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Results from a Phase 1 First-in-human Study of Pemivibart: an Extended–half-life Monoclonal Antibody

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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]
- 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 immunocompromise in March 2024[1]
- Here, we report data from the completed phase 1, single ascending-dose, first-in-human study of pemivibart administered via slow intravenous (IV) push in healthy adults (NCT05791318)[4]

METHODS

Figure 1. Study design

[a]Two sentinel participants (1 receiving pemivibart and 1 receiving placebo) were dosed and monitored for 48 hours. If no safety concerns were observed at 48 hours post-dosing of sentinel participants, then dosing continued to include the rest of participants in the cohort. [b]SRC approval following review of available safety data from Cohort 1 through Day 7 occurred prior to dose escalation in subsequent cohorts.
IV, intravenous; PBO, placebo; SRC, safety review committee.

Trial design and participants

- Phase 1, randomized, triple-blind, placebo-controlled, single ascending-dose study
- Eligible participants were aged 18–65 years, in good health, with body mass index between 18.5 and 32 kg/m^2, tested negative for SARS-CoV-2 infection by rapid antigen test on the day prior to dosing, and were 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 2 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 2 sentinel participants and monitoring for 48 hours was completed before dosing remainder of Cohorts 2 and 3
- A safety review committee reviewed available blinded safety and tolerability data from Cohort 1 through the Day 7 visit and recommended proceeding with dosing in the next 2 cohorts
- Participants remained in the clinical research unit from the day prior to dosing until 24 hours post dosing (Day 2)
- In-person post-dose visits: Days 7, 14, 21, and 45 and Months 3, 6, and 12
  - Phone contact for safety monitoring: Days 3 and 4 and Months 4, 5, 8, and 10

Endpoints and assessment

- **Safety and tolerability:** The primary objective was 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 (PK) assessment:** Secondary objective to evaluate PK parameters of pemivibart
  - Collection of samples for measurement of serum concentrations of pemivibart: pre- and post-dose on Day 1, 24 hours post-dose, Days 7, 14, 21, and 45, and Months 3, 6, and 12
  - Serum PK parameters were calculated using noncompartmental analysis methods
- **Immunogenicity:** Secondary objective to evaluate the development of antidrug antibodies (ADAs) to pemivibart
- **Measured and calculated serum virus neutralizing antibody (sVNA) titers:** Exploratory objective to evaluate neutralizing activity of pemivibart against relevant SARS-CoV-2 variants over time
  - Measured sVNA titers were determined against relevant SARS-CoV-2 variants, including XBB.1.5, B.1.617.2 (Delta), and BA.4/5, 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, and 45 and Months 3, 6, and 12
    - Measured sVNA data from participants with a SARS-CoV-2 infection or vaccination event during the study were excluded from summary analyses at timepoints following the event
  - Calculated sVNA titers are based on the serum concentration of pemivibart at a specified timepoint divided by the half maximal inhibitory concentration (IC_{50}) value of pemivibart against a relevant SARS-CoV-2 variant
  - To investigate the relationship between measured and calculated sVNA titers, an analysis of the 2 titer levels using all data (through Month 12) was performed using Pearson correlation coefficient, a parametric measure of the linear relationship

RESULTS

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) because of an administration error
- Twenty-nine (96.7%) participants completed the study; 1 participant in Cohort 3 withdrew from the study on Day 180
- The median age was 32.5 years; 13.3% of participants were aged 55 years or older; 53.3% of participants were male; most participants were White (83.3%); mean body mass index was 25.78 kg/m^2 across all participants
- At baseline, all participants were negative for SARS-CoV-2 per reverse transcription polymerase chain reaction 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 participants

Safety and tolerability

- Study drug (pemivibart or placebo) was generally safe and well tolerated in healthy adults
- There were no deaths, SAEs, or AEs leading to study drug discontinuation
- Overall, TEAEs were reported in 25/30 (83.3%) of participants:
  - All TEAEs were mild or moderate in severity, apart from 1 placebo-treated participant with 1 grade 4 (potentially life-threatening) AE of exercise-induced elevations in creatine kinase and transaminases
  - There were no hypersensitivity reactions reported
  - A total of 4 participants receiving pemivibart (2 each from Cohorts 2 and 3) experienced mild, self-limited, infusion-related reactions (chest pressure, flushing, presyncope) that were considered 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 Cohorts 2 and 3) until the reactions resolved and then resumed without further signs or symptoms
  - All other AEs were considered unrelated to the study drug (pemivibart or placebo)

Pharmacokinetic assessment

- All participants receiving pemivibart demonstrated observable serum concentrations following IV administration of single doses of 1500 mg, 2500 mg, or 4500 mg
- Noncompartmental analysis of serum concentration data are shown in **Table 1**
- Pemivibart demonstrated linear PK with apparent dose-proportional exposure (**Figure 2**); and extended serum half-life (mean 61, 57, and 51 days in Cohorts 1, 2, and 3, respectively; **Table 1**)

Table 1. Noncompartmental analysis of pemivibart PK parameters

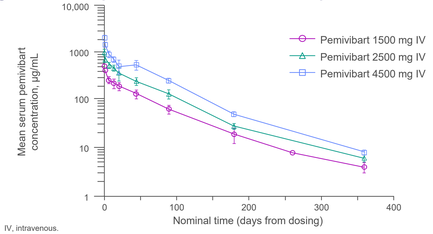
PK parameter (mean ± SD)	Pemivibart 1500 mg IV	Pemivibart 2500 mg IV	Pemivibart 4500 mg IV
C_{max}, µg/mL	535 ± 136	1003 ± 183	2078 ± 246
$AUC_{0\text{-}inf}$, day*µg/mL	19,480 ± 3419	36,930 ± 6094	65,020 ± 7890
$AUC_{0\text{-}inf}$/Dose, day*µg/mL/mg	13.0 ± 2.3	15.0 ± 2.4	14.5 ± 1.8
$T_{1/2}$, day	60.7 ± 4.1	56.9 ± 3.1	51.1 ± 3.3

$AUC_{0\text{-}inf}$, area under the concentration time curve; C_{max}, maximum plasma concentration; IV, intravenous; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life.

Antidrug antibodies

- ADAs were observed at baseline in 1 participant each in the pemivibart 2500 mg and 4500 mg groups, but neither developed into treatment-emergent (TE) ADAs post baseline
- TE ADAs were infrequent, occurring in 1 participant receiving pemivibart 4500 mg and 1 participant receiving placebo. Detected TE ADA titers were low (<minimum required dilution)
- Overall, no substantial ADAs to pemivibart were observed

Figure 2: Serum pemivibart concentration-time profile

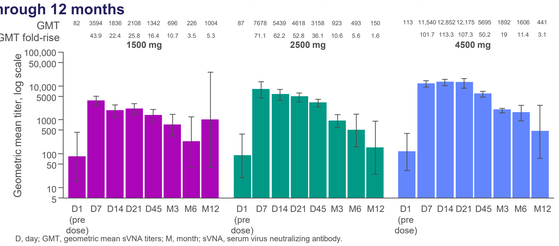


IV, intravenous.

Measured serum virus neutralizing antibody titers

- Measured geometric mean sVNA titers were determined against XBB.1.5, B.1.617.2 (Delta), and BA.4/5 pseudoviruses at all timepoints collected; measured sVNA titers to XBB.1.5 are presented in **Figure 3**
- Participants receiving pemivibart demonstrated a geometric mean fold-rise in XBB.1.5 sVNA titers from pre-dose to Day 7 of 43.9 (1500 mg), 71.1 (2500 mg), and 101.7 (4500 mg)
- Geometric mean sVNA titers (GMTs) to XBB.1.5 on Day 7 were 3594 (1500 mg), 7678 (2500 mg), and 11540 (4500 mg)
- GMTs for all doses remained above pre-dose XBB.1.5 sVNA titers through 12 months

Figure 3. Geometric mean serum virus neutralizing antibody titers against XBB.1.5 following pemivibart 1500 mg, 2500 mg, and 4500 mg from baseline through 12 months

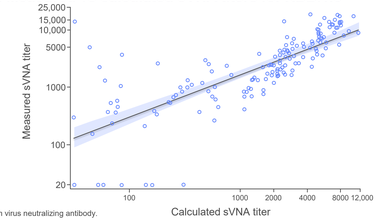


D, day; GMT, geometric mean sVNA titers; M, month; sVNA, serum virus neutralizing antibody.

Measured vs calculated serum virus neutralizing antibody titers

- Measured sVNA titers were strongly correlated with calculated sVNA titers for each variant tested, with Pearson correlation coefficients of 0.75, 0.88, and 0.65 (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 4**

Figure 4. Measured vs calculated sVNA titers for XBB.1.5



sVNA, serum virus neutralizing antibody.

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 61, 57, and 51 days in Cohorts 1, 2, and 3, respectively)

Overall, no substantial ADAs to pemivibart were observed

GMTs for all doses remained above pre-dose XBB.1.5 sVNA titers through 12 months

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

CONCLUSIONS

- **In this completed phase 1, single ascending-dose study, pemivibart was generally safe and well tolerated in healthy adults at doses up to 4500 mg**
- **No 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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DISCLOSURES

AH, YL, DG, AC, and KN are employees of Invivyd, Inc. and may own stock. EC and KM were employees at the time the study was conducted. 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.

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