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

T Evans[1], L Bussey[1], SL Teo[2], A Tria[2], A Brown[3], R Mehta[1], K Anderson[1], A Vardeu[1], WL Chuang[4], CY Chen[5], YS Lim[6], WY Tak[7], K Agarwal[8], S Ryder[9], J Heo[10], BK Jang[11], SH Ahn[12], GH Lo[13], KC Tseng[14], SK Yoon[15], WW Su[16], CT Hu[17], E Barnes[3]

[1]Vaccitech, [2]ICON, [3]Oxford University, [4]Kaohsiung Medical University Chung-Ho Memorial Hospital, [5]Chia-Yi Christian Hospital, [6]Asan Medical Center, [7]Kyungpook National University Hospital, South Korea; [8]King's College Hospital NHS Foundation Trust, [9]Nottingham University Hospitals NHS Trust, [10]Pusan National University Hospital, [11]Keimyung University Dongsan Hospital, [12]Yonsei University College of Medicine, [13]E-Da Hospital, [14]Dalin Tzu Chi General Hospital, [15]Catholic University of Korea Seoul Saint Mary's Hospital, [16]Changhua Christian Hospital, [17]Hualien Tzu Chi Hospital

**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.

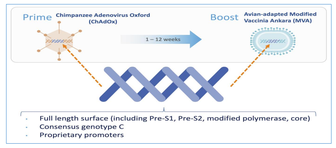
**AIM**: The goal of this study is to assess the immunogenicity and activity on cccDNA of VTP-300 (as measured by surface antigen reduction) as monotherapy and when combined with low-dose checkpoint inhibition, in virally suppressed, chronic hepatitis B patients.

**METHODS**: Vaccitech has developed an HBV immunotherapeutic using a chimpanzee adenoviral vector (ChAdOx1-HBV) and a heterologous Modified vaccinia Ankara boost (MVA-HBV), both encoding the inactivated polymerase, core, and the entire S region from a consensus genotype C virus (VTP-300). A Phase 1b/2a trial has enrolled 55 patients with virally-suppressed CHB (on antivirals for a minimum of one year with viral load undetectable and HBsAg <4,000 IU) in Taiwan, South Korea and the UK (NCT047789). Hepatitis B specific efficacy and immunologic parameters were followed.

As of May 2022, the study had closed recruitment, having exceeded enrolment at n=55 patients. An amendment closed Groups 1 and 4 early due to interim HBsAg data. Visits were conducted at days 0, 7, 28, 35 and months 3, 6 and 9. HBsAg data shown were collected through May 9, 2022. Individual plots show results for those patients with data through at least month 3.

Immunologic assays are performed with peptide pools encompassing core, Pol (4 pools) pre-S1, pre-S2, S for the gamma IFN ELISpot and 4 pools (Core, Pol1, Pol2, S) for the ICS assay. All assays are short, 6-hour to overnight stimulations without *in vitro* expansion. The ICS used the following phenotypic and activation markers: CD3, CD4, CD8, IFNg, IL-2, TNF-α, CCR7, CD45RO, CD107, CD154.

**Construct Design**




## Study Design

**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

| Group | Age (Yrs) | Gender (M:F) | Total participants | Through D 35 | Through Mo 3 | Through Mo 6 | Through Mo 9 |
|---|---|---|---|---|---|---|---|
| 1 | 52.6 ± 6.8 | 8:1 | 10 (9)* | 9 | 9 | 9 | 9 |
| 2 | 53.3 ± 6.7 | 15:3 | 18 | 13 | 10 | 8 | 6 |
| 3 | 49.8 ± 8.3 | 11:7 | 18 | 14 | 11 | 8 | 6 |
| 4 | 49.9 ± 15.4 | 7:2 | 9 | 9 | 9 | 7 | 5 |

*early discontinuation

## Safety

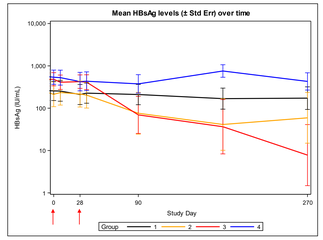
- To date no vaccine-related SAEs
- Two patients with mild, rapidly resolving transaminitis
- Local reactions have been mild or moderate

**Solicited Symptoms by Maximum-Reported Severity (data cutoff: 26 April 2022)**

| | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Participants reporting (out of n=43 dosed) | | | | | |
| Any solicited symptom | 38 | 26 | 11 | 1 | 0 |
| Any local symptom | 35 | 27 | 8 | 0 | 0 |
| Pain | 33 | 26 | 7 | 0 | 0 |
| Redness | 2 | 2 | 0 | 0 | 0 |
| Swelling | 5 | 4 | 1 | 0 | 0 |
| Warmth | 16 | 13 | 3 | 0 | 0 |
| Any systemic symptom | 33 | 24 | 8 | 1 | 0 |
| Chills | 6 | 5 | 1 | 0 | 0 |
| Fatigue | 18 | 14 | 3 | 1 | 0 |
| Fever | 11 | 10 | 1 | 0 | 0 |
| Headache | 14 | 12 | 2 | 0 | 0 |
| Joint Ache | 16 | 10 | 6 | 0 | 0 |
| Malaise | 18 | 13 | 4 | 1 | 0 |
| Muscle Ache | 29 | 23 | 5 | 1 | 0 |
| Nausea | 8 | 6 | 2 | 0 | 0 |

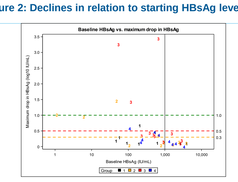
Notes: Includes reactogenicity from both doses of VTP-300.
Participants are included at most once per row.

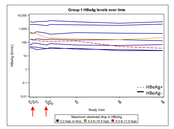
## Figure 1: Surface antigen responses by group and individual



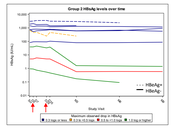

- No response seen in homologous boost in Group 1
- VTP-300 had activity without nivolumab with low starting HBsAg
- Group 3 decline 8 months after VTP-300 as good as 8 months after 2 doses of siRNA; for both approaches more boosts are planned
- Group 4 using anti-PD-1 at prime blocked effect seen in Group 3
- Responses over 0.3 $\log_{10}$ are sustained 8 months after last dose
- One Group 3 patient has non-detectable HBsAg from month 3-9

**Figure 2: Declines in relation to starting HBsAg levels**

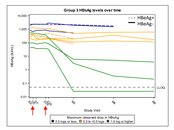


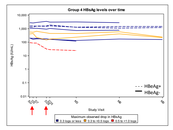

Gr. 1: MVA-HBV Day 0; MVA-HBV Day 28




Gr. 2: ChAdOx1-HBV Day 0; MVA-HBV Day 28

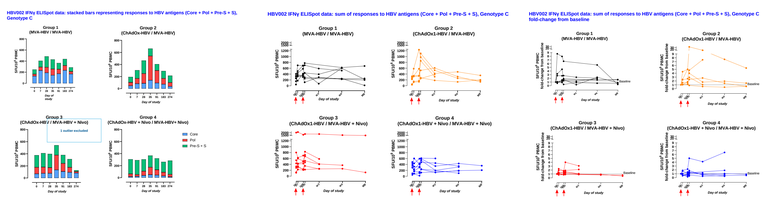



Gr 3:ChAdOx1-HBV Day 0; MVA-HBV + LD nivolumab Day 28

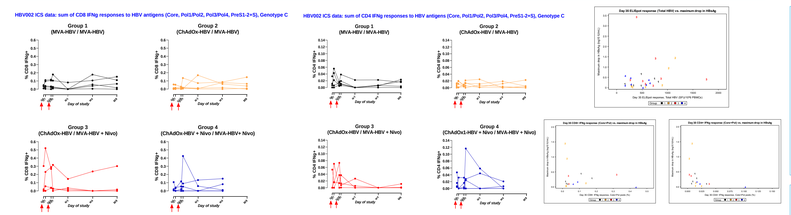



Gr. 4: ChAdOx1-HBV+ LD nivolumab Day 0; MVA-HBV + LD nivolumab Day 28

## Figure 3: T cell immune responses




A. Responses were most pronounced in Group 2, the heterologous prime-boost arm without nivolumab. Despite the difference in HBsAg responses in Group 3 and 4, the data to date show no major difference in peripheral blood T cell responses. Liver aspirates were not performed.




B. Fewer ICS responses have been run, and they are variable, but increases are demonstrated after both the prime and boost, with CD8 T cell responses >>CD4 (note scale) responses, also for TNF/IFNgamma double positive (not shown)
Shown are the correlations between the magnitude of the T cell response at Day 35 (peak time point) and HBsAg declines, but dataset is still small. Correlations trended in the positive direction for CD8, but not CD4

C. Response after boost were best observed in the heterologous prime-boost group without nivolumab. Responses were seen to all encoded antigens

**CONCLUSIONS**

- VTP-300 as monotherapy and in combination with LD nivolumab was safely administered, with no treatment-related SAEs, and infrequent transient transaminitis
- Significant, durable reductions of HBsAg were seen in patients in the VTP-300 monotherapy group (Group 2):
  - 3 patients had 0.7, 0.7 and 1.4 $\log_{10}$ declines 2 mos post last dose
  - These dramatic declines are persisting in all 3 patients at latest follow-up 5 or 8 months after the last dose of VTP-300
  - These 3 patients had baseline HBsAg under 50 IU/mL, implying better response in patients with low baseline HBsAg
- For the first 8 patients who received VTP-300 with a single low dose of nivolumab at the time of the booster dose (Group 3), the mean reduction in HBsAg was over 1 $\log_{10}$ at 6 months
  - This effect persisted with a mean decline of 1.15 $\log_{10}$ at 8 months after the last dose
  - Effect most prominent with starting values HBsAg < 1,000 IU/mL
  - One patient in group 3 developed a non-detectable HBsAg level, which continued 8 months after last dose
- The lowering of HBsAg persisted until the last measurement in all patients with >0.5 $\log_{10}$ reduction. This compares favorably to the lack of durability seen with direct acting agents to date
- No reductions ≥1 $\log_{10}$ 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, notable for marked CD8+ T cell predominance, which had never been achieved by any other immunotherapeutic
- A trial to look at timing of low dose nivolumab and additional doses of the MVA boost component of VTP-300 has been implemented, with first patient dosed expected by Q3 2022 (NCT05343481)
- 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

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

**REFERENCES:** 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).

tom.evans@vaccitech.co.uk; ellie.barnes@ndm.ox.ac.uk