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Pharmacokinetics and Serum Virus Neutralizing Antibody Titers Following the Second Dose of Pemivibart in the Phase 3 CANOPY Trial

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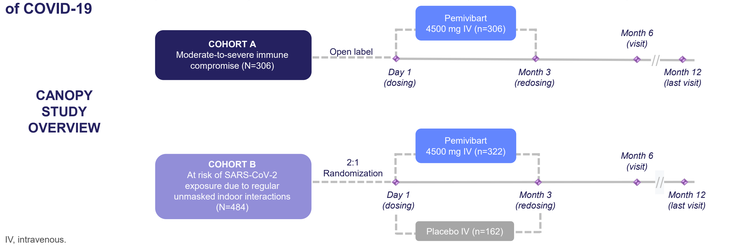
INTRODUCTION

- Given the emergence of SARS-CoV-2 variants that had displayed resistance to monoclonal antibody (mAb) therapies, the development of next-generation mAbs with activity against circulating variants was 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 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[1–3]
- Two clinical studies have evaluated pemivibart
  - A completed phase 1 first-in-human single ascending-dose study (NCT05791318)[4]
  - An ongoing phase 3 study investigating pemivibart for pre-exposure prophylaxis of COVID-19 in immunocompromised participants (Cohort A) and in participants at risk of exposure to SARS-CoV-2 (Cohort B; CANOPY; NCT06039449)[5]
- The US Food and Drug Administration issued pemivibart an emergency use authorization for pre-exposure prophylaxis of COVID-19 in certain adults and adolescents with moderate-to-severe immune compromise in March 2024[1]
- Here, we describe calculated serum virus neutralizing antibody (sVNA) titers for participants in Cohorts A and B following the first and second dose of pemivibart and provide further estimates from a population pharmacokinetic (PPK) model constructed with available data from the phase 1 first-in-human study and the phase 3 CANOPY study

METHODS

Figure 1. CANOPY, a phase 3 study to evaluate efficacy and safety of pemivibart for the prevention of COVID-19



IV, intravenous.

CANOPY trial design

- The CANOPY trial design is illustrated in **Figure 1**
- Participants received an initial dose of study drug administered via IV infusion on Day 1 followed by a second IV dose approximately 3 months later (ie, Month 3)
- Evaluation of the neutralizing activity of pemivibart against relevant SARS-CoV-2 variants over time was conducted
  - Serum samples were collected for PK analysis on Day 1 (end of infusion), Day 14, and Day 28 and at Month 3 prior to and after the second pemivibart dose, and at Months 6 and 12
  - Calculated sVNA titers are based on the serum concentration of pemivibart divided by the half maximal inhibitory concentration (IC_{50}; based on pseudovirus assay) of pemivibart against relevant SARS-CoV-2 variants
- The incidence of reverse transcription polymerase chain reaction (RT-PCR)–confirmed symptomatic COVID-19, COVID-19–related hospitalizations, and all-cause mortality were also evaluated

PPK model

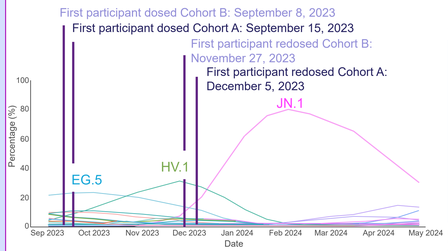
- A PPK model was developed using combined data from pemivibart phase 1 and phase 3 studies; full details of model development were presented previously[6]
- This model was updated with all available phase 1 and phase 3 PK and participant characteristic data
- This dataset contains a total of 3143 concentration records from 627 participants including 2940 concentration records from 604 participants from the phase 3 study

RESULTS

CANOPY

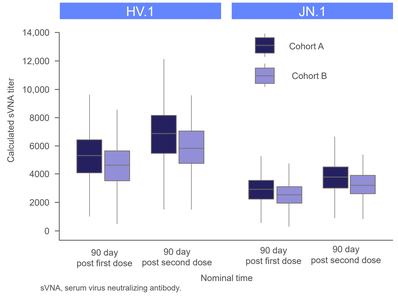
- **Cohort A**: 306 pemivibart-treated participants; 298 (97%) received a full initial dose, and 294 (96%) received a full second dose
  Cohort B: 317 pemivibart-treated participants; 314 (99%) received a full initial dose, and 294 (93%) received a full second dose
- The predominant variants circulating during the conduct of the phase 3 CANOPY study were SARS-CoV-2 Omicron sublineages HV.1 (mean IC_{50}=41.2 ng/mL) and JN.1 (mean IC_{50}=74.6 ng/mL) as displayed in **Figure 2**
- At completion of the second (ie, Month 3) dose of pemivibart, the calculated sVNA geometric mean titers to the HV.1 and JN.1 variants in Cohort A and Cohort B participants were 20% and 25% higher, respectively, than the corresponding values following the initial pemivibart dose
- Calculated sVNA titers 90 days post administration of the first and second dose of pemivibart are listed in **Table 1** and **Figure 3**
- Corresponding clinical efficacy results from the CANOPY trial are displayed in **Tables 2** and **3**, respectively
- These exploratory analyses showed an 84% relative risk reduction of RT-PCR–confirmed COVID-19 through 180 days in Cohort B with pemivibart treatment vs placebo and a low rate of RT-PCR–confirmed COVID-19 (3.7%) in pemivibart-treated participants in Cohort A

Figure 2. SARS-CoV-2 predominant variants circulating during the conduct of the phase 3 CANOPY trial



CDC COVID Data Tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

Figure 3. Calculated sVNA titers against predominant variants circulating during the conduct of the phase 3 CANOPY trial



sVNA, serum virus neutralizing antibody.

Table 1. Calculated sVNA titers 90 days post administration of the first and second dose of pemivibart

	CANOPY	HV.1	JN.1
Day 90 (ie, post dose 1; pre dose 2)	Cohort A (n=278)	5364	2963
	Cohort B (n=287)	4660	2574
Day 180 (ie, post dose 2)	Cohort A (n=278)	6905	3814
	Cohort B (n=273)	5752	3177

Median value listed. PK full analysis set includes all participants who received a full dose of study drug at the initial dosing and had a quantifiable serum concentration result at Day 28.
sVNA, serum virus neutralizing antibody.

Table 2. Incidence of RT-PCR–confirmed symptomatic COVID-19, COVID-19–related hospitalizations, and all-cause mortality among adults with significant immune compromise (Cohort A)

n (%)	Outcomes	Through Day 90	Through Day 180
Pemivibart (n=298)	Composite RT-PCR–confirmed COVID-19	3 (1.0)	11 (3.7)
	Symptomatic COVID-19	3 (1.0)	9 (3.0)
	COVID-19–related hospitalizations	0	0
	All-cause mortality	0	2 (0.6)[a]

Full analysis set includes all participants who received a full dose of study drug at the initial dosing.
[a]Two all-cause deaths (1 due to an unknown cause and 1 due to suicide).
RT-PCR, reverse transcription polymerase chain reaction.

Table 3. Incidence of RT-PCR–confirmed symptomatic COVID-19, COVID-19–related hospitalizations, and all-cause mortality among adults who do not have significant immune compromise (Cohort B)

n (%)	Through Day 90	Through Day 180
Pemivibart (n=317)	1 (0.3)	6 (1.9)
Placebo (n=160)	8 (5.0)	19 (11.9)
RRR	94%	84%
Nominal *P* value	0.0087	0.000061

No COVID-19–related hospitalizations or deaths were observed in Cohort B through Day 180. Modified full analysis set includes all randomized participants without current SARS-CoV-2 infection at baseline as measured by central lab RT-PCR.
RRR, relative risk reduction; RT-PCR, reverse transcription polymerase chain reaction.

Pemivibart population PK model

- A linear, two-compartment model with zero-order IV input and allometric scaling of clearance (CL), volume of the central compartment (Vc), and volume of the peripheral compartment (Vp) provided a robust fit to the data
- No significant relationships were seen between the phase 3 cohorts (ie, Cohort A vs Cohort B), suggesting no systematic differences in PK between participants with and without significant immune compromise
- The PK of pemivibart was not affected by age, race, or obesity
- Summary statistics of post hoc pemivibart PK parameter estimates for participants enrolled in the phase 3 study are listed in **Table 4**
- The median estimate of terminal half-life ($T_{1/2}$ beta) in participants enrolled in the phase 3 study is 49.0 days

Table 4. Summary statistics of post hoc pemivibart PK parameter estimates for participants enrolled in the phase 3 CANOPY study

	Phase 3, Cohort A (n=294)	Phase 3, Cohort B (n=309)	Phase 3, pooled (n=603)
$AUC_{0–3\ months}$,[a] µg•d/mL	41,800 (22.3) 41,900 (18,800–99,000)	39,300 (22.2) 39,100 (16,700–95,900)	40,500 (22.5) 40,700 (16,700–99,000)
C_{max}, µg/mL	1850 (19.2) 1850 (1100–3080)	1800 (17.5) 1800 (1050–2910)	1820 (18.4) 1820 (1050–3080)
C_{Day28}, µg/mL	482 (23.9) 484 (196–1110)	455 (23.7) 456 (163–1070)	468 (23.9) 472 (163–1110)
C_{Day90}[a], µg/mL	204 (35.0) 211 (19.0–1848)	174 (43.5) 187 (16.6–830)	188 (40.4) 197 (16.6–848)
CL, L/day	0.0816 (29.5) 0.0811 (0.0156–0.255)	0.0908 (31.7) 0.0892 (0.0154–0.290)	0.0862 (31.1) 0.0852 (0.0154–0.290)
Vss, L	5.62 (18.6) 5.59 (3.54–9.40)	5.62 (16.0) 5.65 (3.69–8.95)	5.62 (17.3) 5.63 (3.54–9.40)
$T_{1/2,alpha}$, day	2.60 (17.1) 2.57 (1.71–4.17)	2.58 (14.9) 2.58 (1.76–4.01)	2.59 (16.0) 2.58 (1.71–4.17)
$T_{1/2,beta}$, day	51.0 (19.2) 51.8 (18.4–169)	46.1 (23.9) 47.1 (18.5–190)	48.4 (22.3) 49.0 (18.4–190)

Summary statistics presented as geometric mean (CV%) and median (min–max).
[a]$AUC_{0–3months}$ 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).
$AUC_{0–3\ months}$, area under the concentration time curve from 0 to 3 months; CL, clearance; C_{Day28}, maximum plasma concentration at Day 28; C_{Day90}, maximum plasma concentration at Day 90; C_{max}, maximum plasma concentration; PK, pharmacokinetic; $T_{1/2}$, half-life; Vss, volume of distribution under steady state conditions.

KEY FINDINGS

The calculated sVNA titers of pemivibart against SARS-CoV-2 Omicron sublineages HV.1 and JN.1 were approximately 20%–25% higher following completion of the second pemivibart infusion relative to the corresponding values observed after the initial dose

Observed titer values against representative SARS-CoV-2 variants following a pemivibart 3-month dosing interval corresponded to a comparative clinical efficacy of 84% RRR in RT-PCR–confirmed symptomatic COVID-19 relative to placebo in Cohort B through 6 months

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

CONCLUSIONS

A second dose of pemivibart 4500 mg IV administered at Month 3 sustained calculated sVNA titers expected by PPK modeling in both Cohort A (immunocompromised) and Cohort B (immune competent) and corresponded well with clinical efficacy in Cohorts A and B through 6 months

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DISCLOSURES

AH, YL, DG, CK, and PH are employees of Invivyd, Inc, and may own stock. KM and MP were employees at the time the study was conducted. LH is a paid consultant of Invivyd, Inc.
Pemivibart is an investigational product candidate that is not approved for use in any country. The safety and efficacy of pemivibart have not been established.

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