Preliminary safety and antiviral activity of VIR-2218, an X-targeting RNAi therapeutic, in chronic hepatitis B patients

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Disclosures

- Ed Gane has been an advisor and/or speaker for AbbVie, Arbutus, Arrowhead, Assembly, Avalia, Dicerna, Gilead Sciences, GSK, Janssen, Merck, Novartis, Roche and Vir Bio.

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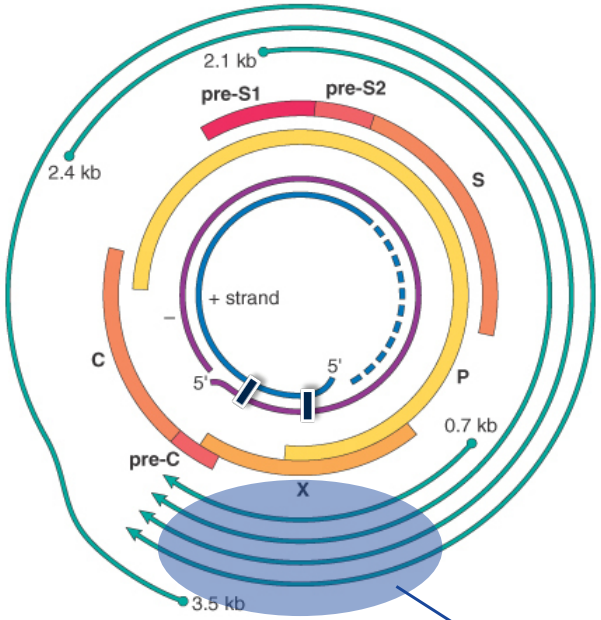
VIR-2218: X-targeting Investigational RNAi therapeutic for the treatment of chronic HBV infection

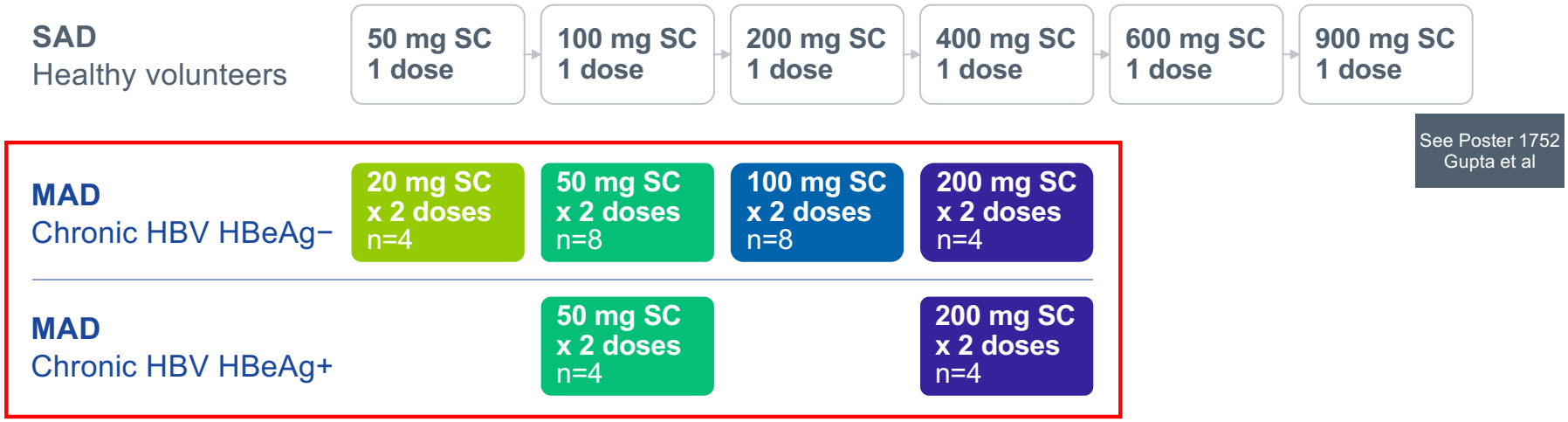
- Targets conserved region in X gene, upstream of integration hotspot, allowing for
  - Single siRNA to suppress HBsAg from both intDNA and cccDNA
  - Suppression of all HBV mRNAs, which overlap in this region
- GalNAc-conjugated ESC+ siRNA
  - Subcutaneous administration with GalNAc ligand for targeted delivery to liver and prolonged pharmacodynamic effect[1,2]
  - ESC+ technology: improved specificity of RNAi activity[3,4]



cccDNA, covalently-closed circular DNA; ESC+, enhanced stabilization chemistry plus; GalNAc, Trivalent *N*-acetylgalactosamine; intDNA, integrated DNA; HBsAg, hepatitis B surface antigen; RNAi, RNA interference; siRNA, small interfering RNA.

1. Nair J, et al. J Am Chem Soc 2014;136:16958-61; 2. Foster D, et al, Nucleic Acids Res 2018; 3. Janas M, et al. Nature Comm 2018;9:723; 4. Schlegel MK, et al. J Am Chem Soc 2017;139:8537-46.

VIR-2218-1001: Phase 1/2 study design



- Double-blind, randomized, placebo-controlled, MAD study in patients with chronic HBV infection
- At each dose level, 4 or 8 patients randomized 3 active:1 placebo

HBeAg, hepatitis B e antigen; MAD, multiple ascending dose; SAD, single ascending dose.

Key inclusion/exclusion criteria

Inclusion

- Age 18–65 years
- Detectable serum HBsAg for ≥6 months
- On NRTI therapy for ≥6 months
- HBsAg >150 IU/mL
- HBV DNA <90 IU/mL
- Serum ALT and AST ≤2 × ULN

Exclusion

- Significant fibrosis or cirrhosis (FibroScan >8.5 kPa at screening or Metavir F3/F4 liver biopsy within 1 year)
- Bilirubin, INR, or prothrombin time >ULN
- Active HIV, HCV, or hepatitis Delta virus infection
- Creatinine clearance <60 mL/min (Cockcroft-Gault)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLcr, creatinine clearance; INR, international normalized ratio; NRTI, nucleoside reverse transcriptase inhibitor; ULN, upper limit of normal.

VIR-2218-1001 Phase 2 Study Results

Demographics and baseline characteristics

	HBeAg-Negative Patients						HBeAg-Positive Patients			
	VIR-2218						VIR-2218			
	20 mg n=3	50 mg n=6	100 mg n=6	200 mg n=3	Overall n=18	Placebo n=6	50 mg n=3	200 mg n=3	Overall n=6	Placebo n=2
Mean age, y (SD)	40 (9)	43 (11)	45 (6)	55 (4)	45 (9)	44 (7)	35 (10)	34 (13)	34 (10)	59 (8)
Male sex, n (%)	2 (67)	5 (83)	5 (83)	0	12 (67)	3 (50)	1 (33)	2 (67)	3 (50)	1 (50)
Race, n (%)										
Asian	3 (100)	5 (83)	5 (83)	3 (100)	16 (89)	6 (100)	3 (100)	3 (100)	6 (100)	2 (100)
White	0	0	1 (17)	0	1 (6)	0	0	0	0	0
Other	0	1 (17)	0	0	1 (6)	0	0	0	0	0
Mean $\log_{10}$ HBsAg (SD)	3.3 (0.3)	3.3 (0.5)	3.4 (0.5)	3.3 (0.4)	3.3 (0.4)	3.5 (0.4)	3.5 (0.3)	3.9 (0.6)	3.7 (0.5)	3.2 (0.3)

SD, standard deviation.

VIR-2218-1001 Phase 2 Study Results

Summary of safety and tolerability

Patients, n (%)	VIR-2218 n=24	Placebo n=8
Any adverse event (AE)	13 (54)	2 (25)
Treatment-related AE	5 (21)	0
Grade ≥3 AE	1 (4)	0
SAE	1 (4)	0

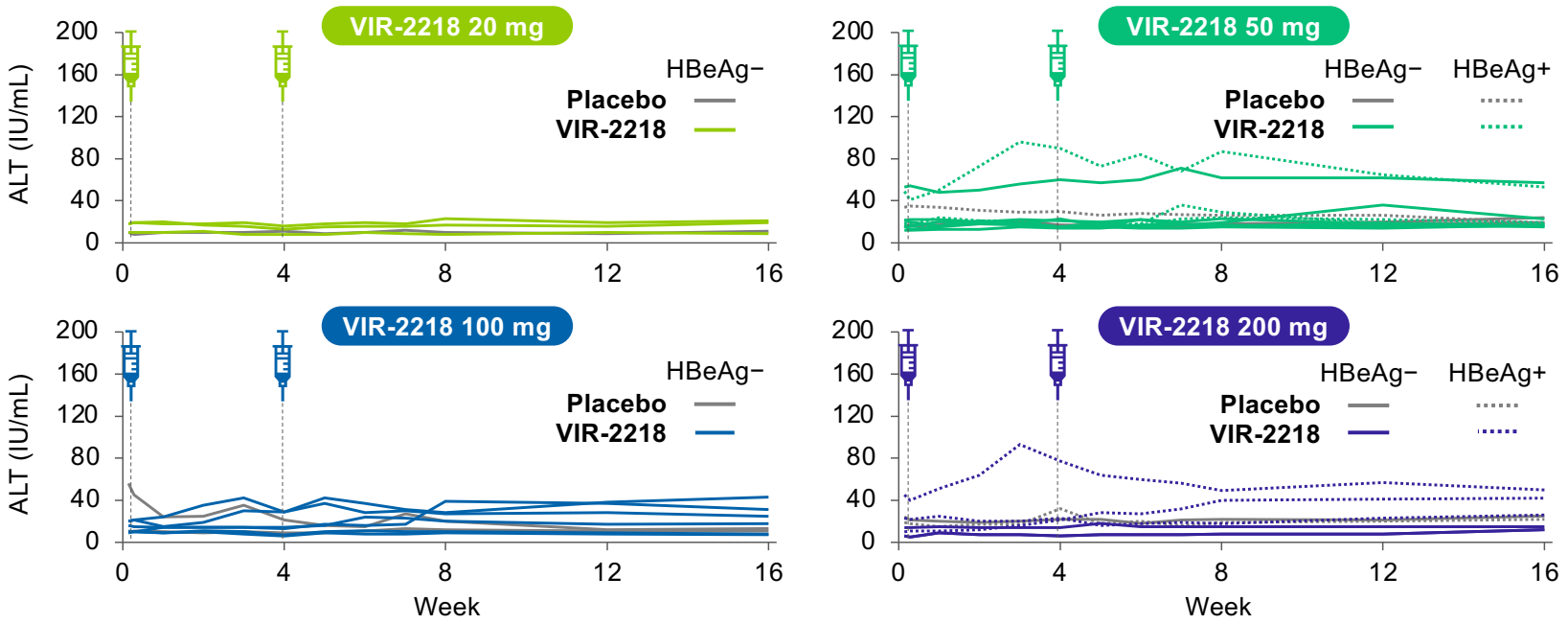
*All AEs included in summary are treatment emergent AEs.

- No clear dose related trend in frequency of AEs
- Most common AE: headache (6/24, 25%)
- Single Grade 3 AE of hypophosphatemia in a patient on tenofovir DF
- Single SAE of Grade 2 headache

DF, disoproxil fumarate; SAE, serious AE.

VIR-2218-1001 Phase 2 Study Results

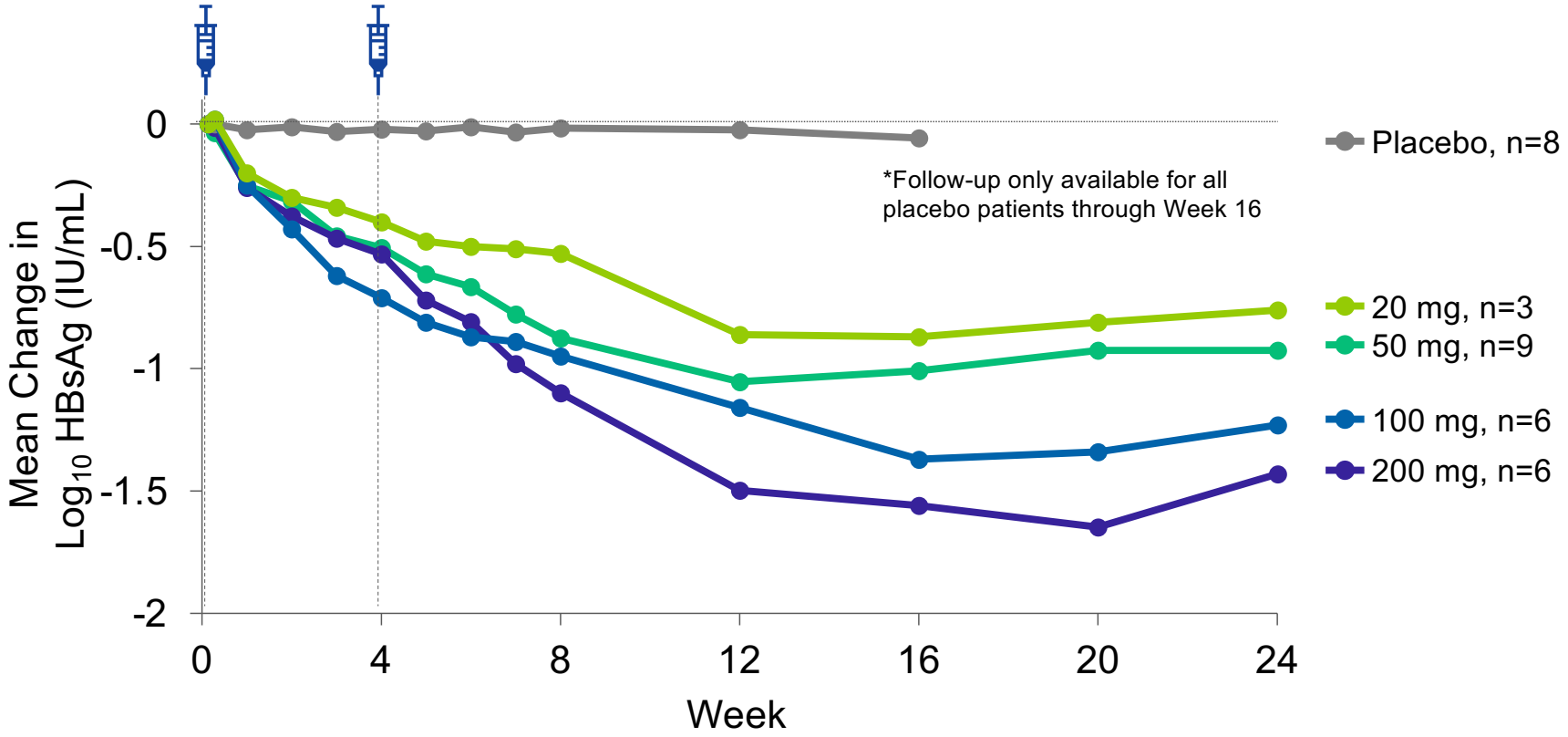
ALT levels in all patients through Week 16 (N=32)



- No Grade ≥2 ALT elevations; no bilirubin >ULN
- No clinically relevant changes or trends in other lab parameters, vital signs, or ECGs

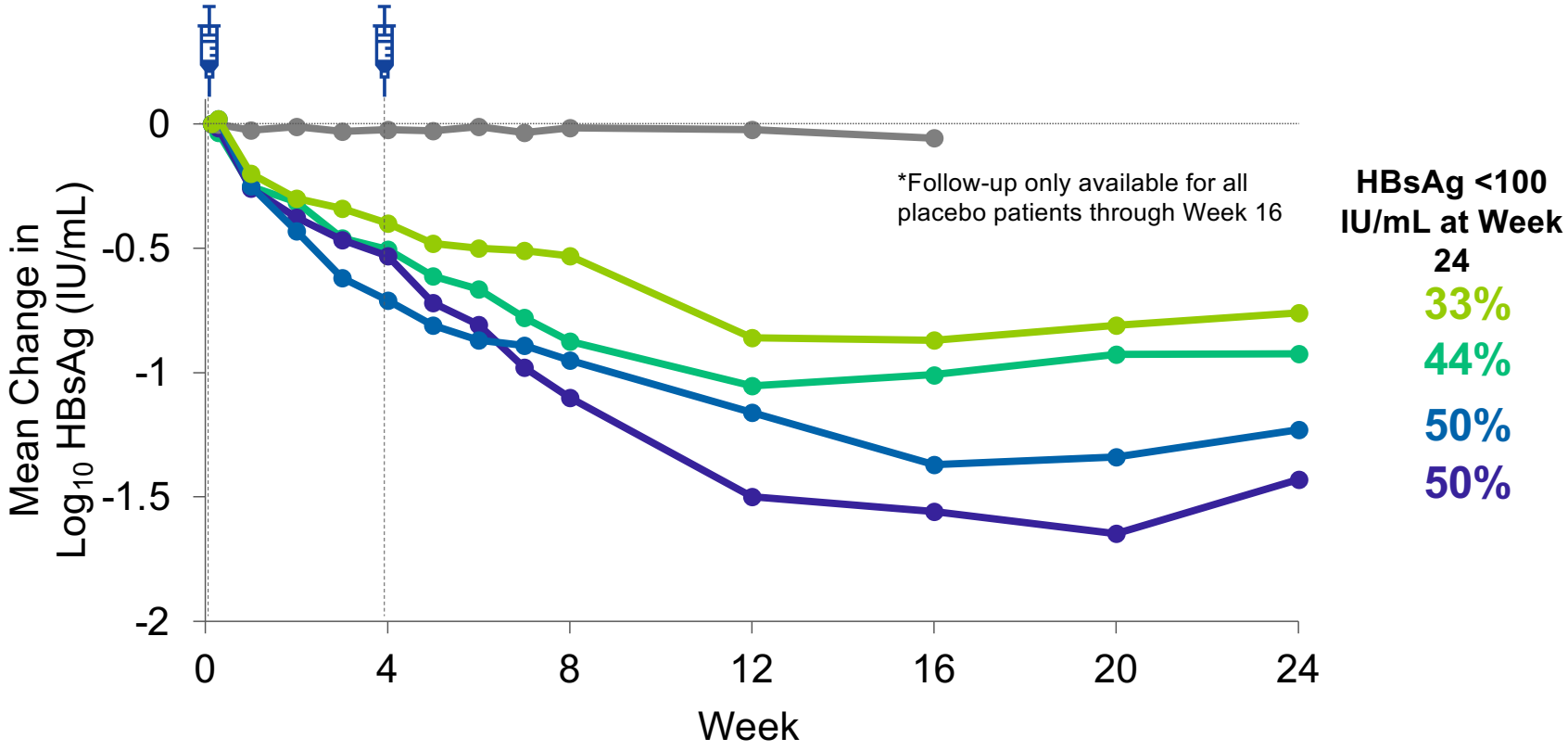
VIR-2218-1001 Phase 2 Study Results

HBsAg change from baseline



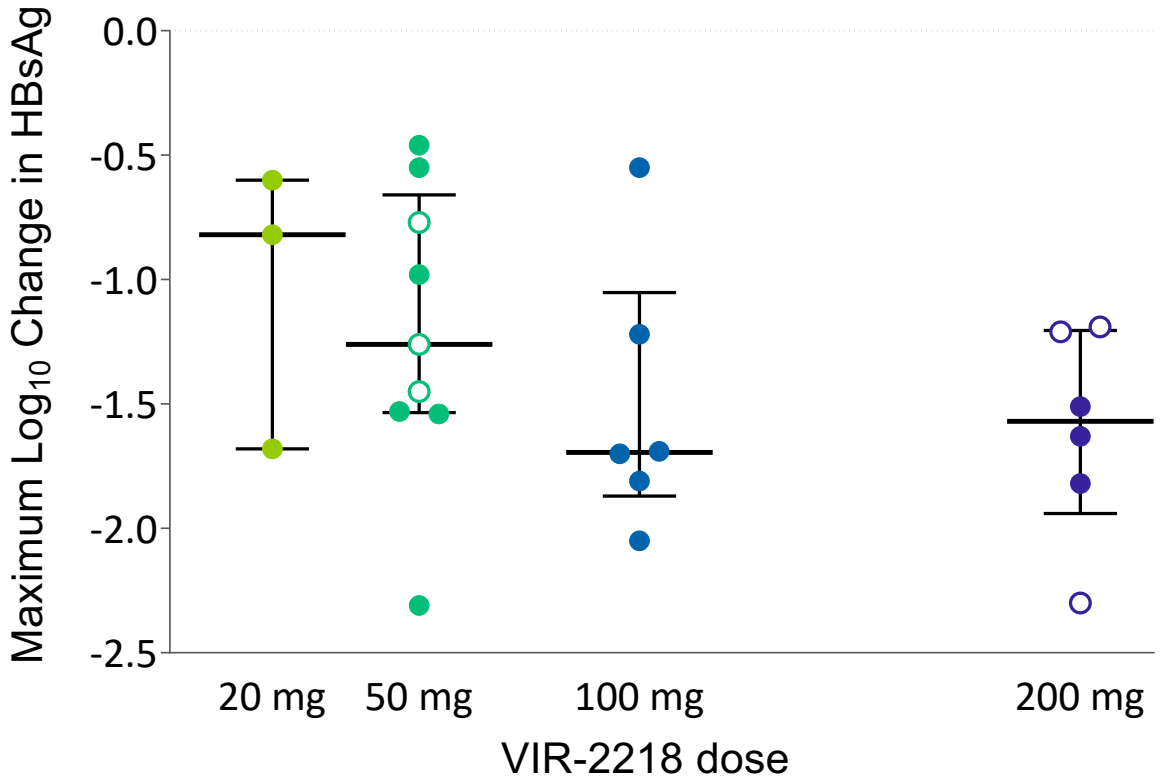
VIR-2218-1001 Phase 2 Study Results

HBsAg change from baseline



VIR-2218-1001 Phase 2 Study Results

Individual maximum HBsAg change from baseline



- All 6 patients who received 2 doses of 200 mg achieved ≥1.0 log_{10} HBsAg decline
- Similar reductions in HBeAg− and HBeAg+ patients
  - HBeAg−
  - HBeAg+

Error bars represent median (interquartile range).

Conclusions

- VIR-2218 was tolerated across all dose levels, with no safety signals observed to date
- Dose dependent HBsAg reductions in HBeAg− and HBeAg+ patients across dose range of 20 to 200 mg of VIR-2218 x 2 doses
- All patients who received 200 mg x 2 achieved a ≥1-log reduction in HBsAg
  - At Week 24, the mean decline in HBsAg was -1.43 $\log_{10}$
- Overall, results support the continued development of VIR-2218 as a backbone for a finite treatment regimen aimed at functional cure of chronic HBV infection

Acknowledgments

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