Contractor) **Donald E. Mager, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Lynn E. Connolly, MD, PhD**, **Adagio Therapeutics, Inc.** (Employee) **Paul G. Ambrose, PharmD**, **Adagio Therapeutics, Inc.** (Employee)

1087. Imipenem-Cilastatin-Relebactam (I/R) Pharmacokinetics (PK) in Critically Ill Patients with Augmented Renal Clearance (ARC)

Andrew J. Fratoni, PharmD[1]; John W. Mah, MD[1]; David P. Nicolau, PharmD[1]; Joseph L. Kuti, PharmD[2]; [1]Hartford Hospital, Hartford, Connecticut; [2]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut

Session: P-62. PK/PD Studies

Background. Imipenem (IMI) and relebactam (REL) are predominantly excreted via glomerular filtration. ARC is a common syndrome in critically ill patients with sepsis, whereby increased renal blood flow may result in enhanced solute clearance; therefore, sub-therapeutic antibiotic concentrations are of concern. Herein, we describe the PK of I/R in critically-ill patients with confirmed ARC.

Methods. Infected patients in the intensive care unit with ARC (CrCl ≥130 mL/min) received a single dose of I/R 1.25g as a 30min infusion. Blood samples were collected over 6 hours (hr) for IMI and REL concentration determination by a validated LC/MS/MS assay. Protein binding was assessed at 0.5hr by ultrafiltration (UF). An 8hr urine creatinine (UCr) collection was performed to confirm ARC. IMI and REL plasma concentrations were fitted to compartmental models in WinNonlin. Simulated concentration vs time profiles were used to assess attainment of pharmacodynamic (PD) targets for IMI (30%*f*T >MIC) and REL (*f*AUC:MIC 18) at the susceptibility breakpoint of 2 mg/L.

Results. Five patients (60% female) completed the study. Mean (SD) age, weight, and APACHE II were 43 (14) years, 90 (15) kg, and 16 (6), respectively. All patients had confirmed ARC with CrCl of 160.6 ± 47.0 mL/min (range: 135-244mL/min) based on UCr. Both IMI and REL concentrations fitted a 2-compartment better than 1-compartment model. IMI PK was: clearance, 17.9 ± 8.7 L/hr; volume of central compartment, 15.6 ± 11.2 L; volume of peripheral compartment, 10.6 ± 5.4 L; and intercompartmental clearance, 16.6 ± 14.5 L/hr. REL PK parameters were 11.9 ± 7.5 L/hr, 17.0 ± 11.3 L, 13.5 ± 9.9 L, and 13.4 ± 11.1 L/hr, respectively. Half-life was 1.5 ± 0.5 for IMI and 2.8 ± 2.2 hr for REL. Protein binding for IMI ranged from 0-10%, while REL was 0-14%. IMI *f*T >MIC ranged from 40-90%, and REL *f*AUC:MIC ranged from 22.6-59.0.

Conclusion. These are the first data to describe IMI and REL PK in critically-ill infected patients with ARC. Despite plasma clearance values greater than those reported in healthy volunteers and patients in clinical trials, I/R 1.25g as a 30 minute infusion provided optimal exposure in all patients for isolates with MICs ≤2 mg/L.

Disclosures. **David P. Nicolau, PharmD**, **Abbvie, Cepheid, Merck, Paratek, Pfizer, Wockhardt, Shionogi, Tetraphase** (Other Financial or Material Support, I have been a consultant, speakers bureau member, or have received research funding from the above listed companies.) **Joseph L. Kuti, PharmD**, **Allergan** (Speaker's Bureau)**BioMérieux** (Consultant, Research Grant or Support, Speaker's Bureau)**Contrafect** (Scientific Research Study Investigator)**GSK** (Consultant)**Merck** (Research Grant or Support)**Paratek** (Speaker's Bureau)**Roche Diagnostics** (Research Grant or Support)**Shionogi** (Research Grant or Support)**Summit** (Scientific Research Study Investigator)

1088. A Whole-Body Quantitative System Pharmacology Physiologically-Based Pharmacokinetic (QSP/PBPK) Model to Support Dose Selection of ADG20: an Extended Half-Life Monoclonal Antibody Being Developed for the Treatment of Coronavirus Disease (COVID-19)

Evan D. Tarbell, PhD[1]; Scott A. Van Wart, PhD[1]; Dhaval K. Shah, PhD[2]; Laura M. Walker, PhD[3]; Andrew Santulli, PhD[1]; Lynn E. Connolly, MD, PhD[4]; Donald E Mager, PharmD, PhD[2]; Ashley N. Brown, PhD[5]; Paul G. Ambrose, PharmD[4]; [1]Enhanced Pharmacodynamics LLC, Buffalo, New York; [2]University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York; [3]Adimab LLC, Lebanon, New Hampshire; [4]Adagio Therapeutics, Inc., Waltham, Massachusetts; [5]University of Florida, College of Medicine, Orlando, Florida

Session: P-62. PK/PD Studies

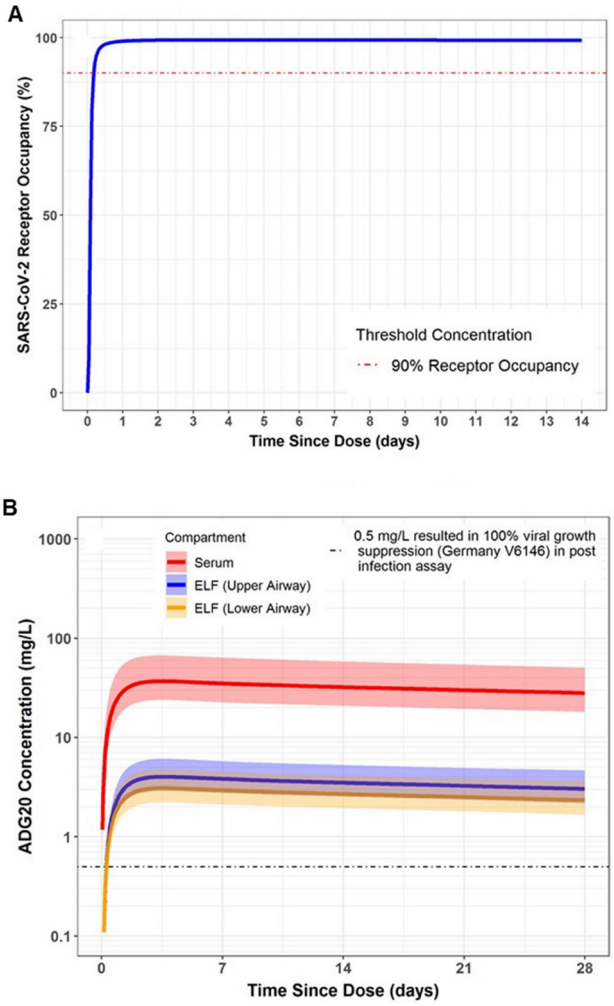
Background. ADG20 is a fully human IgG1 monoclonal antibody engineered to have potent and broad neutralization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other SARS-like CoVs with pandemic potential and an extended half-life. ADG20 is administered intramuscularly (IM). A QSP/PBPK model was constructed to support dose selection for a Phase 2/3 trial of ambulatory patients with mild to moderate COVID-19 (STAMP: NCT04805671).

Methods. A QSP/PBPK model was used to simulate receptor occupancy (RO) and drug exposure in the upper airway (nasopharyngeal/oropharyngeal epithelial lining fluid [ELF] compartment). RO was linked to an existing viral dynamic model to enable the prediction of the natural time course of viral load and the effect of ADG20 on viral clearance and infectivity rate. RO was calculated using: 1) in vitro ADG20–SARS-CoV-2 binding kinetics (association rate constant (k_{on}) of 1.52E+06 M^{-1}•s^{1} and dissociation rate constant (k_{off}) of 2.81E-04 s^{-1} from a Biacore assay; 2) time course of ADG20 concentrations in ELF; and 3) time course of viral load following ADG20 administration. Molar SARS-CoV-2 viral binding site capacity was calculated assuming 40 spike proteins per virion, 3 binding sites per spike, and an initial viral load of log 10^{7} copies/mL for all patients. The QSP/PBPK model and a 2018 CDC reference body weight distribution (45–150 kg) were used to simulate 1000 concentration-time profiles for a range of candidate ADG20 regimens. ADG20 regimens were evaluated against 2 criteria: 1) ability to attain near complete (>90%), and durable (28-day) SARS-CoV-2 RO in the ELF; and 2) ability to maintain ELF ADG20 concentrations relative to a concentration (0.5 mg/L) associated with 100% viral growth suppression in an in vitro post-infection assay.

Results. A single 300 mg IM ADG20 dose met the dose selection criteria in terms of RO (Figure A) and viral growth suppression (Figure B).

Conclusion. These data support the evaluation of an ADG20 300 mg IM dose for the treatment of mild to moderate COVID-19. ADG20 is forecasted to attain near complete (>90%) SARS-CoV-2 RO in the ELF and maintain ELF ADG20 concentrations above that associated with 100% viral growth suppression in vitro.

Figure. QSP/PBPK model forecast of ADG20 300 mg IM in adults



(A) Predicted RO expressed as percent occupancy with the dotted line representing the threshold for 90% RO. (B) Predicted median concentration of ADG20 relative to a concentration (0.5 mg/L) associated with 100% viral growth suppression as indicated by the dotted line; the shaded area represents the 90% prediction interval.

Disclosures. **Evan D. Tarbell, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Scott A. Van Wart, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Laura M. Walker, PhD**, **Adagio Therapeutics, Inc.** (Other Financial or Material Support, Laura M. Walker is an inventor on a patent application submitted by Adagio Therapeutics, Inc., describing the engineered SARS-CoV-2 antibody.) **Andrew Santulli, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Lynn E. Connolly, MD, PhD**, **Adagio Therapeutics, Inc.** (Employee) **Donald E Mager, PharmD, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Paul G. Ambrose, PharmD**, **Adagio Therapeutics, Inc.** (Employee)

1089. Use of a Whole-Body Quantitative System Pharmacology Physiologically-Based Pharmacokinetic (QSP/PBPK) Model to Support Dose Selection of ADG20: an Extended Half-Life Monoclonal Antibody Being Developed for the Prevention of Coronavirus Disease (COVID-19)

Scott A. Van Wart, PhD[1]; Evan D. Tarbell, PhD[1]; Kristin Narayan, PhD[2]; Laura M. Walker, PhD[3]; Lynn E. Connolly, MD, PhD[2]; Paul G. Ambrose, PharmD[2]; [1]Enhanced Pharmacodynamics LLC, Buffalo, New York; [2]Adagio Therapeutics, Inc., Waltham, Massachusetts; [3]Adimab LLC, Lebanon, New Hampshire

Session: P-62. PK/PD Studies

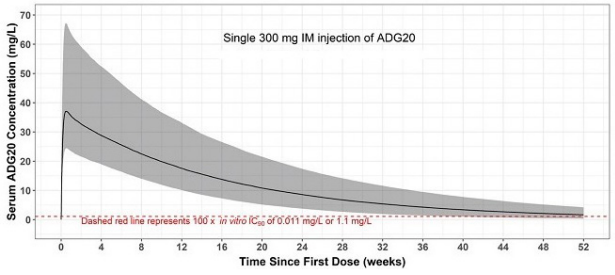
Background. ADG20 is a fully human IgG1 monoclonal antibody engineered to have potent and broad neutralization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other SARS-like CoVs with pandemic potential as well as an extended-half-life. ADG20 is administered intramuscularly (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.

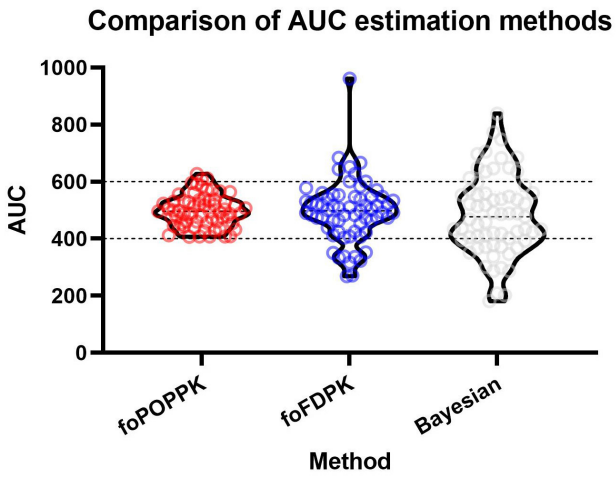
Disclosures. **Scott A. Van Wart, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Evan D. Tarbell, PhD**, **Adagio Therapeutics, Inc.** (Independent Contractor) **Kristin Narayan, PhD**, **Adagio Therapeutics, Inc.** (Employee) **Laura M. Walker, PhD**, **Adagio Therapeutics, Inc.** (Other Financial or Material Support, Laura M. Walker is an inventor on a patent application submitted by Adagio Therapeutics, Inc., describing the engineered SARS-CoV-2 antibody.) **Lynn E. Connolly, MD, PhD**, **Adagio Therapeutics, Inc.** (Employee) **Paul G. Ambrose, PharmD**, **Adagio Therapeutics, Inc.** (Employee)

1090. Does calculation method matter for targeting vancomycin AUC?

Jack Chang, PharmD[1]; Dhara Patel, Student[1]; Kimberly C. Claeys, PharmD[2]; Marc H. Scheetz, PharmD, MSc[3]; Emily Heil, PharmD, BCPS AQ-ID[4]; [1]Midwestern University, Downers Grove, Illinois; [2]University of Maryland School of Pharmacy, Baltimore, Maryland; [3]Midwestern University/Northwestern Memorial Hospital, Chicago, IL; [4]University of Maryland, Baltimore, Maryland

Session: P-62. PK/PD Studies

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.



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.

Disclosures. **Kimberly C. Claeys, PharmD**, **GenMark** (Speaker's Bureau) **Marc H. Scheetz, PharmD, MSc**, **Nevakar** (Grant/Research Support)**SuperTrans Medical** (Consultant)**US Patent #10688195B2** (Other Financial or Material Support, Patent holder)

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

Brent Footer, PharmD, BCPS[1]; Arthur Nguyen, PharmD[1]; Meagan Greckel, PharmD[1]; Colton Taylor, PharmD[2]; Alyssa Christensen, PharmD, BCIDP[2]; Gregory Tallman, PharmD, BCIDP, BCPS[3]; [1]Providence Portland Medical Center, Portland, Oregon; [2]Providence Saint Vincent Medical Center, Portland, Oregon; [3]School of Pharmacy, Pacific University, Portland, Oregon

Session: P-62. PK/PD Studies

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