Evaluation of RNAi therapeutics VIR-2218 and ALN-HBV for chronic hepatitis B: Results from randomized clinical trials

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Supplementary methods

Ethics Committees for Study ALN-HBV-001 and VIR-2218-1001

Each study was reviewed and approved by applicable regulatory bodies and ethics committees. For study ALN-HBV-001, this was London Bridge Research Ethics Committee (UK Health Research Authority). For study VIR-2218-1001, the institutional review boards/independent ethics committees were as follows: Health and Disability Ethics Committees (HDEC); St. Vincent's Human Research Ethics Committee (HREC); Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB); Asan Medical Center Institutional Review Board; Seoul National University Hospital Institutional Review Board; Pusan National University Hospital Institutional Review Board; Ethics Committee of the Faculty of Tropical Medicine, Mahidol University; Siriraj Institutional Review Board Human Research Protection Unit, Faculty of Medicine Siriraj Hospital, Mahidol University; Institutional Review Board, Faculty of Medicine, Chulalongkorn University; Khon Kaen University Ethics Committee in Human Research; and Human Research Ethics Committee, Faculty of Medicine, Prince of Songkla University. For both studies, participants were randomly assigned via an interactive response system.

Criteria for Suspending or Stopping Dosing in Healthy Volunteers

Cohort dosing was suspended or stopped if a sentinel participant experienced a grade ≥3 treatment-related AE, if ≥1 participant experienced a grade 3 study drug–related rash, if ≥2 participants experienced the same grade ≥3 study drug–related AE, if ≥1 participant had a study drug–related serious AE, or if ≥1 participant experienced a grade 4 rash.

Criteria for Suspending or Stopping Dosing in Participants With cHBV Infection

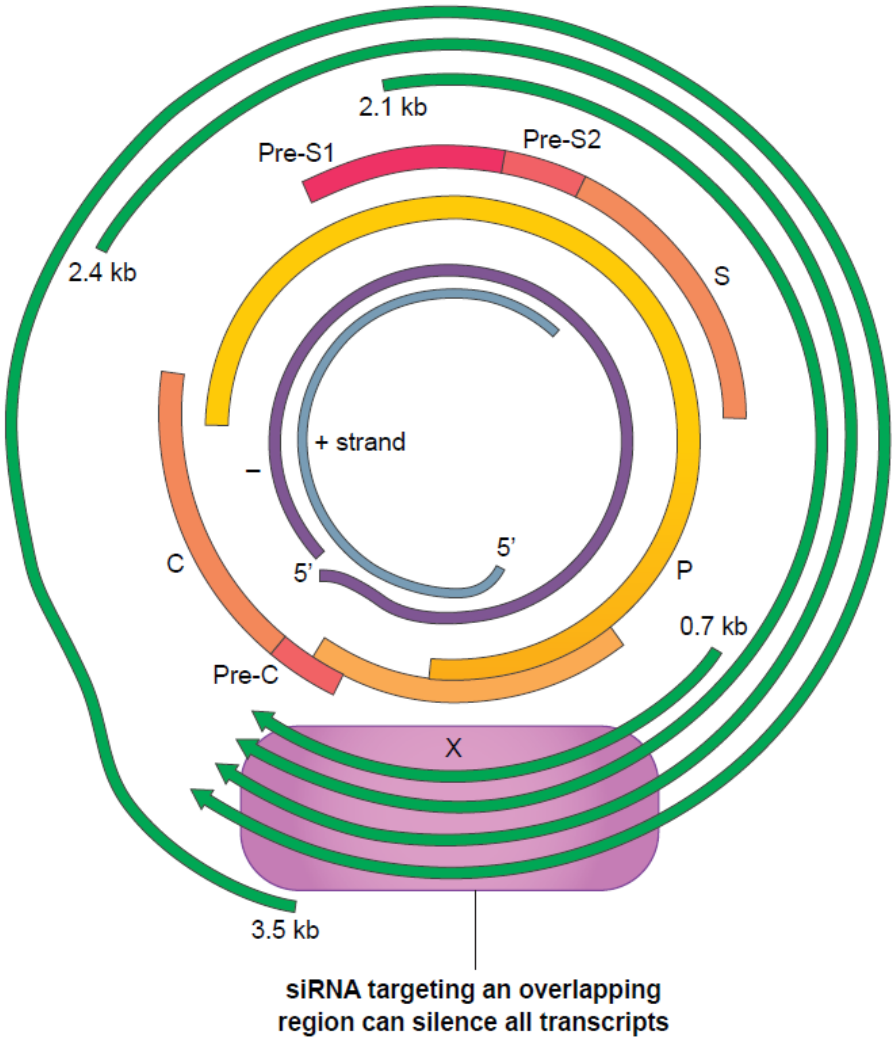
Participants who received 1 dose of study drug continued treatment as scheduled unless serum ALT level >10 × ULN, serum ALT level >5 × ULN with no change in HBsAg (defined as a <50% decrease from the baseline predose value), serum ALT or AST level >3 × ULN with a concomitant total bilirubin level >2 × ULN, or any clinical manifestations of hepatic decompensation.

Supplemental Results

Missing Data in the Analysis of Post-treatment HBsAg Reduction Over Time in Participants With cHBV Infection (Study VIR-2218-1001)

All HBeAg-negative participants completed all follow-up visits except for 1 in the 50-mg dose cohort who missed the Week 28 and 32 visits and 5 participants in the placebo group with last visits at Week 16, 24, 28, and 32, respectively. All HBeAg-positive participants completed all follow-up visits except for 1 participant in the 50-mg dose cohort who had their last follow-up visit at Week 28, 1 participant in the 200-mg dose cohort who missed the Week 28 visit and had last follow-up visit at Week 36, and 2 participants in the placebo group with last visits at Week 16 and 24, respectively.

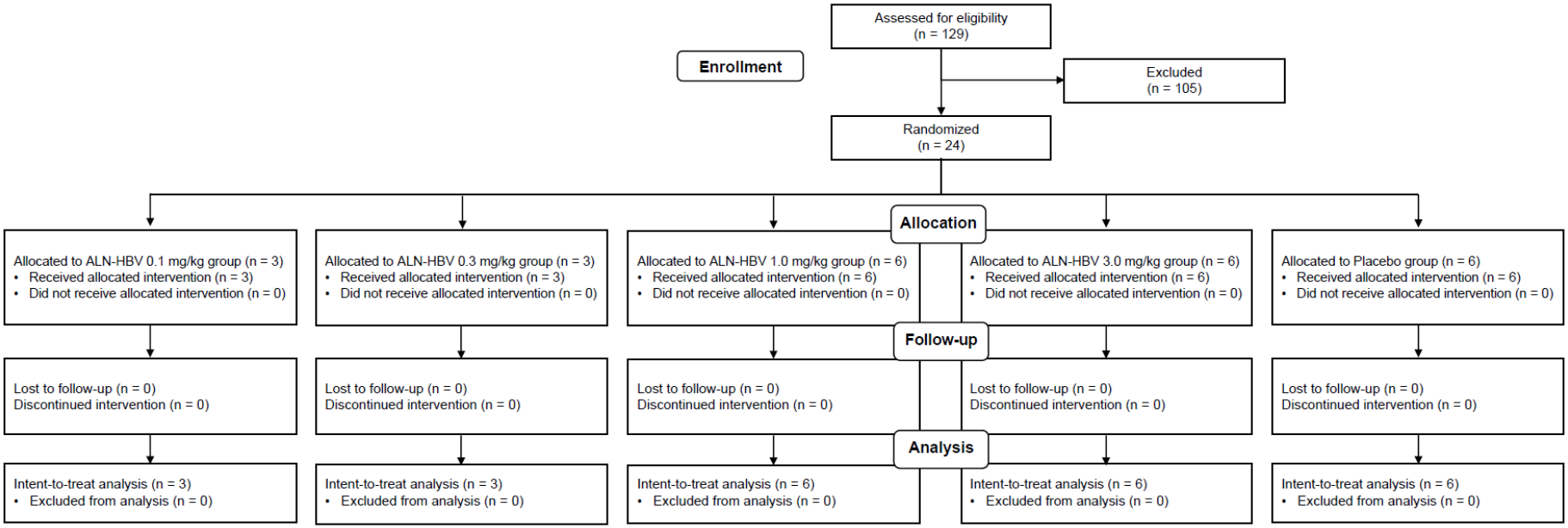
Fig. S1. VIR-2218 target within the HBV genome.



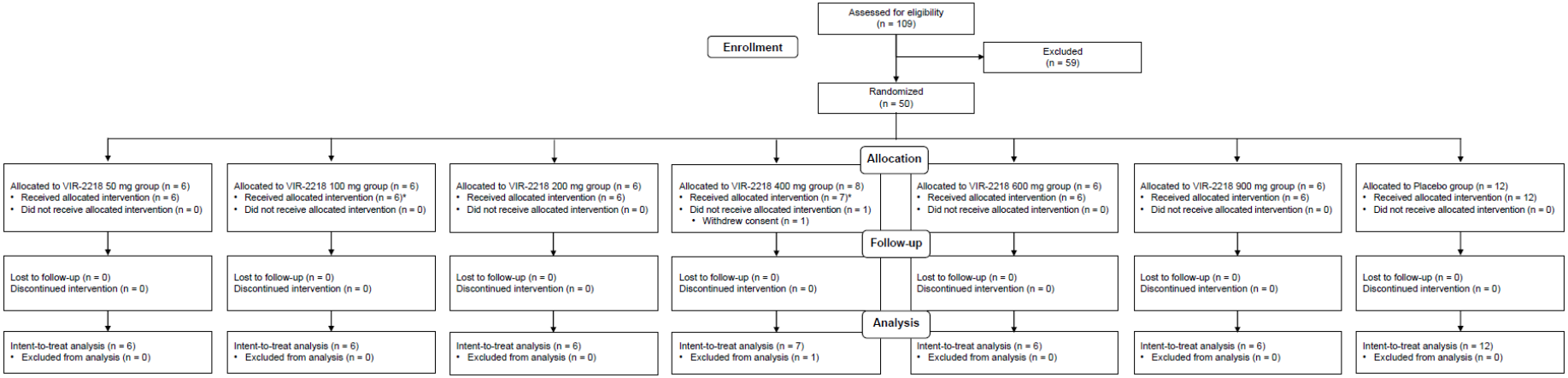
HBV, hepatitis B virus; siRNA, short interfering RNA.

Fig. S2. CONSORT flow diagram for healthy volunteers in the (a) ALN-HBV-001 and (b) VIR-2218-1001 studies.

A.



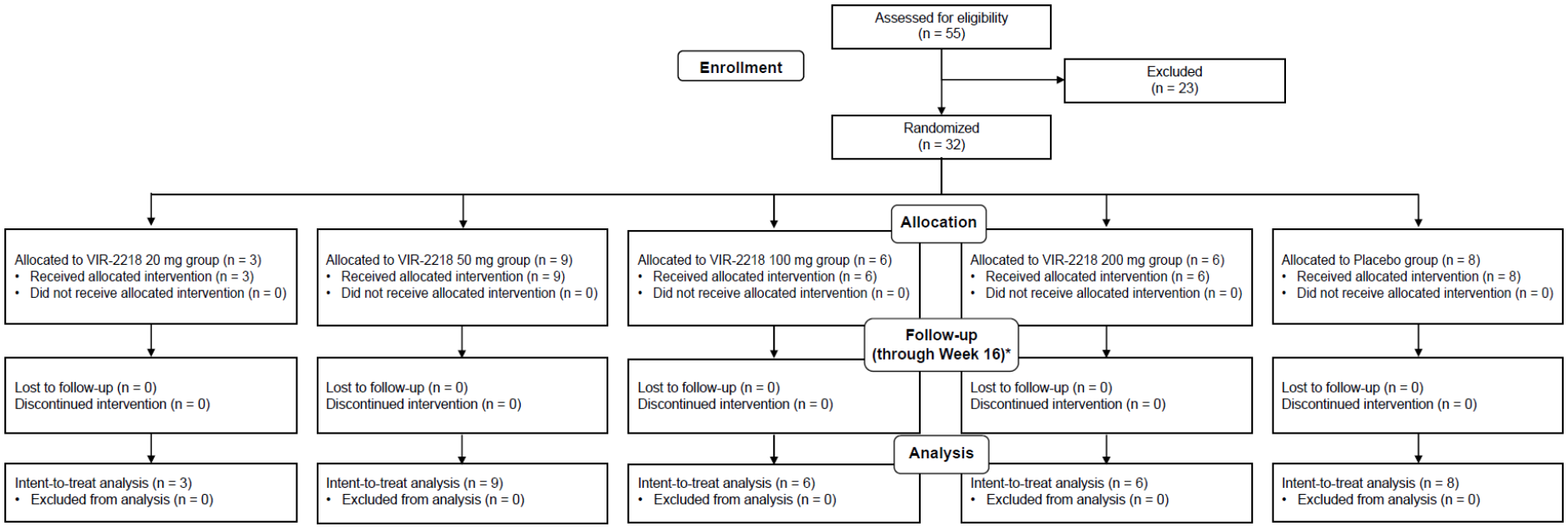
B.



*A total of 2 participants received a partial dose of VIR-2218; 1 participant in the 100-mg cohort received 0.4 mL of the planned 0.5-mL volume and 1 participant in the 400-mg cohort received 1.5 mL or the planned 2.0-mL volume.

CONSORT, Consolidated Standards of Reporting Trials.

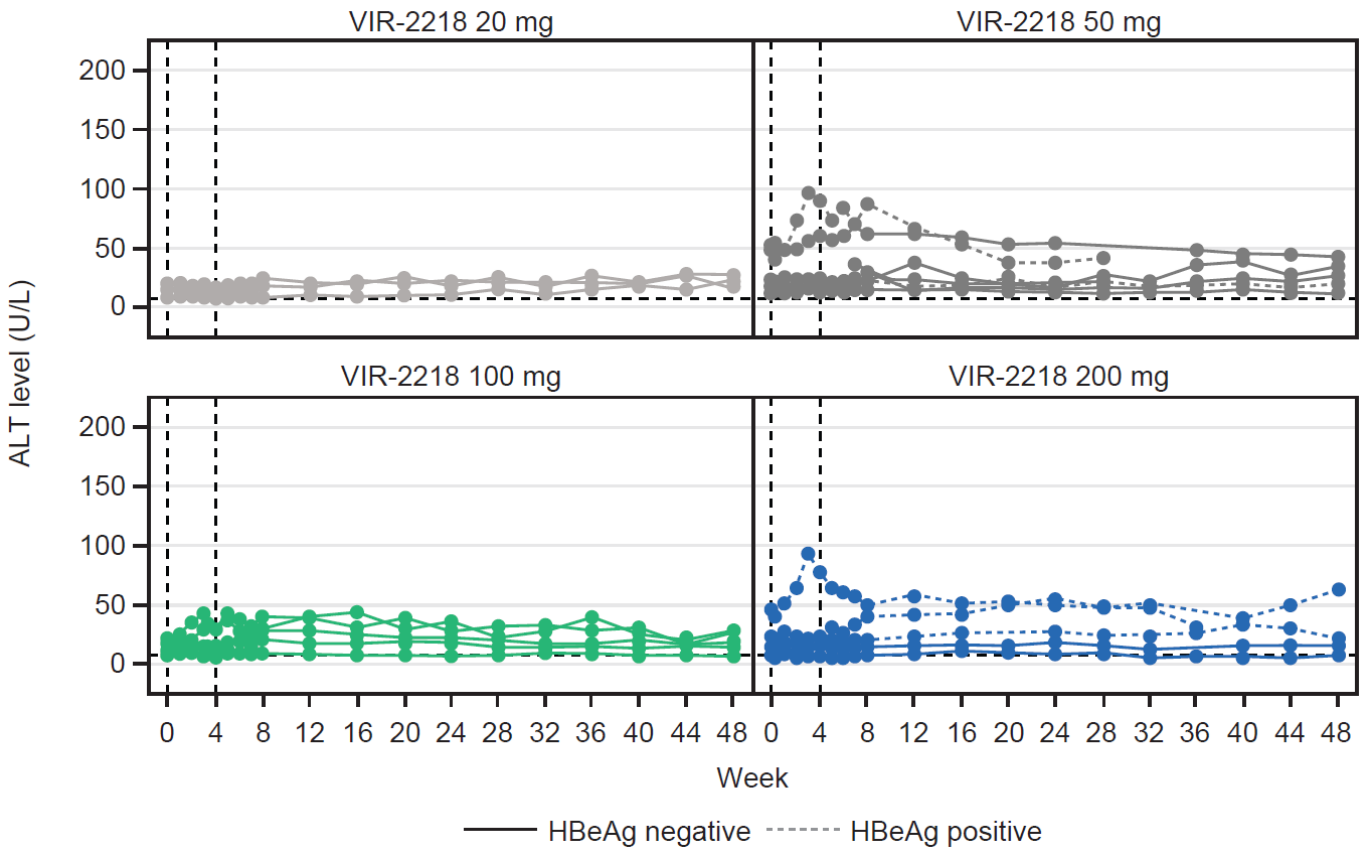
Fig. S3. CONSORT flow diagram for participants with cHBV infection in the VIR-2218-1001 study.



*All participants completed regular follow-up of 16 weeks. Participants with >10% HBsAg level reduction at Week 16 underwent extended follow-up, which was not completed by 2 participants (both of whom were HBeAg positive); 1 participant in the 50-mg cohort had their last follow-up visit at Week 28, and 1 participant in 200-mg cohort missed the Week 28 visit and had their last follow-up visit at Week 36.

CONSORT, Consolidated Standards of Reporting Trials; cHBV, chronic hepatitis B virus; HBsAg, hepatitis B virus surface antigen HBeAg, hepatitis B e antigen.

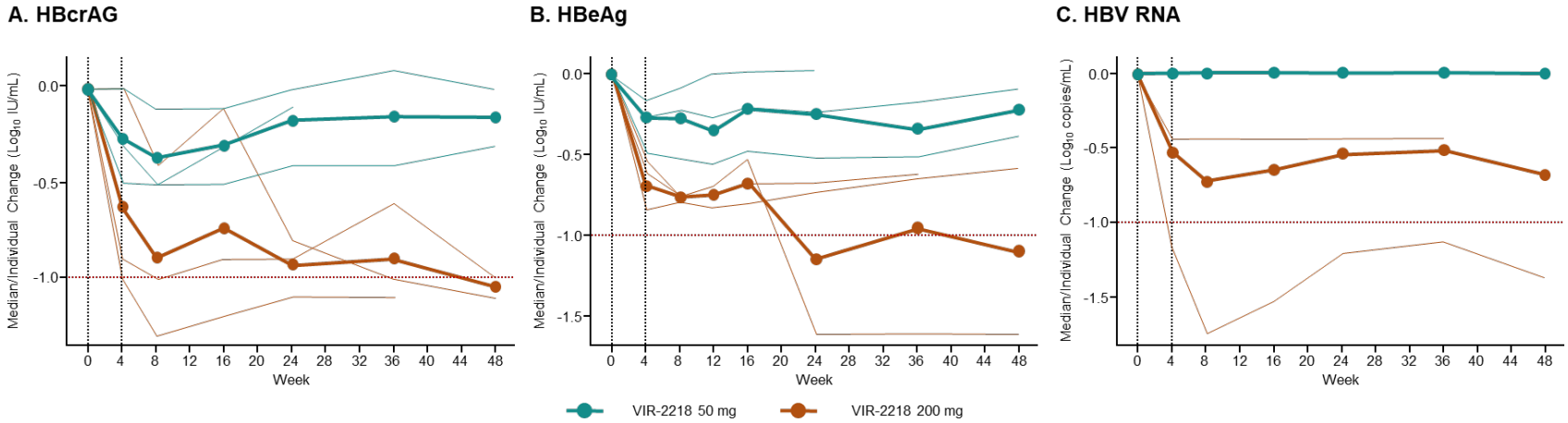
Fig. S4. ALT levels* in all participants with cHBV infection through Week 48 (study VIR-2218-1001).



*The upper limit of normal for male and female participants is 43 U/L and 34 U/L, respectively.

ALT, alanine aminotransferase; cHBV, chronic hepatitis B virus; HBeAg, hepatitis B e antigen.

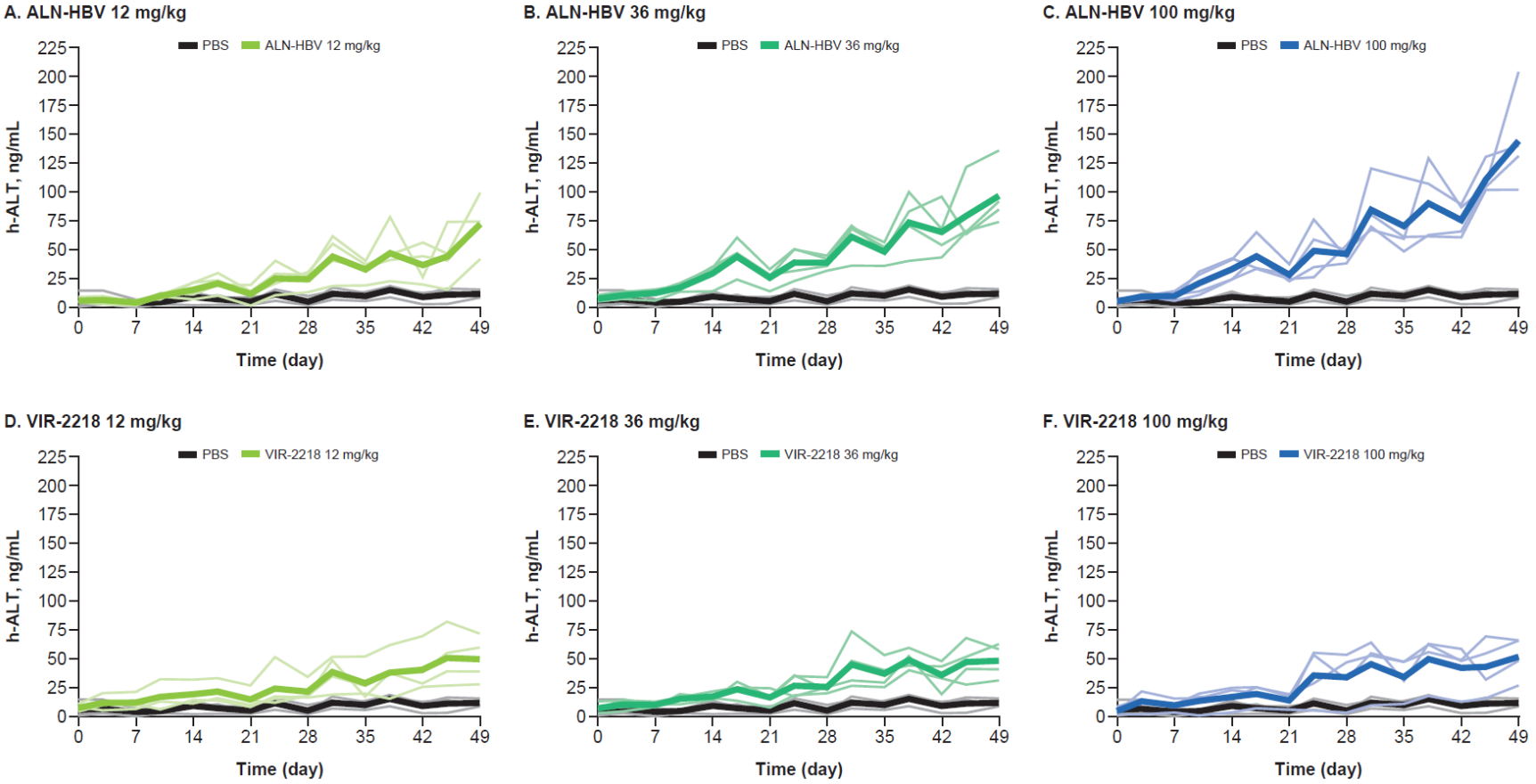
Fig. S5. Dose-dependent reductions in (A) HBcrAg, (B) HBeAg and (C) HBV RNA in HBeAg-positive participants.*



*Individual-level (solid lines) and median (dotted lines) data are shown. All values < LLOQ were imputed to 1 significant unit below LLOQ; 2 of 3 participants in the 50 mg cohort had < LLOQ HBV RNA at baseline.

HBeAg, hepatitis B e antigen; HBcrAg, hepatitis B core-related antigen; LLOQ, lower limit of quantitation.

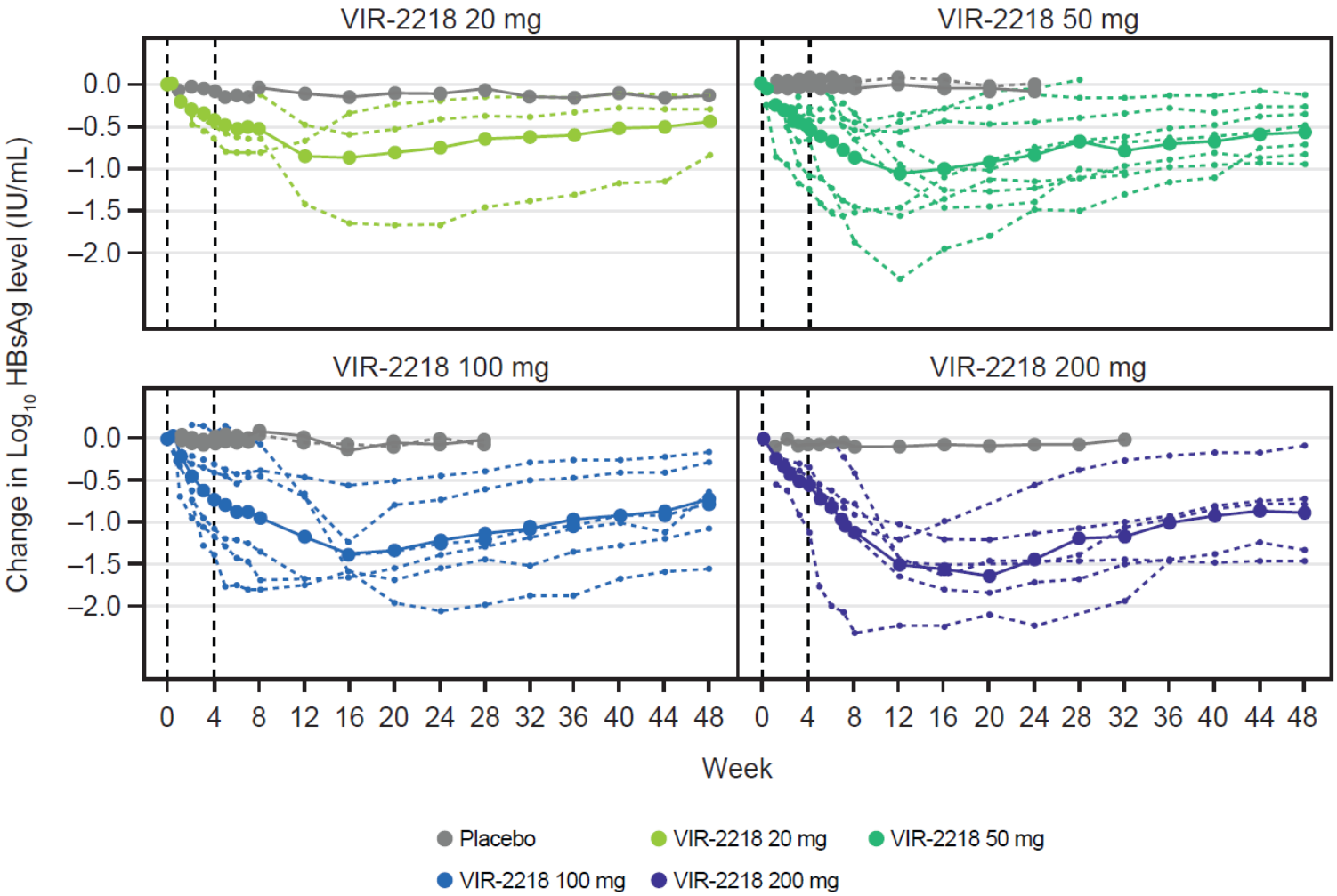
Fig. S6. Individual-level data for comparison of post-treatment ALT levels between ALN-HBV and VIR-2218 in nonclinical studies.*



*Individual-level and mean data are shown; the data correspond to the mean data plotted in Figure 2a.

ALT, alanine aminotransferase; hALT, human alanine aminotransferase.

Fig. S7. Participant-level data for post-treatment mean HBsAg level reduction over time in participants with cHBV infection (study VIR-2218-1001).*



*Individual-level and mean data are shown; the data correspond to the mean data plotted in Figure 3.

HBsAg, hepatitis B virus surface antigen; cHBV, chronic hepatitis B virus.

Table S1. Summary of Demographics of Healthy Volunteers From the ALN-HBV-001 and VIR-2218-1001 Studies

	ALN-HBV					
Participants, n (%)	**Overall (n = 18)**	**0.1 mg/kg (n = 3)**	**0.3 mg/kg (n = 3)**	**1.0 mg/kg (n = 6)**	**3.0 mg/kg (n = 6)**	**Placebo (n = 6)**
Mean age, y (SD)	24.3 (5.9)	30.7 (4.0)	24.3 (6.7)	24.8 (7.2)	20.5 (0.8)	26.8 (5.5)
Male, n (%)	10 (55.6)	2 (66.7)	1 (33.3)	2 (33.3)	5 (83.3)	4 (66.7)
Race, n (%)						
White	10 (55.6)	2 (66.7)	1 (33.3)	4 (66.7)	3 (50.0)	2 (33.3)
Black or African American	4 (22.2)	0 (0.0)	2 (66.7)	1 (16.7)	1 (16.7)	0 (0.0)
Asian	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)
Other	2 (11.1)	1 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	3 (50.0)
Mean BMI, kg/m^2 (SD)	22.0 (3.0)	23.5 (2.4)	19.4 (1.6)	23.0 (3.1)	21.7 (3.3)	25.3 (2.2)

	VIR-2218							
Participants, n (%)	**Overall (n = 49)**	**50 mg (n = 6)**	**100 mg (n = 6)**	**200 mg (n = 6)**	**400 mg (n = 7)**	**600 mg (n = 6)**	**900 mg (n = 6)**	**Placebo (n = 12)**
Mean age, y (SD)	26.7 (6.1)	25.0 (3.0)	23.3 (4.0)	26.7 (3.8)	24.3 (3.7)	28.8 (6.3)	32.5 (9.5)	26.5 (6.7)
Male, n (%)	18 (36.7)	0 (0.0)	2 (33.3)	3 (50.0)	0 (0.0)	3 (50.0)	3 (50.0)	7 (58.3)
Race, n (%)								

Asian	9 (18.4)	2 (33.3)	3 (50.0)	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)	1 (8.3)
White	28 (57.1)	2 (33.3)	2 (33.3)	5 (83.3)	5 (71.4)	3 (50.0)	3 (50.0)	8 (66.7)
Other	12 (24.5)	2 (33.3)	1 (16.7)	1 (16.7)	2 (28.6)	1 (16.7)	2 (33.3)	3 (25.0)
Mean BMI, kg/m^2 (SD)	24.5 (3.1)	23.1 (4.6)	22.9 (2.7)	24.2 (2.0)	25.1 (3.9)	26.0 (1.4)	25.7 (4.0)	24.4 (2.4)

SD, standard deviation; BMI, body mass index.

Table S2. AEs Summary in Healthy Volunteers from the ALN-HBV-001* and VIR-2218-1001* Studies

	ALN-HBV					
Participants, n (%)	**Overall (n = 18)**	**0.1 mg/kg (n = 3)**	**0.3 mg/kg (n = 3)**	**1.0 mg/kg (n = 6)**	**3.0 mg/kg (n = 6)**	**Placebo (n = 6)**
Any AE	12 (66.7)	2 (66.7)	1 (33.3)	3 (50.0)	6 (100.0)	2 (33.3)
Treatment-related AE	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)
Severe AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to discontinuation of study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	VIR-2218							
Participants, n (%)	**Overall (n = 49)**	**50 mg (n = 6)**	**100 mg (n = 6)**	**200 mg (n = 6)**	**400 mg (n = 7)**	**600 mg (n = 6)**	**900 mg (n = 6)**	**Placebo (n = 12)**
Any TEAE	28 (57)	4 (67)	3 (50)	4 (67)	5 (71)	3 (50)	3 (50)	6 (50)
Treatment-related TEAE	3 (6)	0 (0)	1 (17)	0 (0)	1 (14)	1 (17)	0 (0)	0 (0)
Grade ≥3 TEAE[†]	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)
Serious TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Treatment-related serious TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TEAE leading to discontinuation of study	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*Safety population.

[†]One participant in the 600-mg cohort experienced a grade 3 nonserious AE of respiratory tract infection (considered not related to study drug).

AE, adverse event; treatment-emergent adverse event.