VTP-300 combined with low-dose nivolumab is associated with HBsAg loss in chronic hepatitis B participants with HBsAg less than 200 IU/mL: Results from a phase 2b open-label study

Presenter: Chun-Jen Liu MD PhD Hepatitis Research Center, National Taiwan University Hospital, Taipei City, Taiwan

Authors: Liu CJ, Avihingsanon A, Chuang WL, Leerapun A, Wong G, Yuen MF, Kolenovska R, Jones B, Tait D, Hooftman L

Publication Number: 5009

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

BARINTHUS BIOTHERAPEUTICS

Disclosures – Dr. Chun-Jen Liu

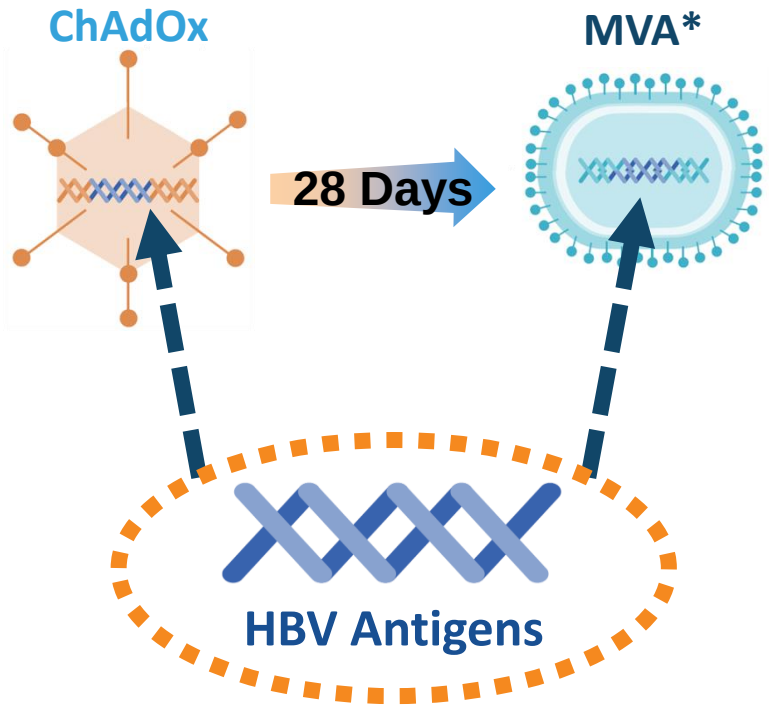
- Declaration of Potential Conflict of Interest:
  - Consultancy: Gilead Sciences, BMS, AstraZeneca
  - Speaker fee: Gilead Sciences

Investigative Approach to Treating CHB Patients With VTP-300

Patient Population	Ongoing VTP-300 Trial	Treatment Approach		
		Inhibit viral replication	Directly **lower** HBsAg burden	**Stimulate** immune response
HBsAg ≤200 IU/mL	HBV003	NUCs	Patients below 200 IU/mL	VTP-300 + ICI
HBsAg >200 IU/mL	IM-PROVE II	NUCs	HBsAg Reducer (*e.g.*: ASO, siRNA)	VTP-300 +/- ICI

ICI: Immune Checkpoint Inhibitor

VTP-300: Targeted Investigational Immunotherapy Designed to Elicit Ag-Specific T Cells



ChAdOx: Chimpanzee Adenovirus Oxford
MVA: Modified Vaccinia Ankara

- **ChAdOx/MVA combination approach:** Has yielded high magnitude, high quality and durable CD8+ T cells, essential for controlling disease in humans.
- **Antigens based on a consensus genotype C**
  - Full length surface (PreS1, PreS2, S)
  - Modified polymerase
  - Core
- **Phase 1b/2a study demonstrated meaningful and sustained reductions in HBsAg** when given alone and with checkpoint inhibitor.

* MVA may be administered more than once.

HBV003: Phase 2b Study Design

Data cut off: 30 September 2024 for lab data, 8 October 2024 for clinical data.

VTP-300 + Low-Dose (LD) nivolumab (N=121) - Initiated in Q4 2022. Enrolment complete across 18 sites in Q3 2024.*

Objective: Evaluating Additional Dosing and PD-1 Inhibition Timing

Inclusion Criteria

- HBV DNA ≤1,000 IU/mL
- HBsAg ≤200 IU/mL**
- On NUCs for ≥6 months

Primary Endpoint

- % participants with a greater than 1 log HBsAg reduction at 6 months (D169) after initiation of therapy

Secondary Endpoints

- Safety: incidence of AEs and SAEs
- T cell response

NUC Discontinuation Criteria

- ALT <2 × ULN, and
- Hepatitis B virus DNA loss, and
- Hepatitis B e antigen negative, and
- Hepatitis B surface antigen <100 IU/mL, and/or
- Hepatitis B surface antibody positive

Study Reference: NCT05343481
ALT: Alanine aminotransferase; **LLOQ:** lower limit of quantitation; **ULN**: upper limit of normal.

* Including Thailand, Hong Kong and Taiwan.

** Protocol amended, from HBsAg ≥10 to <4,000 IU/mL, to include only HBsAg ≥10 to ≤200 IU/ml after Nov 2023 (58%) participants had been randomised.

HBV003 Phase 2b: Patient Demographics and Baseline Characteristics

Table 1: Preliminary Baseline Data (Participants ≤200 IU/mL HBsAg)

	Group 1 (N=22)	Group 2 (N=22)	Group 3 (N=25)	Total (N=69)
Age, mean (SD)	51 (7.4)	50.2 (6.7)	53.7 (7.6)	51.7 (7.3)
Male, %	91%	82%	84%	86%
Day 1 HBsAg IU/mL Median (25th, 75th %tile)	48.7 (30.7, 117.9)	80.2 (41.4, 110.1)	105.1 (43.5, 153.1)	81.5 (35.6, 129.2)
Day 1 ALT U/L, Mean (SD)	27.7 (16.3)	20.4 (10.0)	22.2 (10.5)	23.4 (12.7)
HBeAg positive, %	5%	23%	20%	16%

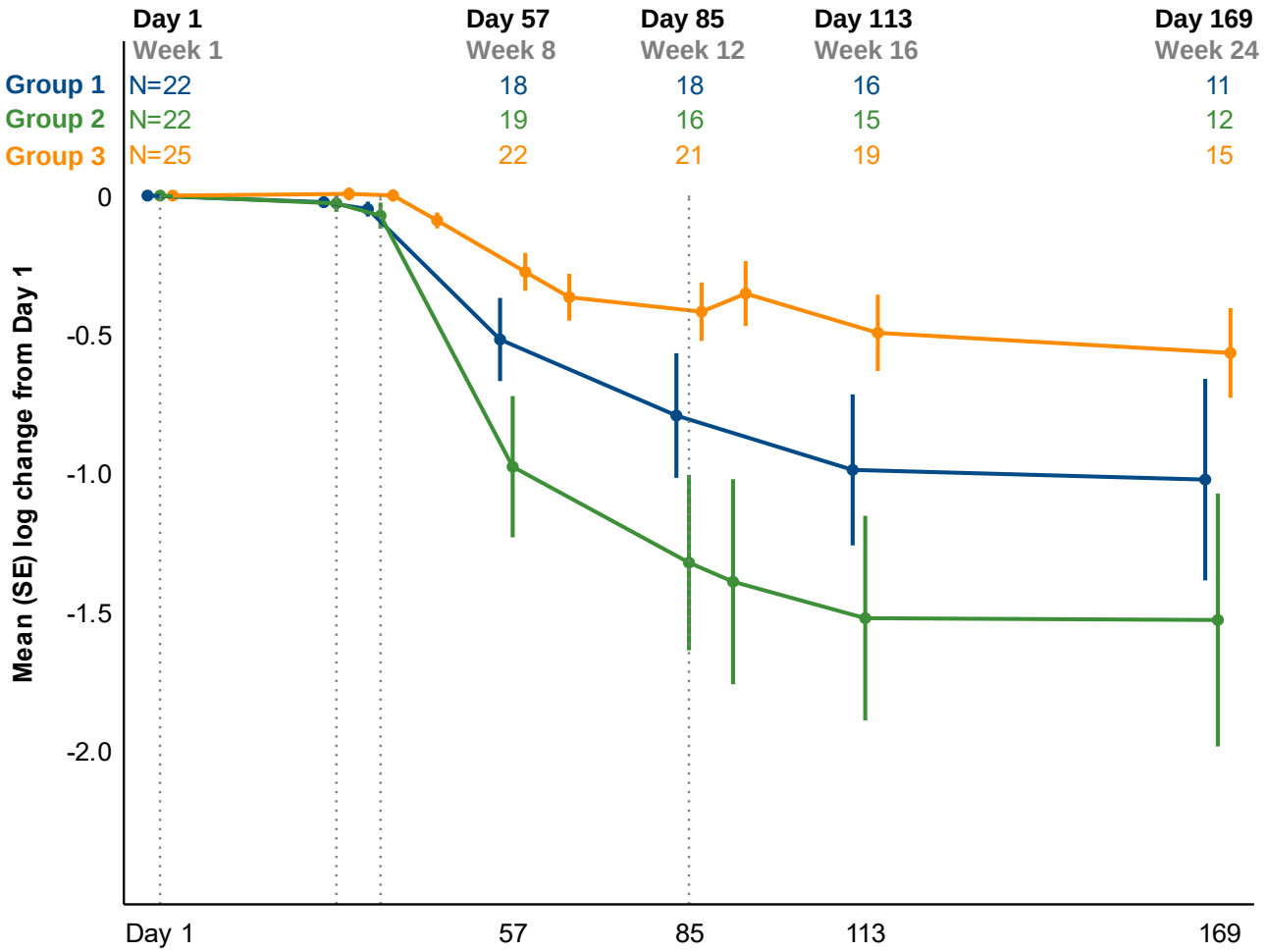
Note: The study was paused for 3 months to implement a protocol amendment to exclude participants with evidence of thyroid abnormalities at screening. The Day 85 dose was delayed by 3–7 months in seven participants (depending on local ethics approvals).

Preliminary Efficacy Data

In Sub-Population of Participants with Baseline HBsAg ≤200 IU/mL

Meaningful, Sustained HBsAg Drops Observed in Participants

Figure 2: Mean (SE) log change from Day 1



HBsAg log reductions at Day 169 by Baseline level

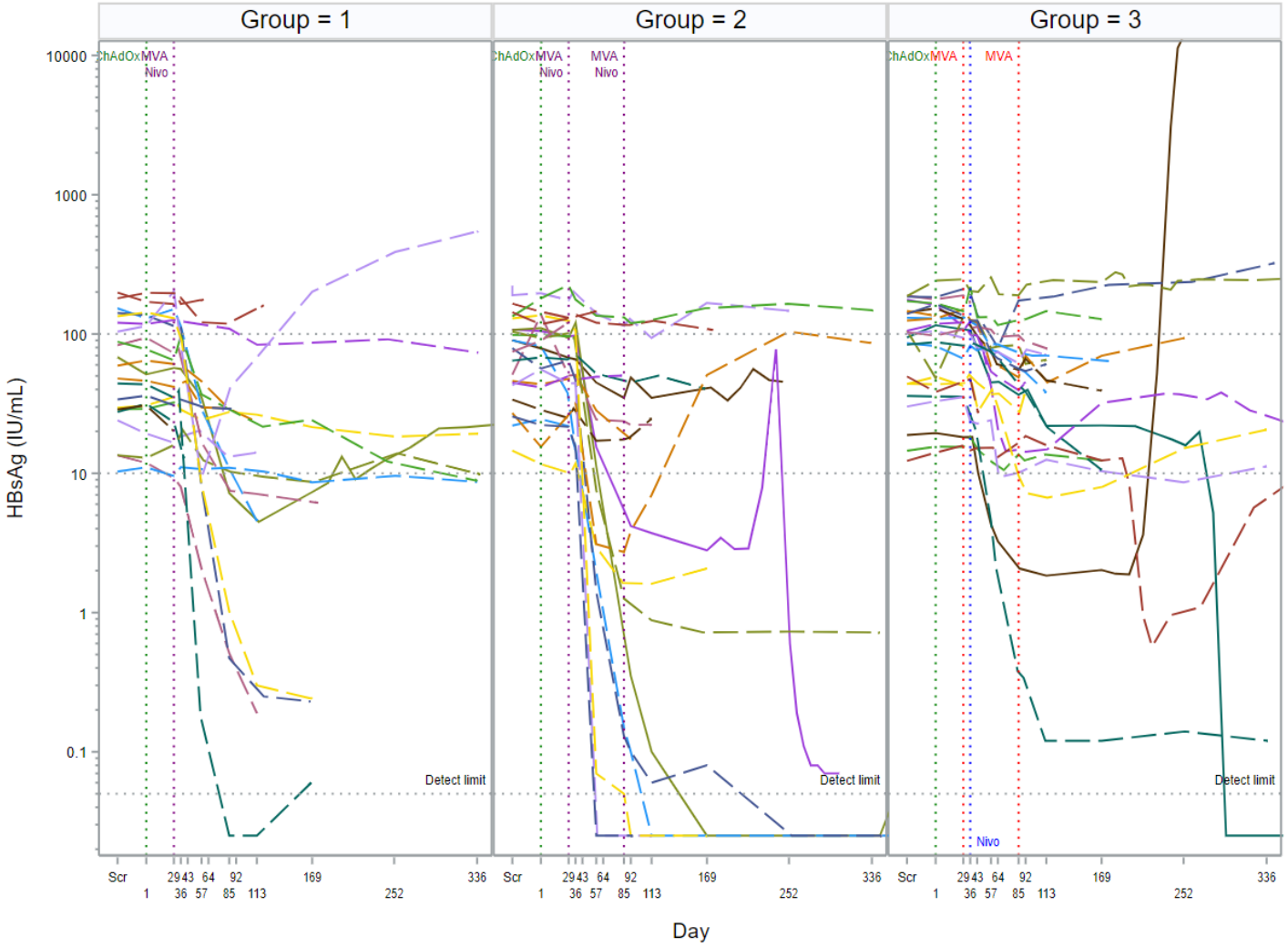
	≤200 IU/mL
>1 log reduction	11/38 (29%)

- The greatest declines were observed by Day 113 in all groups.

- Group 1: Day 1 ChAdOx1-HBV, Day 29 MVA-HBV+Nivo
- Group 2: Day 1 ChAdOx1-HBV, Day 29 & Day 85 MVA-HBV+Nivo
- Group 3: Day 1 ChAdOx1-HBV, Day 29 MVA-HBV, Day 36 Nivo, Day 85 MVA-HBV

HBsAg Loss Observed in 8 Participants to Date

Figure 3: Individual patient plots (n=69)



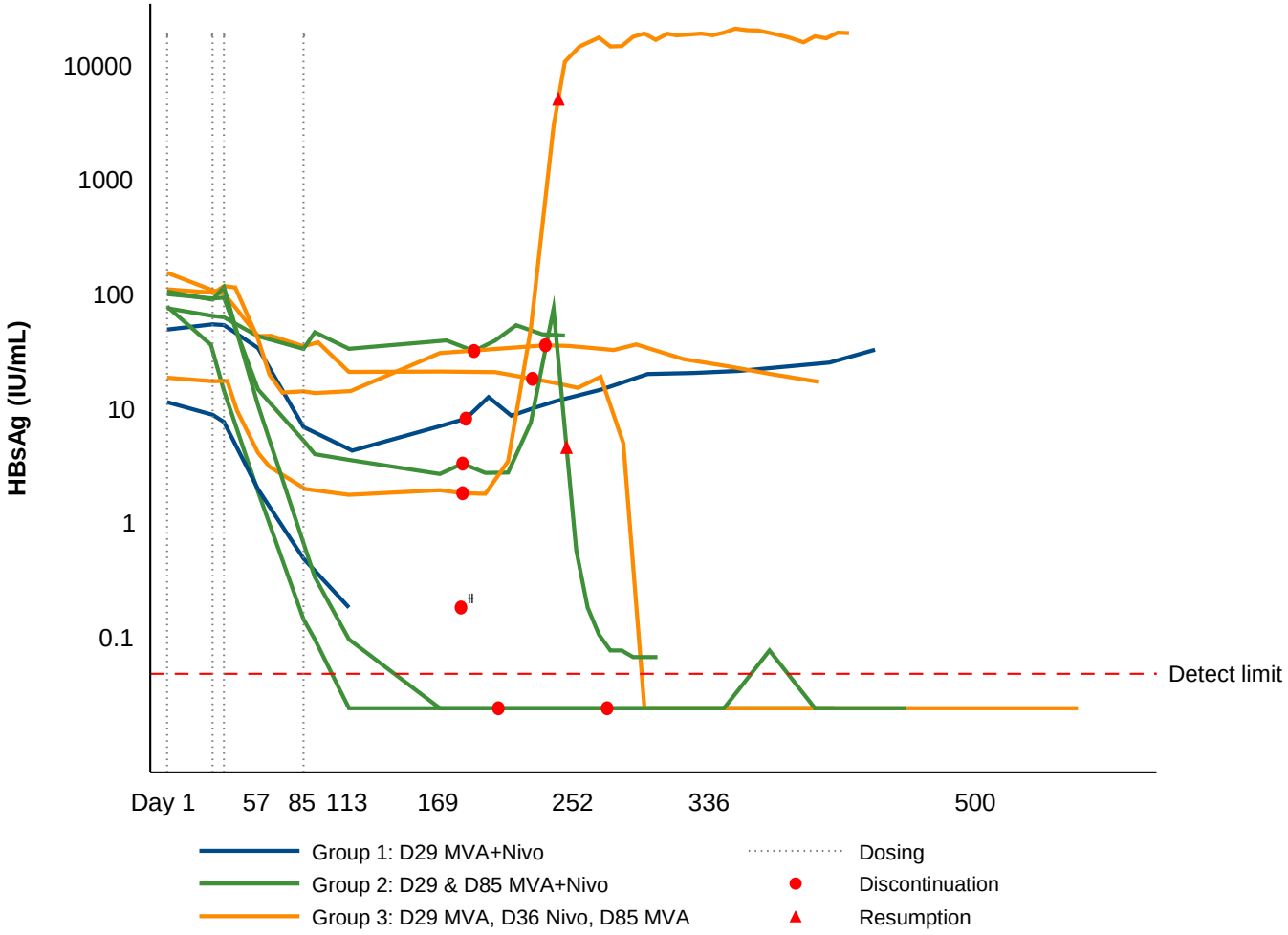
- **8 participants across the groups achieved HBsAg loss (<LLOQ) at any time.**
  - 6 of those who achieved HBsAg loss have remained at that level, to data cut off.
  - 2 participants rose above the limit for HBsAg detection, 1 has achieved loss again. Follow-up continues.
  - **2 participants achieved HBsAb seroconversion.**

- Participant HBsAg
- Participant HBsAg, discontinued NUCs
- ChAdOx dose
- MVA + Nivolumab dose
- MVA dose
- Nivolumab dose
- Detection limit

LLOQ: lower limit of quantitation.

Two Participants Met the Criteria for Functional Cure

Figure 4: Participants who discontinued NUCs (n=9)



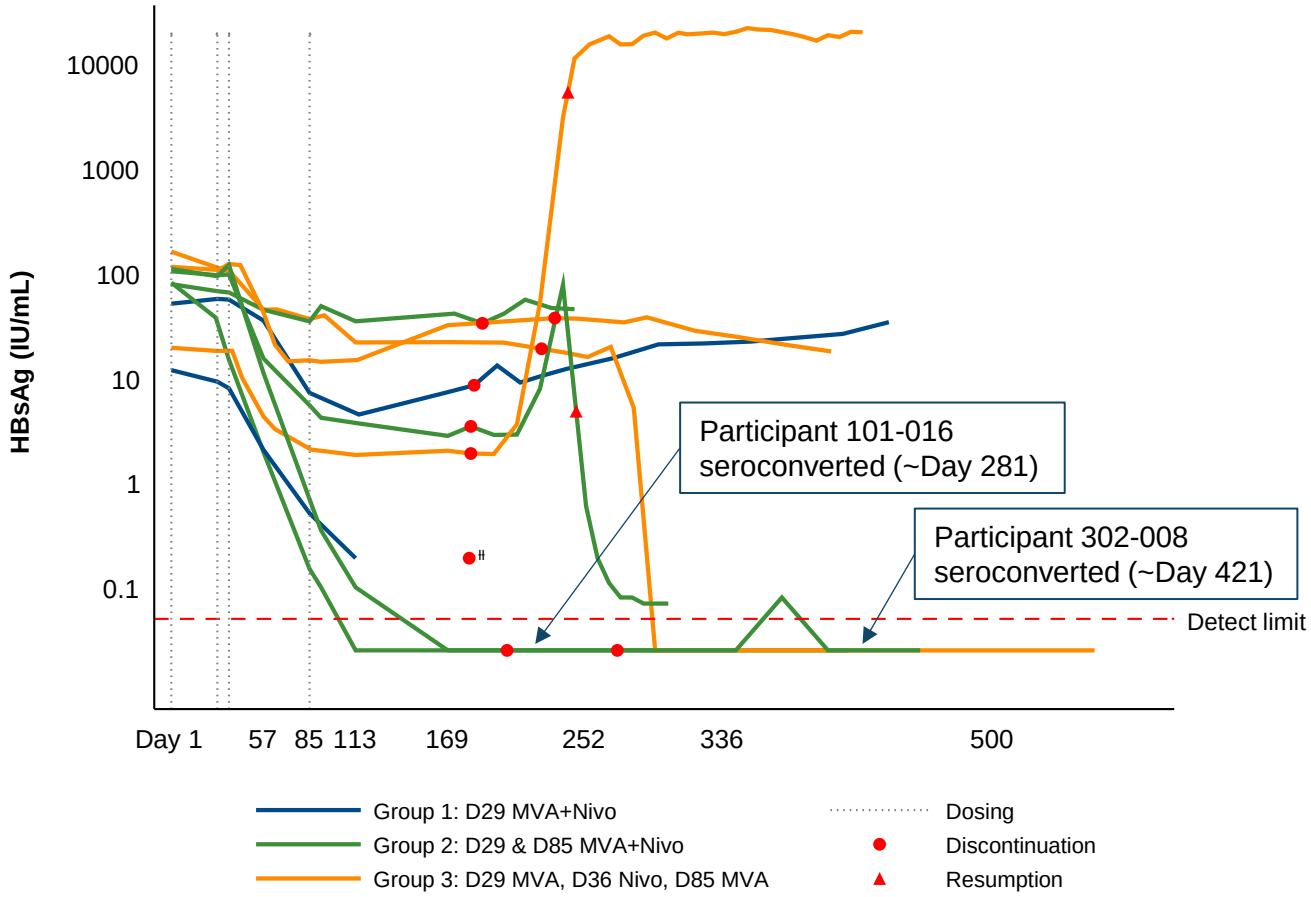
- 60% of assessed participants (n=24) were eligible for NUC discontinuation* at Day 169, 9 of these discontinued.**
  - **6 of the 9 who discontinued NUCs remained off NUC therapy.**
  - 3 participants met the criteria to restart NUCs soon after NUC discontinuation (week 6 or 8)ǂ.
- **2 patients met the criteria for functional cure.**

Functional Cure criteria: HBsAg and HBV DNA loss, maintained for six months off therapy.

* NUC discontinuation criteria: ALT <2 × ULN, and HBV DNA < LLOQ, and HBeAg negative, and HBsAg loss or <100 IU/mL
** If criteria for NUC discontinuation met, PI or participant could elect not to discontinue NUCs.
ǂ An additional participant resumed NUCs following lab data cut-off (30 Sep 2024), but before clinical data cut-off (8 Oct 2024), this patient's NUC resumption is not included in Figure 4.
ǂǂ This patient's HBsAg level for Day 169 had not been yet been processed by data cut-off, due to the difference between lab and clinical data cut-offs.

Two Participants Achieved HBsAb Seroconversion

Figure 4: Participants who discontinued NUCs (n=9)



- **2 patients met the criteria for functional cure.***
  - 1 of these participants had HBsAb seroconversion.
- 1 additional patient seroconverted but has not yet met the criteria for functional cure.

* HBsAg and HBV DNA loss, maintained for six months off therapy.
ǂ This patient's HBsAg level for Day 169 had not been yet been processed by data cut-off, due to the difference between lab and clinical data cut-offs.

Preliminary Safety Data

All enrolled participants, both ≤200 IU/mL and >200 IU/mL

VTP-300 + LD Nivolumab was Generally Well Tolerated in all Patients

- No study discontinuations due to related adverse events.
- 2 SAEs – urinary tract infection + pharyngitis; both unrelated.
- One treatment discontinuation – participant with Bell's Palsy (did not receive Day 85 MVA-HBV); resolved.
- Thyroid dysfunction reported in 7 participants (all groups) attributed to nivolumab; follow-up is ongoing.
  - 5 asymptomatic; thyroid function laboratory values returned to within normal range in 4 out of 5 participants.
  - 2 symptomatic requiring short-term therapy; one had anti-thyroid antibodies at screening; one TSH slightly above ULN.
- ALT
  - ALT elevations above 2x ULN (2.05 to 6.7x ULN) occurred in 17 participants on treatment; observed in all groups.
  - The majority occurred at the Day 57 visit, were transient, and reverted to <2x ULN or within normal range over the next few visits.
  - 9 were associated temporally with declines in HBsAg.
  - A transient ALT elevation >2xULN (2.29xULN) was observed in a single participant 8 weeks after discontinuing NUCs.

Data cut off: 30 September 2024 for safety data.

HBV003 Phase 2b

Conclusions

Conclusions (Patients with Baseline HBsAg ≤200 IU/mL)

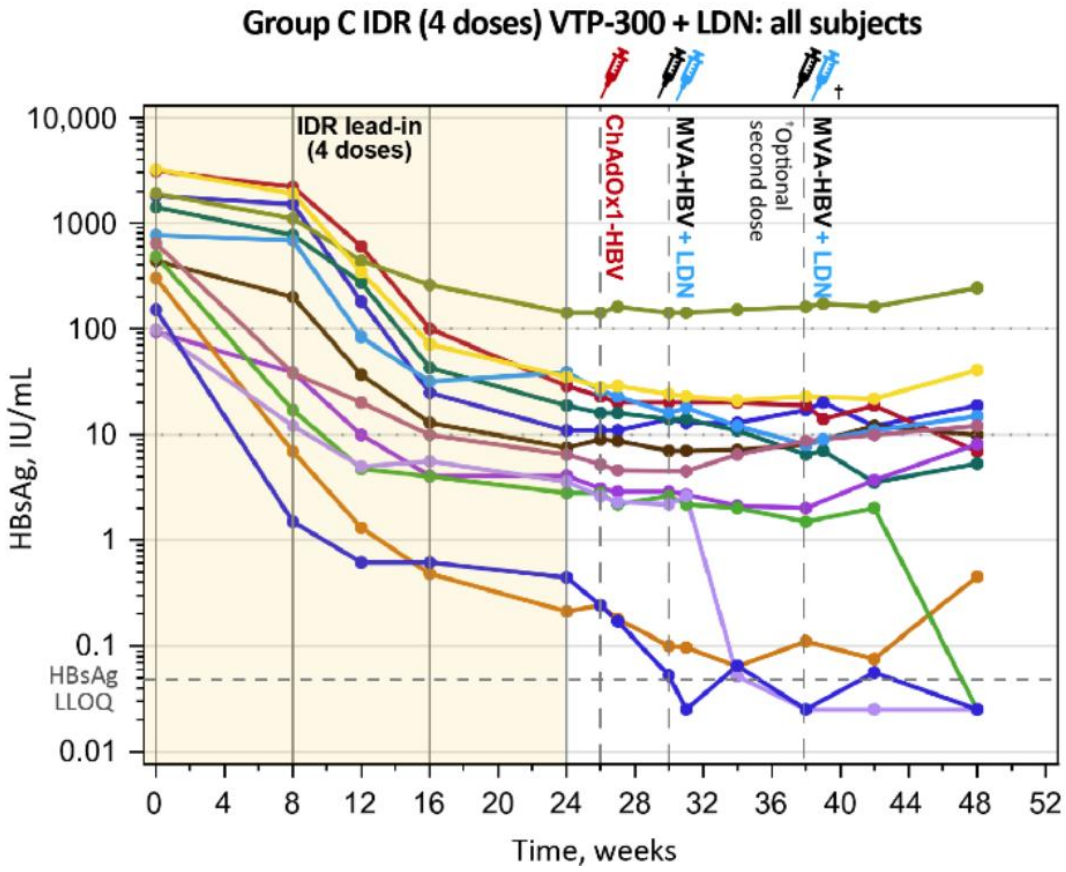
- HBsAg declines were observed in all treatment groups.
- 8 participants to date have reached HBsAg <LLOQ.
- 60% of participants (24/40) were eligible for NUC discontinuation at Day 169, and 9 of these discontinued NUCs.
- Of the 9 who discontinued NUCs.
  - 2 participants met the criteria of functional cure.
  - 2 participants seroconverted to HBsAb positive, one of whom had met the criteria for functional cure.
- Preliminary safety data indicate that VTP-300 in combination with low-dose nivolumab was generally well tolerated with no treatment-related SAEs observed or reported.
- We believe these early data are encouraging and, in combination with interim data from an ongoing study with imdusiran/VTP-300, suggest that VTP-300 may be an important component of a future functional cure regimen.
  - The HBV003 trial is continuing, and the primary analysis (including immunology) will be conducted after all participants have reached Day 169.

BARINTHUS

VTP-300 Could be a Critical Component to Functional Cure Regimen for Patients with Higher Baseline HBsAg

Directly **lower** HBsAg burden

Stimulate immune response



IMPROVE-II Study

- VTP-300 and low-dose nivolumab regimen is also being studied after a 24-week lead-in of the siRNA imdusiran (IDR), which reduced HBsAg levels prior to administration of VTP-300 with or without low-dose nivolumab (AASLD 2024 Poster 5025).
- **23% participants (3/13) in Group C, receiving imdusiran + VTP-300 + low-dose nivolumab had achieved HBsAg loss by Week 48.**

Arbutus BIOPHARMA

BARINTHUS

Acknowledgements

Barinthus Biotherapeutics thanks:

- All trial participants and their families;
- Investigators and site staff;
- S-cubed CRO for statistical assistance;
- Novotech;
- Barinthus Bio staff and VTP-300 Research and Development Team.

The HBV003 study was sponsored by Barinthus Biotherapeutics.