Poster # 33 OR

Six-Month Interim Analysis from a Phase 1 First-in-Human Study of Pemivibart: an Extended Half-Life Monoclonal Antibody (mAb) Authorized for Pre-Exposure Prophylaxis for COVID-19 in Certain Adults and Adolescents with Moderate to Severe Immune Compromise

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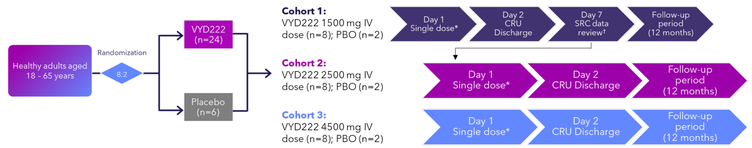
INTRODUCTION

- 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 a re-engineered version of adintrevimab; substitutions in the Fc region (M435L/N441A) of pemivibart extend its serum half-life[1,2,3]
- The US Food & Drug Administration (FDA) granted pemivibart an emergency use authorization (EUA) for pre-exposure prophylaxis of COVID-19 in certain adults and adolescents with moderate-to-severe immune compromise in March 2024[1]
- Here, we report six-month interim analysis from this Phase 1, single-ascending dose, first-in-human study of pemivibart administered via intravenous (IV) push in healthy adults (NCT05791318)[4]

METHODS

Figure 1. Study Design



VYD222, pemivibart; CRU, clinical research unit; PBO, placebo; SRC, safety review committee.
*Two sentinel participants (1 receiving pemivibart and 1 receiving placebo) were dosed and monitored for 48 hours. If no safety concerns observed at 48 hours post-dosing of sentinel participants, then dosing continued to include rest of participants in cohort.
†SRC approval following review of available safety data from Cohort 1 through Day 7 occurred prior to dose escalation in subsequent cohorts.

Trial Design and Participants

- Phase 1, randomized, triple-blind, placebo-controlled, single ascending dose study
- Eligible participants were aged 18 – 65 years old, in good health, with BMI between 18.5 – 32 kg/m^2, tested negative for current SARS-CoV-2 infection by rapid antigen test on the day prior to dosing, and seropositive to nucleocapsid (N) and/or spike (S) SARS-CoV-2 antigens at screening
- Participants (N=30) were randomized 8:2 (n=10 per cohort) to receive either pemivibart (VYD222) or placebo (normal saline) delivered by slow IV push over 3 to 5 minutes **(Figure 1)**
  - Cohort 1: Pemivibart 1500 mg IV push
  - Cohort 2: Pemivibart 2500 mg IV push
  - Cohort 3: Pemivibart 4500 mg IV push
- Cohort 1 was dosed first (starting with two sentinel participants [n=1 pemivibart 1500 mg and n=1 placebo]). Dosing continued to include the rest of participants in Cohort 1 as no safety concerns were observed at 48 hours post-dosing in sentinel participants (safety data reviewed by Investigator).
  - Same process of dosing two sentinel participants and monitoring for 48 hours before dosing remainder of the cohort was completed for Cohorts 2 and 3
- A Safety Review Committee reviewed available blinded safety and tolerability data through the Day 7 visit from Cohort 1; upon data review the SRC recommended proceeding with the study
- Participants stayed overnight at the clinical research unit (CRU) from the day prior to dosing until 24 hours post-dosing (Day 2)
- In-person post-dose visits: Days 7, 14, 21, 45, Months 3, 6 and 12
  - Phone contact for safety monitoring: Days 3 and 4 and at Month 4, 5, 8 and 10

Endpoints and Assessment

- **Safety & Tolerability:** The primary objective is evaluation of the safety and tolerability of multiple dose levels of pemivibart after a single IV administration in healthy participants, as measured by incidence of treatment-emergent adverse events (TEAEs) including serious adverse events (SAEs)
- **Pharmacokinetic Assessment:** Secondary objective to evaluate pharmacokinetic parameters of pemivibart
  - Collection of samples for measurement of serum concentrations of pemivibart: pre- and post-dose administration on Day 1, 24 hours post dose, and Days 7, 14, 21, 45, Months 3, 6, and 12
  - Serum PK parameters were calculated using noncompartmental analysis methods
- **Measured vs Calculated sVNA:** An exploratory objective to evaluate neutralizing activity of pemivibart against relevant SARS-CoV-2 variants over time
  - Serum virus neutralizing antibody (sVNA) titers were measured using a pseudovirus neutralization assay and expressed as 1/dilution; clinical samples for measured sVNA testing were collected on Days 1 (pre-dose), 7, 14, 21, 45, and Months 3, 6, and 12
  - Calculated sVNA titers are based on the serum concentration of pemivibart divided by the IC_{50} value of pemivibart against a relevant SARS-CoV-2 variant
  - Measured sVNA titer is the assay-determined sVNA titer against a relevant SARS-CoV-2 variant from clinical samples
  - To investigate the relationship between measured and calculated sVNA titers, an analysis was performed to understand the correlation between the two titer levels
  - Pearson correlation coefficient, a parametric measure of the linear relationship, was calculated

RESULTS

- This study is ongoing, and data are presented in a blinded manner

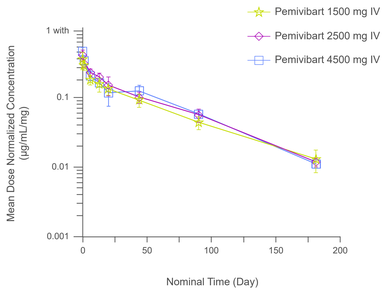
Participants

- Overall, 30 participants were randomized to receive either pemivibart (n=24) or placebo (n=6)
- Two participants in Cohort 2 received 93% of the full dose (18.55 mL instead of 20 mL) due to an administration error
- Full data were available through the 6-month timepoint for 29 (96.7%) participants
- The median age was 32.5 years; 13.3% of participants were 55 years or older; most participants were white (83.3%)
- Mean BMI was 25.78 kg/m^2 across all participants
- At baseline, all participants were negative for SARS-CoV-2 per RT-PCR testing
- At baseline, all participants had detectable antibodies to SARS-CoV-2 S protein; antibodies to SARS-CoV-2 N protein were detected in 80% of the study population

Safety and Tolerability

- Study drug (pemivibart or placebo) was generally safe and well-tolerated in healthy adults at doses up to 4500 mg
- There were no deaths, SAEs, or AEs leading to permanent study drug discontinuation
- Overall, TEAEs were reported in 25/30 (83.3%) of participants:
  - All TEAEs were mild or moderate in severity, with the exception of one participant with two Grade 3 (severe) AEs of exercise induced elevations in creatine kinase and transaminase
  - There were no hypersensitivity reactions
  - A total of 4 participants (2 each from Cohort 2 and 3, respectively) experienced mild, self-limited, infusion-related reactions (chest pressure, flushing, presyncope) that were considered to be study drug-related
    - The reactions started approximately 2 minutes into the 3 to 5 minute slow IV push infusion and resolved without treatment within a few seconds to 5 minutes
    - The infusion was briefly interrupted for 2 participants (one each from Cohort 2 & 3) until the reactions resolved and then resumed without further signs or symptoms
  - The infusion-related reactions observed are consistent with reactions observed with previously authorized SARS-CoV-2 mAbs administered intravenously
  - All other AEs were considered to be unrelated to the study drug (placebo or pemivibart)

Figure 2: Mean ± Standard Deviation Serum Pemivibart Dose-Normalized Concentration-Time Profile



Pharmacokinetic Assessment

- All participants receiving pemivibart demonstrated observable serum concentrations following IV administration of single doses of 1500 mg, 2500 mg, or 4500 mg
- Preliminary noncompartmental analysis (through Month 6) of serum concentration data are shown in **Table 1**
- Pemivibart demonstrated linear PK with apparent dose-proportional exposure and extended serum half-life (mean 46, 44, and 50 days in Cohort 1, 2, and 3, respectively; **Figure 2**)

Table 1. Preliminary Noncompartmental Analysis of Pharmacokinetic Parameter Estimates of Pemivibart (Mean ± SD)

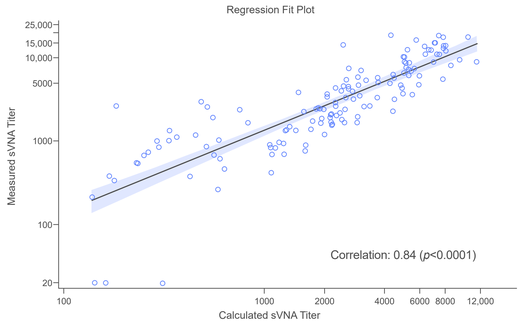
	Pemivibart		
PK Parameter	**1500mg IV**	**2500mg IV**	**4500mg IV**
C_{max} (µg/mL)	534.6 ± 135.5	1002.5 ± 182.5	2077.5 ± 246.4
$AUC_{0\text{-}181.5}$ (Day*µg/mL)	17203 ± 3081	33611 ± 5727	61422 ± 8057
$AUC_{0\text{-}181.5}$/Dose (Day*µg/mL/mg)	11.5 ± 2.1	13.6 ± 2.3	13.6 ± 1.8
$t_{½}$ (Day)	45.8 ± 4.8	44.3 ± 2.1	49.9 ± 27.4

Mean half-life for Cohort 3 should be interpreted with caution. The NCA-calculated half-life may be unreliable in the terminal slope calculation for one subject (117 days). Half-life for the remaining subjects in Cohort 3 was similar to that of Cohort 1 and 2.

Measured vs Calculated sVNA

- Measured sVNA titers against SARS-CoV-2 XBB.1.5, B.1.617.2 (Delta) and BA.4/5 variants were assessed in serum samples using a pseudovirus neutralization assay
- Measured sVNA titers were strongly correlated with calculated sVNA titers for each variant tested, with Pearson correlation coefficients of 0.84, 0.85, and 0.77 (all $p<0.0001$) against XBB.1.5, B.1.617.2 (Delta) and BA.4/5, respectively
- The correlation plot for XBB.1.5 is displayed in **Figure 3**

Figure 3. Measured sVNA vs. Calculated sVNA for XBB.1.5



KEY FINDINGS

Mild infusion-related reactions were reported in 4 participants, consistent with reactions observed with previously authorized SARS-CoV-2 mAbs that were administered intravenously. No other study drug-related AEs were reported and no AEs leading to discontinuation or SAEs were reported

Pemivibart demonstrated linear PK with apparent dose-proportional exposure and extended serum half-life (mean 46, 44, and 50 days in Cohort 1, 2, and 3, respectively)

Comparison of preliminary data on measured versus calculated sVNA titers found a linear correlation for all variants tested

CONCLUSIONS

- **In this Phase 1 study of healthy adults no SAEs or adverse events leading to discontinuation were reported with pemivibart administered by slow IV push at doses up to 4500 mg**
- **Measured sVNA titers correlated well with calculated sVNA titers across all variants evaluated, supporting the use of calculated sVNA titers as a biomarker for immunobridging studies to support further development**

REFERENCES

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2. Ison MG, et al. Open Forum Infect Dis. 2023 May 24;10(6):ofad279.
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DISCLOSURES

KM, DG, YL, NB, EC, AC, KN, and AH are employees of Invivyd, Inc. and may own stock. AD, LM, and AR are paid consultants 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.

Acknowledgments

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