Poster E0504

Safety, Tolerability, Pharmacokinetics, and Immunogenicity in a Phase 1 First-in-Human Study With VYD2311, a SARS-CoV-2-Directed Monoclonal Antibody

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KEY FINDINGS

- A single dose of VYD2311 administered IV up to 4500 mg, IM at 1000 mg, and SC at 1250 mg showed a favourable safety and tolerability profile in healthy adults, with no SAEs or TEAEs leading to permanent study discontinuation or death
- In the dose range and administration routes studied, VYD2311 demonstrated linear PK characteristics
- There were no treatment-emergent ADAs and no ADA trends observed following VYD2311 administration

INTRODUCTION

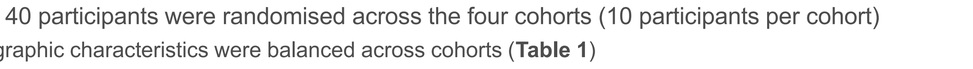
- COVID-19 remains a significant threat, putting those infected with newly emerging variants at risk for developing severe disease requiring hospitalization, potentially leading to death or Long COVID, or impacting daily activity[1-3]
- Previous exposure or vaccination to prevent future SARS-CoV-2 infections is suboptimal[4]
- Monoclonal antibodies targeted to SARS-CoV-2 spike protein represent an alternative preventive strategy against COVID-19[5]
- VYD2311 is a novel immunoglobulin G1 (IgG1) monoclonal antibody that targets the spike glycoprotein receptor–binding domain (RBD) of SARS-CoV-2[6]
- VYD2311 was engineered from the same lineage as pemivibart, its parent molecule, and adintrevimab[6]
  - Pemivibart was granted emergency use authorization (EUA) in the US (Mar 2024) for pre-exposure prophylaxis of COVID-19 in certain adults and adolescents with moderate-to-severe immune compromise[7,8]
  - Ongoing in vitro neutralisation testing has shown that pemivibart continues to demonstrate potency against the latest dominant Omicron sublineages, including KP.3.1.1, XEC, LP.8.1, and XFG[8]
  - In the Phase 3 trial CANOPY, pemivibart was generally well tolerated; anaphylaxis was an important safety risk[9]
- VYD2311 has been optimised for improved binding affinity to contemporary Omicron variants and has demonstrated broad and potent in vitro neutralisation activity[6]
- Here we summarise the results of a Phase 1 study of safety, tolerability, pharmacokinetics (PK), and immunogenicity of VYD2311 in healthy participants (NCT06523153[10]) to inform design of future studies for prevention and treatment of COVID-19

METHODS

Trial Design and Participants

- Phase 1, randomised, double-blind, placebo-controlled study, conducted at a single center in Australia
- Eligible participants were healthy adults aged 18 to 65 with a negative SARS-CoV-2 rapid antigen test during screening and on the day prior to dosing
- Participants in four cohorts were randomised (8:2) to receive one dose of VYD2311 (n=8) or placebo (n=2) by either intravenous (IV) infusion (2000 mg or 4500 mg), intramuscular (IM) injection (1000 mg), or subcutaneous (SC) injection (1250 mg) using a sentinel dosing approach (**Figure 1**)
- Participants received a single dose of the assigned study drug on Day 1 and were followed for 6 months

Figure 1: Phase 1 Study Design



Dosing Regimen*	VYD2311	Placebo
Cohort 1 (1000 mg IM)	N=8	N=2
Cohort 2 (2000 mg IV)	N=8	N=2
Cohort 3 (4500 mg IV)	N=8	N=2
Cohort 4 (1250 mg SC)	N=8	N=2

EOS, end of study; IM, intramuscular(ly); IV, intravenous(ly); SC, subcutaneous(ly); SRC, Safety Review Committee.
*After C1 sentinel participants (1:1 VYD2311; placebo) completed 72 hrs of safety monitoring, the remaining C1 participants and the C2 sentinel participants began dosing. C1 non-sentinel participant dosing occurred in parallel with dosing of all C2 participants. Upon SRC approval, C3 sentinel participants (1:1 VYD2311; placebo) began dosing followed by remaining C3 participants. After C4 sentinel participants completed 72 hours of safety monitoring, the remaining C4 non-sentinel participants began dosing.

Endpoints and Assessments

- The primary objective was to evaluate the safety and tolerability of multiple dose levels of VYD2311 after a single dose via IV, IM, or SC administration in healthy participants
  - The primary endpoint was incidence of treatment-emergent adverse events (TEAEs), including adverse events (AEs) and serious AEs (SAEs)
- Secondary and exploratory objectives were to evaluate PK, immunogenicity, and calculated serum virus neutralising antibody (sVNA) titers of VYD2311 after IV, IM, or SC administration in healthy participants
  - PK endpoints included PK parameters of VYD2311: AUC, C_{max}, T_{max}, CL, $t_{1/2}$, V_{ss}, and V_z
  - Immunogenicity endpoints included incidence of anti-drug antibodies (ADAs) against VYD2311
    - Treatment emergent ADAs were defined as seroconversion from negative at baseline to positive post-baseline or as ≥4-fold rise in ADA from baseline. The minimum required dilution was 12.5, and blood samples were collected for PK and immunogenicity throughout the follow-up period
  - Calculated sVNA titer endpoint included sVNA titers summarized by study day evaluated across the 3 dominant variants circulating during the study (KP.3.1.1, XEC, and LP.8.1)
    - Calculated sVNA titers were obtained using the serum concentrations of VYD2311 divided by IC_{50} value of VYD2311 against relevant SARS-CoV-2 variants, and expressed as 1/dilution
    - Levels were compared against protective efficacy threshold of 500 established using the parent molecule pemivibart[11]

RESULTS

Participants

- A total of 40 participants were randomised across the four cohorts (10 participants per cohort)
  - Demographic characteristics were balanced across cohorts (**Table 1**)
- All participants were negative for SARS-CoV-2 by central lab reverse transcription-polymerase chain reaction (RT-PCR) at baseline
- All participants completed the study, except for one participant in Cohort 2 (lost to follow-up after 149 days)

Table 1: Baseline Characteristics

Parameter	VYD2311 Cohort 1 1000 mg IM (N=8)	VYD2311 Cohort 2 2000 mg IV (N=8)	VYD2311 Cohort 3 4500 mg IV (N=8)	VYD2311 Cohort 4 1250 mg SC (N=8)	VYD2311 Total (N=32)	Placebo Cohorts 1–4 (N=8)	Total Cohorts 1–4 (N=40)
Age (years), median (range)	28.5 (20–48)	28.0 (18–57)	39.5 (21–57)	37.0 (24–57)	35.0 (18–57)	43.5 (20–59)	35.0 (18–59)
Female, n (%)	8 (100)	7 (87.5)	7 (87.5)	7 (87.5)	29 (90.6)	5 (62.5)	34 (85.0)
Race, n (%)							
White	8 (100)	3 (37.5)	3 (37.5)	6 (75.0)	20 (62.5)	5 (62.5)	25 (62.5)
Asian	0	4 (50.0)	4 (50.0)	2 (25.0)	10 (31.3)	3 (37.5)	13 (32.5)
Unknown	0	0	1 (12.5)	0	1 (3.1)	0	1 (2.5)
Other	0	1 (12.5)	0	0	1 (3.1)	0	1 (2.5)
Weight (kg), median (range)	81.55 (65.8–95.9)	71.90 (50.7–90.2)	64.30 (45.4–100.1)	72.45 (58.3–91.6)	72.40 (45.4–100.1)	69.40 (49.9–91.2)	72.40 (45.1–100.1)
Baseline central lab SARS-CoV-2 RT-PCR							
Not detected, n (%)	8 (100)	8 (100)	8 (100)	8 (100)	32 (100)	8 (100)	40 (100)

RESULTS

Safety and Tolerability

- Overall, 21 of 32 (65.6%) participants who received VYD2311 and 2 of 8 (25.0%) who received placebo experienced at least one TEAE (**Table 2**)
- Across all cohorts, 13 of 32 (40.6%) participants who received VYD2311 and none who received placebo experienced a study drug–related TEAE (**Table 3**)
- All TEAEs were mild (Grade 1) or moderate (Grade 2) in severity (**Table 2**)
  - There were no serious AEs (SAEs) and no TEAEs leading to permanent study discontinuation or death
- No hypersensitivity reactions were reported in any cohort. All injection site reactions (ISRs) and infusion related reactions (IRRs) were considered related to the study drug
  - ISRs were less frequent after IM (12.5%; 1/8) administration than after SC (100%; 8/8; **Table 3**). All ISRs were mild and did not require treatment
  - IRRs occurred in 3 of 8 (37.5%) participants receiving 4500 mg VYD2311 in Cohort 3
- No participants experienced COVID-19 TEAEs during the study

Table 2: TEAE Summary

Event, n (%)	VYD2311 Cohort 1 1000 mg IM (N=8)	VYD2311 Cohort 2 2000 mg IV (N=8)	VYD2311 Cohort 3 4500 mg IV (N=8)	VYD2311 Cohort 4 1250 mg SC (N=8)	VYD2311 Total (N=32)	Placebo Cohorts 1–4 (N=8)
Any TEAEs	4 (50.0)	5 (62.5)	4 (50.0)	8 (100)	21 (65.6)	2 (25.0)
Any TEAS ≥ Grade 3	0	0	0	0	0	0
Any serious TEAEs	0	0	0	0	0	0
Any TEAEs leading to death	0	0	0	0	0	0
Any TEAEs leading to permanent study discontinuation	0	0	0	0	0	0
Any TEAEs leading to study treatment interruption	0	0	1 (12.5)	0	1 (3.1)	0
Study-drug related TEAEs	1 (12.5)	1 (12.5)	3 (37.5)	8 (100)	13 (40.6)	0

The safety population included all participants who received any amount of study drug.
%=percentage of participants with at least one AE in each category relative to the total number of participants in the relevant analysis set.
Participants with multiple AEs in each category are counted only once.
A TEAE is an AE that occurs at any time during or after administration of study treatment through the end of study (EOS), or any preexisting condition that has worsened during or after the administration of study treatment through the EOS.

Table 3: Study Drug–Related TEAEs by System Organ Class and Preferred Term

System Organ Class, n (%) Preferred Term Maximum Severity	VYD2311 Cohort 1 1000 mg IM (N=8)	VYD2311 Cohort 2 2000 mg IV (N=8)	VYD2311 Cohort 3 4500 mg IV (N=8)	VYD2311 Cohort 4 1250 mg SC (N=8)	VYD2311 Total (N=32)	Placebo Cohorts 1–4 (N=8)
Any drug-related TEAEs	1 (12.5)	1 (12.5)	3 (37.5)	8 (100)	13 (40.6)	0
Grade 1	1 (12.5)	1 (12.5)	2 (25.0)	6 (75.0)	10 (31.3)	
Grade 2	0	0	1 (12.5)	2 (25.0)	3 (9.4)	
General disorders and administration site conditions	1 (12.5)	0	0	8 (100)	9 (28.1)	0
Injection site erythema	0	0	0	7 (87.5)	7 (21.9)	0
Injection site pain	1 (12.5)	0	0	2 (25.0)	3 (9.4)	0
Injection site swelling	0	0	0	3 (37.5)	3 (9.4)	0
Pyrexia	0	0	0	1 (12.5)	1 (3.1)	0
Nervous system disorders	0	1 (12.5)	0	3 (37.5)	4 (12.5)	0
Headache	0	1 (12.5)	0	3 (37.5)	4 (12.5)	0
Dizziness	0	1 (12.5)	0	1 (12.5)	2 (6.3)	0
Injury, poisoning, and procedural complications	0	0	3 (37.5)	0	3 (9.4)	0
Infusion-related reaction	0	0	3 (37.5)*	0	3 (9.4)	0
Gastrointestinal disorders	0	0	0	1 (12.5)	1 (3.1)	0
Nausea	0	0	0	1 (12.5)	1 (3.1)	0
Vomiting	0	0	0	1 (12.5)	1 (3.1)	0

The safety population included all participants who received any amount of study drug.
%=percentage of participants with at least one AE in each category relative to the total number of participants in the relevant analysis set.
*Two of the IRRs were mild and did not require treatment. One IRR was moderate (Grade 2), lasted for 2 minutes, resolved 3 minutes after study drug interruption, treated with paracetamol and loratadine, study drug restarted at half-rate then increased to full-rate without recurrence of symptoms, but resulted in the participant not receiving the full IV dose (received 89% of the full dose [4005 mg out of 4500 mg] due to expiration of the 4-hour window following preparation of IP.

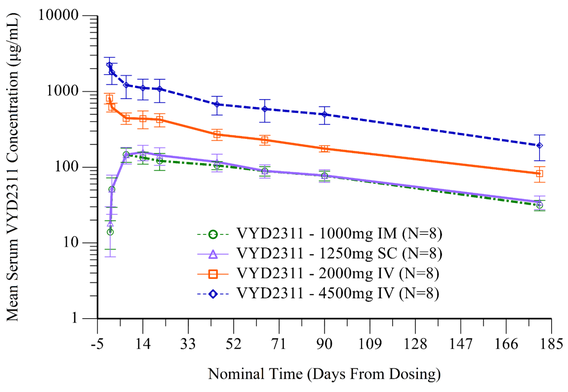
PK Profile and Immunogenicity

- VYD2311 demonstrated linear PK and extended serum half-life (range: 72–78 days; **Figure 2**)
  - Following a single IV administration of 2000 mg or 4500 mg VYD2311, maximum observed serum concentration (C_{max}) was observed at the first sample (5 min after infusion), then concentrations declined bi-exponentially
  - Following a single IM administration of 1000 mg VYD2311 or a single SC administration of 1250 mg VYD2311, C_{max} was observed within 6-14 days in most participants (7/8), then concentrations declined mono-exponentially
- There were no treatment-emergent ADAs in the study
  - One participant in Cohort 4 (1250 mg SC arm) tested positive for ADAs predose, with a low ADA titer of 25 (2-fold above the minimum required dilution of 12.5); all post-baseline, postdose samples from this participant were negative for ADA

Calculated sVNA titers following administration of VYD2311 1000 mg IM

- As IM is the preferred route of administration for later stage clinical trials, calculated sVNA titers following VYD2311 1000 mg IM dosing are presented
  - Peak calculated sVNA titers after 1000 mg IM dosing were observed on Day 7 with GMT of 3421.4, 10119.6, and 7603.1 against KP.3.1.1, XEC, and LP.8.1, respectively
  - Calculated sVNA values after 1000 mg IM dosing at Month 6 of the study remained above 500 against all dominant variants (KP.3.1.1: 740; XEC: 2188.7; LP.8.1: 1644.4)[11]

Figure 2: Mean (± SD) VYD2311 Serum Concentration Over Time (PK Population)



Select Serum PK Parameter	VYD2311 1000 mg IM (N=8)	VYD2311 1250 mg SC (N=8)	VYD2311 2000 mg IV (N=8)	VYD2311 4500 mg IV (N=8)
C_{max}, µg/mL, mean (SD) (CV%)	149.5 (33.166) (22.2)	165.5 (46.170) (27.9)	814.8 (131.49) (16.1)	2243 (572.16) (25.5)
AUC_{0-inf}, day*µg/mL, mean (SD) (CV%)	16820 (2783.1) (16.5)	18330 (3796.5) (20.7)	48090 (6412.8) (13.3)*	117300 (38432) (32.8)
T_{max}, days, median (range)	5.978 (5.85–21.9)	9.513 (5.11–13.9)	0.003471 (0.00347–0.00347)	0.003471 (0.00347–0.00347)
$t_{1/2}$, days, mean (SD) (CV%)	75.06 (5.2633) (7.0)	78.34 (8.9237) (11.4)	73.38 (10.466) (14.3)*	71.79 (14.983) (20.9)

AUC_{0-inf}, area under the serum concentration–time curve from time zero to infinity; C_{max}, maximum observed concentration; CV, coefficient of variation; T_{max}, time to reach C_{max}; SD, standard deviation; $t_{1/2}$, terminal phase half-life.
The PK population included all participants who received any amount of study drug and had VYD2311 quantifiable concentration data for at least two time points. Plot shows arithmetic mean ± SD values on a semi-logarithmic scale.
*N=7; Terminal PK parameters from a participant who had no concentration records beyond Day 45, and for whom terminal phase was, hence, not apparent, were not calculated.

CONCLUSIONS

- **The Phase 1 study results show a favourable safety, tolerability, PK, and immunogenicity profile of VYD2311 and support further clinical investigation of VYD2311 at doses and routes of administration evaluated. This includes 1000 mg IM injection, 2000 and 4500 mg IV infusions, and 1250 mg SC injection**
- **At lowest the dose evaluated (1000 mg IM), neutralising antibody responses were demonstrated against dominant circulating variants through 6 months**
- **A Phase 3 randomised, placebo-controlled trial (NCT07298434)[12] evaluating the efficacy and safety of single and multiple IM dosing regimens of 250 mg VYD2311 compared with placebo for prevention of RT-PCR-confirmed symptomatic COVID-19 in adults and adolescents is currently ongoing**

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DISCLOSURES

This study was funded by Invivyd, Inc.
KN, KT, RG, and IY are employees of Invivyd, Inc. and may own stock. DW and LH are paid consultants of Invivyd. PR has served on vaccine scientific advisory boards (non-COVID-19) for Pfizer, Moderna, AstraZeneca, and Clover Pharmaceuticals and as an investigator in investigator-led and industry-sponsored (Sanofi, Novavax) multicenter COVID-19 vaccine trials on behalf of his institution.

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