

BACKGROUND AND AIMS

- Pevifoscorvir sodium (ALG-000184) is a prodrug of ALG-001075, a potent HBV capsid assembly modulator-empty (CAM-E)
- ALG-001075 inhibits viral replication and cccDNA establishment *in vitro* by inducing rapid assembly of core viral proteins to small, morphologically normal spherical capsids
- The multipart Phase 1 study ALG-000184-201 (NCT04536337) demonstrated that PEVY 300 mg oral once daily (QD) ± entecavir (ETV) for ≤ 96 weeks was well tolerated and demonstrated potent antiviral activity, achieving profound suppression of HBV DNA and RNA, along with additional declines in HBV antigens in treatment-naïve/currently-not-treated (TN/CNT) subjects with chronic hepatitis B virus (HBV) infection
- This analysis aimed to provide a robust characterization of the dose–exposure relationship and identify key covariates influencing ALG-001075 pharmacokinetics to provide rationale for safe and effective dosing for pevifoscorvir sodium and inform Phase 2 dose selection

METHODS

- PK data were collected from Study ALG-000184-201 across five parts in healthy subjects (n=47) and subjects with chronic HBV infection (n= 115) following single or multiple once-daily or twice-daily dosing of 10-300 mg PEVY or placebo followed by PEVY
 - Part 1: SAD (40-500 mg) in healthy volunteers (HV)
 - Part 2: MAD (150, 250 mg QD x 7d) in HV
 - Part 3: 28-day (10-300 mg QD) in chronic HBV infection
 - Part 4: Combo with ETV (100, 300 mg QD) + monotherapy (300 mg QD) in chronic HBV infection for up to 96 weeks
 - Part 5: BID dosing (200 mg) with ETV in chronic HBV infection for up to 40 weeks
- The final analysis dataset included 3158 evaluable PK samples from 162 subjects. Majority of the population was Asian (71.0%) and male (80.9%), with a median age of 36 yr and weight (WT) of 66.5 kg. Among 115 Asian subjects, 76 subjects were of Chinese origin. Of 75 subjects (46.3%) who were HBeAg+, 73 subjects were also Asian (Table 1).
- Plasma concentration of ALG-001075 was quantified using a validated LC-MS/MS assay with a lower limit of quantification (LLOQ) of 1 ng/mL.
- A nonlinear mixed-effects model was developed and implemented with NONMEM (v7.5.1) to characterize the population PK:
 - Two-compartment model with first-order absorption (KA), lag time (ALAG), and dose-dependent duration (D1). IIV on CL, V2, KA, D1; log-additive residual error
 - Covariates tested included body weight (WT), age, sex, race (Asian vs non-Asian), Chinese origin, albumin (ALB), ALP, AST, ALT, bilirubin, CrCl, eGFR, HBeAg status
 - Covariate search was conducted using a stepwise forward addition (p<0.05) + backward elimination process using likelihood ratio test
 - Model selection was based on goodness-of-fit diagnostic plots, precision and plausibility of parameter estimates and prediction-corrected VPC (pcVPC)
- A schematic representation of the final popPK model structure is shown in Figure 1

Figure 1: PopPK Model Schematic

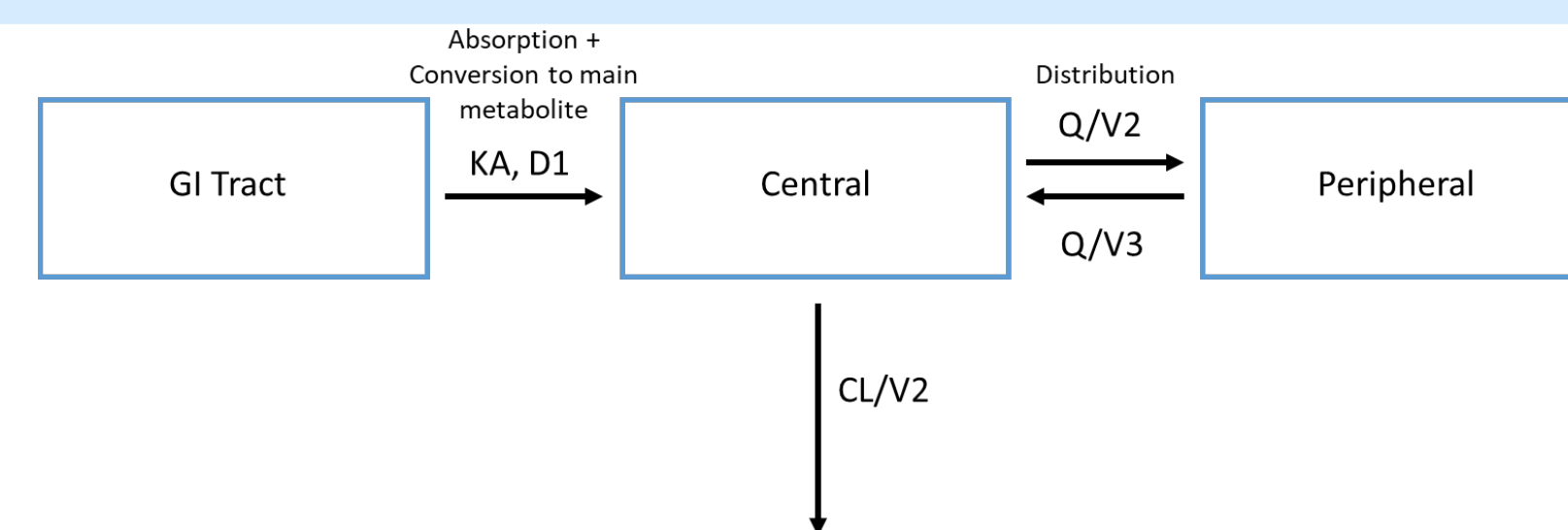


Table 1: Summary of Baseline Demographics and Lab Values in the PopPK Dataset

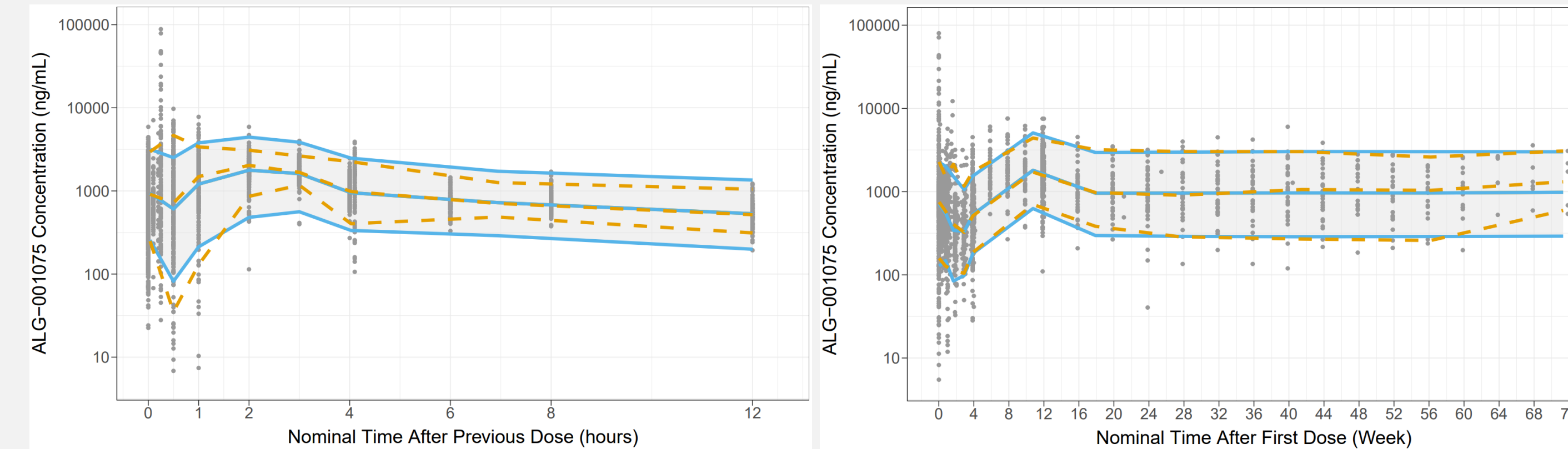
Covariate	Part 1 SAD (N=31)	Part 2 MAD (N=16)	Part 3 28-d MD (N=59)	Part 4 Combo w/ETV and Mono in CHB (N=45)	Part 5 BID Combo w/ETV in CHB (N=11)	Overall (N=162)
Age (yr)	28	33	37	38	37	36
Median [Min, Max]	[18, 51]	[21, 54]	[20, 57]	[22, 66]	[25, 57]	[18, 66]
Sex						
Male	31 (100.0%)	14 (87.5%)	30 (50.8%)	45 (100.0%)	11 (100.0%)	131 (80.9%)
Female	0 (0.0%)	2 (12.5%)	29 (49.2%)	0 (0.0%)	0 (0.0%)	31 (19.1%)
Weight (kg)	76.2	75.8	62.1	64.3	62.0	66.5
Median [Min, Max]	[49.3, 104.4]	[50.0, 91.5]	[42.2, 115.0]	[40.4, 104.2]	[47.3, 85.9]	[40.4, 115.0]
Race						
Asian	16 (51.6%)	11 (68.8%)	42 (71.2%)	36 (80.0%)	10 (90.9%)	115 (71.0%)
Non-Asian	15 (48.4%)	5 (31.2%)	17 (28.8%)	9 (20.0%)	1 (9.1%)	47 (29.0%)
Chinese						
Yes	13 (41.9%)	8 (50.0%)	25 (42.4%)	28 (62.2%)	2 (18.2%)	76 (46.9%)
No	18 (58.1%)	8 (50.0%)	34 (57.6%)	17 (37.8%)	9 (81.8%)	86 (53.1%)
HBeAg Status						
Negative	31 (100.0%)	16 (100.0%)	29 (49.2%)	11 (24.4%)	0 (0.0%)	87 (53.7%)
Positive	0 (0.0%)	0 (0.0%)	30 (50.8%)	34 (75.6%)	11 (100.0%)	75 (46.3%)

Data shown as median [minimum, maximum]

Final PopPK Model Characteristics for ALG-001075:

- A linear, two-compartment with sequential first-order and zero-order oral absorption with a lag time provided best fit to the Phase 1 data. A dose-dependent zero-order duration (D1) was included to capture the increased lag-time in peak concentrations observed with increasing dose
- The between-subject variability on CL, V2, Ka using log-additive intersubject variability was able to capture the data
- The population PK parameters were sufficiently precise (Table 2)
- The pcVPC plots show that simulations from the model were able to recapture the data used to develop the model (Figure 2)

Figure 2: Population PK Model Visual Predictive Check



Notes: Grey dots are individual prediction-corrected values. Yellow dashed lines represent the 5th, 50th (median) and 95th percentiles of the observed ALG-001075 concentrations over time. Solid blue lines represent the 5th, 50th (median) and 95th percentiles of the predictions from 1000 simulations. Left panel shows concentrations after each dose; right panel shows profiles over 72 weeks after the first dose.

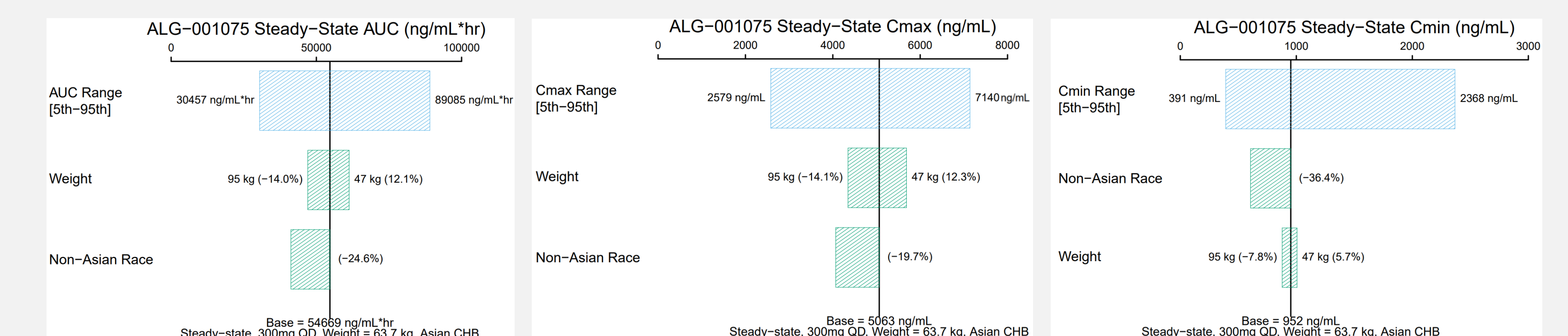
Table 2: Parameter Estimates for the Final ALG-001075 PopPK Model

Model Parameter	Estimate	SE	RSE (%)	CV (%)
Central Clearance (CL, L/hr)	6.56	0.50	7.7	--
Central Volume (V2, L)	2.43	0.88	36.0	--
Dist Clearance (Q, L/hr)	13.5	2.06	15.2	--
Dist Volume (V3, L)	52.9	1.68	3.2	--
Absorption Rate (KA, 1/hr)	0.382	0.052	13.5	--
Zero Order Absorption Duration (D1, hr)	0.915	0.173	19.0	--
Lag Time (ALAG, hr)	0.192	0.003	1.4	--
Dose Effect on D1	0.551	0.116	21.1	--
WT on CL/Q	0.376	0.168	44.8	--
WT on V2/V3	0.648	0.101	15.5	--
Non-Asian on CL	0.282	0.072	25.5	--
Non-Asian on V2	1.021	0.518	50.7	--
CHB on CL	-0.395	0.081	20.5	--
Residual Variance	0.221	0.002	1.1	47
Variance CL	0.08	0.01	15.2	29
Variance V2	3.26	0.96	29.4	181
Variance KA	0.08	0.03	40.2	28
Variance D1	0.96	0.27	28.3	98
Terminal half-life HV (hr)	8.5			
Terminal half-life CHB (hr)	11.3			

Impact of Covariates on ALG-001075 PK

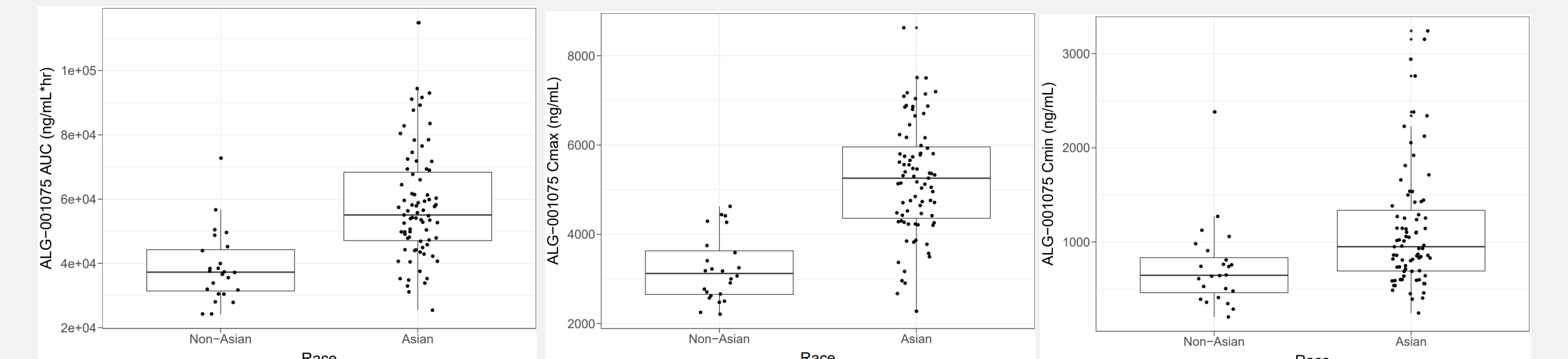
- Final ALG-001075 covariate effects included WT on clearances and volumes, race on CL and V2, and population (CHB vs HV) on CL (Table 2).
- The relative covariate effects on ALG-001075 PK parameters are shown in Figure 3 where covariates were varied one-at-a-time relative to a base case reference subject, who was selected to be Asian with CHB and a median weight of 63.7 kg.
- Simulations indicate approximately 50-60% higher exposure in Asians (Figure 4) and a greater exposure in subjects with lower weight for C_{max}, and less so for AUC and C_{min} (Figure 5).
- Overall, the magnitude of the covariate effects (<30%) is not likely to be clinically meaningful, given the relatively flat exposure–efficacy and safety relationship for ALG-000184 over a large range of doses from 10 mg to 300 mg QD¹.

Figure 3: Effect of Covariates on Steady-State PK Parameters for PEVY 300 mg QD



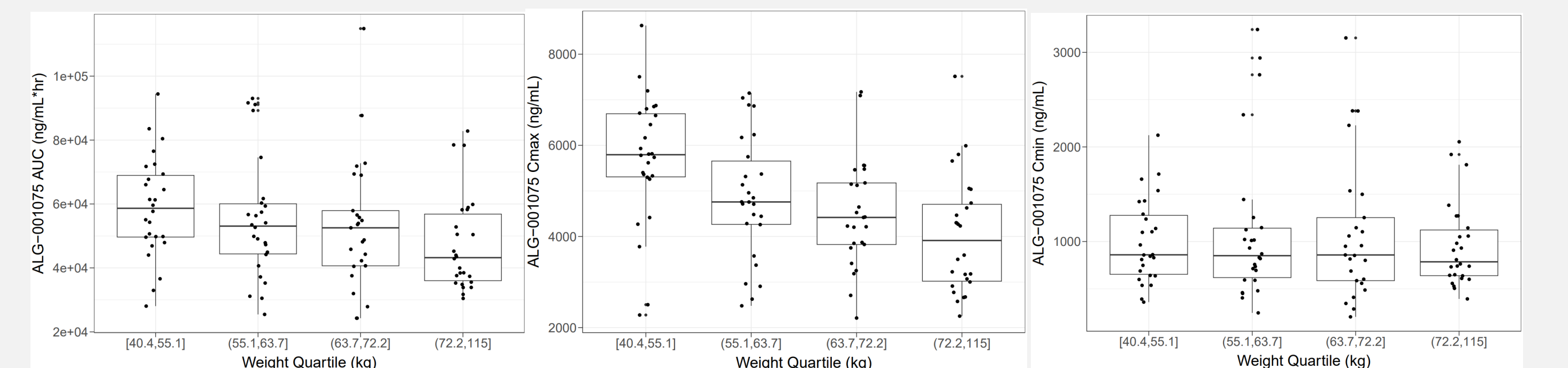
Abbreviations: AUC = area-under-the-curve concentration; CHB = chronic HBV infection; QD = once daily. Notes: 'Base' exposure values were the simulated exposures from the typical Asian CHB subject, with WT of 63.7 kg.

Figure 4: Steady-State ALG-001075 Exposure Boxplots in Asian versus non-Asian CHB Subjects for PEVY 300 mg QD



Abbreviations: AUC = area-under-the-curve; CHB = chronic hepatitis B; Cmax = maximum concentration; Cmin = trough concentration; QD = once daily. Notes: Boxplots indicate the interquartile range and the median; whiskers indicate the furthest point within 1.5 times the interquartile range. Steady-state was simulated after 364 QD doses.

Figure 5: Steady-State ALG-001075 Exposure Boxplots by Weight Quartile in CHB Subjects for PEVY 300 mg QD



The PK of ALG-001075 was described adequately using a two-compartment model with sequential first-order and zero-order oral absorption with a lag time.

- Apparent clearance of ALG-001075 was 6.56 L/hr for the typical Asian HV subject. Apparent central volume of distribution was 2.43 L, and apparent peripheral volume was 52.9 L. Terminal half-life was 8.5 hr.
- Detected covariates included WT on clearances and volumes, non-Asian race on elimination clearance and central volume, and CHB on elimination clearance.
- No effects of age, sex, CrCl, ALP, AST, ALT, ALB, BILI, and HBeAg status on PK parameters were determined.
- The most influential covariates on AUC, C_{max}, and C_{min} in chronic HBV infection were non-Asian race and WT.
- Asians had a 1.5 to 1.6-fold increase in exposure relative to non-Asians, attributed to both race and weight effects on pharmacokinetics. This magnitude of the differences (<60%) is not likely to be clinically meaningful, given the relatively flat exposure–efficacy and safety relationship for ALG-000184 over a large range of doses from 10 mg to 300 mg QD.

REFERENCES

1. Yuen MF, Agarwal K, Jucov A, Hou J, Niu J, Ding Y, Hacetrean A, Liang X, Xu J, Wu M, Le K, Lin T, Blatt L, Chanda S, Fry J, Gane E. ALG-000184 (pevifoscorvir sodium) monotherapy in participants with chronic HBV infection: a phase 1, multicentre, randomised, dose escalation trial. *Lancet Gastroenterol Hepatol.* 2026 Mar;11(3):218-231.