HBsAg declines, and T cell increases, observed in CHB patients: Interim results from P1b trial of VRON-0200, a novel checkpoint modifier, following prime only, and prime and boost dosing

Viral Hepatitis
Abstract #1404

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BACKGROUND

- Despite preventative vaccines, chronic HBV infection remains a high unmet medical need[1]
- Immune-based treatments are now considered necessary for HBV functional cure[2]
- VRON-0200 is an immune modulator for functional cure of HBV infection designed to enhance and broaden CD8+ T cells to HBV core & pol[3-6]
- In chronically HBV-infected patients, VRON-0200 has previously demonstrated[7]
  - A favorable safety and tolerability profile
  - Immunogenicity
  - Anti-HBV activity (HBsAg declines)
- VRON-0200 P1b study expanded to add a cohort to evaluate the safety and efficacy of VRON-0200 with the addition of other therapeutics agents [**See EASL 2025 Abstract #LBP-033**]

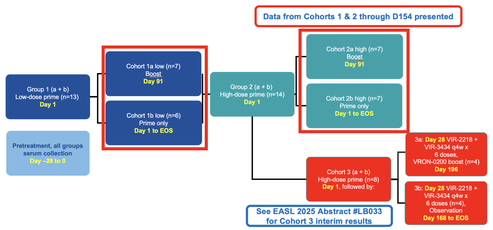
PURPOSE

- **To report safety, immunogenicity, and HBsAg changes in chronically HBV-infected patients dosed with VRON-0200 prime only, and prime and boost regimens**

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 (**Figure 1**) (**NCT06070051**)
  - Cohort 1($1x10^{10}$vp: low dose): patients are randomized to receive either an i.m. injection of VRON-0200 low dose plus a VRON-0200 low dose boost at Day 91 (Cohort 1a), or VRON-0200 low dose prime only (Cohort 1b)
  - Cohort 2 ($5x10^{10}$vp: high dose): repeats Cohort 1 design but with a higher dose
  - Cohort 3 (combination cohort): patients are randomized to receive a high dose VRON-0200 prime on Day 1, plus monthly elebsiran plus tobevibart dosing, starting on Day 28, alone, or in combination with a VRON-0200 high dose boost on Day 196 [**See EASL 2025 Abstract #LBP-033**]
- Patients were evaluated for safety, immunologic and virologic measures at multiple time points
- **This analysis includes VRON-0200 monotherapy Cohort 1 and Cohort 2 safety, immunogenicity and HBsAg data through Day 154, with a data cutoff of March 31, 2025, and PBMC ELISpot data, with a data cutoff of January 6, 2025**

Figure 1. Study Schema



METHODS II: Clinical Assessments

Safety

- Physical exams were performed, and serum were collected for clinical laboratory assessments, including liver function tests

HBsAg (Quantitative)

- ELISA HBsAg II Quant; LLOD: 0.05 IU/mL
- Absolute changes (log_{10}IU/mL)

Immunologic assessments (PBMC)

- IFNγ ELISpot to core, pol, and surface peptide pools; LLOD < 30 SFU/million PBMCs
- **Prime Only**: Immunologic "**responder**" – 2 consecutive core + pol ELISpot measurements at Day 28 > average of the 2 pre-treatment timepoints, and above the LLOD
  - One-side paired t-test – assess sum of core + pol ELISpot measurements from average of the pre-treatment values compared to Day 28, and Day 91, respectively, for each patient
- **Boost**: Cohorts 1a/2a included patients with evaluable samples at Day 104 (14 days post-Boost)
  - One-sided paired t-test – assess sum of core + pol ELISpot measurements from Day 104 compared to Day 91 (pre-boost value), respectively, for each patient

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS (N=27)

- **Table 1** lists the demographics for 27 patients
  - 22 were male (82%), mean age of 46 years, and baseline HBsAg of 177 IU/mL (range: 10-623 IU/mL)

Table 1: Patient Demographics (N=27)*

	Cohort 1a (n=6)	Cohort 1b (n=7)	Cohort 2a (n=7)	Cohort 2b (n=7)	Overall (N=27)
Median age, yrs (range)	43 (37-52)	49 (41-54)	47 (45-54)	46 (41-55)	46 (37-55)
Sex, n (%)					
Male	6(100%)	6 (86%)	4 (57%)	6 (86%)	22 (81%)
Female	0 (0%)	1 (14%)	3 (43%)	1 (14%)	5 (19%)
Race, n (%)					
Asian	5 (83%)	6 (86%)	6 (86%)	7(100%)	24 (89%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	1 (14%)	0 (0%)	1 (4%)
White	0 (0%)	1 (14%)	0 (0%)	0 (0%)	1 (4%)
Other	1 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
BMI (kg/m²), median (range)	29.3 (27.3 - 31.7)	24.8 (20.2 – 32)	27.4 (22.9 – 31.6)	23 (19.7 – 27.7)	26.7 (19.7 – 32)
Baseline HBsAg Levels (IU/mL), median (range)	222 (29 - 319)	273 (16 - 623)	124.8 (17.1 – 322.2)	226 (9.66 – 562.6)	177.1 (9.66 – 623*)
Baseline HBsAg Levels, n (%)					
>500 IU/mL	0 (0%)	1 (14%)	0 (0%)	1 (14%)*	2 (7%)*
200 – <500 IU/mL	4 (67%)	2 (29%)	1 (14%)	3 (43%)	10 (37%)
100 – 199 IU/mL	0 (0%)	2 (29%)	4 (57%)	1 (14%)	7 (26%)
<100 IU/mL	2 (33%)	2 (29%)	2 (29%)	2 (29%)	8 (30%)
Baseline ALT (x ULN), n (%)					
<1 x ULN	5 (83%)	7 (100%)	6 (86%)	6 (86%)	24 (89%)
1 to 1.5x ULN	0 (0%)	0 (0%)	1 (14%)	1 (14%)	2 (7%)
1.6 x ≤2x ULN	1 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
HBsAg Status at Baseline, n (%)					
Negative	6 (100%)	6 (80%)	7 (100%)	7 (100%)	26 (96%)
Positive	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (4%)

SAFETY AND TOLERABILITY

- There are **8,295** total patient safety days reported. VRON-0200 was well tolerated with 43 adverse event being reported in 16 patients (**Table 2**)
  - There were no SAEs, treatment discontinuations, or treatment-related clinical laboratory abnormalities, including liver function tests (not shown)
  - Twenty treatment-related adverse events (TRAEs) were reported; 3 were Grade 2 (eczema; myalgia, injection site reaction); all other TRAEs were Grade 1
  - Symptoms have resolved in all patients

Table 2: Safety & Tolerability (N=27)

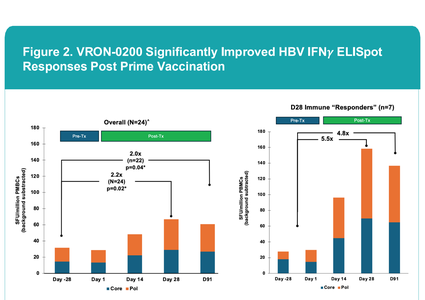
	Cohort 1a (n=6)	Cohort 1b (n=7)	Cohort 2a (n=7)	Cohort 2b (n=7)	Overall (N=27)
Any AE, n	7	9	18	9	43
Grade 1	6	7	12	6	32
Grade 2	1	2	6	3	12
Grade 3 or 4	0	0	0	0	0
SAE, n	0	0	0	0	0
TRAEs, n	2	3	10	5	20
AEs leading to Study Drug Discontinuation, n	0	0	0	0	0
Study Discontinuations, n	0	0	0	0	0
ALT elevations, n					
Grade 1	0	0	0	0	0
Grade 2	0	0	0	0	0

IMMUNOLOGY

ELISpot Data cutoff date January 6, 2025

- **After a single VRON-0200 prime dose only** (**Figure 2**):
  - IFNγ ELISpot responses were available for 24 patients at Day 28, and 22 patients at Day 91
  - Overall, there was a significant 2.2- and 2.0-fold increase from baseline at Days 28 (p=0.02) and Day 91 (p=0.04), respectively
  - 7 patients (29%) were classified as "Day 28 immune responders" with 5.5- and 4.8-fold increases being observed at Days 28 and 91, respectively
    - No differences in baseline parameters, including demographics, age, HBsAg levels, HBV ELISpot and control immune panel measurements, among others, were observed between "responders" and "non responders"
- **After a prime and boost VRON-0200 regimen** (**Figure 3**):
  - 9 patients had IFNγ ELISpot responses at both Days 91 and 104 (14 days after a Boost dose)
    - 4 of the 9 patients had increased responses at Day 104 (post-boost) from Day 91 (pre-boost); however, this was not statistically significant (p=0.06)

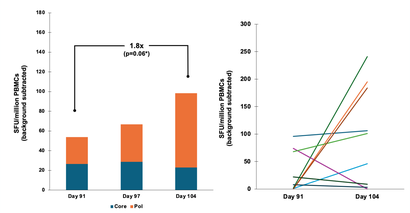
Figure 2. VRON-0200 Significantly Improved HBV IFNγ ELISpot Responses Post Prime Vaccination



*One sided paired t-test
^D91 unavailable for 2 patients – replaced with D104

D28 Responders are defined as having ELISpot measurements above the LOD with 2 consecutive timepoint measurements greater than the average of the two pre-treatment timepoints

Figure 3. IFNγ ELISpot Responses Post Boost Dosing (n=9)



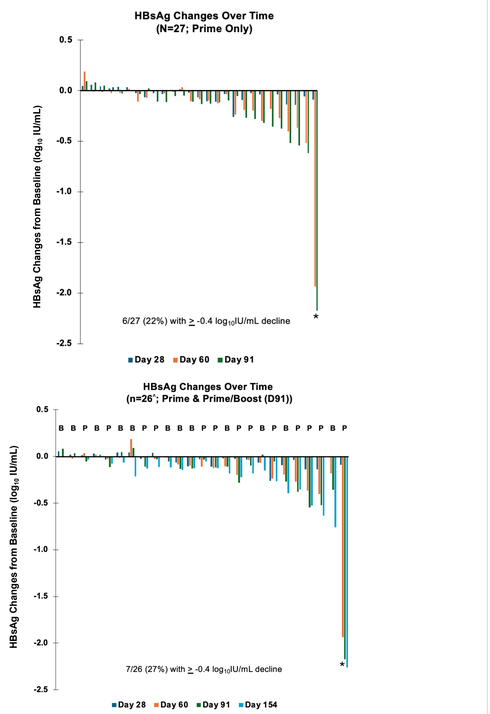
*One sided paired t-test

HBsAg RESULTS

Data cutoff: March 31, 2025

- **Figure 4** shows HBsAg changes over time:
  - The top figure shows changes in 27 patients, following a single VRON-0200 prime only dose
    - Six patients (22%) had a ≥ 0.4log_{10}IU/mL HBsAg change from baseline
    - HBsAg declines were observed in patients starting at Day 28
    - HBsAg declines were observed in both low- and high-dose VRON-0200 treated patients
  - The bottom figure shows changes in 26 patients following a Day 1 VRON-0200 prime, alone, or in combination with a boost, at Day 91, through Day 154
    - Seven patients (27%) had a ≥0.4 log_{10}IU/mL decline from baseline
    - For patients with HBsAg declines, the decline deepened over time
    - HBsAg declines were not enhanced following a boost dose at Day 91

Figure 4. HBsAg Changes Over Time



*D91 missing; Replaced with D104; P – Prime only Day 1; B – Prime on Day 1, Boost on Day 91; ^One patient at D118 with -0.6 log_{10}IU/mL decline included

CONCLUSIONS

Treatment with VRON-0200 Prime, and Prime and Boost, in chronically HBV-infected patients:

- Was safe and well-tolerated with 8,295 patient safety days reported (N=27)
  - No differences were observed between low- and high-dose, prime, and prime boost regimens
- S-antigen declines were observed in ~25% of patients, despite the fact VRON-0200 does NOT target S
  - Declines initiated at Day 28 and deepened over time
  - Factors associated with HBsAg declines are being evaluated further
    - The impact of IFNγ in the blood is unclear
    - A VRON-0200 boost dose at Day 91 did not improve responses
- The VRON-0200 high dose was well tolerated and displayed anti-HBV activity
  - This dose can be conveniently administered and will be used for future VRON-0200 studies
- Initial results from the first VRON-0200 combination regimen (Cohort 3) are available at EASL 2025 Abstract #LBP-033
- **These data support the continued study of VRON-0200 as a safe and well tolerated, easy-to-administer, potential IFN-sparing immunotherapy, alone or in combination, for HBV Functional Cure**

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ABBREVIATIONS

AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BMI, body mass index; core – HBV core enzyme; ECG, end of study; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ICS, intracellular cytokine staining; IFNγ, interferon-gamma; IU, international unit; LLOD, lower limit of detection; PBMC, peripheral blood mononuclear cell; Pol, polymerase; SAE, serious adverse event; SFU, spot-forming unit; TRAE, treatment-related 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,Aligos, Arbutus, Arrowhead, Assembly, Dicerna, Gilead Sciences, GlaxoSmithKline, Intellia, Janssen, Merck, Novartis, Pharalex-Biosciences, Genentech-Roche, Tune, Vaccitech, Vir Biotechnology, and Virion Therapeutics.

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