

Introduction

Induction of a CD8+ T cell response to HBV is considered to be a needed mechanism to achieve a functional cure of chronic hepatitis B (CHB). The highest magnitude CD8+ T cell responses achieved to date in man have used replication incompetent adenoviral vectors followed by attenuated poxvirus vector boosts. The goal of this study is to assess the immunogenicity and activity on cccDNA of VTP-300 (as measured by surface antigen reduction) as a monotherapy and when combined with low-dose checkpoint inhibition, in virally-suppressed, chronic hepatitis B patients.

Methods and Materials

HBV002 Phase 1b/2a (South Korea, Taiwan, UK)

Group 1 (N=10)
MVA-HBV [1 x 10^8 pfu]; MVA-HBV [1 x 10^8 pfu]

Group 2 (N=18)
ChAdOx1-HBV [2.5 x 10^{10} vp]; MVA-HBV [1 x 10^8 pfu]

Group 3 (N=18)
ChAdOx1-HBV [2.5 x 10^{10} vp]; MVA-HBV [1 x 10^8 pfu] + LD nivolumab [0.3 mg/kg]

Group 4 (N=9)
ChAdOx1-HBV [2.5 x 10^{10} vp] + LD nivolumab [0.3 mg/kg]; MVA-HBV [1 x 10^8 pfu] + LD nivolumab [0.3 mg/kg]

Major enrollment criteria

- On effective antiviral treatment for one year
- HBV DNA <40 copies/mL
- HBsAg <4,000 IU/mL

Results

Group	Age (Yrs)	Sex (M:F)	Total # Ppts	Baseline HBsAg GeoMean (Avg)	Through Mo 3	Through Mo 6	Through Mo 9
1	52.6 ± 7.3	8:1	9*	259 (746)	9	9	9
2	53.3 ± 6.9	15:3	18	306 (928)	18	12	8
3	49.8 ± 8.5	11:7	18	326 (806)	18	10	7
4	49.9 ± 9.7	7:2	9	550 (905)	9	9	7

* A 10th participant has been omitted from the Group 1 summary due to well-controlled HBsAg (< LLoQ) at Baseline.

Safety

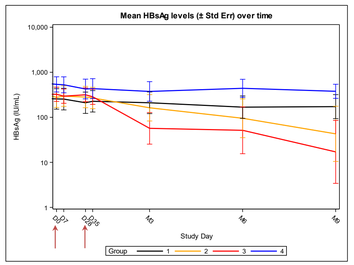
Solicited Symptoms by Maximum-Reported Severity (data cutoff: 28 Sep 2022)

Participants reporting (out of n=55 dosed)	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any solicited symptom	47	30	16	1	0
Pain	44	33	11	0	0
Redness	3	2	1	0	0
Swelling	5	4	1	0	0
Warmth	18	15	3	0	0
Chills	8	7	1	0	0
Fatigue	26	22	3	1	0
Feverishness	18	17	1	0	0
Headache	20	17	3	0	0
Joint Ache	21	15	6	0	0
Malaise	24	19	4	1	0
Muscle Ache	34	26	7	1	0
Nausea	11	8	3	0	0
Fever	0	0	0	0	0

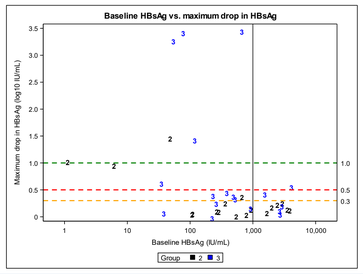
Notes: Table includes reactogenicity from both IMP administrations.
Participants are included at most once per row.

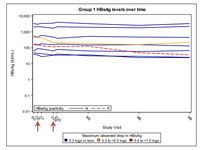
- No vaccine-related SAE has been reported
- Two participants have experienced mild, rapidly resolving transaminitis
- All local reactions have been mild or moderate

Surface Antigen Responses

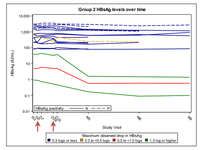


- No response seen in homologous boost in Group 1
- VTP-300 had activity without nivolumab with low starting HBsAg
- Group 3 decline 8 months after VTP-300 as good as 8 months after 2 doses of siRNA
- Group 4 using anti-PD-1 at prime blocked effect seen in Group 3
- Responses over 0.3 $\log_{10}$ are sustained 8 months after last dose
- Two Group 3 patients have non-detectable HBsAg by Month 3

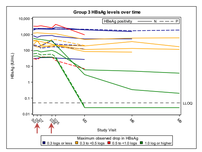




Group 1
Day 0: MVA-HBV
Day 28: MVA-HBV

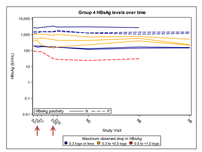


Group 2
Day 0: ChAdOx1-HBV
Day 28: MVA-HBV



Group 3
Day 0: ChAdOx1-HBV
Day 28: MVA-HBV + LD nivolumab

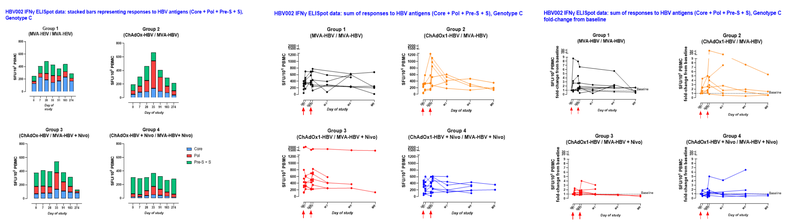
Two patients have non-detectable HBsAg by Month 3



Group 4
Day 0: ChAdOx1-HBV + LD nivolumab
Day 28: MVA-HBV + LD nivolumab

Genotyping and pgRNA data to be completed Q4 2022.

T cell Immune Responses



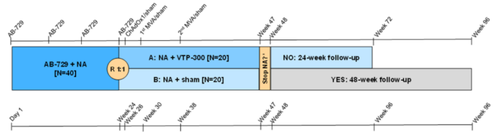
Discussion

- VTP-300 as monotherapy and in combination with LD nivolumab was safely administered, with no treatment-related SAE and infrequent transient transaminitis
- Significant, durable reductions of HBsAg were seen in patients in the VTP-300 monotherapy group (Group 2):
  - 3 of 5 patients with HBsAg below 100 IU/mL at baseline had 0.9, 1.0 and 1.4 $\log_{10}$ declines 5 months post last dose, that persisted in all 3 patients at last follow-up 8 months post last dose
- For patients who received VTP-300 with a single low dose of nivolumab at the time of the Day 28 booster dose (Group 3), the mean $\log_{10}$ reduction in HBsAg was 0.8 (n=18), 0.9 (n=10), and 1.3 (n=7) at Months 3, 6, and 9, respectively
  - Effect most prominent with starting values of HBsAg < 1,000 IU/mL
  - 2 of 5 patients with HBsAg < 100 IU/mL at baseline developed non-detectable HBsAg level at Month 3, which, in one patient with Month 6 and 9 visits, remained non-detectable (see figure)
  - 4 of 5 patients with HBsAg < 100 IU/mL at baseline had declines > 0.6 $\log_{10}$
  - The lowering of HBsAg persisted in all patients with > 0.5 $\log_{10}$ reduction
- No meaningful reductions were seen in Group 1 patients, who received 2 doses of MVA-HBV, or in patients who received low-dose nivolumab with both doses of VTP-300 (Group 4). These groups were discontinued after interim analysis
- A robust T cell response against all encoded antigens is observed following VTP-300 administration, notable for marked CD8+ T cell predominance
- An additional trial to look at the timing of low dose nivolumab and additional MVA-HBV boosts has been implemented, with first patient dosed expected by Q4 2022 (NCT05343481)

Group	Day 1	Day 29	Day 36	Day 85
1	ChAdOx1-HBV	MVA-HBV+ LD nivolumab		
2	ChAdOx1-HBV	MVA-HBV+ LD nivolumab		MVA-HBV+ LD nivolumab[1]
3	ChAdOx1-HBV	MVA-HBV	LD nivolumab	MVA-HBV[1]

Abbreviations: LD = Low-dose (0.3 mg/kg)
[1] Boost is not given if the HBsAg is less than 10 IU/ml

- These results portend well for the collaborative study with Arbutus 729 siRNA, in which HBsAg is expected to be lowered to < 100 IU/mL in the majority of the patients prior to receiving VTP-300



Conclusions

VTP-300, an immunotherapeutic that induces CD8+ T cell responses and durable HBsAg reduction, is a promising component of a potential functional cure of chronic hepatitis B with a well-tolerated safety profile.

CONTACT
Tom Evans, MD
tom.evans@vaccitech.co.uk
+1 781-775-1373

TRIAL SITES RECRUITING PATIENTS [4]Kaohsiung Medical University Chung-Ho Memorial Hospital (W-L Chuang); [5]Asan Medical Center (Y-S Lim); [9]King's College Hospital NHS Foundation Trust (K Agarwal); [10]Nottingham University Hospitals NHS Trust (S Ryder); [11]Pusan National University Hospital (J Heo); [12]Keimyung University Dongsan Hospital (B Jang); [7]Kyungpook National University Hospital (W Tak); [13]Yonsei University College of Medicine (S Ahn); [3]Chia-Yi Christian Hospital (C-Y Chen); [6]E-Da Hospital (G-H Lo); [8]Dalin Tzu Chi General Hospital (K-C Tseng).

REFERENCE

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 Vaccines. 2020 Apr 14;8(2).

DISCLOSURES

Professor Lim YS is an advisor and clinical trial investigator for Vaccitech. He is also an advisor to Gilead Sciences and received research grant/support from Gilead Sciences.