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

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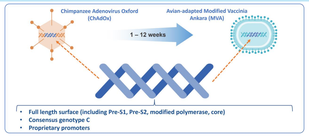
INTRODUCTION: Induction of a CD8+ T cell response to HBV is likely a required mechanism to achieve a functional cure of chronic hepatitis B (CHB). The highest magnitude CD8+ T cell responses achieved to date in man have used sequential combination of replication incompetent adenoviral vectors followed by attenuated poxvirus vector.

AIM: The goal of this study was to assess the impact of VTP-300 on T cell function and efficacy (as measured by surface antigen reduction) as monotherapy and when combined with Low-Dose (LD) checkpoint inhibition, in virally suppressed, CHB patients.

METHODS: VTP-300 is a HBV investigational immunotherapeutic candidate 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. This Phase 1b/2a trial enrolled 55 patients with virally-suppressed CHB (on antivirals for a minimum of one year with viral load undetectable and HBsAg <4,000 IU/mL) in Taiwan, South Korea and the UK (NCT047789). Results from the locked database are reported here.

Construct Design[1]



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]

Visits were conducted at Days 0, 7, 28, 35 and Months 3, 6 and 9. Data presented are for all participants through the Month 9/EOS visit.

Demographics and Safety Evaluation

Group	Age (Yrs)	Gender (M:F)	Total participants
1	50.8 ± 8.8	9:1	10 (9)*
2	53.3 ± 6.9	15:3	18
3	49.8 ± 8.5	11:7	18
4	49.9 ± 9.7	7:2	9

*1 participant in Group 1 was early terminated due to a protocol deviation

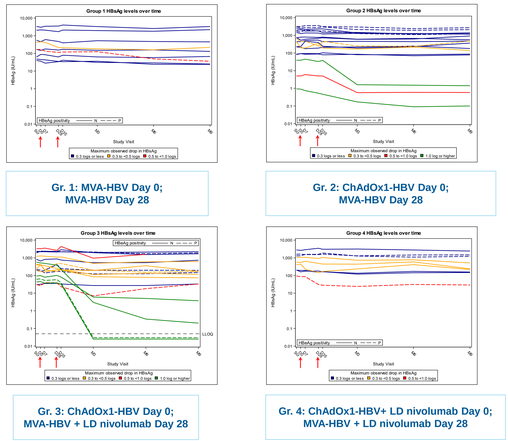
- No discontinuation due to AE
- No treatment-related SAEs or Grade 3 Adverse Events
- Three Treatment Emergent Adverse Events related to nivolumab
  - Two patients with mild, rapidly resolving increases ALT/AST (both Group 3)
  - One instance of urticaria
- Local reactions were mild or moderate

Table 1: Summary of Solicited Symptoms, Overall and by Maximum-Reported Severity

Number of participants with	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any Solicited Symptom	48	30	17	1	0
Any Local Symptom	46	33	13	0	0
Pain	45	34	11	0	0
Erythema	3	2	1	0	0
Induration	6	5	1	0	0
Warmth	18	15	3	0	0
Any systemic symptom	41	29	11	1	0
Arthralgia	21	14	7	0	0
Chills	8	7	1	0	0
Fatigue	26	21	4	1	0
Feverishness	18	17	1	0	0
Headache	20	16	4	0	0
Malaise	26	21	4	1	0
Myalgia	34	26	7	1	0
Nausea	11	8	3	0	0
Fever	0	0	0	0	0

Notes: Solicited symptoms are summarized across all four treatment arms and both IMP administrations. Participants are counted at most once per row in the "Any Grade" column and at most once per row in the column reflecting their maximum-reported severity grading.

Figure 1: Surface antigen responses by group and individual



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 2: HBsAg declines in relation to starting HBsAg levels

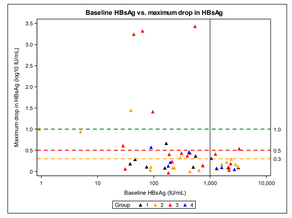


Figure 3: pgRNA data

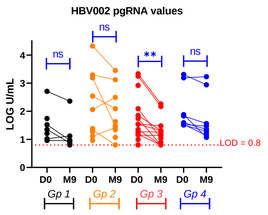
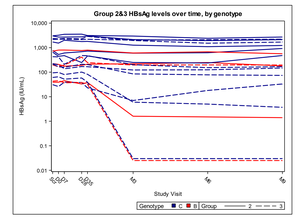


Figure 4: Genotyping data

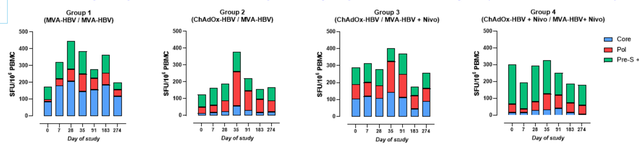


Genotypes were detected in approximately 80% of patients using a sensitive assay: (https://doi.org/ 10.1002/jmv.26249)

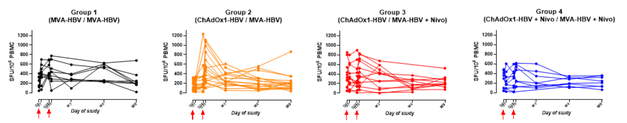
Figure 5: T cell immune responses

A

HBV002 IFNγ ELISpot data: stacked bars representing responses to HBV antigens (Core + Pol + Pre-S + S)

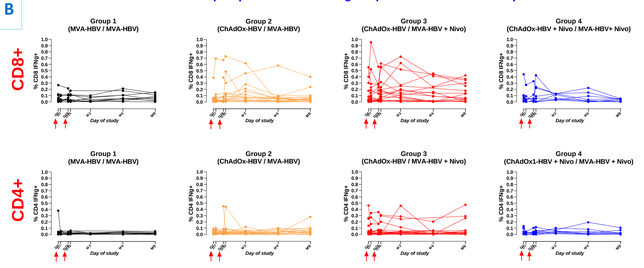


IFNγ ELISpot data: sum of responses to HBV antigens (Core + Pol + Pre-S + S), Genotype C

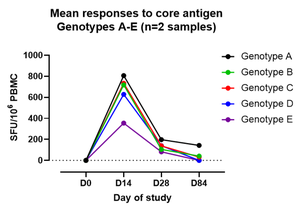


B

ICS data: sum of CD8 & CD4 IFNγ responses to HBV antigens (Core + Pol + PreS1-2 + S)



C



IFNγ ELISpot and intracellular cytokine staining (ICS) assays to measure T cell responses are performed with peptide pools encompassing core, Pol (4 pools) pre-S1 and S. 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, CD45RA, CD107, CD154. Groups 3 and 4, the data to date show no major difference in peripheral blood T cell responses. Liver aspirates were not performed.

A. Responses were most pronounced in Group 2, VTP-300 alone arm.
B. Increases are demonstrated after administration of each component of VTP-300, with CD8 T cell responses >> CD4 responses (note scale), also for TNF/IFNg double positive (not shown).
C. Responses to peptides of Core from genotype A-E in healthy subjects (n=2) receiving ChAdOx1-HBV alone

Figure 6: HBsAg vs ELISpot response (Groups 2 and 3)

T cell responses of HBsAg "responders" (log_{10} change D0 to M3 > 0.5)

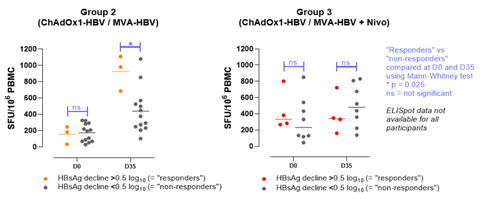
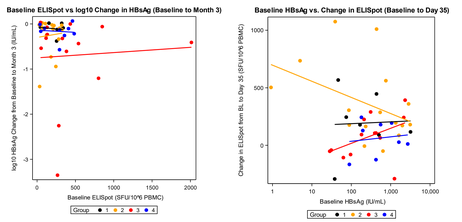


Figure 7: Baseline HBsAg, T cell responses



Group	Day 1	Day 29	Day 36	Day 85	Day 169 (or later)
1	ChAdOx1-HBV	MVA-HBV + LD nivolumab			Optional NA discontinuation and follow-up
2	ChAdOx1-HBV	MVA-HBV + LD nivolumab		MVA-HBV + LD nivolumab[1]	
3	ChAdOx1-HBV	MVA-HBV	LD nivolumab	MVA-HBV[1]	

[1] Boost is not given if HBsAg is <10 IU/mL
NA discontinuation if criteria met: If ALT <2 × ULN, HBV DNA is <LLOQ, HBeAg is negative and at least one of the following is met on two occasions at least 1 month apart: HBsAg undetectable and/or HBsAg <100 IU/mL

CONCLUSIONS

Safety Evaluation:

- VTP-300 as monotherapy and in combination with LD nivolumab was administered with no treatment-related SAEs and infrequent transient elevated liver enzymes.

Efficacy Evaluation:

- Significant, durable reductions of HBsAg were seen in patients in the VTP-300 monotherapy group (Group 2):
  - 3 of 18 patients had 0.7, 0.7, and 1.4 log_{10} declines 2 months post last dose, with durable responses 8 months after the last dose.
  - These 3 patients had baseline HBsAg <50 IU/mL, implying better response in patients with low baseline HBsAg.
- For the patients receiving VTP-300 with a single LD of nivolumab together with MVA-HBV (Group 3), the mean reduction in HBsAg was 0.76 log_{10} at 3 months (p<0.001).
  - This effect persisted with a mean decline of 0.98 log_{10} at 8 months (p<0.001) after the last dose and is most prominent with starting values HBsAg < 1,000 IU/mL.
  - 2 of 18 patients 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 (Groups 2 and 3).
- Patients who received low-dose nivolumab with both doses of VTP-300 (Group 4) did not have HBsAg declines.

Immunology & pgRNA readouts:

- A robust T cell response was generated and was highest in the VTP-300 alone group (Group 2). In that group there was a relation between ELISpot response and HBsAg decline.
- VTP-300 (based on genotype C) led to a decline in HBsAg in both genotype B and C CHB patients (Groups 2 & 3). Cross-reactivity to core was shown in ELISpot assays using genotype-specific peptides A-E (healthy subjects).
- pgRNA levels fell significantly only in Group 3, consistent with the decline in HBsAg levels.

A phase 2b trial (NCT05343481) to look at timing of LD nivolumab, additional doses of the MVA-HBV component of VTP-300 and NA discontinuation has been implemented, with over 40% of the 120 patients enrolled to date (40 per group).

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. Vaccines. 2020 Apr 14;8(2).

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