Poster 1089

Use of a Whole-Body Quantitative System Pharmacology Physiologically Based Pharmacokinetic Model to Support ADG20 Dose Selection for the Prevention of Coronavirus Disease (COVID-19)

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INTRODUCTION

- ADG20 is a fully human IgG1 monoclonal antibody engineered to have high potency and broad neutralization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other SARS-like CoVs with pandemic potential by binding to a highly conserved epitope in the receptor-binding domain of the spike protein[1]
- The Fc region of ADG20 has been modified to provide an extended half-life[1]
- In vitro, ADG20 displays high binding affinity and potent neutralization against all SARS-CoV-2 variants tested, including variants being monitored and variants of concern (B.1.1.7/Alpha, B.1.351/Beta, P.1/Gamma, B.1.617.2/Delta)[2-4]
- ADG20 can be administered intramuscularly (IM) and is currently in clinical development and being evaluated for the potential treatment and prevention of COVID-19
- The quantitative systems pharmacology whole-body physiologically based pharmacokinetic (QSP/PBPK) modeling and simulation analyses presented here were used to support an ADG20 dose regimen decision for a Phase 2/3 COVID-19 prevention study (EVADE: NCT04859517)

METHODS

Objectives

- To utilize a platform ADG20 QSP/PBPK model to support dose selection for a Phase 2/3 COVID-19 prevention trial

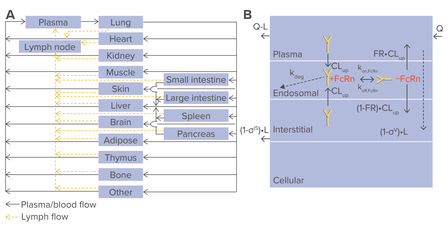
QSP whole-body PBPK model

- The QSP/PBPK model had previously been shown to adequately predict first-in-human serum ADG20 concentrations with good precision and minimal bias[5]
- The model comprised 15 specific tissues and one representing the rest of the body (**Figure 1A**); each tissue was connected through blood and lymph flow to the systemic circulation
- In the endothelial space of each tissue, monoclonal antibodies enter by pinocytosis and via the interaction with neonatal Fc receptor (FcRn), FcRn-bound drug is recycled, and unbound drug is eliminated (k_{deg}; **Figure 1B**)
  - The dissociation rate constant for FcRn ($K_{D,FcRn}$) was estimated based on human PK data from other extended half-life monoclonal antibodies (**Figure 1B**)
  - The distribution of patches of positive charge was used as a covariate on the rate of pinocytosis into the endosomal space (CL_{up}; **Figure 1B**)

Model-based simulations and dose regimen discrimination

- Using the ADG20 QSP/PBPK model and a US Centers for Disease Control (CDC) reference body weight distribution[6] truncated to 45 to 150 kg, 1000 concentration-time profiles were simulated for a range of candidate single-injection regimens
- Prior to availability of human PK data, the QSP whole-body PBPK model forecasts in humans were based upon the estimated IM bioavailability from NHP, while the $K_{D,FcRn}$ value of 9.55 nM was derived based upon multiplying the mean NHP:human $K_{D,FcRn}$ ratio for other extended half-life antibodies to the NHP $K_{D,FcRn}$ value for ADG20
- The QSP whole-body PBPK model was later optimized by estimating $K_{D,FcRn}$ (4.27 nM) and IM bioavailability (92.2%) using the interim human PK data, along with estimating inter-individual variability for some key parameters to better reflect observed variability
- ADG20 IM dosing regimens were evaluated against two criteria
  - Ability to maintain serum ADG20 concentrations 100-fold higher than the in vitro 90% inhibitory concentration (IC_{90}) of 0.011 µg/mL[7] against authentic SARS-CoV-2 (USA-WA1/2020) for a minimum of 6 months in ≥90% of simulated patients
    - This threshold was based on a precedent with respiratory syncytial virus and HIV, in which serum concentrations approximately 100-fold higher than the in vitro IC_{50} were associated with protection in animal models and/or in humans[8-10]
  - Ability to attain measured 50% neutralization (MN50) serum virus-neutralizing antibody (sVNA) titers within the range of peak sVNA titers for COVID-19 vaccine recipients[11]
- After measured human ADG20 serum concentrations became available, the QSP/PBPK model was optimized by refitting to the human data, allowing for formal estimation of interindividual variability, and ADG20 dose regimen simulations were updated

Figure 1. QSP whole-body PBPK model in (A) tissues and (B) cells



σ^{x}, vascular reflection coefficient; σ^{ls}, interstitial fluid reflection coefficient; CL_{up}, rate of pinocytosis of antibody entry and exit from the epithelial space; FR, fraction of FcRn bound antibody that recycles to the vascular space; L, lymphatic flow rate; k_{deg}, degradation rate constant; $k_{on,FcRn}$, first-order dissociation rate constant of antibody from FcRn; $k_{on,FcRn}$, second-order association rate constant for binding of antibody to FcRn; Q, blood or tissue flow rate.

RESULTS

QSP whole-body PBPK model–based simulation

- Histograms of the simulated human body weight and $K_{D,FcRn}$ distributions in humans are shown in **Figure 2**
- Using the original model, single ADG20 IM injections of 300 mg or greater were forecasted to maintain serum concentration in most simulated patients for up to 12 months (**Figure 3**)
- **Table 1** shows ADG20 potency against SARS-CoV-2 variants of concern
- The optimized model confirmed these predictions and suggests that the single 300 mg IM injection provides a margin of coverage for SARS-CoV-2 variants with higher IC_{90} values than those of the original variant used to support this target (**Figure 4**)
- Based on data from a first-in-human Phase 1 study, ADG20 maintains MN50 titers within the range of those achieved by COVID-19 vaccine recipients following 2 doses (AZD1222, mean titer 80; mRNA-1273, mean titer 327)[11]
  - Given a QSP/PBPK forecasted ADG20 52-week post-dose median serum concentration of 5.3 mg/L and a regression relating ADG20 concentration and MN50 titer,[11] the predicted MN50 is 231 one year post-dose

Figure 2. Simulated human body weight (A) and calculated $K_{D,FcRn}$ values for other extended half-life antibodies in healthy humans (B)

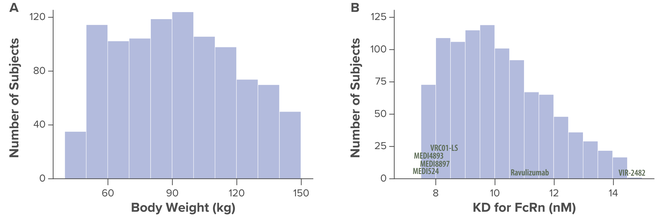
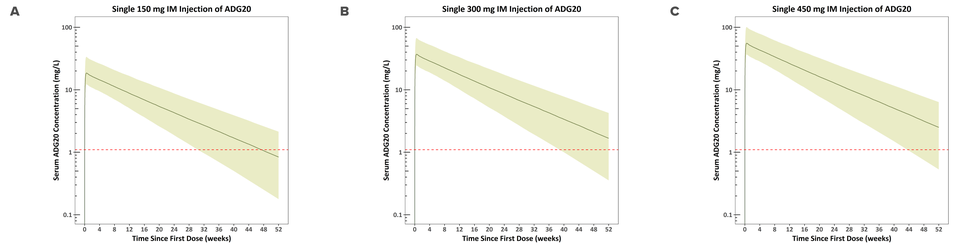


Table 1. ADG20 potency against SARS-CoV-2 variants of concern[12]

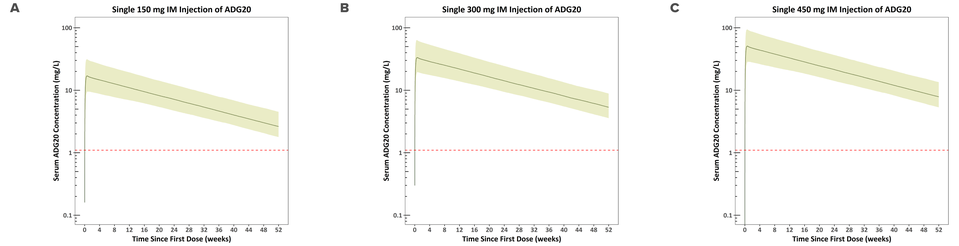
Lineage	WHO Designation	IC_{50}, µg/mL	IC_{90}, µg/mL	100 × IC_{90}, µg/mL
Victoria	–	0.004	0.015	1.5
B.1.1.7	Alpha	0.007	0.023	2.3
B.1.351	Beta	0.013	0.095	9.5
P.1	Gamma	0.008	0.034	3.4
B.1.617.2	Delta	0.007	0.04	4

Figure 3. QSP model–predicted median (90% PI) serum ADG20 PK profiles following a single IM 150 mg (A), 300 mg (B), and 450 mg (C) injection in humans predicted a priori based on distributions shown in Figure 2



Dashed red line represents 100 × in vitro IC_{90} of 0.011 µg/mL or 1.1 mg/L against the USA-WA1/2020 strain. PI, prediction interval.

Figure 4. Optimized QSP model–predicted median (90% PI) serum ADG20 PK profiles following a single IM 150 mg (A), 300 mg (B), and 450 mg (C) injection in humans



Dashed red line represents 100 × in vitro IC_{90} of 0.011 µg/mL or 1.1 mg/L against the USA-WA1/2020 strain.

KEY FINDINGS

A QSP whole-body PBPK modeling and simulation approach was used to evaluate candidate ADG20 dose regimens for a Phase 2/3 COVID-19 prevention study (EVADE)

Candidate ADG20 dosing regimens were evaluated for their ability to

- **Maintain serum ADG20 concentrations 100-fold higher than the in vitro IC_{90} against authentic wild-type SARS-CoV-2 for a minimum of 6 months**

And

- **Attain measured peak serum virus-neutralizing titers within range of those achieved at peak for COVID-19 vaccine recipients**

A single 300 mg IM ADG20 injection is projected to maintain targeted serum ADG20 concentrations for up to 12 months and is predicted to maintain vaccine-like titers for one year[11]

This innovative modeling and simulation approach was a key element in the rapid advancement of the ADG20 program during the COVID-19 pandemic

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CONCLUSIONS

- These data support the evaluation in clinical trials of a single 300 mg IM injection of ADG20 for the prevention of COVID-19 in both pre- and post-exposure settings
- Data compiled to date suggest that the single 300 mg IM injection of ADG20 has a projected ability to rapidly exceed the IC_{90} target in the majority of simulated patients, to maintain effective concentrations for up to 12 months, and to provide greater efficacy margins than lower doses for coverage against SARS-CoV-2 variants

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DISCLOSURES

LEC, LMW, and PGA are employees of Adagio Therapeutics, Inc. EDT and SAVW received funding from Adagio Therapeutics, Inc. for the conduct of this work. LMW is an inventor on a patent application submitted by Adagio Therapeutics, Inc., describing the engineered SARS-CoV-2 antibody.

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