Poster: 32 OR

Population Pharmacokinetics of Pemivibart (VYD222), an Extended–Half-Life Monoclonal Antibody in Development for the Pre-Exposure Prophylaxis of COVID-19

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INTRODUCTION

- Given the emergence of SARS-CoV-2 variants that display resistance to monoclonal antibody (mAb) therapies, the development of next-generation mAbs with activity against circulating variants is needed to protect certain immunocompromised populations
- Pemivibart (VYD222) is a recombinant human monoclonal IgG1λ antibody that targets the SARS-CoV-2 spike protein receptor binding domain, thereby inhibiting virus attachment to the human angiotensin converting enzyme 2 (ACE2) receptor on host cells[1]
- Pemivibart is an engineered version of adintrevimab; substitutions in the Fc region (M435L/N441A) of pemivibart extend its serum half-life[1,2,3]
- Two studies are currently ongoing: a Phase 1 first-in-human single ascending dose study (NCT05791318) and a Phase 3 study investigating pemivibart for pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in immunocompromised participants (Cohort A) and in participants at risk of exposure to SARS-CoV-2 (Cohort B) (NCT06039449 /CANOPY)[4,5]
- The US Food & Drug Administration (FDA) granted pemivibart an emergency use authorization (EUA) in certain adults and adolescents with moderate-to-severe immune compromise in March 2024[1]
- The objective of the current analysis was to develop a population pharmacokinetic (PPK) model that describes the serum concentration-time profile of pemivibart following intravenous (IV) administration

METHODS

Analysis Dataset

- These data represent an interim pemivibart PPK model including a total of 2101 evaluable pemivibart serum concentrations from 641 participants
- Phase 1 first-in-human study (pemivibart 1500 mg, 2500 mg & 4500 mg doses, intravenous (IV) administration, through 6-months):
  - 190 samples from 24 participants (ages: 20-62 years)
- Phase 3 CANOPY study (pemivibart at 4500 mg dose, IV administration, through 3-months):
  - 1911 samples from 617 participants (ages: 18–84 years)

Population Pharmacokinetic (PPK) Model Development

The primary aims of the interim analyses were to:

1) Construct a PPK model for pemivibart using the available data from the Phase 1 study
2) Assess the ability of the Phase 1 PPK model to capture data from the Phase 3 study, and
3) Explore potential for differences in PK parameters based on subject characteristics

- The Phase 1 PPK model was developed using the data from the Phase 1 study only
- The Phase 1 PPK model was fit to the pooled dataset and modifications were made to the model as required to obtain an adequate fit to both the Phase 1 and Phase 3 data
- The resultant model fit to the pooled Phase 1 and 3 data was then used for the covariate assessment

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DISCLOSURES

NB, JJ, MP and YL are employees of and stockholders of Invivyd, Inc.
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RESULTS

Final PPK Model Characteristics for Pemivibart

- A linear, two-compartment model with zero-order IV input and allometric scaling of clearance (CL) and volume of the central compartment (Vc) provided a robust fit to the Phase 1 data
- The interindividual variability (IIV) in CL and Vc was modelled using a joint omega term with a scalar to define the relative extent of IIV for the two parameters. A proportional residual variability (RV) model was found to be most appropriate.
- The population PK parameters were sufficiently precise but moderate shrinkage was observed
- The model produced relatively precise and unbiased fits to the Phase 1 data based on both traditional goodness-of-fit plots and the individual fitted profiles compared to observed data
- The prediction-corrected visual predictive check (PC-VPC) plots show that simulations from the model were able to recapture the data used to develop the model
- Minimal changes were required to the Phase 1 PPK model to obtain a robust fit to the pooled Phase 1 and Phase 3 dataset

Impact of Covariates on the PPK Model

- The model fit to the pooled dataset was used for an interim analysis of the impact of covariates (e.g., immunocompromised status, body weight, age, sex, race, etc.) on pemivibart serum disposition
- No significant relationships were seen based on Phase 3 cohort, which suggests that there were no systematic differences in PK parameters between participants with and without significant immune compromise
- The PK of pemivibart was not affected by age, race, or obesity
- Body weight is related to the variability in PK such that heavier adults are predicted to have lower exposure
- Sex is related to the variability in Vc but the effect is modest (10% lower Vc in females), which suggest that the differences in drug exposure between males in females is most likely due to lower body weight in females
- Population mean CL and Vp are higher in Phase 3 participants. The lack of a mechanistic/physiologic basis for these observations suggests that study design differences may account for the observed differences between Phase 1 and Phase 3 participants.

$$CL\ (L/d) = 0.0829 \times \left(\frac{\text{WTKG}}{84}\right)^{0.641} \times (1 + 0.113)^{Phase3}$$

$$\text{Vc}\ (L) = 2.98 \times \left(\frac{\text{WTKG}}{84}\right)^{0.534} \times (1 - 0.0966)^{SEXF}$$

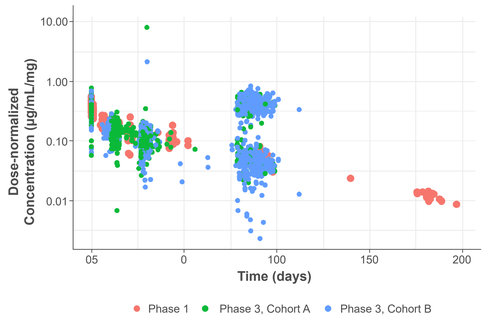
$$CLd\ (L/d) = 0.423$$

$$\text{Vp}\ (L) = 2.15 \times \left(\frac{\text{WTKG}}{84}\right)^{0.677} \times (1 + 0.303)^{Phase3}$$

Pemivibart PPK Model

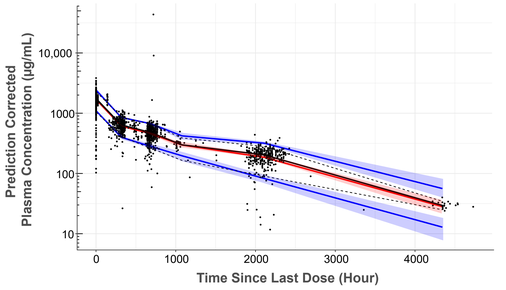
- **Figure 1** shows the observed dose-normalized pemivibart concentrations over time following a single ascending dose of either 1500, 2500 or 4500 mg IV in the Phase 1 study or 4500 mg IV in the Phase 3 study. Peak concentrations following the second pemivibart 4500 mg dose administered at the Month 3 visit among Phase 3 study participants are also displayed.
- The PPK model provided a robust fit to the data based on goodness-of-fit plots and PC-VPC plots
  - The goodness-of-fit plots indicated good precision: $R^2 = 0.86$ for population predictions versus observations and $R^2 = 0.92$ for individual predictions versus observations
  - The PC-VPC plots show good agreement between median simulated serum concentrations based on the population PK model fit to the pooled dataset and the median observed serum concentrations for the pooled dataset (**Figure 2**)
- Summary statistics of post-hoc PK parameter estimates for participants enrolled in the Phase 1 and Phase 3 studies are listed in **Tables 1** and **2**, respectively
  - PK parameter estimates are similar between Phase 3 Cohorts A and B, suggesting that there are no systematic differences in pemivibart PK based on immunocompromised status (**Table 2**)
- The median estimate of serum half-life ($T_{1/2\ beta}$) from the model-based simulations was 45.6 days

Figure 1: Plot of observed pemivibart concentrations over time in the Phase 1 and Phase 3 studies



Peak concentrations from day 77 to 98 represent the 2nd pemivibart dose administered at the Month 3 visit among Phase 3 study participants. Phase 1 study participants received a single dose only.

Figure 2: Prediction-corrected visual predictive check plot for the population PK model fit to the pooled Phase 1 and Phase 3 dataset following a single dose of pemivibart



Circles are observed concentrations, thicker black lines are the median observed concentrations, thinner black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th and 95th percentiles from the simulations.

Table 1: Summary statistics of post hoc PK parameter estimates for participants enrolled in the Phase 1 study

	Cohort 1 (1500 mg) (n=8)	Cohort 2 (2500 mg[a]) (n=8)	Cohort 3 (4500 mg) (n=8)
$AUC_{0\text{-}3\ months}$ (µg•d/mL)	14,300 (13.7) 14,000 (12,500–18,600)	26,100 (11.8) 25,100 (22,600–31,600)	48,500 (7.68) 49,100 (42,800–53,900)
$AUC_{0\text{-}6\ months}$ (µg•d/mL)	17,600 (14.6) 17,200 (15,200–23,300)	32,300 (12.7) 30,900 (27,700–39,800)	60,100 (8.26) 61,000 (52,600–67,300)
$AUC_{0\text{–}\infty}$[b] (µg•d/mL)	18,600 (15.3) 18,100 (16,000–25,100)	34,400 (13.3) 32,800 (29,300–42,700)	64,000 (8.65) 65,000 (55,700–72,000)
C_{max} (µg/mL)	508 (20.2) 490 (416–751)	979 (17.7) 921 (789–1310)	1830 (11.6) 1860 (1520–2160)
C_{day28} (µg/mL)	187 (12.9) 184 (165–240)	341 (11.1) 329 (299–409)	633 (7.23) 641 (563–699)
C_{day90} (µg/mL)	69.9 (16.6) 68.0 (59.7–96.7)	130 (14.5) 124 (109–165)	243 (9.40) 247 (209–276)
CL (L/d)	0.0807 (15.3) 0.0827 (0.0599–0.0935)	0.0718 (13.3) 0.0744 (0.0585–0.0854)	0.0703 (8.65) 0.0693 (0.0625–0.0808)
Vss (L)	4.95 (11.7) 5.03 (3.97–5.58)	4.51 (9.81) 4.62 (3.88–5.14)	4.43 (6.50) 4.39 (4.05–4.93)
$T_{1/2,alpha}$ (d)	1.52 (8.77) 1.55 (1.28–1.65)	1.42 (8.15) 1.46 (1.25–1.57)	1.41 (5.27) 1.40 (1.30–1.53)
$T_{1/2,beta}$ (d)	43.6 (3.89) 43.2 (42.1–47.2)	44.7 (3.65) 44.1 (42.7–47.3)	44.9 (2.28) 45.1 (43.4–46.2)

Note: Summary statistics presented as geometric mean (geometric CV%) and median (min–max).
[a]Two participants from Cohort 2 did not receive the full 2500 mg dose, but the dose received was only 5% lower (2375 mg), so all participants were pooled for Cohort 2. [b]$AUC_{0\text{–}\infty}$ was calculated as dose/CL.

Table 2: Summary statistics of post hoc PK parameter estimates for participants enrolled in the Phase 3 study (4500 mg dose)

	Phase 3, Cohort A (n=303)	Phase 3, Cohort B (n=314)	Phase 3, Pooled (n=617)
$AUC_{0\text{-}3\ months}$[a] (µg•d/mL)	36,700 (45.3) 38,200 (64.6–63,400)	36,500 (35.1) 37,400 (410–58,300)	36,600 (40.4) 37,800 (64.6–63,400)
$AUC_{0\text{-}6\ months}$[b] (µg•d/mL)	79,700 (49.3) 84,300 (79.9–150,000)	79,600 (38.6) 82,700 (503–133,000)	79,600 (44.2) 83,200 (79.9–150,000)
C_{max} (µg/mL)	1760 (43.5) 1820 (2.69–3000)	1740 (32.3) 1780 (17.9–2730)	1750 (38.2) 1800 (2.69–3000)
C_{day28} (µg/mL)	461 (45.7) 478 (0.800–799)	459 (35.4) 467 (5.18–746)	460 (40.7) 475 (0.800–799)
C_{day90}[a] (µg/mL)	176 (48.9) 188 (0.313–359)	174 (39.6) 182 (1.95–316)	175 (44.4) 183 (0.313–359)
CL (L/d)	0.0897 (24.1) 0.0883 (0.0495–0.234)	0.0921 (22.5) 0.0910 (0.0562–0.159)	0.0909 (23.3) 0.0895 (0.0495–0.234)
Vss (L)	5.49 (17.8) 5.46 (3.56–9.38)	5.59 (16.2) 5.63 (3.80–8.70)	5.54 (17.0) 5.53 (3.56–9.38)
$T_{1/2,alpha}$ (d)	2.12 (16.6) 2.11 (1.41–3.48)	2.16 (15.1) 2.18 (1.50–3.26)	2.14 (15.8) 2.14 (1.41–3.48)
$T_{1/2,beta}$ (d)	44.8 (10.3) 45.2 (28.7–59.1)	44.5 (10.6) 44.5 (28.1–64.6)	44.6 (10.4) 44.8 (28.1–64.6)

Note: Summary statistics presented as geometric mean (CV%) and median (min–max).
[a]$AUC_{0\text{-}3months}$ and C_{day90} calculated assuming that the second dose was administered at exactly 90 days (ie, the values do not include additional area/concentration that would be apparent in participants who received their second dose prior to Day 90). [b]The $AUC_{0\text{-}6months}$ estimates include additional area subsequent to the second VYD222 dose and therefore are not directly comparable to those reported for participants enrolled in the Phase 1 study.

KEY FINDINGS

Using serum samples from participants enrolled in Phase 1 and Phase 3 studies, a PPK model was developed that provided a precise and unbiased fit to observed pemivibart concentration-time data

- The PK of pemivibart was not affected by age, race, or obesity
- There was no systematic difference in PK between participants with and without significant immune compromise
- The estimated half-life of pemivibart is approximately 45 days

CONCLUSIONS

- When fit to the pooled Phase 1 and 3 data, the pemivibart PPK model provided a robust fit to the data from CANOPY Cohort A and B with reliable estimation of both population and individual PK parameters in participants
- Model-based simulations captured the central tendency and variability in observed concentrations adequately
- The PPK model will be useful for future PK-pharmacodynamic analyses

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