Primary analysis of a phase 2b open-label study demonstrates VTP-300 administered with low-dose nivolumab is associated with meaningful reductions of HBsAg in chronic hepatitis B participants with HBsAg of 200 IU/mL or less

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Introduction and Objectives

- Currently available therapies for chronic hepatitis B (CHB) may delay or prevent hepatitis B virus (HBV)–related hepatic complications but do not usually result in functional cure (FC). The achievement of HBV FC requires a combination of suppressed HBV replication and the enhancement of HBV-specific T-cell responses[1].
- VTP-300[2] is a targeted antigen-specific investigational immunotherapy consisting of two viral vectors, chimpanzee adenovirus vectored hepatitis B - ChAdOx1-HBV (ChAdOx) and modified vaccinia virus Ankara - MVA-HBV (MVA), encoding HBV genotype C sequences: full length surface antigen, modified polymerase, and core.
- HBV003 (NCT05343481) is an open-label, randomised, Phase 2b trial designed to evaluate the safety, immunogenicity, and efficacy of three different regimens of VTP-300 in combination with low-dose nivolumab (LD nivo) in participants with non-cirrhotic CHB who are on antiviral therapy with nucleos(t)ide analogues (NUCs).
- Herewith we report the primary analysis of the trial: the proportion of participants with ≥1 $\log_{10}$ HBsAg reduction at Day 169. Data previously presented [3,4,5] demonstrated greater efficacy in participants with HBsAg ≤200 IU/mL at baseline therefore the protocol was amended to restrict enrolment to these participants. This presentation will focus on participants with HBsAg ≤200 IU/mL at baseline.

Method

Figure 1: Study Design

VTP-300 + Low-Dose nivolumab (N=121) – Data cut off 12FEB2025 (D169)

	Day 1	Day 29	Day 36	Day 85	Day 169	
Group 1 (n= 40)	ChAdOx	MVA + LD nivo			Decision	Patients to discontinue NUCs*
Group 2 (n=41)	ChAdOx	MVA + LD nivo		MVA + LD nivo		Patients to receive additional course of VTP-300 + LD nivolumab*
Group 3 (n=40)	ChAdOx	MVA	LD nivo	MVA		

Inclusion Criteria
- HBV DNA ≤1,000 IU/mL.
- HBsAg ≤4,000 IU/mL later amended to ≤ 200 IU/mL.
- On NUCs for ≥6 months.

Primary Endpoint
- % participants with a greater than 1 $\log_{10}$ HBsAg reduction 6 months after initiation of therapy.

Secondary Endpoints
- Safety and reactogenicity.
- Immunogenicity.
- Eligibility for, and efficacy, of NUC discontinuation

* If eligible and if the participant consents. NUC - nucleos(t)ide analogues. ChAdOx - ChAdOx-1HBV. MVA - MVAHBV

- HBV003 was designed to assess the efficacy of VTP-300 in combination with LD nivo in well-controlled CHB infection. Three different treatment regimens were evaluated in a 1:1:1 randomisation.
- All 3 groups received ChAdOx1-HBV (2.5×10^{10} viral particles IM) followed by MVA-HBV (1×10^{8} plaque forming units IM) and LD nivolumab (0.3 mg/kg IV).
- Participants randomised to Group 2 or 3 did not receive the second (Day 85) MVA dose if HBsAg was < 10 IU/mL.
- As previously reported, thyroid dysfunction and autoimmune thyroiditis were observed in a small number of participants [5] and the protocol was therefore amended to exclude participants considered to be at risk of auto-immune thyroiditis.
- Participants were assessed for NUC discontinuation at Day 169 with optional discontinuation at investigator's discretion and with participant consent. Follow up post-NUC discontinuation is for 48 weeks and NUCs must be restarted if HBV DNA and ALT levels meet criteria defined in the protocol.
- Safety data, immunology data, and biomarkers of HBV are collected throughout the study.
- Participants could elect to receive a second course of VTP-300 and LD nivo (Part 2) if their ALT was <3xULN and they had no evidence of thyroid dysfunction. As the study is ongoing and data from the second course is limited, no data is presented.
- The HBV003 trial is ongoing beyond the point of analysis of the primary efficacy endpoint and the data presented may vary from that in the final CSR.

Results

Table 1: Analysis sets

	Group 1	Group 2	Group 3	Total
Dosed (Intent to Treat - ITT)	40	41	40	121
Baseline HBsAg ≤200 IU/mL	22	23	25	70
As treated*	48	33	40	121
Immunogenicity Analysis set**	12	13	17	42

*Participants randomised to Group 2 and did not receive the second (Day 85) MVA dose as their HBsAg was <10 IU/mL were removed from their randomised Group and included in Group 1.
**All participants who have available immunogenicity data no protocol deviations that may potentially bias the results of the immunological analysis.

Table 2: Baseline characteristics

ITT	Group 1 (N=40)	Group 2 (N=41)	Group 3 (N=40)	Total (N=121)
Male, n (%)	34 (85.0)	30 (73.2)	31 (77.5)	95 (78.5)
Age (years), Mean (SD)	50.3 (8.2)	49.3 (7.4)	52.4 (8.3)	50.6 (8.0)
Ethnicity/Race: Asian, n (%)	40 (100)	41 (100)	40 (100)	121 (100)
Avg years on NUCs prior to enrolment, Mean	4.5	6.4	7.8	6.2
Median Day 1 HBsAg (IU/mL)	156.7	144.7	162.5	161.2
HBeAg positive, n (%)	8 (20.0)	8 (19.5)	7 (17.5)	23 (19.0)
Non-detectable HBV DNA, n (%)	34 (85.0)	33 (80.5)	38 (95.0)	105 (86.8)
HBV genotype B, n *	5	4	8	17
HBV genotype C, n *	6	8	6	20

* 50 participants selected for genotyping; 25 with HBsAg response (>0.5 log drop) and 25 controls with no response. Data currently available for 37/50 participants.

- Demographics were similar across all groups in the study other than time on NUC therapy prior to enrolment which was shorter in Group 1.
- Demographics in those with baseline HBsAg levels ≤200 IU/mL analysis set are generally similar in all groups. Although, baseline HBsAg levels are lower in Group 1.

Table 3: Safety (all participants, as treated)

Time period: Any time after treatment n (%) [n events]	Group 1* (N=48)	Group 2 (N=33)	Group 3 (N=40)
TEAE	25 (52.1%) [50]	17 (51.5%) [27]	24 (60.0%) [57]
VTP-300 related TEAE	2 (4.2%) [2]	0	5 (12.5%) [9]
Nivolumab related TEAE	0	3 (9.1%) [4]	7 (17.5%) [9]
Grade ≥3 TEAE	2 (4.2%) [2]	1 (3.0%) [1]	1 (2.5%) [2]
SAE	2 (4.2%) [2]	0	1 (2.5%) [1]
AESI for VTP-300	0	0	0
AESI related to Nivolumab (Immune mediated thyroiditis)	0	1 (3.0%) [1]	4 (10.0%) [4]
AESI not related to either (Immune mediated thyroiditis)	1 (2.1%) [1]	0	0

*Group 1 includes participants who received one MVA/LD nivo dose only, Group 2 includes those who received 2 MVA/LD nivo doses

- No related SAEs were reported. One death due to unrelated ventricular fibrillation.
- Two early discontinuations of treatment (both in Group 3):
  - Bell's Palsy; ALT >3xULN (individual stopping rule met).
- Post-baseline Grade 3 or 4 laboratory abnormalities:
  - Isolated neutropenia; ALT elevations in 2 participants with concurrent loss of HBsAg.
    - ALT elevations >3x ULN in 8 participants, all occurred after first dose of MVA/LD nivo. Generally resolved rapidly and all had resolved by D169.
- Six AESIs of immune mediated thyroiditis reported; 5 were related to LD nivo. Thyroid dysfunction observed in 14 participants across all treatment groups; transient, resolved in 12 participants; required short-term treatment in two cases.

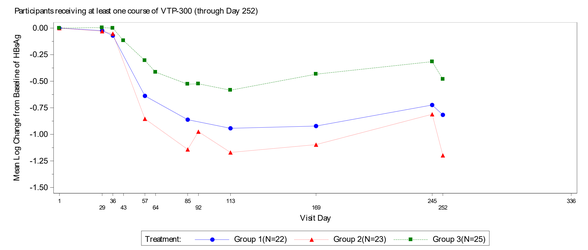
Table 4: Primary Endpoint: HBsAg ≥1 $\log_{10}$ decline from baseline at Day 169

	Intent To Treat			
	Group 1 (N=40)	Group 2* (N=41)	Group 3 (N=40)	Total (N=121)
Participants with ≥1 log drop at Day 169	8 (20.0%)	8 (19.5%)	1 (2.5%)	17 (14.0%)
	HBsAg ≤200IU/mL at baseline			
	Group 1 (N=22)	Group 2* (N=23)	Group 3 (N=25)	Total (N=70)
Participants with ≥1 log drop at Day 169	7 (31.8%)	8 (34.8%)	1 (4.0%)	16 (22.9%)
	As treated analysis set **			
	Group 1* (N=48)	Group 2 (N=33)	Group 3 (N=40)	Total (N=121)
Participants with ≥1 log drop at Day 169	13 (27.1%)	3 (9.1%)	1 (2.5%)	17 (14.0%)

* Includes participants who did not receive Day 85 dose because HBsAg was < 10 IU/mL
** Participants who did not receive second MVA/LD nivolumab dose in Group 2 were included in Group 1

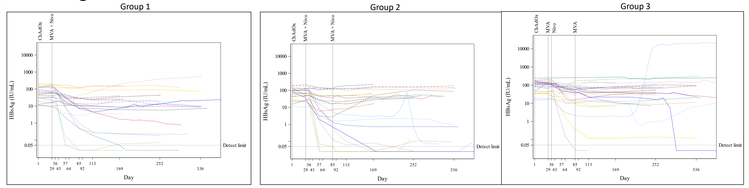
- Participants with baseline HBsAg ≤ 200 IU/mL were more likely to achieve a ≥1 $\log_{10}$ drop in HBsAg compared to the overall population with baseline HBsAg ≤ 4000 IU/mL (22.9% vs 14.0%).
- The efficacy outcomes in Groups 1 and 2 are similar for ITT and those with HBsAg ≤ 200IU/mL at baseline; the increase in participants with ≥ 1log drop at Day 169 in Group 1 in the 'as treated analysis' set reflects the addition of participants from Group 2 who only received a single MVA/LD nivo dose. A single participant in Group 3 achieved a ≥1 $\log_{10}$ drop in HBsAg.

Figure 2: HBsAg $\log_{10}$ Changes from Baseline in Participants with Baseline HBsAg ≤200 IU/mL (ITT)



- Mean HBsAg $\log_{10}$-change from baseline at Day 169 is –0.92, –1.10 and –0.43 for Groups 1,2, and 3 respectively in participants with baseline HBsAg ≤200 IU/mL.
- HBsAg declines occurred in all groups soon after the Day 29 dose of study product and were maintained to Day169 (data still accruing post Day 169).
- The decline at Day 252 corresponds with an optional second course of VTP-300, which was introduced via a protocol amendment (full data pending).

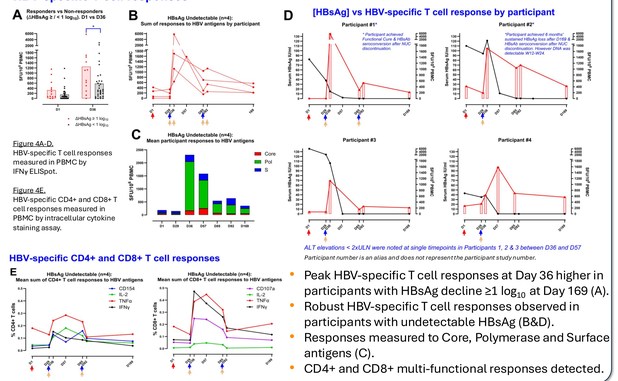
Figure 3: Individual HBsAg declines by treatment group in participants with HBsAg ≤200 IU/mL



- 11/70 (16%) participants with Baseline HBsAg ≤200 IU/mL across all Groups achieved HBsAg loss at any timepoint. The greatest proportion of these (n=6) were in Group 2 (as randomised) and received either one or two doses of MVA/LD nivo.
- 2 participants achieved functional cure: one of these also underwent HBsAb seroconversion; and the other became HBsAg undetectable 12 weeks after NUC discontinuation.
  - Sustained HBsAg loss (≥6 months) has been observed in 4/70 (6%) participants including the two participants with functional cure.
- 48/68 (71%) participants were eligible for NUC discontinuation; 2 participants were not evaluated for NUC discontinuation due to SAE; 15 discontinued NUCs and three met protocol criteria to resume NUC therapy.

Figure 4: VTP-300 elicits robust HBV-specific T cell responses

HBV-specific T cell responses



HBV-specific CD4+ and CD8+ T cell responses

- Peak HBV-specific T cell responses at Day 36 higher in participants with HBsAg decline ≥1 $\log_{10}$ at Day 169 (A).
- Robust HBV-specific T cell responses observed in participants with undetectable HBsAg (B&D).
- Responses measured to Core, Polymerase and Surface antigens (C).
- CD4+ and CD8+ multi-functional responses detected.

Conclusions

- HBsAg declines of ≥1 log at Day 169 were observed in 16/70 (23%) participants with HBsAg ≤200 IU/mL at baseline and in 1/51 (2%) participant with HBsAg >200 IU/mL.
- HBsAg became undetectable at any time in 11 (16%) participants with HBsAg ≤200 IU/mL.
- Functional cure was observed in 2 participants accompanied by HBsAb seroconversion in 1 participant.
- One or two doses of MVA/LD nivo appear to provide similar efficacy. However, it is noteworthy that declines in HBsAg generally occurred soon after the first dose and before the second dose. There is no evident benefit to delaying LD nivo administration as in Group 3.
- VTP-300 elicited robust HBV-specific CD4+ and CD8+ T cell responses which peaked at Day 36; strong magnitudes of T cell response were generated in participants with undetectable HBsAg.
- VTP-300 and LD nivo was generally well tolerated in all regimens. Transient thyroid dysfunction was observed and resolved in 12 of 14 cases with no participant requiring long term treatment.

References

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