Poster P2161

ADG20, a half-life–extended monoclonal antibody in development for the prevention and treatment of COVID-19, demonstrated broad in vitro neutralisation against SARS-CoV-2 variants

Chengzi I. Kaku,[1] Kristin Narayan,[2] Pete Schmidt,[2] Frank Engler,[3] Yong Li,[2] Laura M. Walker[1,2]

[1]Adimab LLC, Lebanon, NH, USA; [2]Adagio Therapeutics, Inc., Waltham, MA, USA; [3]Clinical Pharmacology, Certara, Buffalo, NY, USA

INTRODUCTION

- ADG20 is a fully human immunoglobulin (Ig)G1 monoclonal antibody (mAb) engineered to have improved potency and broad neutralisation against SARS-CoV-2 and other SARS-like CoVs with pandemic potential[1-4]
- In addition, the Fc region of ADG20 has been modified to provide an extended half-life[1]
- ADG20 can be administered intramuscularly (IM) and is being assessed in 2 separate phase 2/3 clinical trials: the EVADE trial for prevention of COVID-19 in both post-exposure and pre-exposure settings and the STAMP trial for treatment of COVID-19[5,6]
- During the COVID-19 pandemic, variants of SARS-CoV-2 have rapidly emerged and dominated global populations, likely due to selective pressure from natural and vaccine-induced immunity[7-9]
- Notably, some variants of concern (VOCs), including Omicron, exhibit enhanced transmissibility and/or decreased susceptibility to neutralisation by vaccine-elicited responses and some mAb therapies[7-9]
- Here we report the in vitro neutralising activity of ADG20 against a panel of circulating SARS-CoV-2 variants, including Omicron and other VOCs with reduced susceptibility to some currently authorised mAbs
- We also present serum virus neutralising antibody (sVNA) titres collected up to 6 months after a single 300 mg IM injection of ADG20 in healthy adults

METHODS

In vitro neutralising activity

- In vitro neutralising activity of ADG20 against 38 SARS-CoV-2 variants encoding the full set of spike mutations in circulating lineages, including Alpha/B.1.1.7, Beta/B.1.351, Gamma/P.1, Delta/B.1.617.2, and Omicron lineages BA.1, BA.1.1, and BA.2, was assessed in an HIV lentiviral pseudovirus assay[9-11]
  - D614G, an early variant of SARS-CoV-2, was used as a reference to calculate the half maximal inhibitory concentration (IC_{50}) fold change in neutralising activity for ADG20
- In vitro neutralising activity of ADG20 against 27 SARS-CoV-2 variants, including those reported to exhibit reduced susceptibility to emergency-use authorised (EUA) mAbs, was assessed in a non-replicative vesicular stomatitis virus pseudovirus assay[12,13]
  - Fold reduction was calculated by dividing the IC_{50} of a variant by the mean IC_{50} (14.6 ng/mL) of the D614G reference strain

ADG20 sVNA titres

- A phase 1 randomised, double-blind, placebo-controlled, single-ascending dose study was initiated at a single center in the United States in February 2021[14]
  - Eligible participants were healthy adults aged 18–50 years at low risk of SARS-CoV-2 infection and with no evidence of prior or current SARS-CoV-2 infection
  - Three cohorts (n=10 per cohort) were randomised (8:2) to receive ADG20 or placebo; here, we report exploratory sVNA data for the cohort that received a single 300 mg ADG20 IM injection
  - As a non-prespecified exploratory research analysis, the 80% neutralisation (MN80) sVNA titres following ADG20 administration were determined by a plaque reduction neutralisation test against authentic SARS-CoV-2 D614G (BavPat), Beta/B.1.351, and Delta/B.1.617.2 variants (Delta data are preliminary)
  - For each variant ADG20 sVNA titres were compared with peak responses 7–30 days after the second dose of the mRNA-1273 (Moderna) vaccine in a separate cohort of healthy volunteers

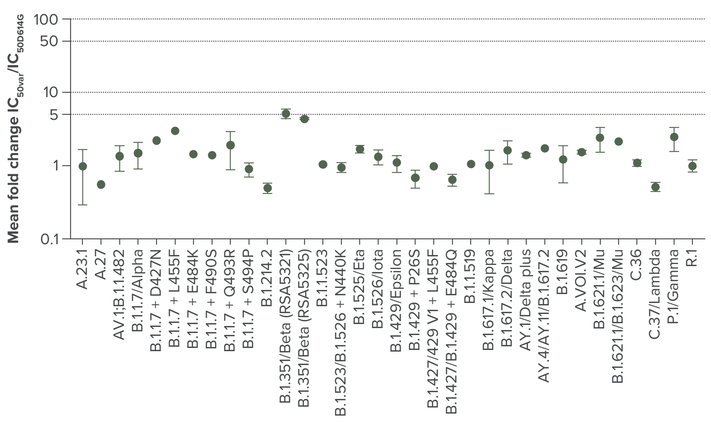
RESULTS

In vitro neutralising activity of ADG20

- ADG20 displayed in vitro neutralisation activity within 0.5- to 5.1-fold of reference D614G strain for all pseudovirus variants tested (**Figure 1A**)
  - Delta plus/AY.1, Lambda/C.37, and Mu/B.1.621 variants remained sensitive to ADG20
- ADG20 maintained neutralising activity against all tested SARS-CoV-2 variants incorporating mutations reported to confer increased resistance to EUA mAbs (**Figure 1B**)
  - IC_{50} values for ADG20 (within 0.6- to 2.4-fold of the D614G strain) were lower than those observed for bamlanivimab, etesevimab, casirivimab, imdevimab, and sotrovimab

Figure 1. In vitro ADG20 neutralising activity against SARS-CoV-2 variants

A. ADG20 neutralising activity against circulating SARS-CoV-2 variants



Adagio has utilised the non-clinical and pre-clinical services offered by the National Institute of Allergy and Infectious Diseases.

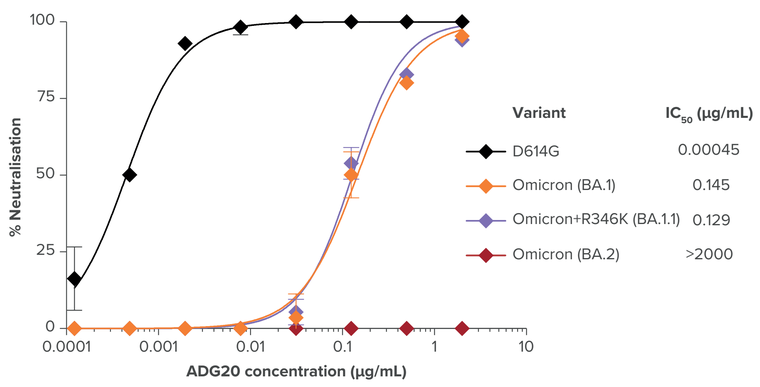
At least 2 independent experiments were performed for each variant. The bars represent standard deviation.

B. ADG20 in vitro neutralising activity against SARS-CoV-2 variants associated with resistance to EUA mAbs

The points represent neutralising activity of ADG20 against SARS-CoV-2 variants.

- ADG20 demonstrated in vitro neutralising activity against BA.1 and BA.1.1, but not BA.2, sub-lineages of Omicron (**Figure 2**)

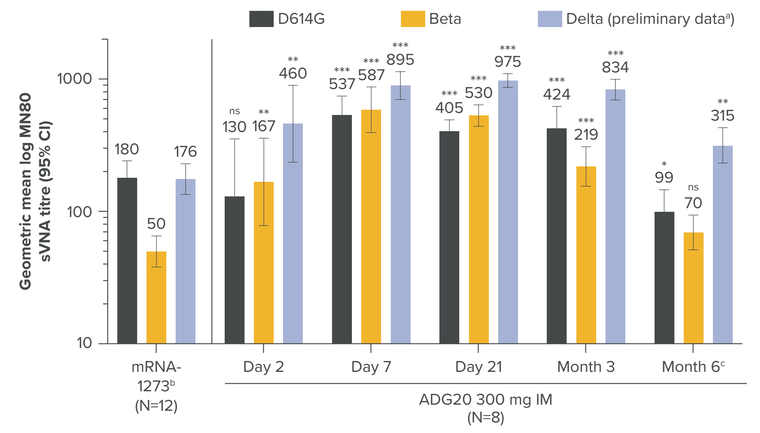
Figure 2. In vitro ADG20 neutralising activity against the Omicron variant and subvariants



ADG20 sVNA titres

- sVNA titres following a single 300 mg IM injection of ADG20 exceeded titres against D614G, Beta, and Delta variants 7–30 days after 2-dose mRNA-1273 vaccination, and this trend was maintained for at least 3 months (**Figure 3**)
  - By 6 months, ADG20 sVNA titres were 0.6-, 1.4-, and 1.8-fold of peak titres induced by mRNA-1273 vaccination for variants tested

Figure 3. ADG20-associated sVNA titres against D614G, Beta, and Delta variants compared with peak responses following mRNA-1273 vaccination



[a]Statistical comparisons for Delta are based on preliminary results.

[b]Peak vaccine response timepoint: 7–30 days post second dose.

[c]Excludes samples taken following SARS-CoV-2 vaccination from participants who received vaccination during the trial.

Statistical comparisons of titres achieved by ADG20 against each variant was performed using 2-sided Mann Whitney U tests: *P<0.05; **P<0.01; ***P<0.001; ns, non-significant vs mRNA-1273 vaccination response against the corresponding variant.

KEY FINDINGS

ADG20 demonstrated broad in vitro neutralising activity against SARS-CoV-2 VOCs, including Alpha, Beta, Delta, Gamma, and the Omicron BA.1 and BA.1.1 sub-lineages

ADG20 displayed no detectable neutralising activity against the Omicron BA.2 sub-lineage at the highest concentration tested

Anti–SARS-CoV-2 sVNA titres after a single 300 mg IM injection of ADG20 exceeded titres after 2-dose mRNA-1273 vaccination in healthy adults for variants tested

CONCLUSIONS

- ADG20 retained neutralising activity with varying potencies against SARS-CoV-2 variants tested, including Delta and Omicron BA.1 and BA.1.1 (but not BA.2) VOCs
- sVNA titres from a phase 1 study support the potential for a single 300 mg injection of ADG20 to provide prolonged protection against symptomatic COVID-19 for susceptible SARS-CoV-2 variants
- Preliminary data from phase 2/3 clinical trials demonstrated that in the pre-Omicron population, ADG20 met the primary endpoints with statistical significance across pre- and post-exposure prophylaxis and treatment for COVID-19

REFERENCES

1. Rappazzo CG, et al. *Science*. 2021;371:823-829.
2. Dejnirattisai W, et al. *Cell*. 2021;184:2939-2954.
3. Liu C, et al. *Cell*. 2021;184:4220-4236.e13.
4. Kaku CI, et al. Presented at ISIRV-WHO; October 19-21, 2021; Virtual. Poster 130.
5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04859517. Accessed April 4, 2022.
6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04805671. Accessed April 4, 2022.
7. Lauring AS, Hodcroft EB. *JAMA*. 2021;325:529-531.
8. Liu L, et al. *Nature*. 2022;602:676-681.
9. Lusvarghi S, et al. *bioRxiv*. 2021. DOI:/10.1101/2021.07.16.452748.
10. Neerukonda SN, et al. *PloS One*. 2021;16:e0248348.
11. ADG-DOF-007; Waltham, MA: Adagio Therapeutics, Inc.; 2022.
12. ADG-DOF-008; Waltham, MA: Adagio Therapeutics, Inc.; 2022.
13. ADG-DOF-009; Waltham, MA: Adagio Therapeutics, Inc.; 2022.
14. Schmidt P, et al. Presented at ISIRV-WHO; October 19-21, 2021; Virtual. Poster 131.

DISCLOSURES

CIK is an employee of Adimab LLC. KN, PS, and YL are employees and stockholders in Adagio Therapeutics, Inc. FE has received consulting fees from Adagio Therapeutics, Inc. LMW is an employee of Adagio Therapeutics, Inc., and an inventor on a patent application submitted by Adagio Therapeutics, Inc., describing the engineered SARS-CoV-2 antibody.

Acknowledgments

The authors would like to thank Carol Weiss, MD, PhD, Laboratory of Immunoregulation, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, US Food and Drug Administration, for performing the HIV-based pseudovirus assays. Collection and processing of blood from mRNA-1273–vaccinated donors conducted at DartLab, the Immune Monitoring and Flow Cytometry Shared Resource at the Norris Cotton Cancer Center Dartmouth College, was supported by NCI Cancer Center Support Grant 5P30CA023108-42.

This study was funded by Adagio Therapeutics, Inc. Writing assistance was provided by Georgiana Manica, PhD, of Parexel, and was funded by Adagio Therapeutics, Inc.

Poster presented at the 32nd European Congress of Clinical Microbiology & Infectious Diseases (ECCMID); April 23–26, 2022; Lisbon, Portugal