QSP Strategy to Support Development of Adintrevimab for Prevention and Treatment of COVID-19

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SYM 6: Clinical Pharmacology Considerations for Monoclonal Antibodies Developed to Combat COVID-19

Location:Grand Ballroom D

Chair & Faculty: Sonia Pahwa, PhD – US Food & Drug Administration

Faculty: Scott Van Wart, PhD – Enhanced Pharmacodynamics LLC

Faculty: Timothy Bensman, PharmD, PhD – US Food & Drug Administration

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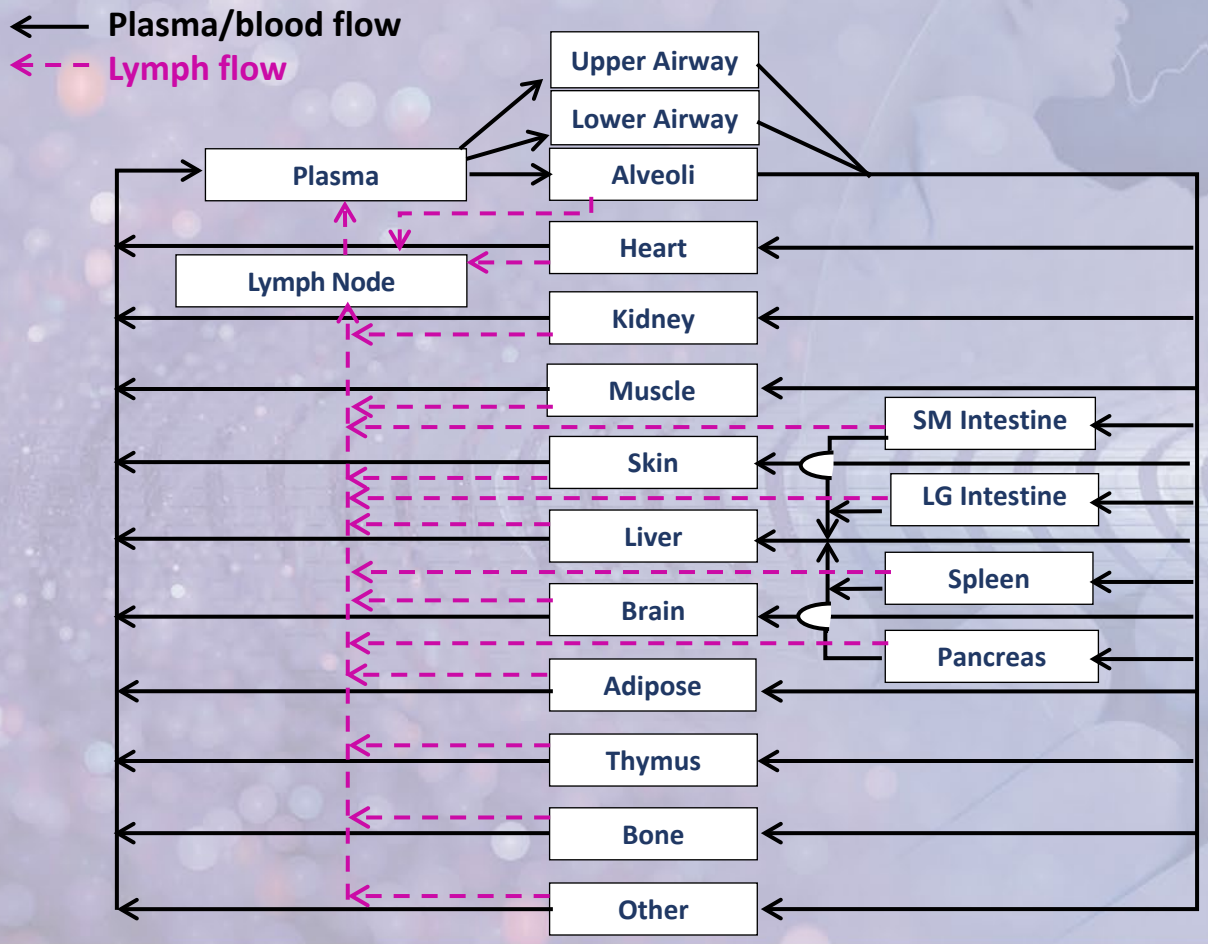
Introduction

- Adintrevimab is a fully human mAb developed by Invivyd, Inc. which was engineered to have an extended $T_{1/2}$ (alteration in Fc region) while maintaining high-affinity binding to SARS-CoV-2 spike protein
- Adintrevimab has demonstrated *in vitro* potency and broad neutralization against most SARS-CoV-2 variants until Omicron BA.2
- A QSP strategy was used to support clinical development of adintrevimab, and illustrates how we can support next-generation mAbs and evaluate efficacy against emerging SARS-CoV-2 variants

QSP Model to Predict Lung mAb PK



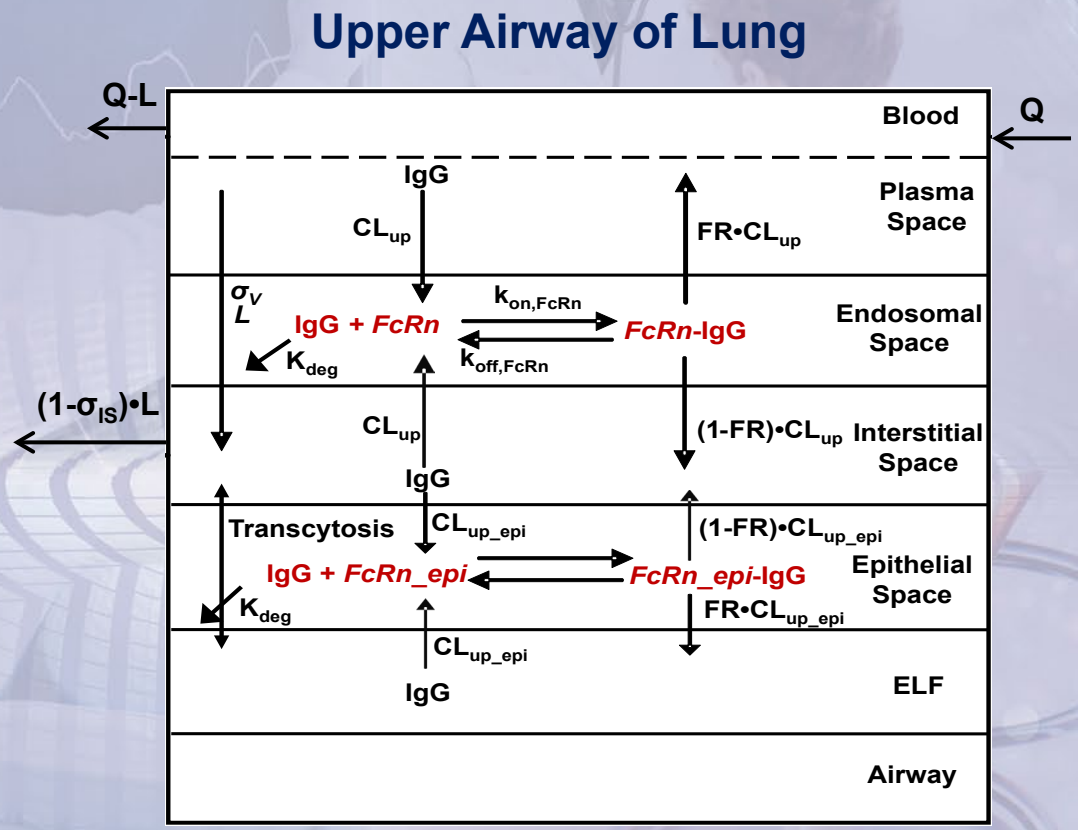
- A platform whole-body QSP model was developed to predict serum and lung concentrations for adintrevimab
- Lung was subdivided to more specifically quantify mAb distribution to upper airway (nasopharyngeal)

Tarbell E et al. 1088. Open Forum Infectious Diseases. 2021;8(Suppl 1):S635-S635.

Jagdale et al. *J Pharmacokinet Pharmacodyn.* 2022;49(6):607-624.

QSP Model Calibration to Serum/Lung Data

- Tissue uptake occurs via pinocytosis; FcRn bound mAb is recycled while unbound mAb is eliminated.
- Binding affinity of mAb to FcRn ($k_{off,FcRn}$) controls elimination half-life and is calibrated to serum PK data.
- Lung transport/uptake in platform model was previously calibrated to NHP and human BALF and NP swab data from literature
  - ❑ Sponsor lung PK data not initially required



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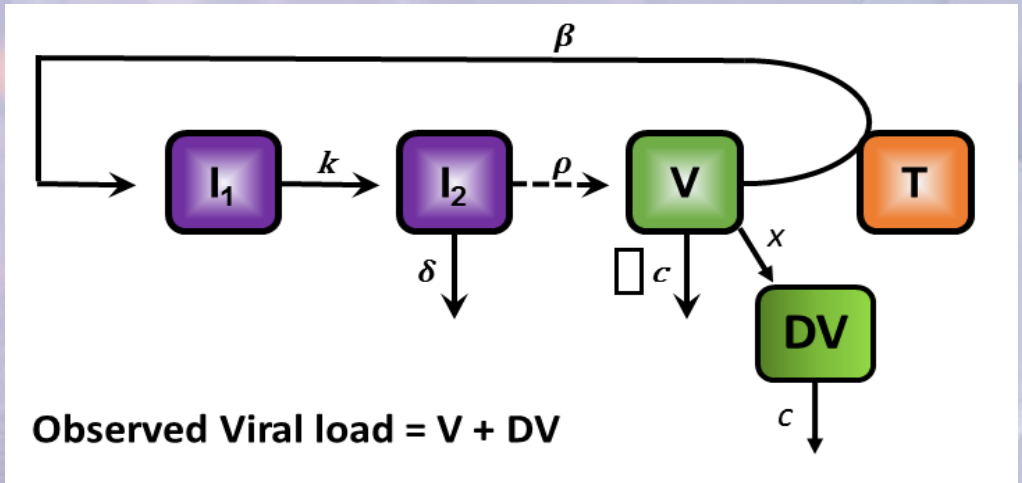
Viral Dynamic Model



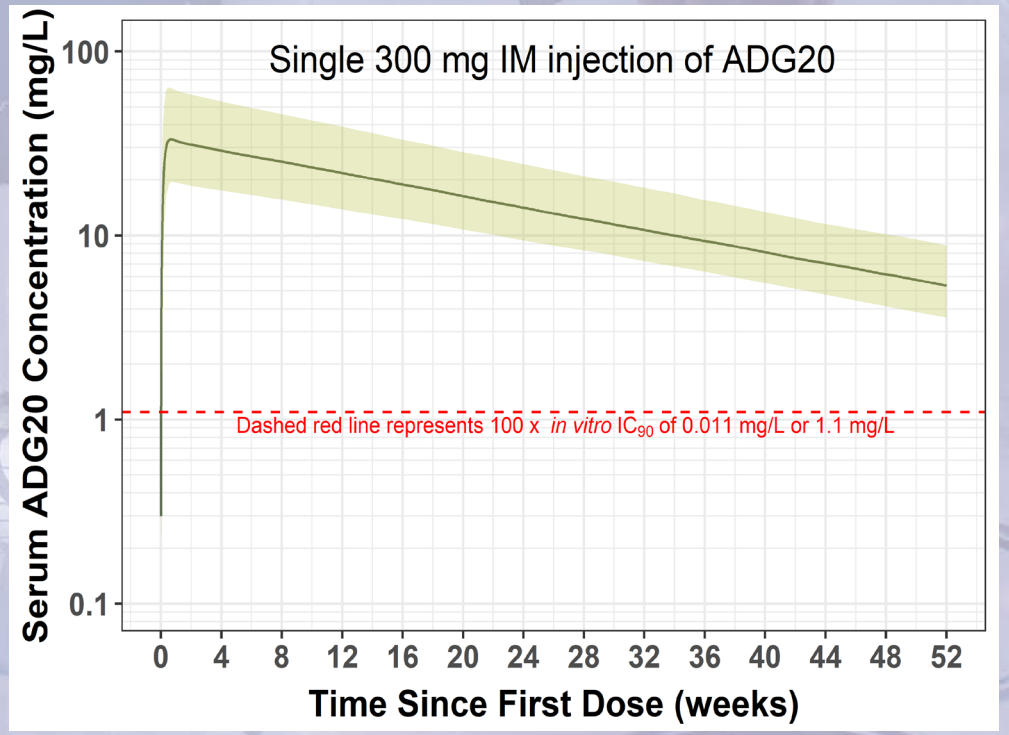
$$\text{Viral CL}\,(c) = TVc \cdot \left(1 + S_{Max} \cdot \frac{[\text{Lung UA ELF}]}{(SC_{50} + [\text{Lung UA ELF}])}\right)$$

- A QSP-linked viral dynamic model[1,2] was used to predict viral load based on lung UA ELF conc
- The viral dynamic model included both:
  - ❑ Active virus (V) which can continue infecting cells
  - ❑ Deactivated virus (DV) which is detectable by PCR but is no longer structurally intact and cannot bind to or be affected by adintrevimab
- The viral dynamic model was fit to individual NP swab data from clinical trials for adintrevimab
  - ❑ Maximal fold-change in viral clearance (S_{max}) and was informed by Regeneron program[3]
  - ❑ Viral production/replication rate and the SC_{50} was estimated separately for each variant

1. Tarbell E at al. ID Week poster; Oct 19-23, 2022
2. Gonçalves A et al. Clin Pharmacol Ther. 2020;9:509-514.
3. Regeneron COVID-19 Antibody Program Update. Sept 29 2020.

Evaluation of Doses for COVID-19 Prevention

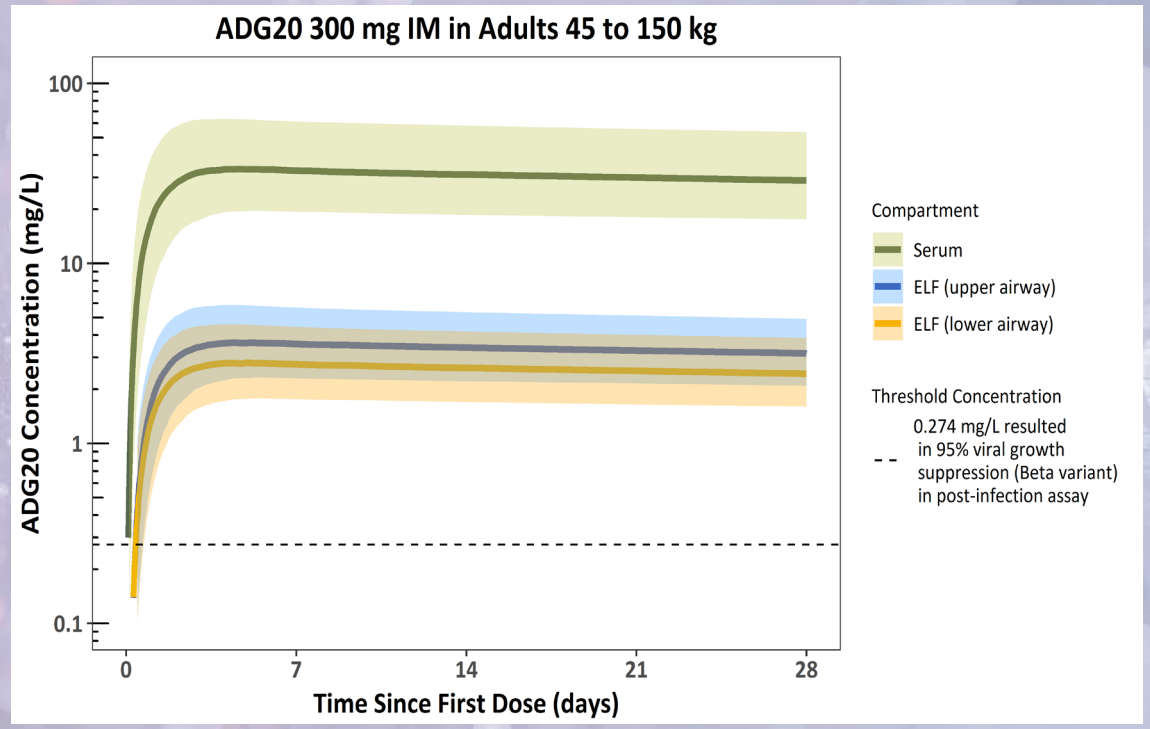
- Using the QSP model, adintrevimab PK dosing regimens were evaluated against two criteria:
  - ❑ Ability to maintain serum mAb concentrations 100-fold higher than *in vitro* IC_{90} of 0.011 mg/L
  - ❑ Ability to attain measured serum virus neutralizing titers (sVNT) within the range for COVID-19 vaccine recipients



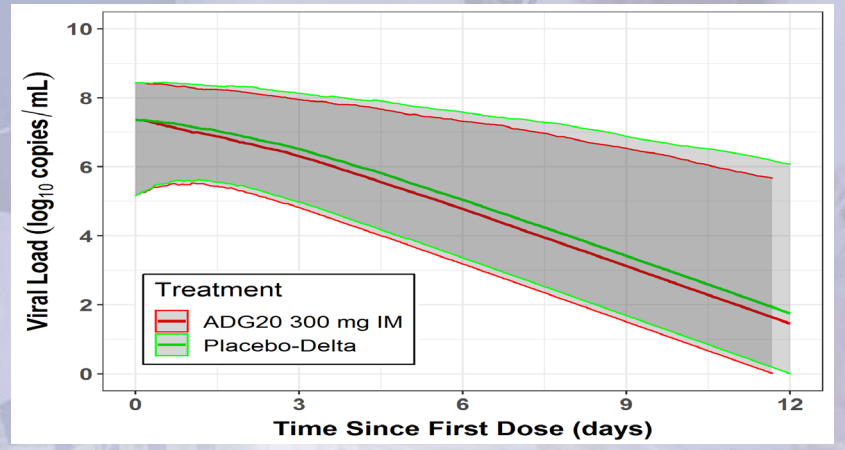
Van Wart SA et al. 1089. In Open Forum Infectious Diseases, vol. 8, no. Supplement 1, pp. S635-S636. US: Oxford University Press, 2021.

Evaluation of Doses for COVID-19 Treatment

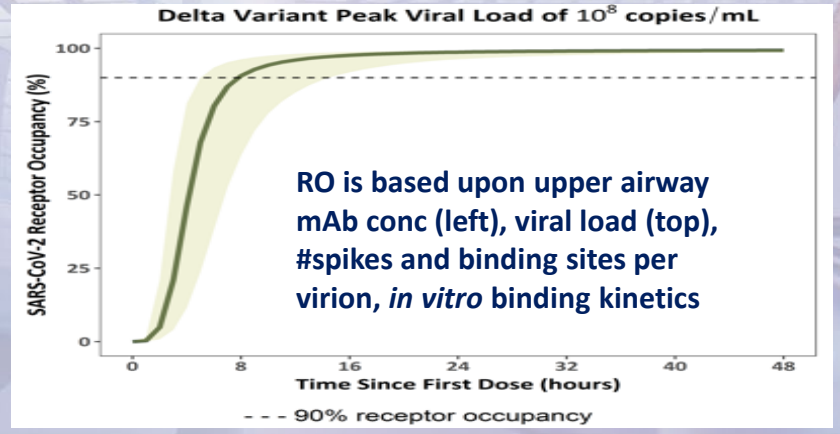
#1: Achieve Lung Upper Airway Conc. ≥ IC_{90} Associated with Growth Suppression in a Post-Infection Assay



#2: Achieve % Reduction in Viral Load Relative to Placebo



#3: Achieve and Maintain ≥90% SARS-CoV-2 RO



Tarbell E et al. 1088. Open Forum Infectious Diseases. 2021;8(Suppl 1):S635-S635

Summary

- This case study illustrates how combining PBPK modeling, *in vitro* binding and neutralization potency data, and meta-analysis of clinical trial data can provide a scientifically sound approach to develop the next generation SARS-CoV-2 mAbs.

- QSP modeling represents a universal approach to rapidly assess efficacy of SARS-CoV-2 targeting mAbs when future variants emerge simply by leveraging these prior data and adjusting *in vitro* binding and potency inputs or other assumptions (e.g., viral replication rate).