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NVD200 potently neutralises Omicron and its sublineages

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KEY FINDINGS

Affinity optimisation of adintrevimab led to generation of ADI-80222, a monoclonal antibody with potent and broader neutralizing activity against SARS-CoV-2 VOC, including Omicron subvariants

ADI-80222, the parent of VYD222, demonstrated high binding affinity across variants tested and a panel of sarbecoviruses

VYD222 demonstrated potent neutralisation against all VOCs tested including XBB.1.5

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 and future variants is needed to protect vulnerable populations
- NVD200 consists of two fully human IgG1 mAbs, VYD222 and VYD224, and was considered for further research
- VYD222 is the Fc-modified version of ADI-80222, an optimised version of adintrevimab (ADG20). Adintrevimab was a mAb that met Phase 2/3 primary endpoints in both treatment and prevention of COVID-19 in previous clinical studies (STAMP, NCT04805671; EVADE, NCT04859517)
- Here, we characterize the optimisation of adintrevimab which lead to the generation of ADI-80222
- Additionally, we explored the binding of ADI-80222 to spike glycoprotein RBDs from SARS-CoV-2 variants of concern (VOCs), breadth to related sarbecoviruses, and in vitro neutralising potency against a panel of SARS-CoV-2 VOCs
- VYD222 has been moved forward for clinical development

METHODS

Optimisation of adintrevimab[1, 2]

- The adintrevimab affinity maturation library was stained with the SARS-CoV-2 BA.1 S1 and pressured for higher affinity to BA.1 relative to adintrevimab
- The broadest and most potent progeny from this selection was then subjected to a second cycle of optimisation to pressure for enhanced binding to the BA.2 RBD
- Diversification was done using NNK complementarity determining region (CDR) libraries
- To determine binding following optimisation, biotinylated SARS-CoV-2 RBDs corresponding to WT D614G, BA.1, BA.2, BA.4/5, Beta, and Delta variants were loaded onto streptavidin (SA) sensor and then exposed to 100 nM Fab in solution for 5 min before transfer to assay buffer for off-rate measurement
- Kinetics were analyzed using the 1:1 binding model
- In vitro binding to determine breadth was assessed in a surface-displayed RBD using serial dilutions of antibody against a panel of yeast-surface displayed sarbecovirus RBD-SD1 proteins

In vitro neutralising activity[3, 4]

Authentic Virus

- Neutralising potency of ADI-80222 was evaluated against a panel of SARS-CoV-2 variants
- An immune–detection assay was performed to determine the expression of viral nucleoprotein in infected Vero E6 cells by staining with a SARS-CoV-2 nucleoprotein-specific antibody
- To compute IC_{50} values, the data were subjected to logistic regressional (sigmoidal) analyses using GraphPad Prism version 9.4.1

Pseudovirus

- SARS-CoV-2 pseudovirus neutralisation assays were performed using the PhenoSense SARS-CoV-2 Neutralising Antibody Assay (LabCorp Monogram Biosciences)
- Pseudovirus-bearing SARS-CoV-2 D614G or variant spike proteins were produced by co-transfecting HEK293 cells with codon optimised spike sequence expression vector and an HIV genomic vector containing a firefly luciferase reporter gene in place of the HIV envelope gene
- To establish neutralisation, a predetermined amount of pseudovirus was incubated with titrating amounts of test mAb before adding to HEK293 cells expressing hACE2 and TMPRSS2
- Inoculated cells were incubated for three days before cells were assessed for luciferase activity (NOTE: this is a single cycle assay, meaning the virus is replication-defective)
- Neutralization IC_{50} values were determined based on a four parameter logisitic regression of mAb dilution versus % inhibition of luciferase activity

RESULTS

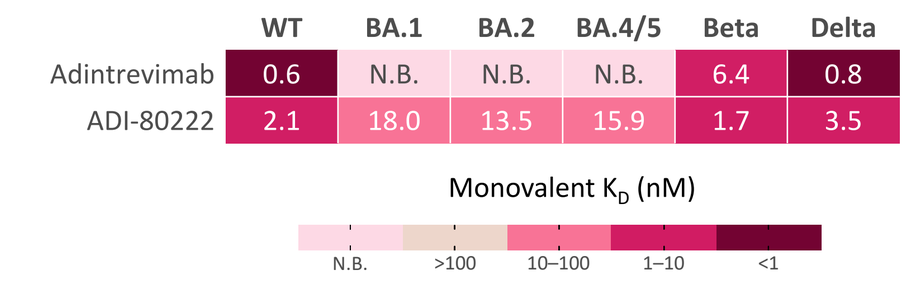
Optimisation of adintrevimab

- Optimisation of adintrevimab occurred in 2 cycles
- After a second cycle of affinity optimisation, the resultant molecule, ADI-80222, displayed high affinity binding to BA.2 and BA.4/5, with K_D = 13.5 nM and 15.9 nM, respectively, and maintained binding to pre-Omicron VOCs such as Delta **(Figure 1)**
- ADI-80222 bound with high affinity to all tested hACE2-binding sarbecovirus RBD-SD1 proteins **(Figure 2)**

In vitro neutralising activity

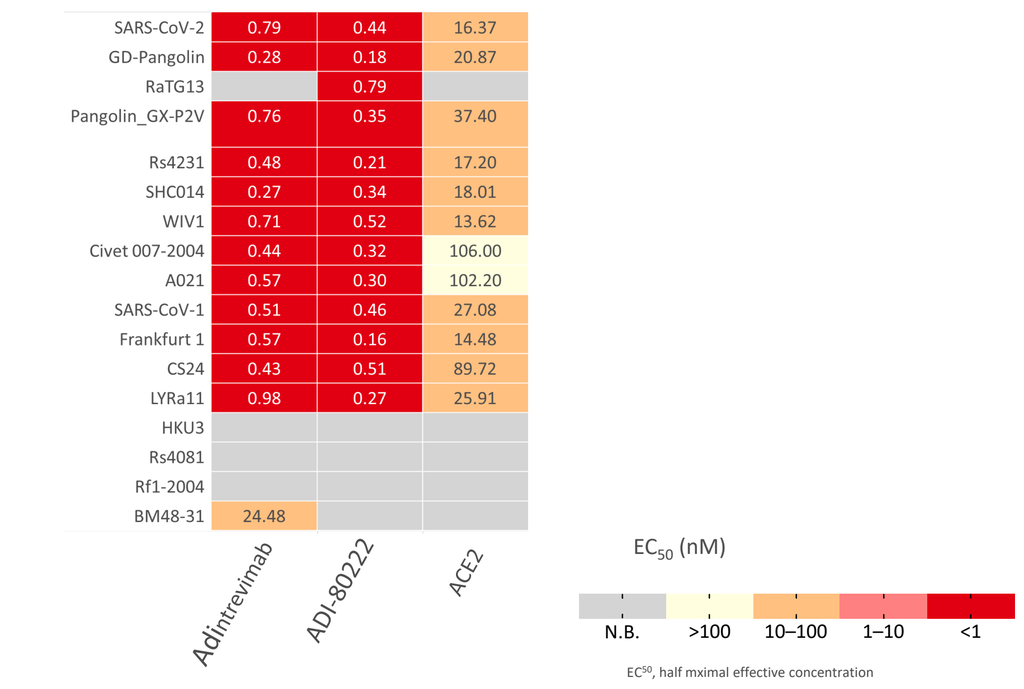
- ADI-80222 demonstrated potent neutralisation against all SARS-CoV-2 VOC tested in authentic virus assay **(Figure 3)**
- VYD222 demonstrated potent in vitro neutralisation in pseudovirus assays against variants tested including BQ.1.1, XBB.1, and XBB.1.5 **(Figure 4)**

Figure 1. In vitro binding affinity after optimisation



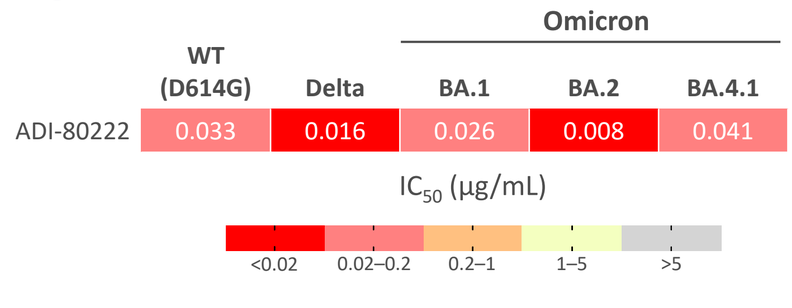
Monovalent Fab affinity of adintrevimab and ADI-80222. Cell values indicate binding KDs. N.B. indicates no binding was observed. >100 indicates binding was observed but sensorgrams could not be fit to a 1:1 binding model

Figure 2. Binding of ADI-80222 against panel of sarbecoviruses



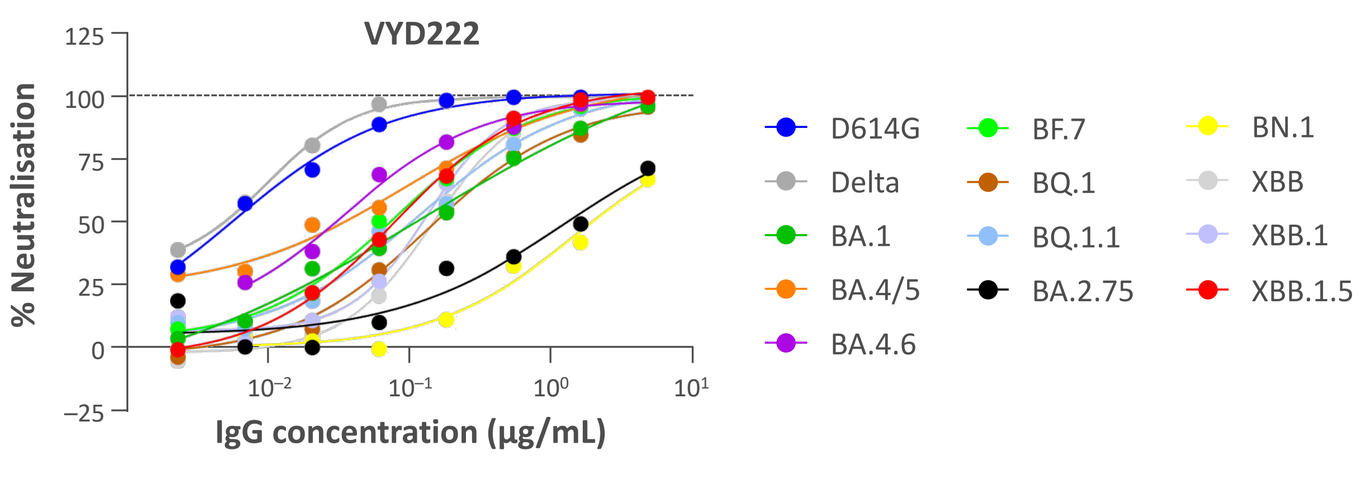
EC_{50}, half maximal effective concentration

Figure 3. Authentic Virus neutralisation



Half-maximal inhibitory concentration (IC50)

Figure 4. Pseudovirus neutralisation



CONCLUSIONS

- **VYD222 demonstrates potential to be an effective prophylactic and therapeutic agent against emergent variants of SARS-CoV-2**
- **These data support further clinical investigation of VYD222 for COVID-19**

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DISCLOSURES

BW, AW, KN, PH, and LD are all employees of Invivyd, Inc. and may own stock. LW, MD, and CK are former employees 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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