Positive clinical and immune responses following a single dose of VRON-0200: Interim results from a Phase1b study for HBV functional cure in chronic HBV-infected patients

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LATE-BREAKER
Abstract LBA-5029

AASLD The Liver Meeting® Nov. 15-19, 2024

AASLD Congress
San Diego, CA, USA, November 15–19, 2024

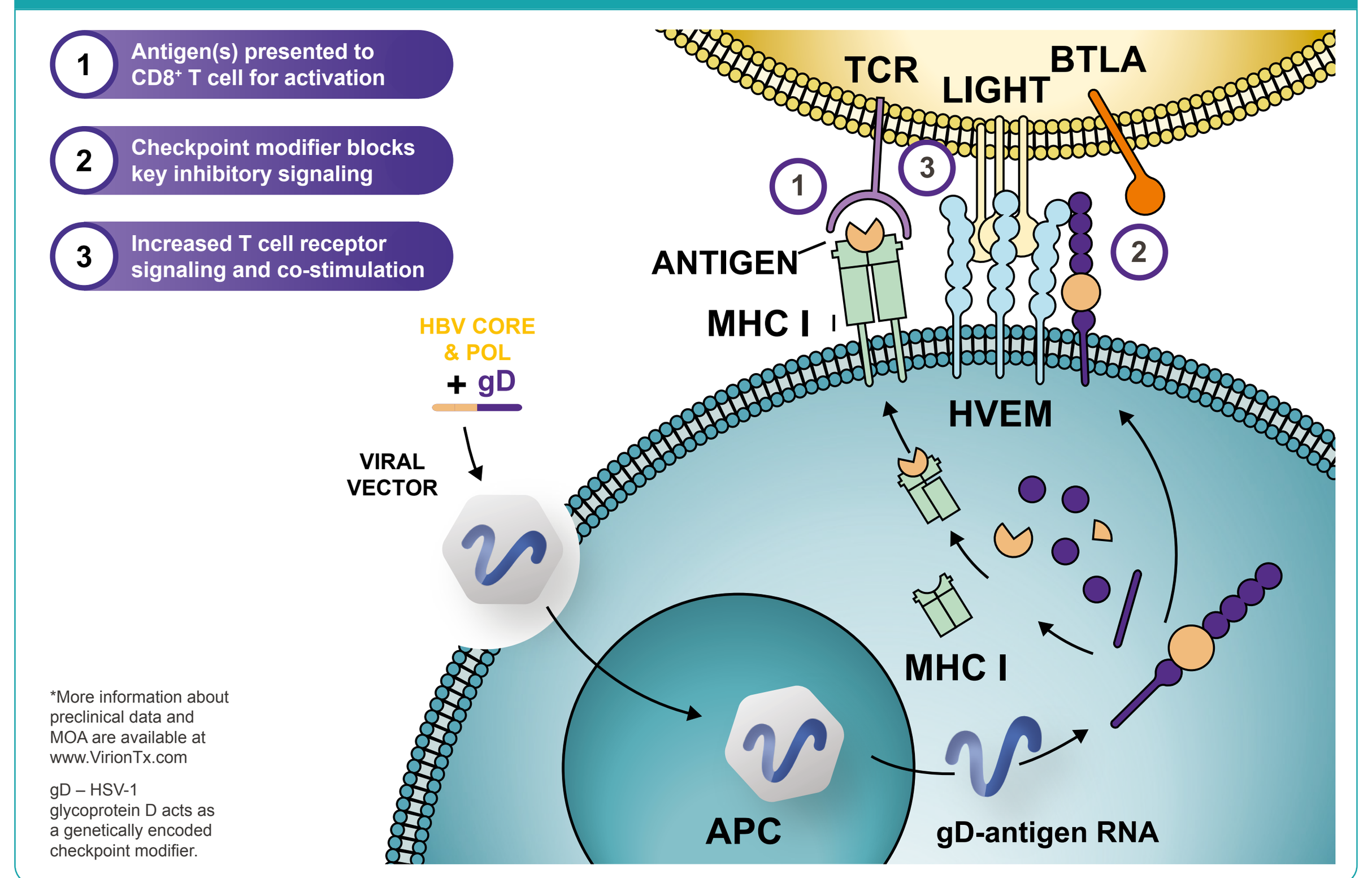
BACKGROUND

- Despite preventative vaccines, chronic HBV infection remains a high unmet medical need[1]
- The use of immune-based treatments is now considered necessary for HBV functional cure[2]
- VRON-0200 is a therapeutic vaccine for the functional cure of HBV infection that expresses a genetically encoded checkpoint modifier (herpes simplex virus type 1 [HSV1] glycoprotein D [gD]) fused with HBV core and pol (but not S) antigens, which is designed to enhance, broaden, and prolong $CD8^+$ T cell responses (Figure 1)[3–6]
- In chronically HBV-infected patients, VRON-0200 has recently been shown to be safe, well tolerated, and immunogenic following a single low-dose IM injection[7]

PURPOSE

- To evaluate the safety, immunogenicity, and HBsAg responses in chronically HBV-infected patients vaccinated with VRON-0200

Figure 1. Checkpoint modification of T cell activation enhances and broadens T cell responses*


1 Antigen(s) presented to CD8+ T cell for activation
2 Checkpoint modifier blocks key inhibitory signaling
3 Increased T cell receptor signaling and co-stimulation
TCR
LIGHT
BTLA
ANTIGEN
MHC I
HVEM
HBV CORE & POL
+ gD
VIRAL VECTOR
MHC I
APC
gD-antigen RNA

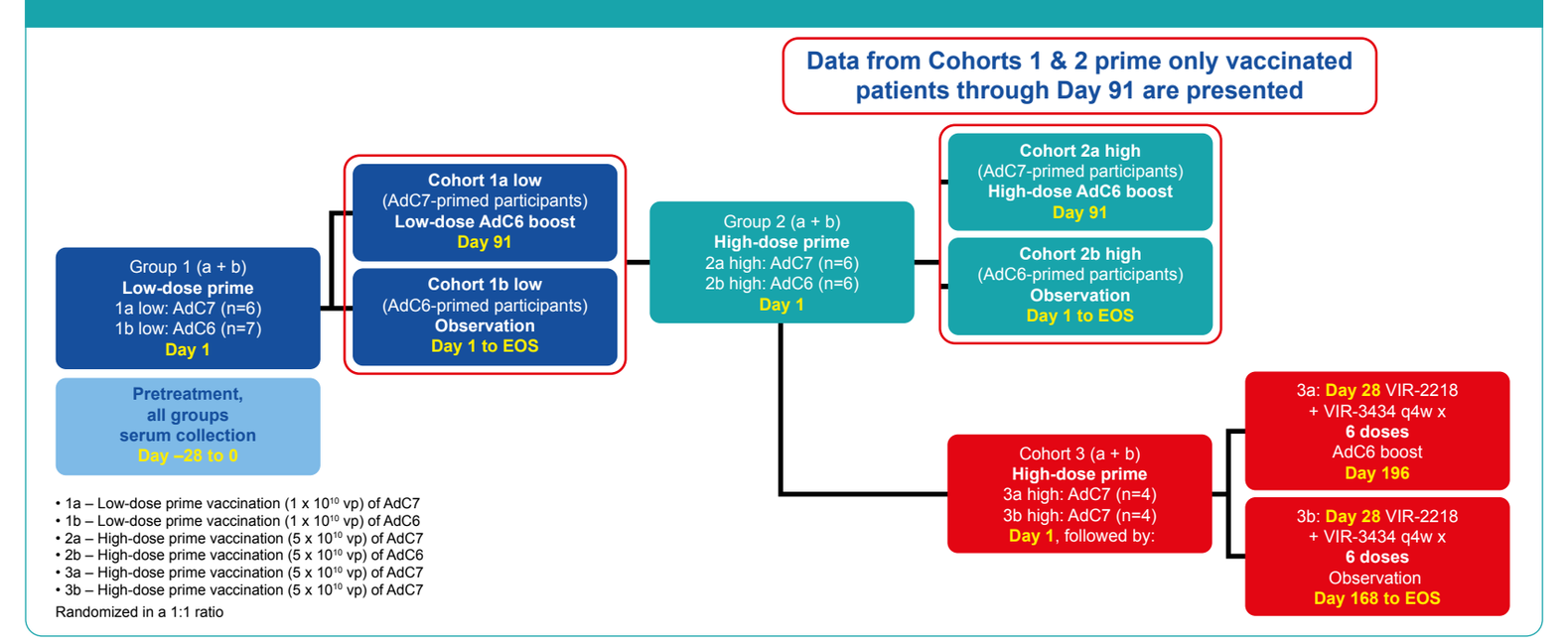
*More information about preclinical data and MOA are available at www.VirionTx.com

gD – HSV-1 glycoprotein D acts as a genetically encoded checkpoint modifier.

METHODS

- This is a Phase 1b multi-center, multi-national, open-label clinical trial in chronic-HBV infected, virally suppressed adults between 18 and 55 years of age, with HBsAg levels ≤500 IU/mL and no evidence of advanced liver fibrosis or cirrhosis
  - Patients were randomized to receive an IM injection of VRON-0200 1×10^{10} vp via one of two chimpanzee adenoviral vectors (AdC7 or AdC6) (Figure 2)
    - Cohort 1a received a prime (AdC7), followed by a heterologous boost (AdC6) on Day 91
    - Cohort 1b received a prime (AdC6) vaccination only
    - Cohorts 2a/2b repeated the Cohort 1a/1b design but used a higher vector dose (5×10^{10} vp)
- Patients were evaluated for safety, immunologic and virologic measures at multiple time points, and blood samples were collected at every visit
- **This analysis includes safety, immunogenicity, and the first-ever HBsAg data for VRON-0200 prime only vaccinated patients in Cohorts 1 and 2 through Day 91**

Figure 2. Study schema


Data from Cohorts 1 & 2 prime only vaccinated patients through Day 91 are presented
Group 1 (a + b) Low-dose prime 1a low: AdC7 (n=6) 1b low: AdC6 (n=7) Day 1
Pretreatment, all groups serum collection Day –28 to 0
Cohort 1a low (AdC7-primed participants) Low-dose AdC6 boost Day 91
Cohort 1b low (AdC6-primed participants) Observation Day 1 to EOS
Group 2 (a + b) High-dose prime 2a high: AdC7 (n=6) 2b high: AdC6 (n=6) Day 1
Cohort 2a high (AdC7-primed participants) High-dose AdC6 boost Day 91
Cohort 2b high (AdC6-primed participants) Observation Day 1 to EOS
Cohort 3 (a + b) High-dose prime 3a high: AdC7 (n=4) 3b high: AdC7 (n=4) Day 1, followed by:
3a: Day 28 VIR-2218 + VIR-3434 q4w x 6 doses AdC6 boost Day 196
3b: Day 28 VIR-2218 + VIR-3434 q4w x 6 doses Observation Day 168 to EOS
• 1a – Low-dose prime vaccination (1 x 10¹⁰ vp) of AdC7
• 1b – Low-dose prime vaccination (1 x 10¹⁰ vp) of AdC6
• 2a – High-dose prime vaccination (5 x 10¹⁰ vp) of AdC7
• 2b – High-dose prime vaccination (5 x 10¹⁰ vp) of AdC6
• 3a – High-dose prime vaccination (5 x 10¹⁰ vp) of AdC7
• 3b – High-dose prime vaccination (5 x 10¹⁰ vp) of AdC7
Randomized in a 1:1 ratio

Clinical assessments

- Sera were collected at multiple timepoints throughout the study and HBsAg level was assessed by ELISA for absolute changes ($\log^{10}$ IU/mL; LLOD 0.05 IU/mL)
- HBsAg results were included for those with a prime vaccination
  - Prime only cohorts (1b/2b) were included after Day 91
  - Boost cohorts (1a/2a) were censored at Day 91, pre-boost

Immunologic assessments

- T cell frequencies were assessed at two pre-vaccination timepoints (Days –28 to –7, and pre-treatment on Day 1) and at post-vaccination time points (Days 7, 14, 28, and 91) via ELISpot (IFNγ; LLOD <30 SFU/million) from PBMCs isolated from whole blood and incubated overnight, using three separate peptide pools (core and pol [N- and C-terminus] representing the vaccine peptides, and peptides representing S-antigen)
- An immunologic "responder" was defined as having two consecutive core plus pol ELISpot measurements at Day 28 greater than the average of the two pre-treatment timepoints, that were above the LLOD
- A one-sided paired sample t-test was conducted to determine whether there was a difference between the mean of the sum of core plus pol ELISpot measurements from pre-treatment compared to Day 28 for each patient
- A Day 91 "response" was defined as a patient with a core plus pol ELISpot measurement above the average of the two pre-treatment timepoints at Day 91

RESULTS

PATIENT DEMOGRAPHICS

- There were no observed differences between cohorts
- Twenty patients were male (80%), mean age of 46 years and baseline HBsAg of 179 IU/mL (range: 9.7–623) (Table 1)
- All but one patient were HBeAg negative

Table 1. Demographics and baseline characteristics (N=25)*

	Cohort 1a (n=6)	Cohort 1b (n=7)	Cohort 2a (n=6)	Cohort 2b (n=6)	Overall (N=25)
Median age, yrs (range)	43 (37–52)	49 (41–54)	47 (45–54)	50 (41–55)	46 (37–55)
Sex, n (%)					
Male	6 (100)	6 (86)	3 (50)	5 (83)	20 (80)
Female	0 (0)	1 (14)	3 (50)	1 (17)	5 (20)
Race, n (%)					
Asian	5 (83)	6 (86)	5 (83)	6 (100)	22 (85)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	1 (17)	0 (0)	1 (5)
White	0 (0)	1 (14)	0 (0)	0 (0)	1 (5)
Other	1 (17)	0 (0)	0 (0)	0 (0)	1 (5)
BMI (kg/m^2), median (range)	29.3 (27.3–31.7)	24.6 (20.2–32)	28.1 (23–31.6)	23.8 (19.7–27.7)	26.7 (20.2–32)
Baseline HBsAg levels (IU/mL), median (range)	222 (29–319)	273 (16–623)	124.8 (17.1–322.2)	248.5 (9.7–562.6)	178.9 (9.7–623†)
Baseline HBsAg levels, n (%)					
>500 IU/mL	0 (0)	1 (14†)	0 (0)	1 (17†)	2 (8†)
200–500 IU/mL	4 (67)	2 (29)	1 (17)	3 (50)	10 (40)
100–199 IU/mL	0 (0)	2 (29)	3 (50)	1 (17)	6 (24)
<100 IU/mL	2 (33)	2 (29)	2 (33)	1 (17)	7 (28)
Baseline ALT (x ULN), n (%)					
<1 x ULN	5 (83)	7 (100)	5 (83)	5 (83)	22 (88)
1 to 1.5 x ULN	0 (0)	0 (0)	1 (17)	1 (17)	2 (8)
1.6 x ≤2 x ULN	1 (17)	0 (0)	0 (0)	0 (0)	1 (4)
HBeAg status at baseline, n (%)					
Negative	6 (100)	6 (80)	6 (100)	6 (100)	24 (96)
Positive	0 (0)	1 (20)	0 (0)	0 (0)	1 (4)

*As of the clinical cut-off date, October 18, 2024; †As per protocol, the participant had prior HBsAg ≤500 IU/mL at screening.

SAFETY AND TOLERABILITY

- A total of 4,952 patient safety days were reported. VRON-0200 was well tolerated, with 29 AEs reported in 14 patients (Table 2)
  - There were no SAEs, treatment discontinuations, or laboratory abnormalities, including liver function tests (not shown)
  - Sixteen TEAEs were reported, including one Grade 2 eczema; all other TEAEs were Grade 1
  - Symptoms have resolved in all patients

Table 2. Safety and tolerability (N=25)*

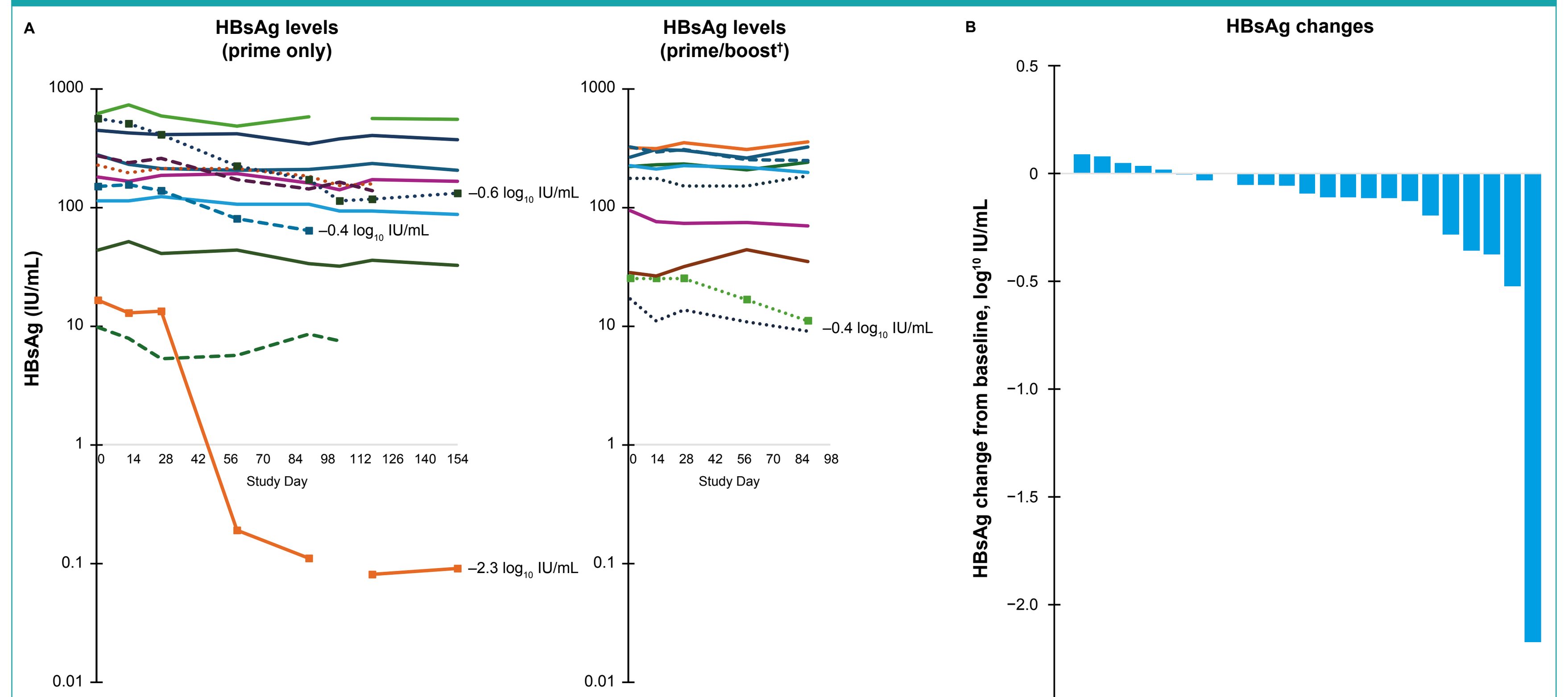
	Cohort 1a (n=6)	Cohort 1b (n=7)	Cohort 2a (n=6)	Cohort 2b (n=6)	Overall (N=25)
Any AE, n	5	9	7	8	29
Grade 1	5	7	6	6	24
Grade 2	0	2	1	2	5
Grade 3 or 4	0	0	0	0	0
SAE, n	0	0	0	0	0
TEAEs, n	2	3	6	5	16
AE leading to study drug discontinuation, n	0	0	0	0	0
Study discontinuations, n	0	0	0	0	0
ALT elevations, n					
Grade 1	0	0	0	0	0
Grade 2	0	0	0	0	0

*As of the clinical cut-off date, October 18, 2024.

HBsAg DECLINES OBSERVED IN SEVERAL PATIENTS

- Four patients had HBsAg ≥0.4 $\log_{10}$ IU/mL from baseline (Figure 3A & B)
  - For each of the four patients, HBsAg declines initiated on Day 28 (Figure 3A)
  - No patients experienced any significant ALT changes over time (Figure 4)

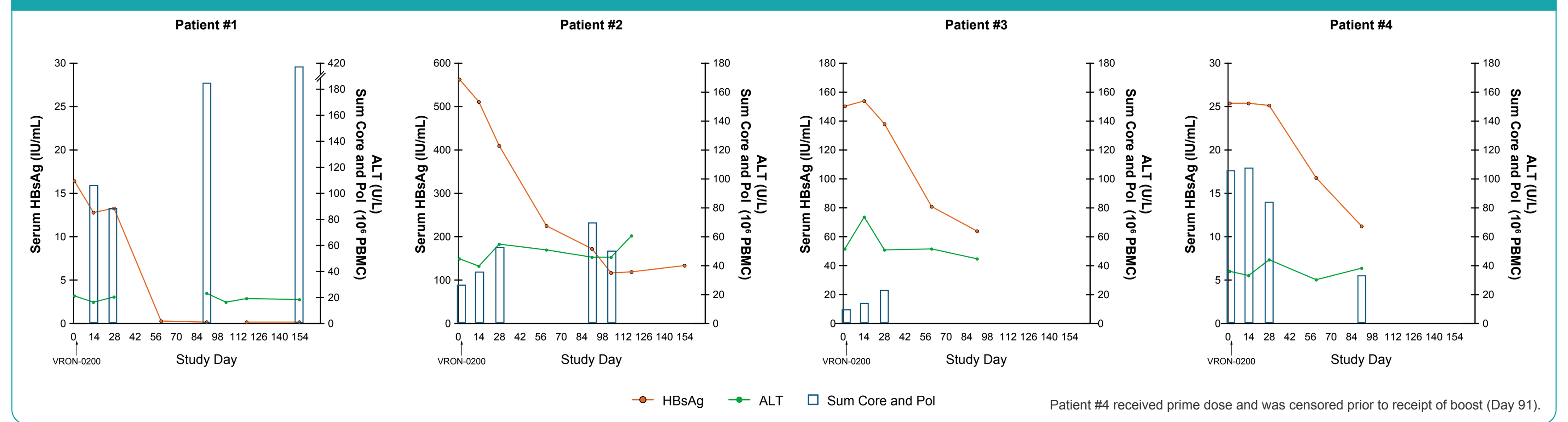
Figure 3. HBsAg levels over time, after a prime only VRON-0200 dose*



Dashed lines – High dose.

*VRON-0200 does not target S-antigen; †Data censored to prime only (Day 91).

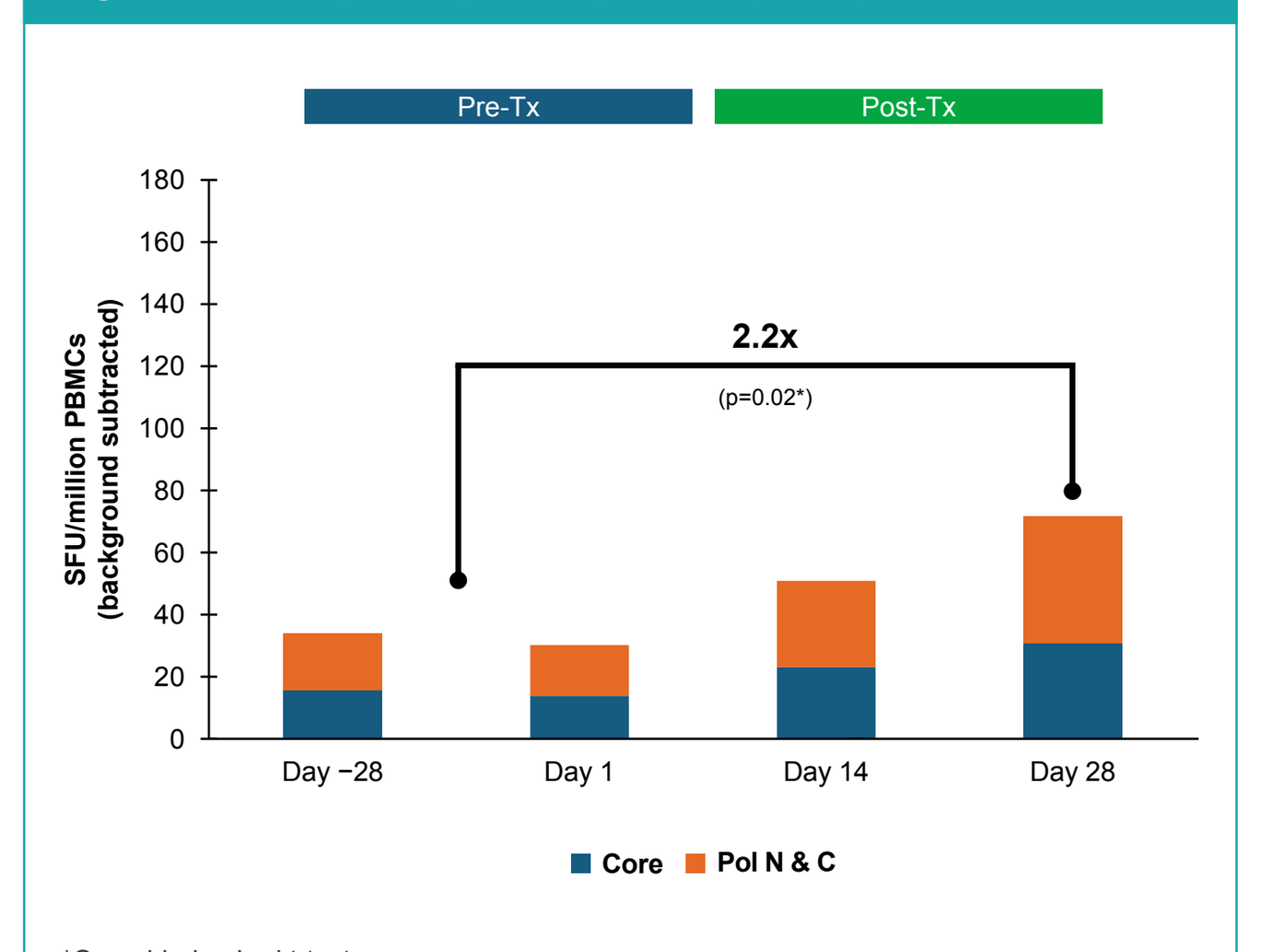
Figure 4. Four patients with S-antigen declines observed over time



Patient #4 received prime dose and was censored prior to receipt of boost (Day 91).

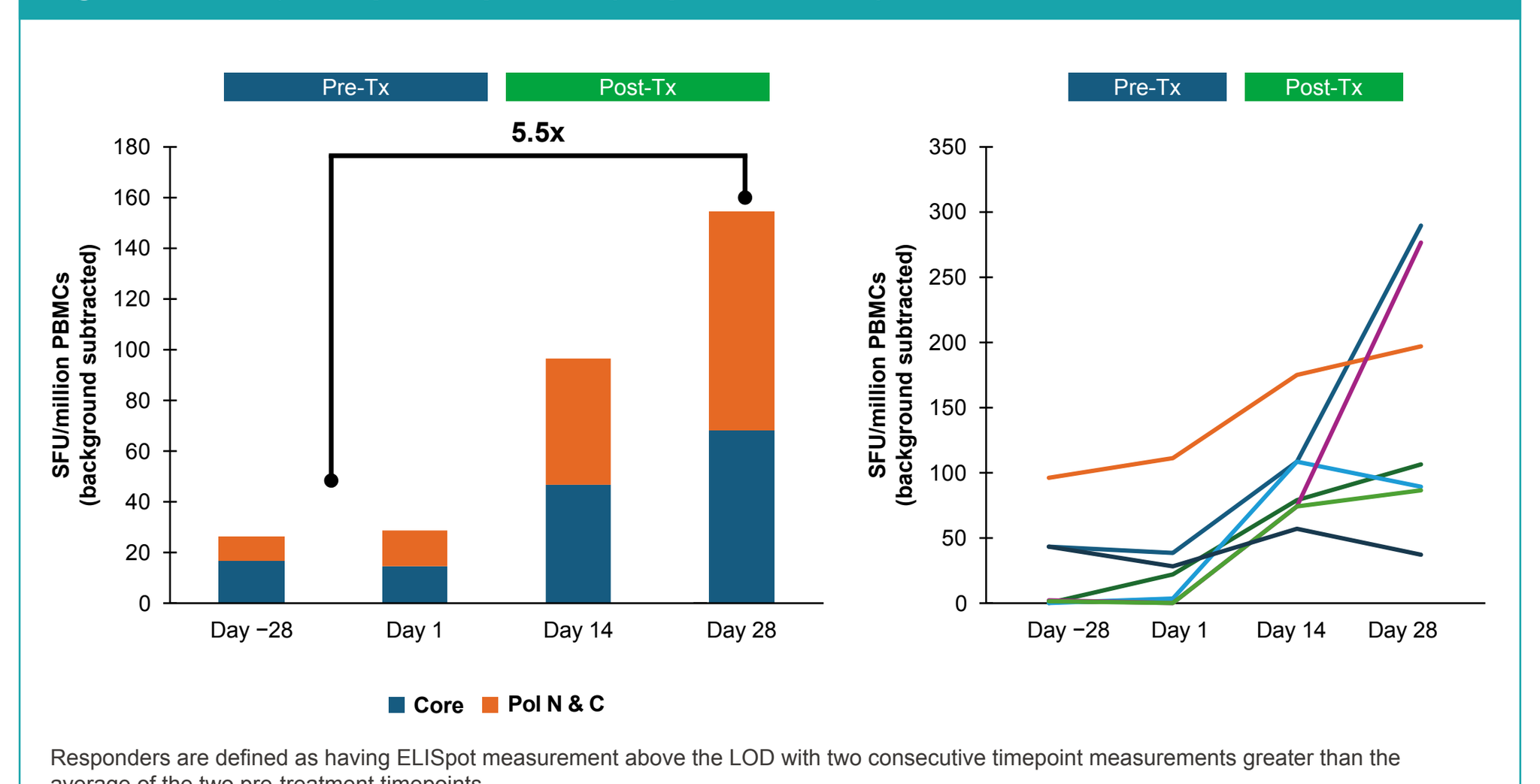
IMMUNOLOGY

Figure 5A. IFNγ ELISpot responses (N=22)



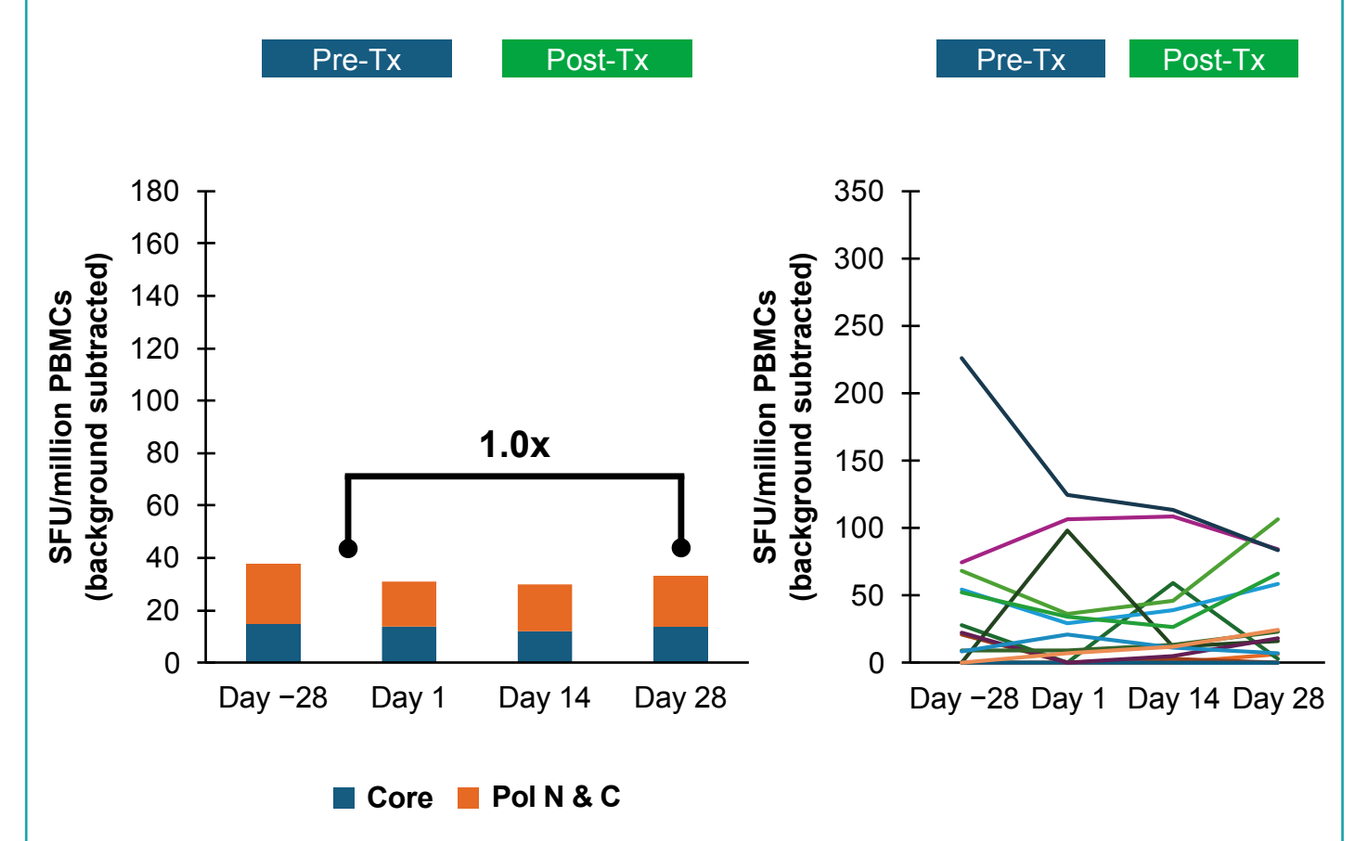
*One-sided paired t-test.

Figure 5B. IFNγ ELISpot responses (responders; n=7)



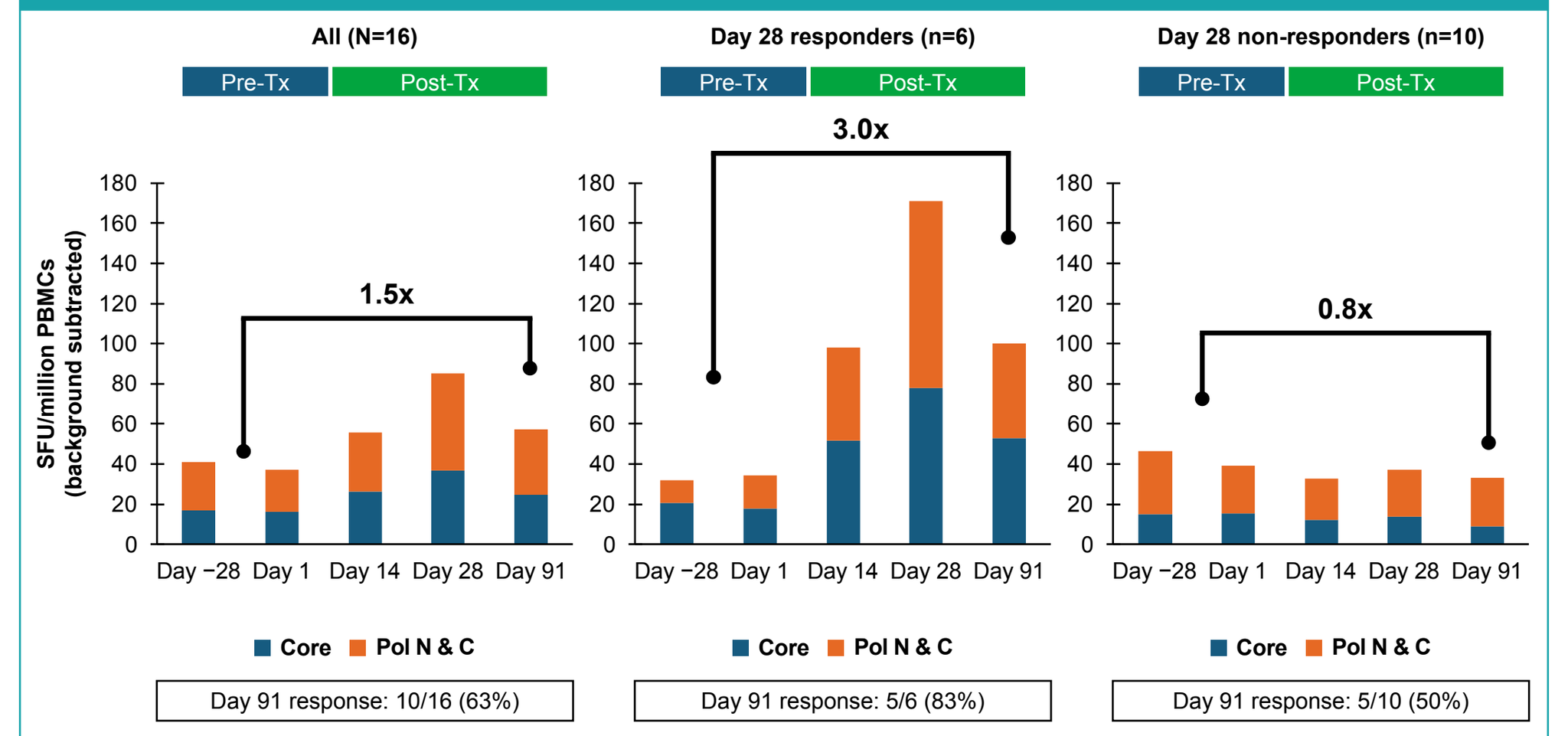
Responders are defined as having ELISpot measurement above the LOD with two consecutive timepoint measurements greater than the average of the two pre-treatment timepoints.

Figure 5C. IFNγ ELISpot responses (non-responders; n=15)



Responders are defined as having ELISpot measurement above the LOD with two consecutive timepoint measurements greater than the average of the two pre-treatment timepoints. Non-responders do not meet the criteria for being a responder.

Figure 6. Day 91 IFNγ ELISpot responses



Day 91 Response: Day 91 sum of core plus pol IFNγ ELISpot above average of two pre-Tx values.

- There are ELISpot measurements for 22 and 16 patients at Days 28 and 91, respectively
- Prior to vaccination, 12/22 patients (55%) had BOTH pre-treatment ELISpot results below the LLOD to all three peptide pools
  - 14 (64%) and 20 (91%) patients had both or one of the two pre-treatment samples below LLOD against both peptide pools contained within the vaccine (core and pol), respectively
- **At Day 28, post VRON-0200 vaccination (Figure 5):**
  - Overall, there was a significant 2.2-fold increase from baseline (p=0.02; Figure 5A)
  - Seven patients (32%) were classified as "responders" (Figure 5B), and 15 patients (68%) were classified as "non-responders" (Figure 5C)
    - Among "responders", there was a 5.5-fold increase; in contrast, "non-responders" had no changes
    - There were no apparent differences in baseline demographics and patient characteristics, including HBsAg levels and HBV ELISpot measurements between "responders" and "non-responders"
- **At Day 91, post VRON-0200 vaccination (Figure 6):**
  - Overall, there was a 1.5-fold change from baseline
    - Day 28 "responders" had a 3.0-fold change
    - Day 28 "non-responders" had a 0.8-fold change
  - Overall, 63% of vaccinated patients had Day 91 levels above their baseline measurements, with Day 28 "responders" having greater proportions (83%) than "non-responders" (50%)
- One patient with an HBsAg decline was a Day 28 ELISpot immune "responder" (Figure 4; patient #1)

CONCLUSIONS

This is the first clinical report of anti-HBV activity for VRON-0200, a novel checkpoint modifier:

- With 4,952 patient safety days reported, VRON-0200 was safe and well-tolerated
- Although VRON-0200 does not target S-antigen, declines in S-antigen were observed in several patients
- At Day 28, a single IM VRON-0200 dose significantly improved T cell responses, even in patients with documented, limited pre-existing anti-HBV immunity, at baseline
  - Enhanced T cell responses were observed in the blood in one-third of patients
- Factors associated with immunologic responses and HBsAg declines are being evaluated further
- Cohorts 1 and 2 are enrolled, with boost dosing underway/completed, and Cohort 3 (combinations of VRON-0200 plus VIR-2218 + VIR-3434) is now enrolling

These data support the continued study of VRON-0200 as a simple, easy-to-administer, IFN-sparing immunotherapy, alone or in combination, for HBV functional cure

DISCUSSION

- Current treatment options for HBV functional cure offer a less than 2–8% response rate, which is not clinically meaningful[8]
- To date, the non-immunologic/artificial removal of S-antigen (e.g., siRNA, small molecules), has not achieved durable S-antigen suppression, after end of treatment, and may not restore immunity
  - In contrast, these VRON-0200 data have been shown to induce immune responses and anti-HBV activity, without directly targeting S-antigen
  - These findings question the role/need for targeting of S-antigen with immune-based treatments
- Can VRON-0200 induce immune responses that translate to sustained off treatment responses, in chronically HBV-infected patients (e.g., functional core)?
  - Are there untreated, chronically HBV-infected patients that could benefit from VRON-0200 alone?
  - Can VRON-0200, combined with other HBV treatments, further improve functional core response rates?
  - With immune-based therapies, are new measures/endpoints needed to assess functional core?

ABBREVIATIONS

AE, adverse event; AdC6/7, chimpanzee adenovirus serotype 6/7; ALT, alanine transaminase; APC, antigen-presenting cell; BMI, body mass index; BTLA, B and T lymphocyte attenuator; CD, cluster of differentiation; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immunosorbent spot; EOS, end of study; gD, glycoprotein D; HBeAg; hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HSV, herpes simplex virus; HVEM, herpes virus entry mediator; IFNγ, interferon-gamma; IM, intramuscular; IU, international unit; LIGHT, lymphotoxin-like, exhibits inducible expression, and competes with HSV gD for HVEM, a receptor expressed by T lymphocytes; LLOD, lower limit of detection; MHC, major histocompatibility complex; MOA, mechanism of action; PBMC, peripheral blood mononuclear cell; pol, polymerase; q4w, every 4 weeks; SAE, serious adverse event; siRNA, small interfering RNA; SFU, spot-forming unit; TCR, T cell receptor; TEAE, treatment-emergent adverse event; Tx, treatment; ULN, upper limit of normal; vp, viral particles.

ACKNOWLEDGMENTS

We wish to thank all the study patients and their families, the study investigators, study coordinators, and study teams, including:

- **NZ – Auckland City Hospital:** Ed Gane, William Abbott, Manish Patel, Mitee Kapadia, and Ghada Sarah
- **Hong Kong – The Chinese University of Hong Kong/Prince of Wales Hospital:** Grace Wong, Angel Chim, Sally Shu, Julie Leung, Pete Tse, Kat Kwan, Christy Fong, Jackie Fung, Jennifer Ng, and Cheryl Leung
- **PPD/BioALabs:** Olivia Briskin, Jason Duncan, and Mark Zavorin
- **ProTrials/Novotech:** Brock Boyce, Paul Donnelly, Sazlyna Mohd Sazlly Lim, Sabiqah Muhammad, Marta Urbanek, and Jody Wu
- **Virion Therapeutics:** Tony Baca, Janice Bennett, Larissa Haut, and Paula MacDonald

All authors contributed to and approved the poster. Monica E. Burgett, PhD, of BOLDSCIENCE Inc., provided editorial assistance, which was funded by Virion Therapeutics, LLC. Virion Therapeutics, LLC provided funding for this study.

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DISCLOSURES

Grace Wong has served as an advisory committee member for AstraZeneca, Gilead Sciences, GlaxoSmithKline, and Janssen and as a speaker for Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gilead Sciences, Janssen, and Roche. She has also received a research grant from Gilead Sciences.

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