Poster # 1363

Preliminary Safety Results from a Phase 1 First in Human Study of VYD222: an Extended Half-Life Monoclonal Antibody (mAb) in Development for COVID-19 Prevention

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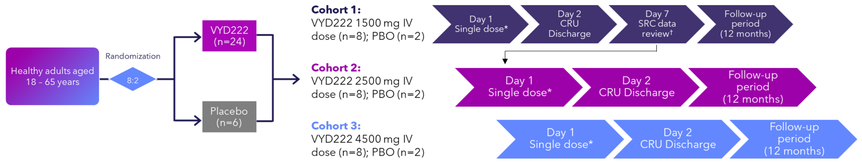
INTRODUCTION

- VYD222 is a fully human IgG1 mAb demonstrating broad and potent in vitro neutralizing activity across SARS-CoV-2 variants, including XBB.1.5 and XBB.1.5.10[1, 2]
- VYD222 is a re-engineered version of adintrevimab, an Fc-modified mAb administered intramuscular (IM) with a robust safety data package that demonstrated clinically meaningful results in Phase 2/3 clinical trials for treatment and prevention (pre-exposure and post-exposure prophylaxis) of COVID-19 (NCT04805671, NCT04859517)[1, 3-4]
- VYD222 functions as a human angiotensin-converting enzyme 2 (hACE2) competitor that targets an epitope on the spike glycoprotein receptor binding domain (RBD) of SARS-CoV-2[5]
- VYD222 is currently in development for the prevention of COVID-19
- Here, we report interim safety and serum virus neutralizing antibody (sVNA) titers from this Phase 1, single-ascending dose, first in human study of VYD222 administered via intravenous (IV) push in healthy adults (NCT05791318)

METHODS

Figure 1. Study Design



CRU, clinical research unit; PBO, placebo; SRC, safety review committee.
*Two sentinel participants (1 receiving VYD222 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, testing 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 VYD222 or placebo (normal saline) delivered by slow IV push over 3 to 5 minutes
  - Cohort 1: VYD222 1500 mg IV push
  - Cohort 2: VYD222 2500 mg IV push
  - Cohort 3: VYD222 4500 mg IV push
- Cohort 1 was dosed first (starting with two sentinel participants [n=1 VYD222 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 all three cohorts
- 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 occurred on Days 7, 14, 21, 45 and Month 3 and will continue to occur at Months 6 and 12 post-dosing
  - Phone contact for safety monitoring occurred on Days 3 and 4 and at Month 4 and is scheduled to occur at Months 5, 8, and 10

Endpoints and Assessment

- The primary objective is evaluation of the safety and tolerability of multiple dose levels of VYD222 after a single IV administration in healthy participants, as measured by incidence of treatment-emergent adverse events (TEAEs) including adverse events (AEs) and serious adverse events (SAEs)
- Secondary objectives include evaluating pharmacokinetic parameters and immunogenicity of VYD222
- The exploratory objective is evaluation of sVNA titers and neutralizing activity against relevant SARS-CoV-2 variants over time
  - sVNA titer collection occurs on Days 1 (pre-dose), 7, 14, 21, 45, and Months 3, 6, and 12

Measured vs Calculated sVNA

- Calculated sVNA titers represent the estimated reciprocal of the 50% inhibitor dilution based on the serum concentration of VYD222 divided by the IC50 value of VYD222 against a relevant SARS-CoV-2 variant
- 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. A scatterplot between measured and calculated sVNA titers (log10 scale) was produced with an overlaid linear regression line.

RESULTS

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

Participants

- Overall, 30 participants were randomized to receive either VYD222 (n=24) or placebo (n=6)
- Baseline characteristics of all randomized participants are presented in **Table 1**

Table 1. Demographic Characteristics (Randomized Participants)

Parameter	1500 mg (n=10)	2500 mg (n=10)	4500 mg (n=10)
Age (years)			
Median	35.5	36.0	24.0
≥55, n (%)	1 (10)	2 (20)	1 (10)
Female, n (%)	3 (30)	4 (40)	7 (70)
Race, n (%)			
White	10 (100)	6 (60)	9 (90)
Asian	0	3 (30)	0
Black	0	0	1 (10)
Other	0	1 (10)	0
Ethnicity, n (%)			
Hispanic or Latino	0	1 (10)	1 (10)

Safety and Tolerability

- As of September 6, 2023, a single administration of VYD222 or placebo was generally well-tolerated at all three dose levels tested with no SAEs reported
- There were no reports of study drug-related serious TEAEs, discontinuations, hypersensitivity reactions or deaths
- TEAEs were reported in 22 participants with the majority being mild in severity
  - Four participants experienced study drug-related TEAEs, all of which were considered mild

Measured sVNA Titers

- At 7 days post-dosing, the following geometric mean fold rises were observed from baseline (against Omicron XBB.1.5):
  - VYD222 1500 mg: 38.87-fold rise (95% CI: 10.3, 146.8)
  - VYD222 2500 mg: 92.82-fold rise (95% CI: 21.2, 406.6)
  - VYD222 4500 mg: 120.97-fold rise (95% CI: 31.4, 466.2)
- Measured geometric mean sVNA titers at baseline and Day 7 are presented in **Figure 2**

Measured sVNA vs Calculated sVNA

- Comparison of preliminary data from measured sVNA vs calculated sVNA against XBB.1.5 found the following:
  - A strong positive linear correlation (**Figure 3,** data cutoff August 12, 2023)
  - Regardless of endogenous antibody level at baseline, a positive relationship existed between measured and calculated sVNA
  - The linear correlation was stronger for participants with negative baseline sVNA titers, where almost all neutralizing activity was derived from mAb receipt (data not shown)
- Similar findings were seen for SARS-CoV-2 variants B.1.617.2 and BA.4/BA.5 (data not shown)

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

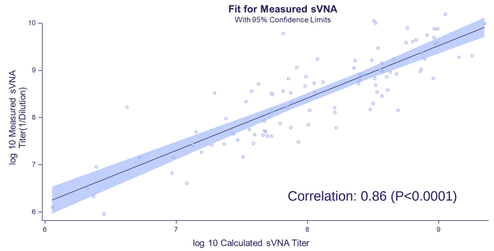
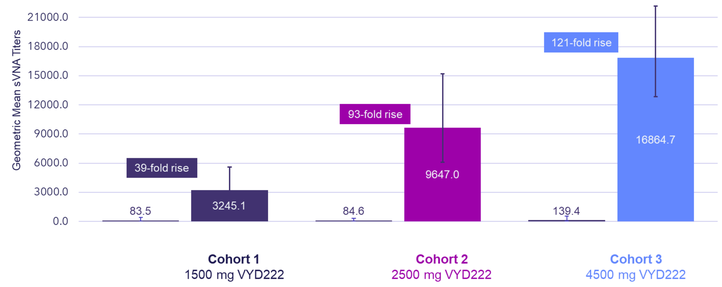


Figure 2. Geometric Mean sVNA Titers Against XBB.1.5 and Fold-Rise of VYD222 (1500 mg, 2500 mg, 4500 mg) from Baseline through Day 7



KEY FINDINGS

A single dose of VYD222 up to 4500 mg showed a favorable safety and tolerability profile

Measured sVNA titers of VYD222 found a rapid increase in titers between baseline and Day 7 at all doses tested

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

CONCLUSIONS

- The preliminary linear correlation between measured and calculated sVNA titers support the use of calculated sVNA as a potential correlate of protection for mAb use in COVID-19 prophylaxis
- Data from the 4500 mg VYD222 cohort support selection of this dose for later phase prevention studies that are currently underway

REFERENCES

1. VYD222 Investigator's Brochure, Edition 3, 08 Aug2023.
2. Invivyd Data on File (VYD-DOF-005).
3. Ison MG, et al. Open Forum Infect Dis. 2023 May 24;10(6):ofad279.
4. Ison MG, et al. Open Forum Infect Dis. 2023 Jun 13;10(7):ofad314.
5. Invivyd Data on File (VYD-DOF-006).

DISCLOSURES

KM, DG, YL, NB, AD, EC, and PS are all employees of Invivyd, Inc. and may own stock.

Adintrevimab and VYD222 are investigational product candidates that are not approved for use in any country. The safety and efficacy of adintrevimab and VYD222 have not been established.

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