*Background.* ADG20 is a fully human IgG1 monoclonal antibody engineered to have potent and broad neutralization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other SARS-like CoVs with pandemic potential as well as an extended-half-life. ADG20 is administered intramuscularly (IM). A QSP/PBPK model was constructed to support dose selection for a COVID-19 Phase 2/3 prevention trial (EVADE: NCT04859517).

Methods. A QSP/PBPK model and a CDC reference adult body weight distribution (45–150 kg) were used to simulate 1000 concentration-time profiles for candidate single-dose regimens of ADG20 (150–450 mg IM). As serum virus neutralizing antibody (sVNA) titers are reportedly a key correlate of protection from COVID-19, a regression equation between time-matched serum ADG20 concentrations (following a 300 mg IM dose) and sVNA titers was developed using measured titers against authentic SARS-CoV-2 determined by a plaque reduction neutralization assay. Projected ADG20 serum concentrations relative to neutralization potency in vitro (90% inhibitory concentration [IC_{90}]) for authentic SARS-CoV-2 were also evaluated.

Results. The measured 50% neutralization titer (MN50; geometric mean [coefficient of variation, %]) was 1382 (32.7%) 13 days after a single 300 mg IM dose of ADG20. This was within the range of peak sVNA titers reported for COVID-19 vaccine recipients. Using the linear equation relating serum ADG20 concentration to time matched individual MN50 titers and the QSP/PBPK median PK prediction, the anticipated median MN50 exceeded the threshold for protection from SARS-CoV-2 infection established in a non-human primate adoptive transfer model for up to 52 weeks. Based on the QSP/PBPK median PK prediction, median ADG20 serum concentrations are projected to remain >100-fold above the ADG20 IC_{90} value of 0.011 mg/L against authentic SARS-CoV-2 for up to 52 weeks (Figure).

Conclusion. Following administration of a single 300 mg IM dose, sVNA titers and concentrations of ADG20 are projected to remain above thresholds anticipated to be required for protection against COVID-19 for up to 52 weeks. These data support the evaluation of a single ADG20 300 mg IM dose for the prevention of COVID-19.

Figure. QSP/PBPK model forecast of ADG20 300 mg IM in adults.
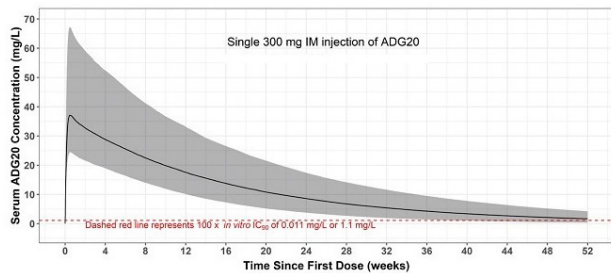
Predicted median serum ADG20 concentration is shown with the dotted line representing 100× in vitro IC90 of 0.011 mg/L or 1.1 mg/L; the solid black line represents the simulated median; the shaded area represents the 90% prediction interval. The predicted median half-life of ADG20 300 mg IM exceeded 74 days. PBPK model inputs include Ln-normal Kd,FcRn of 9.55 nM (10% IIV); IM bioavailability of 100%; 15% IIV on muscle lymph RC; and Centers for Disease Control and Prevention weight distribution of 45–150 kg. FcRn, neonatal Fc receptor; IIV, inter-individual variability; Kd, dissociation constant; Ln, log-normal; RC, reflection coefficient.

1090. Does calculation method matter for targeting vancomycin AUC?

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Background. Recent vancomycin (VAN) guidelines recommend targeting an area under the curve (AUC) concentration of 400-600 for treatment of methicillin resistant *Staphylococcus aureus* infections. Multiple strategies for calculating AUC exist, including first order pharmacokinetic (foPK) equations and Bayesian models. Most clinical applications of foPK assume unchanged patient status and project ideal administration times to estimate exposure. Bayesian modeling provides the best estimate of true drug exposure and can incorporate changing patient covariates and exact doses. We compared two commonly used foPK methods to Bayesian estimates of VAN AUC.

Comparison of AUC estimation methods
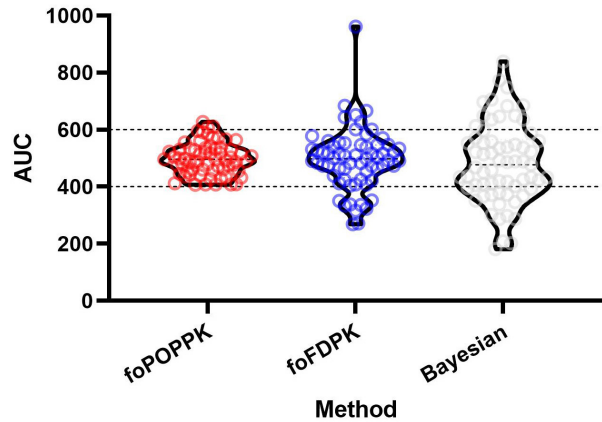
Graphs depict calculated AUCs using the three different methods: 1) Population PK estimated (foPOPPK) 2) Two-level first dose estimated (foFDPK) 3) Bayesian estimated.

Methods. First order equations were performed using population PK estimates (foPOPPK) to estimate steady state (SS) AUC and initial doses. Two concentrations after first dose were used to estimate SS AUC (foFDPK). A 2-compartment Bayesian model allometrically scaled for weight and adjusted for creatinine clearance was used to determine 24-48 hour AUCs. Differences between AUCs were compared using a mixed-effects analysis, and correlation of foPK equations to Bayesian estimates was described using Spearman's correlation. Patient results from each method were classified as below (< 400), within (400-600), or above (>600) targets.

Results. 65 adult patients were included. The median and IQR for calculated AUCs using foPOPPK, foFDPK, and Bayesian methods were 495.6 (IQR: 76.6), 498.2 (IQR: 107.4), and 472.1 (IQR: 177.9), respectively with p >0.65 for both foPK methods vs. the Bayesian method. AUCs predicted by foPK equations were poorly correlated with Bayesian AUCs (Spearman's rho= -0.08, p=0.55), while AUCs from foFDPK better correlated with Bayesian AUCs (Spearman's rho= 0.48, p=0.00). AUCs were within, above, and below target for 54%, 20%, and 26% for the Bayesian model; 95%, 5% and 0% for foPOPPK; and 74%, 12%, and 14% for foFDPK. foPK AUC estimates concurred with Bayesian estimates only 52% of the time.

Conclusion. AUCs calculated by the three methods did not differ on average, but dosing recommendations for foPK at the patient level varied substantially compared to the Bayesian method. This difference is because Bayesian estimation incorporates actual patient exposures while foPK equations rely on idealized dose timing to predict AUCs.

1091. Validation of an Allometrically Scaled Body Weight Equation to Predict Vancomycin Clearance and Guide 24-Hour Vancomycin AUC Dosing in Obese Patients

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Background. Accurately determining empiric vancomycin (VAN) doses in obese patients represents a clinical challenge. A recent population pharmacokinetic (PK) study provided an equation to estimate vancomycin clearance (CL) based on age, sex, serum creatinine (Scr), and allometrically scaled body weight. The purpose of this study was to validate this equation in a population of obese adults treated with vancomycin at eight community-based hospitals and use the CL estimate to guide empiric VAN dosing.

Methods. The study period was November 1, 2020 and March 30, 2021. Patients were included if they were ≥ 18-year-old with a body mass index (BMI) ≥ 30 kg/m^2, had an empiric dose targeting an AUC24 determined using the above referenced equation, and had a calculated AUC24. Only the first vancomycin course and AUC calculation for each patient were included. Patients with a creatinine clearance < 30ml/min and pregnant women were excluded. AUC24 and other PK parameters were calculated using two levels and noncompartmental analysis. Observed versus predicted CL and AUC24 were plotted to determine correlation.

Results. Sixty patients were included, of which 60% were male and 33% had a confirmed methicillin-resistant *Staphylococcus aureus* infection. The mean age, BMI, and baseline Scr were 61.8 years, 37.8 kg/m^2, and 0.99 mg/dL, respectively. Fifty-three