Poster P0453

Characterisation of Monoclonal Antibody VYD2311: Molecular Structure and In Vitro Neutralisation Profile Against Recent SARS-CoV-2 Variants

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KEY FINDINGS

VYD2311 spike complex structure demonstrated conservation of critical interaction determinants and mechanism of binding to parental mAbs adintrevimab and pemivibart

VYD2311 demonstrated sustained in vitro neutralisation activity against all variants tested, including current dominant circulating variants

INTRODUCTION

- The clinical use of monoclonal antibodies (mAbs) for COVID-19 has been impacted by the complexity of SARS-CoV-2 variant evolution and dynamics[1]
- VYD2311 is a fully human, long-acting mAb targeting a highly conserved and functionally constrained epitope of SARS-CoV-2 spike protein, thereby inhibiting virus attachment to the human angiotensin-converting enzyme 2 (hACE2) receptor on host cells[2]
- The overall mechanism of binding remains the same between VYD2311 and parental mAbs (pemivibart, adintrevimab), all targeting a similar epitope and having strong structural overlap[2-6]
  - Pemivibart was granted emergency use authorization (EUA; Mar 2024) for pre-exposure prophylaxis of COVID-19 in certain adults and adolescents with moderate-to-severe immune compromise[7]
- VYD2311 previously demonstrated potent neutralising activity against both pseudovirus and authentic SARS-CoV-2 wild-type (WT), Delta, and Omicron variants[2,8]
- Here we report *in vitro* neutralising activity of VYD2311 against a panel of recent circulating SARS-CoV-2 variant pseudoviruses

METHODS

VYD2311 Cryogenic Electron Microscopy (Cryo-EM) Structure

- A high-resolution structure of the VYD2311 fragment antigen-binding (Fab) domain bound to XEC spike was determined using Cryo-EM
  - Data were collected using a Krios™ microscope and processed using cyroSPARC[9]
  - Both receptor binding domain (RBD) “Up” and “Down” conformations of the Spike were observed bound to VYD2311
  - The “Up” model shown here was generated from 33,000 particles and refined using Phenix[10] to a resolution of 3.6 Å
- The VYD2311:XEC spike complex structure was aligned, using the RBD domain, to the previously solved x-ray crystal structure of adintrevimab:WT RBD complex (PDB accession code 7UD2)[11]

SARS-CoV-2 variant monitoring

- CDC Variant Proportion data from the COVID Data Tracker[12] were used as the foundational dataset for the proportion of variants present in the U.S. over a given period of time

Weighted average EC_{50} calculation

- The weighted average EC_{50} (WA-EC_{50}) for a mAb against a mixture of variants over time was calculated by summing the product of each variant proportion multiplied by the EC_{50} value for that variant, divided by the total proportional sum of all represented variants.
  - The following formula was used to determine the WA-EC_{50}: $\text{weighted average}_{\text{EC}_{50}} = \frac{\Sigma(w)_n(X)_n}{\Sigma(w)_n}$ where $(w)_n$ is the proportion of total sampled viruses for variant n, and $(X)_n$ is the closest representative variant for which PVNA EC_{50} data is available for variant n
  - EC_{50} values for bebtelovimab, tixagevimab and cilgavimab were obtained from the Stanford Coronavirus Antiviral and Resistance Database[13]
  - If the pseudovirus EC_{50} was not available for a specific SARS-CoV-2 variant, the variant was matched to the closest variant for which pseudovirus EC_{50} data was determined experimentally[14]

RESULTS

VYD2311 Cryo-EM Structure

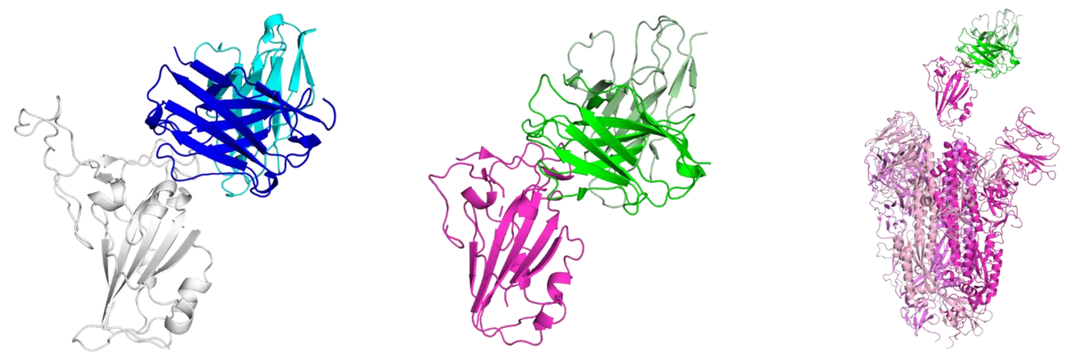
- Alignment of the VYD2311:XEC Spike structure to the adintrevimab:WT RBD structure showed strong structural overlap (**Figure 1**)

VYD2311 Neutralising Activity

- VYD2311 showed in vitro neutralisation activity against the SARS-CoV-2 pseudovirus variants that were tested, including WT (D614G), Delta, BA.1, BA.2, and JN.1 variants, as well as recent and current dominant variants such as KP.3.1.1, XEC, LP.8.1, NB.1.8.1, and XFG (**Figures 2 and 3**)

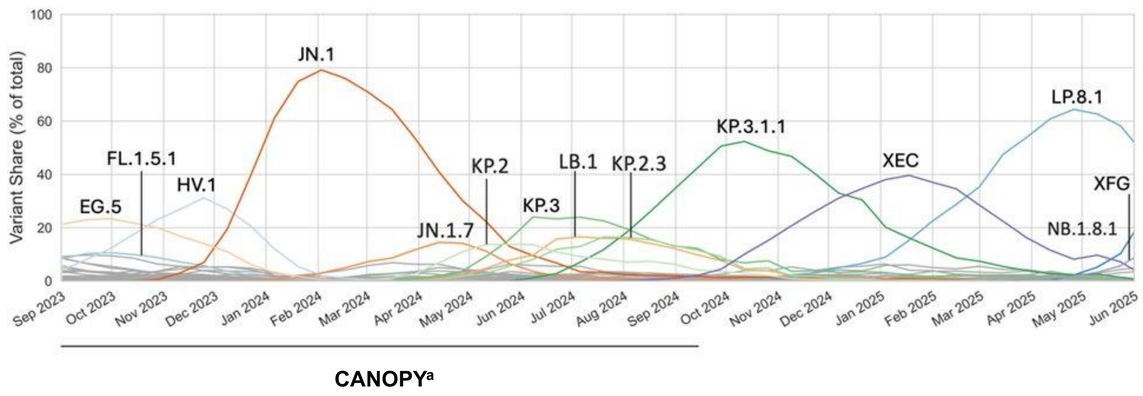
RESULTS - Figures and Tables

Figure 1: VYD2311 Binding Motif



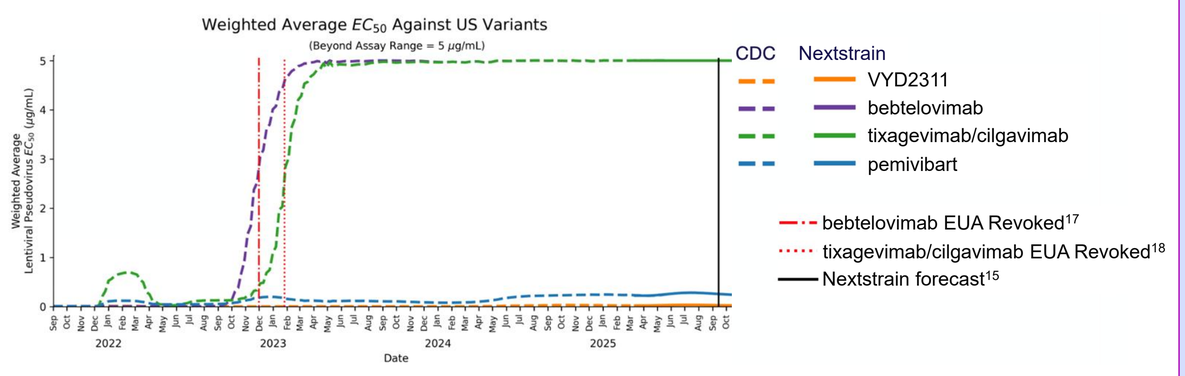
The Cryo-EM structure of the VYD2311 Fv domain (dark green/light green) bound to XEC Spike (pink) was aligned using the RBD domain to the previously solved structure of the adintrevimab Fv domain (blue/cyan) bound to WT RBD (white), PDB ID 7U2D[11]. The VYD2311:XEC spike structure displays a high degree of similarity to the adintrevimab:WT RBD structure with Cα root mean square deviation of only 0.52 Å².

Figure 2: Circulating Proportions of US CDC Tracked Variants[8,15-16]



[a]Line denotes the period during which the Phase 3 CANOPY study (NCT06039449) was conducted.

Figure 3: Weighted Average EC_{50} Estimates of mAb activity against circulating SARS-CoV-2 Variant Population Over Time[8]



The weighted average half-maximal effective concentration (WA-EC_{50}) values for variants which circulated in the US as tracked by the CDC are graphed over time for VYD2311 (orange), bebtelovimab (purple), tixagevimab/cilgavimab (green), and pemivibart (blue). The vertical dashed lines indicate the date of EUA revocation and share the color code with the corresponding drug as indicated in the legend.

CONCLUSIONS

- **The sustained in vitro antiviral potency of VYD2311 against current dominant circulating SARS-CoV-2 variants supports further investigation of VYD2311**
- **A Phase 3 randomised, placebo-controlled trial (NCT07298434)[18] evaluating the efficacy and safety of single and multiple intramuscular dosing regimens of VYD2311 compared with placebo for prevention of symptomatic COVID-19 in adults and adolescents is under way**

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DISCLOSURES

This study was funded by Invivyd, Inc.
CP, RM, DC, BW, JH, FG, RA are employees of Invivyd, Inc. and may own stock.

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