SAT462

Pharmacokinetics of VIR-2218, an RNAi Therapeutic for the Treatment of HBV Infection, in Healthy Volunteers

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Introduction

- Chronic hepatitis B virus (HBV) infection remains an important global public health problem with significant morbidity and mortality[1,2]
- Continued HBV DNA suppression with nucleoside reverse transcriptase inhibitors (NRTIs) requires lifelong treatment and rarely results in hepatitis B surface antigen (HBsAg) loss
- An RNA interference (RNAi) therapeutic targeting HBV RNAs has the potential to contribute to functional cure with finite treatment by decreasing expression of viral antigens, including tolerogenic HBsAg
- VIR-2218 is an investigational, N-acetylgalactosamine (GalNAc)-conjugated, double-stranded RNAi therapeutic that targets within the HBx gene region shared by all HBV transcripts[3,4]
  - The GalNAc moiety enables targeted delivery of VIR-2218 into the liver via uptake by asialoglycoprotein receptor (ASGPR) expressed primarily on the surface of hepatocytes

Objective

- To characterize plasma and urine pharmacokinetics (PK) of VIR-2218 and primary circulating (N-1)3' antisense metabolite following single dose administration of VIR-2218 in healthy volunteers

Methods

Study Design

VIR-2218

50 mg SC n=8 → 100 mg SC n=8 → 200 mg SC n=8 → 400 mg SC n=8 → 600 mg SC n=8 → 900 mg SC n=8

- First-in-human, Phase 1, randomized, double-blinded, placebo-controlled, single-ascending dose study in healthy volunteers (VIR-2218-1001 [ClinicalTrials.gov identifier NCT03672188])
- 6 cohorts (n=8/cohort) randomized (6:2) to receive single dose VIR-2218 or placebo
- Intensive plasma and urine PK samples were collected for 1 week
  - Plasma: serial samples over 24 h, at 48 h and 1-week post dose
  - Urine:
    - Pooled urine samples over 24 h
    - Single void samples at 48 h and 1-week post dose
- Concentrations of VIR-2218 and (N-1)3' antisense metabolite in plasma and urine measured using validated liquid chromatography–time-of-flight mass spectrometry assays; lower limit of quantitation (LLOQ) 10 ng/mL in plasma and urine
- PK parameters estimated using standard noncompartmental methods in WinNonlin®, V6.3.0 (Certara L.P., Princeton, NJ)

Key Eligibility Criteria

- Age 18 to 55 y
- Body mass index (BMI) 18.0 to ≤32 kg/m^2, creatinine clearance (CL_{cr}) ≥90 mL/min (Cockcroft-Gault)
- No clinically significant electrocardiogram abnormalities or clinically significant chronic medical condition

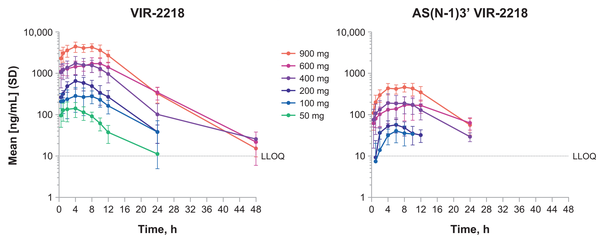
Results

Demographics

	VIR-2218							
	50 mg n=6	100 mg n=6	200 mg n=6	400 mg n=7[a]	600 mg n=6	900 mg n=6	Overall n=37	Placebo n=12
Mean age, y (SD)	25 (3)	23 (4)	27 (4)	24 (4)	29 (6)	33 (10)	27 (6)	27 (7)
Male sex, n (%)	0	2 (33)	3 (50)	0	3 (50)	3 (50)	11 (30)	7 (58)
Mean weight, kg (SD)	62 (12)	63 (7)	75 (5)	65 (10)	72 (8)	72 (12)	68 (10)	76 (10)
Mean BMI, kg/m^2 (SD)	23 (5)	23 (3)	24 (2)	25 (4)	26 (1)	26 (4)	25 (3)	24 (2)
Race, n (%)								
Asian	2 (33)	3 (50)	0	0	2 (33)	1 (17)	8 (22)	1 (8)
White	2 (33)	2 (33)	5 (83)	5 (71)	3 (50)	3 (50)	20 (54)	8 (67)
Native Hawaiian or Other Pacific Islander	1 (17)	1 (17)	0	1 (14)	0	0	3 (8)	2 (17)
Other	1 (17)	0	1 (17)	1 (14)	1 (17)	2 (33)	6 (16)	1 (8)

[a]Includes replacement volunteer. SD, standard deviation.

Plasma Concentration vs Time Profiles for VIR-2218 and AS(N-1)3' VIR-2218 After Single SC Dose in Healthy Volunteers



- VIR-2218 exhibits linear kinetics in plasma after SC injection
  - Median time of maximum concentration (C_{max}; t_{max}) of 4–8 h
  - Not quantifiable in plasma beyond 48 h in any volunteer
- AS(N-1)3' VIR-2218, primary circulating metabolite with equal potency to VIR-2218, is formed by the loss of one nucleotide from the 3' end of the antisense strand of VIR-2218
  - Median t_{max} of 2–10 h
  - Quantifiable only at doses ≥100 mg; not quantifiable in plasma beyond 48 h in any volunteer
  - Concentrations were ~10-fold lower compared with VIR-2218

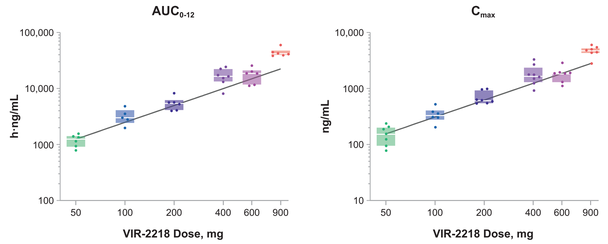
Plasma PK Parameters for VIR-2218 and AS(N-1)3' VIR-2218 After Single SC Dose in Healthy Volunteers

	50 mg n=6	100 mg n=5[a]	200 mg n=6	400 mg n=7[b]	600 mg n=6	900 mg n=6
VIR-2218						
$AUC_{0\text{-}12}$, h·ng/mL	1200 (24.6)	3230 (32.5)	5480 (28.2)	16800 (32.9)	17700 (30.9)	44300 (17.9)
AUC_{last}, h·ng/mL	1260 (21.2)	3700 (31.9)	6570 (17.6)	21400 (25.9)	28000 (27.0)	59000 (15.5)
C_{max}, ng/mL	155 (42.1)	355 (32.9)	711 (29.2)	1940 (41.2)	1830 (33.5)	5014 (12.6)
t_{max}, h	4.00 (1.00, 4.00)	4 (4.00, 6.00)	5.00 (4.00, 6.50)	8.00 (4.00, 8.00)	7.00 (5.50, 10.0)	4.00 (3.50, 8.50)
t_{last}, h	12.0 (12.0, 15.0)	12.0 (12.0, 24.0)	24.0 (21.0, 24.0)	24.0 (24.0, 24.0)	24.0 (24.0, 48.0)	24.0 (24.0, 48.0)
AS(N-1)3' VIR-2218						
$AUC_{0\text{-}12}$, h·ng/mL	BLQ	NC	233 (27.3)	871 (47.2)	726 (52.4)	2030 (23.3)
AUC_{last}, h·ng/mL	BLQ	205 (186)[c]	475 (31.2)	2253 (39.2)	2670 (54.7)	6380 (23.4)
C_{max}, ng/mL	BLQ	26.3 (168)[c]	62.4 (28.2)	234 (52.2)	177 (55.9)	515 (20.6)
t_{max}, h	NC	6.00 (5.00, 6.00)[c]	6.00 (4.00, 6.50)	8.00 (4.00, 10.0)	10.0 (8.00, 10.0)	8.00 (4.00, 10.0)
t_{last}, h	NC	8.00 (6.00, 9.00)[c]	12.0 (10.0, 10.0)	12.0 (12.0, 24.0)	24.0 (21.0, 24.0)	24.0 (24.0, 24.0)
$MR_{C_{max}}$	NC	0.074[c]	0.088	0.121	0.097	0.103
$MR_{AUC_{0\text{-}12}}$	NC	NC	0.094	0.115	0.09	0.11

Time parameters expressed as median (quartile [Q]1, Q3); all other data are mean (% coefficient of variation [% CV]); due to short VIR-2218 half-life ($t_{1/2}$) and PK sampling schedule limitations, terminal phase was not adequately characterized; therefore, apparent clearance and $t_{1/2}$ have not been reported.
[a]Excludes 1 volunteer who received partial dose; [b]Includes PK from replacement volunteer; [c]Measurable in 3/6 volunteers.
AUC, area under curve; $AUC_{0\text{-}12}$, AUC from time 0 to 12 h; AUC_{last}, AUC from time of dosing to last measurable time point; BLQ, below limit of quantitation; MR, metabolite-to-parent ratio; NC, not calculable; t_{last}, last measurable time.

- Interpatient variability of PK parameters was generally low (~30% CV) for VIR-2218
- Plasma PK profile of AS(N-1)3' VIR-2218 mirrored that of VIR-2218
- $AUC_{0\text{-}12}$ and C_{max} of AS(N-1)3' VIR-2218 in plasma were ≤11% of total drug-related material
- Both VIR-2218 and AS(N-1)3' VIR-2218 were eliminated from plasma with a similar short $t_{1/2}$ of ~2–8 h

Plasma VIR-2218 Dose Proportionality From 50 to 900 mg Following Single SC VIR-2218 Administration

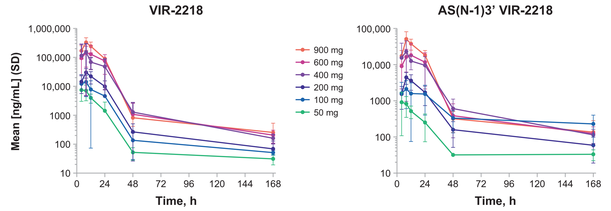


	Dose Range	Fold-Change	$AUC_{0\text{-}12}$	C_{max}
Fold-change Between VIR-2218 Plasma Exposure and Dose	50 – 200 mg	4	4.57	4.59
	200 – 900 mg	4.5	8.08	7.05

Boxes represent median (Q1, Q3); trendline indicates dose proportionality relative to 50 mg dose.

- VIR-2218 plasma exposures ($AUC_{0\text{-}12}$ and C_{max}) appeared to increase in a dose-proportional manner up to 200 mg and exhibited slightly greater than dose-proportional increase at doses above 200 mg
- Similar trend observed with active metabolite AS(N-1)3' VIR-2218 (data not shown)

Urine Concentration vs Time Profiles for VIR-2218 and AS(N-1)3' VIR-2218



- Low concentrations of VIR-2218 and AS(N-1)3' 2218 were detected in urine through the last measured time-point at 1 week postdose in all cohorts
- PK profile of VIR-2218 in urine mirrored that of plasma

Urine PK Parameters for VIR-2218 and AS(N-1)3' VIR-2218

PK Parameter	50 mg n=6	100 mg n=5[a]	200 mg n=6	400 mg n=7[b]	600 mg n=6	900 mg n=6
VIR-2218						
Plasma $AUC_{0\text{-}24}$, h·ng/mL	1360 (15.8)[c]	4080 (29.1)[c]	6920 (26.9)	21100 (26.8)	26700 (29.4)	57400 (15.9)
CL_{ss}/F, L/h	6.21 (16.4)	5.32 (22.4)	6.71 (11.9)	5.24 (17.8)	7.28 (20.2)	7.22 (19.1)
Urine $fe_{0\text{-}24}$, %	17.0 (18.8)	18.3 (34.0)	23.2 (18.7)	27.6 (26.0)	32.3 (36.1)	46.1 (20.6)
AS(N-1)3' VIR-2218						
Urine $fe_{0\text{-}24}$, %	1.95 (24.8)	4.20 (54.8)	3.31 (20.1)	4.62 (26.5)	4.15 (55.6)	6.96 (21.1)

All PK parameters expressed as mean (% CV). [a]Excludes 1 volunteer who received partial dose; [b]Includes PK from replacement volunteer; [c]$AUC_{0\text{-}24}$ is extrapolated.
$AUC_{0\text{-}24}$, AUC from time 0 to 24 h; CL_{ss}/F, apparent renal clearance; $fe_{0\text{-}24}$, fraction excreted from time 0 to 24 h.

- Approximately 17–46% and 2–7% of the administered dose (50–900 mg) was excreted in urine as unchanged VIR-2218 and AS(N-1)3' VIR-2218, respectively, over the first 24-h period
- Fraction of VIR-2218 excreted into urine over 24 h postdose increased with dose level
- The renal clearance of VIR-2218 approached glomerular filtration rate

Discussion & Conclusions

Plasma and urine PK support further development of VIR-2218

- Plasma PK:
  - VIR-2218 was absorbed after SC administration with median t_{max} of 4–8 h, and was not detectable beyond 48 h
  - VIR-2218 converted to metabolite AS(N-1)3' VIR-2218; metabolite concentrations ~10-fold lower than parent
  - Short plasma half-life of VIR-2218 and AS(N-1)3' VIR-2218 is attributable to the rapid and specific ASGPR-mediated uptake into the liver
  - VIR-2218 plasma exposures increased dose-proportionally up to 200 mg and slightly greater than dose-proportionally above 200 mg
    - Indicative of transient saturation of ASGPR-mediated hepatic uptake of VIR-2218 resulting in higher circulating concentrations at higher doses[5]
- Urine PK:
  - In all cohorts, VIR-2218 and AS(N-1)3' VIR-2218 were detectable in urine through the last measured time-point, 1 week postdose
  - Fraction of unchanged VIR-2218 excreted into urine over 24 h postdose increased with dose
    - Likely due to transient saturation of ASGPR[5]
    - Mirrors greater than dose-proportional increases in plasma VIR-2218
  - The renal clearance of VIR-2218 approached glomerular filtration rate
- **Evaluation in patients with chronic HBV infection is ongoing**

References: 1. EASL 2017 HBV Clinical Practice Guidelines. J Hepatol. 2017;67:370-98; **2.** World Health Organization. Hepatitis B. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b; **3.** Janas MM, et al. Nat Commun. 2018;9:723; **4.** Schlegel MK, et al. J Am Chem Soc 2017;139:8537-46; **5.** Agarwal S, et al. Clin Pharmacol Ther 2020;108:63-72.
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