Promising first-in-human, first-in-class, Phase 1b immunogenicity data of VRON-0200, a novel checkpoint modifier containing immunotherapy, for HBV functional cure

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LATE-BREAKER
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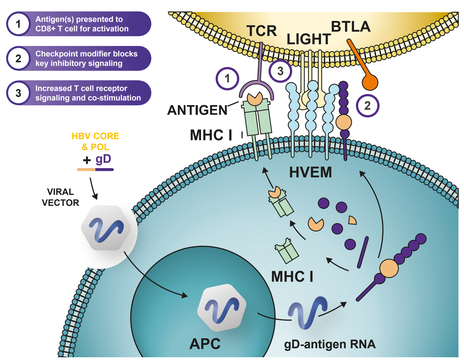
BACKGROUND

- Despite preventative vaccines, chronic HBV infection remains a high unmet medical need[1]
- The use of immune-based treatments are now considered necessary for HBV functional cure[2]
- VRON-0200 is a therapeutic vaccine for 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 polymerase 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 and well tolerated following a single low-dose intramuscular injection[7]

PURPOSE

- To report the first-ever immunogenicity, and ongoing safety data, in chronically HBV-infected patients vaccinated with VRON-0200

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



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

METHODS

- This is a Phase 1b multicenter, multinational, 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 are randomized to receive an intramuscular injection of VRON-0200 1x10[10] vp via one of two chimpanzee adenoviral vectors (AdC7 or AdC6) (**Figure 2**)
  - Cohort 1a receives a prime (AdC7), followed by a heterologous boost (AdC6) on Day 91
  - Cohort 1b receives a prime (AdC6) vaccination only
  - A higher-dose cohort (Cohort 2; 5x10[10] vp) has recently been initiated following review of the first 12 patients in Cohort 1
- Patients were evaluated for safety, immunological, and virologic measures at multiple time points, and blood samples were collected at every visit
- **This analysis includes the first-ever immunogenicity data and ongoing safety for Cohort 1, prime only VRON-0200 vaccinated patients, through Day 91, with a data cutoff of May 1, 2024**

Figure 2. Study schema

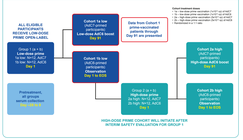
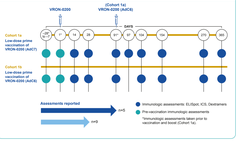


Figure 3. Immunologic assessments



Immunologic assessments

- T cell frequencies are assessed pre-vaccination (two timepoints) and at multiple timepoints post-vaccination (**Figure 3**) via ELISpot (IFNγ; LLOD <30 SFU/million) from PBMCs isolated from whole blood and incubated overnight, using three separate peptide pools (core and polymerase [N- and C-terminus] representing the vaccine peptides, and peptides representing S antigen)
- A "responder" is defined as having an ELISpot measurement above the LLOD, with two consecutive timepoint measurements post-vaccination that are greater than the average of the two pre-treatment timepoints

RESULTS

Data cutoff: May 1, 2024

SAFETY AND TOLERABILITY (N=13)

- Of the 13 patients, 12 were male; mean age of 46 years, and baseline HBsAg of 244 IU/mL (range: 16–623) (**Table 1**)
- **Table 2** lists the overall study disposition – 12 and 5 patients have study visits at 28 and 91 days post-vaccination, respectively
  - As of May 1, 2024, 870 total on-treatment prime (up to and including Day 91) patient safety days are included in this analysis
- VRON-0200 was well tolerated; five Grade 1 AEs were reported in three patients (**Table 3**)
  - One patient had a leg cramp and flu-like symptoms; another patient had left arm numbness and papular rash, and the third patient had diarrhea
  - All symptoms resolved without treatment, except for the papular rash
- There were no significant changes in any liver function (**Figure 4**) or laboratory test post-vaccination

Table 1. Demographic and baseline characteristics (N=13)

	Cohort 1a (n=6)	Cohort 1b (n=7)	Overall (N=13)
Median age, yrs (range)	43 (37–52)	49 (41–54)	46 (37–54)
Sex, n (%)			
Male	6 (100)	6 (86)	12 (92)
Female	0 (0)	1 (14)	1 (8)
Race, n (%)			
Asian	5 (83)	6 (86)	11 (85)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0)
White	0 (0)	1 (14)	1 (8)
Other	1 (17)	0 (0)	1 (8)
BMI (kg/m^2), median (range)	29.3 (27.3–31.7)	24.6 (20.2–32)	28.9 (20.2–32)
Baseline HBsAg levels (IU/mL), median (range)	222 (29–319)	273 (16–623)	244 (16–623*)
Baseline HBsAg levels, n (%)			
>500 IU/mL	0 (0)	1 (14*)	1 (8*)
200–≤500 IU/mL	4 (67)	2 (29)	6 (46)
100–199 IU/mL	0 (0)	2 (29)	2 (15)
<100 IU/mL	2 (33)	2 (29)	4 (31)
Baseline ALT (x ULN), n (%)			
<1 x ULN	5 (83)	7 (100)	12 (92)
1 to 1.5 x ULN	0 (0)	0 (0)	0 (0)
1.6 x ≤2 x ULN	1 (17)	0 (0)	1 (8)
HBeAg status at baseline, n (%)			
Negative	6 (100)	6 (80)	12 (92)
Positive	0 (0)	1 (20)	1 (10)

* As per protocol, participant had prior HBsAg ≤500 IU/mL at screening.

Table 2. Study subject disposition (N=13)

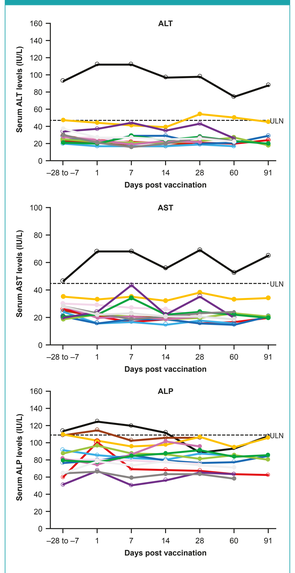
	Number of patients with study visit at day of follow-up					
	Day 1	Day 7	Day 14	Day 28	Day 60	Day 91*
Cohort 1a (n=6)	6	6	6	6	5	3
Cohort 1b (n=7)	7	7	7	6	4	2
Overall (N=13)	13	13	13	12	9	5

*For those subjects randomized to receive a boost vaccination, this visit is prior to receipt of the boost vaccination.

Table 3. Safety and tolerability

	Cohort 1a (n=6)	Cohort 1b (n=7)	Overall (N=13)
Any AE, n	1	4	5
Grade 1	1	4	5
Grade 2	0	0	0
Grade 3 or 4	0	0	0
SAE, n	0	0	0
TEAEs, n	1	4	5
AE leading to study drug discontinuation, n	0	0	0
Study discontinuations, n	0	0	0
ALT elevations, n			
Grade 1	0	0	0
Grade 2	0	0	0

Figure 4. Select liver function tests (N=13)

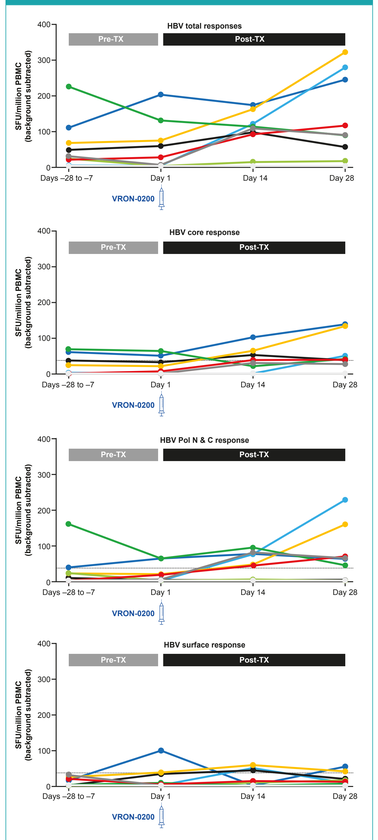


Day 1 samples taken prior to vaccination.
Open symbols – Cohort 1a; solid symbols – Cohort 1b.

IMMUNOLOGY (n=9)

- Despite a relatively younger age and lower baseline HBsAg values, most patients had limited pre-existing T cell immunity, with **BOTH** pre-treatment ELISpot results below the LLOD prior to VRON-0200 vaccination (**Table 4**)
  - 5 (55%) and 6 (66%) patients had both pre-treatment samples below LLOD against all three peptide pools, and the two peptide pools contained within the vaccine (core and polymerase), respectively
- **At Day 28, post VRON-0200 vaccination (n=9):**
  - 5 of 9 patients were classified as "responders" with increases in both core and polymerase T cell responses observed (**Figure 5**)
  - Overall, there was a 2.4-fold increase from baseline (**Figure 6**)
  - For the 5 "responders", the increase was more pronounced (4.0-fold)
  - No baseline demographic differences were observed between the overall study population (N=13) and the five responders.
- **At Day 91, post VRON-0200 vaccination (n=5; Figure 7):**
  - 3 of 5 patients had maintained T cell responses above their pre-treatment values

Figure 5. HBV responses to Day 28 (n=9)



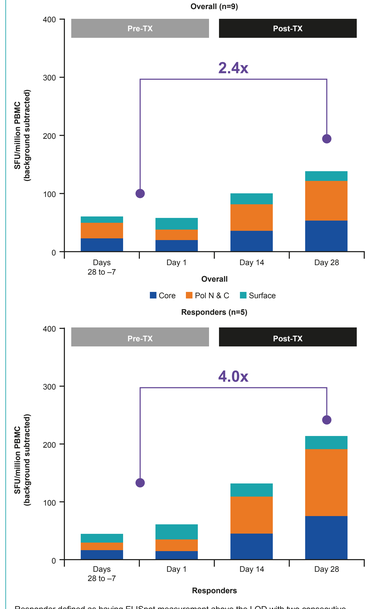
Dashed line – LLOD <30 SFU/million PBMCs.
VRON-0200 targets core and polymerase (Pol N & C), but not S-antigen.

Table 4. Number of patients with ELISpot values below LLOD* at both pre-treatment timepoints (n=9)

# of peptide pools	Core, Pol N & C, Surface	Core and/or Pol N & C
0	1	2
1	2	1
2	1	6
3	5	NA

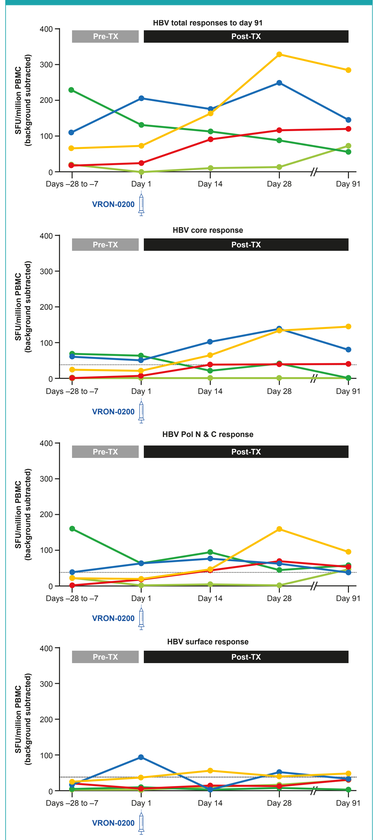
*LLOD <30 SFU/million PBMCs; pre-treatment assessments at Days –28 to –7 and Day 1 (pre-vaccination)

Figure 6. Overall T cell immune responses



Responder defined as having ELISpot measurement above the LOD with two consecutive timepoint measurements greater than the average of the two pre-treatment timepoints.
VRON-0200 targets core and polymerase (Pol N & C), but not S antigen.

Figure 7. HBV responses to Day 91 (n=5)



Dashed line – LOD <30 SFU/million PBMCs.
VRON-0200 targets core and polymerase (Pol N & C), but not S-antigen.

CONCLUSIONS

- These are the first-ever immunogenicity data for any checkpoint modifier-containing vaccine of any kind
- Following a single intramuscular low-dose VRON-0200 vaccination (Cohort 1):
  - **Safety**
    - Has been well tolerated with no SAEs or safety concerns
    - No unexpected laboratory abnormalities, including liver function tests
  - **Immunogenicity**
    - Even in patients with limited pre-existing immunity, VRON-0200 showed increases in T cell responses in the majority of treated patients
    - At Day 91, several patients maintain T cell responses above their pre-treatment values
- Cohort 1 is ongoing with boost vaccinations underway; Cohort 2 (high-dose) is now enrolling; and Cohort 3, which is VRON-0200 in combination with investigational agents, is planned for later in 2024
- **These data demonstrate that VRON-0200 is safe, well tolerated, easy to administer, and immunogenic, and support its continued evaluation as a potential IFN-sparing option for HBV functional cure**

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ABBREVIATIONS

AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; APC, antigen-presenting cell; BMI, body mass index; BTLA, B and T lymphocyte attenuator; CD, cluster of differentiation; EOS, end of study; gD, HSV-1 glycoprotein D acts as a genetically encoded checkpoint modifier; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HVEM, herpes virus entry mediator; ICS, intracellular cytokine staining; IFNγ, interferon-gamma; IU, international unit; LIGHT, lymphotoxin-like; exhibits inducible expression, and competes with herpes simplex virus glycoprotein D 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; SAE, serious adverse event; SFU, spot-forming unit; TCR, T cell receptor; TEAE, treatment-emergent adverse event; Tx, treatment; ULN, upper limit normal; vp, viral particles.

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DISCLOSURES

Ed Gane has served as an advisor and/or speaker for AbbVie, Abbott Diagnostics, Allgos, Arbutus, Arrowhead, Assembly, Dicerna, Gilead Sciences, GlaxoSmithKline, Intellia, Janssen, Merck, Novartis, Precision Biosciences, Genentech-Roche, Tune, Vaccitech, Vir Bio, and Virion Therapeutics.

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