Adintrevimab population pharmacokinetics in phase 1 and phase 2/3 COVID-19 prevention and treatment study participants

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INTRODUCTION

- Adintrevimab is a fully human IgG1 monoclonal antibody engineered to have an extended half-life with high potency and broad neutralization against SARS-CoV-2 and other SARS-like coronaviruses[1–3]
- Adintrevimab pharmacokinetics (PK) were evaluated in a first-in-human, phase 1, randomized, double-blind study in healthy adults[4]
  - Results were consistent with the intended PK characteristics of adintrevimab (ie, prolonged half-life and high intramuscular bioavailability)[5]
- Safety and PK data from the phase 1 study supported the initiation of 2 phase 2/3 studies, EVADE (prevention of symptomatic COVID-19)[6] and STAMP (treatment of mild to moderate COVID-19)[7,8]
- The objective of the current analysis was to develop a population PK (PPK) model that describes the serum concentration–time profile of adintrevimab following intravenous (IV) and intramuscular (IM) administration

METHODS AND MODEL CHARACTERISTICS

Analysis Dataset

- A total of 1590 evaluable serum concentrations from 864 participants (both adolescents and adults) were available for development of the model
  - Phase 1 (300 mg IM, 500 mg IV, 600 mg IM): 196 samples from 24 participants (age 18–55 years)
  - EVADE (300 mg IM): 1069 samples from 653 participants (age 13–83 years)
  - STAMP (300 mg IM): 325 samples from 187 participants (age 15–93 years)

PPK Model Development

- Development of the model involved 3 main steps:
  1. Construction of the base structural/statistical model
  2. Conduct of a covariate analysis to identify descriptors associated with the interindividual variability (IIV) in PK
  3. Evaluation and qualification of the final model
- Base structural model development
  - Initially conducted using the phase 1 intensive PK sampling data only and consisted of the fitting of 1, 2, and 3 compartmental PPK models with linear elimination and first-order drug absorption
  - The model was then fit to pooled phase 1 and phase 2/3 data and refined as necessary to ensure a robust fit across all participants
- After an appropriate base structural model was identified, PPK covariate model development was undertaken using forward selection followed by a backward elimination procedure
- The resultant final PPK model was then evaluated for potential revisions such as removal of extraneous covariate relationships or modifications to the IIV and residual variability models
- The model was qualified by a prediction-corrected visual predictive check (PC-VPC)

Final PPK Model for Adintrevimab

- The final PPK model comprises 2 systemic compartments with zero-order infusion for IV administration and first-order absorption for IM administration
- IIV was estimated for apparent clearance (CL/F) and apparent volume of the central compartment (Vc/F) using a single shared IIV term with a scalar to allow for partitioning of the IIV
- There is moderate IIV in adintrevimab PK based on the IIV estimate of 52.2%. The shrinkage in the IIV estimate is relatively low (16.9%)

Impact of Covariates on the PPK Model

- Three participant characteristics were associated with variability in adintrevimab PK: body weight, race, and age
  - Body weight influenced clearance, intercompartmental clearance, and central and peripheral volume compartments; however, the relationship between body weight and clearance did not suggest the need for a dose adjustment
  - CL/F is 35.5% faster in Black participants
  - Vc/F increases with increasing age
- There was no apparent impact of baseline viral load or age on adintrevimab clearance
- The relationships were quantified using a power function and the coefficients identified during base structural model development

$$(1)\quad CL/F = 34.1 \times \left(\tfrac{WTKG}{75}\right)^{0.658} \times (1 + 0.355)^{Race:Black}$$

$$(2)\quad Vc/F = 3700 \times \left(\tfrac{WTKG}{75}\right)^{1.00} \times \left(\tfrac{AGE}{48}\right)^{0.411}$$

$$(3)\quad CLd/F = 613 \times \left(\tfrac{WTKG}{75}\right)^{0.658}$$

$$(4)\quad Vp/F = 3140 \times \left(\tfrac{WTKG}{75}\right)^{1.00}$$

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DISCLOSURES

RESULTS

Adintrevimab PPK Model

- **Figure 1** shows the PPK model median (90% CI) concentration-time profile of adintrevimab following a single 300 mg IM dose in the phase 2/3 studies
- The PPK model provided a robust fit to the data based on goodness-of-fit plots (**Figure 2**) and PC-VPC plots (**Figure 3**)
  - The goodness-of-fit plots indicated good precision: $R^2 = 0.66$ for population predictions versus observations and $R^2 = 0.94$ for individual predictions versus observations
  - The PC-VPC plots showed good agreement between median simulated concentrations based on the final PPK model and median observed concentrations for the pooled dataset

- Additionally, the model robustly captured the variability in observed concentrations as the 5th and 95th percentiles of the observed data generally fall within or close to the CIs of the corresponding simulated values
- The median adintrevimab half-lives in days by study were phase 1 (α 1.69; β 118), EVADE (α 1.89; β 141), and STAMP (α 1.93; β 152; **Table 1**)
- The population mean IM bioavailability estimate was 90.5%

Figure 1. Observed adintrevimab concentrations over time following a 300 mg IM dose in the EVADE and STAMP studies

Figure 2. Goodness-of-fit plots for the model. (A) Population predictions vs observations and (B) individual predictions vs observations. Conditional weighted residuals vs (C) population fitted concentration and (D) time since last dose

Table 1. Predicted parameters by study[a]

Parameter	Phase 1 (n=8)	EVADE (n=653)	STAMP (n=187)
AUC_{0-180} (mg*d/L)	4920 (2730–6830)	4350 (1440–10,900)	4230 (1560–8720)
C_{max} (mg/L)	44.6 (23.1–62.4)	37.3 (11.7–94.2)	35.3 (14.1–72.3)
T_{max} (days)	7.00 (6.00–12.0)	8.00 (3.00–13.0)	8.00 (3.00–13.0)
CL/F (L/d)	0.0339 (0.0266–0.0636)	0.0370 (0.0116–0.122)	0.0361 (0.0128–0.117)
Q/F (L/d)	0.560 (0.482–0.778)	0.644 (0.396–1.08)	0.659 (0.444–0.967)
Vc/F (L)	2.85 (1.94–8.80)	3.79 (0.673–18.4)	3.98 (0.788–13.1)
Vp/F (L)	2.73 (2.18–4.51)	3.39 (1.61–7.48)	3.51 (1.92–6.28)
Vss/F (L)	6.13 (4.22–11.0)	7.29 (2.71–22.0)	7.65 (4.14–18.5)
$T_{1/2,α}$ (days)	1.69 (1.44–2.50)	1.89 (0.673–3.17)	1.93 (0.599–2.99)
$T_{1/2,β}$ (days)	118 (106–163)	141 (76.4–252)	152 (84.2–237)

[a]Adintrevimab 300 mg IM only. Data are median (range). AUC, area under the curve; CL, clearance; C_{max}, maximum serum concentration; F, fraction absorbed (bioavailability); Q, intercompartmental CL; T_{max}, time to reach C_{max}; $T_{1/2}$, half-life; Vc, volume of central compartment; Vp, volume of peripheral compartment; Vss, steady state volume of distribution.

Figure 3. PC-VPC plot for the final PPK model using the pooled dataset

Circles represent the prediction-corrected observed adintrevimab concentrations. Long dashed and short dashed black lines represent the median and 5th/95th percentiles of the prediction-corrected observed data, respectively. Red line and shaded region represent the median and 90% prediction interval for the median simulated prediction-corrected concentrations. Blue lines and shaded regions represent the medians and 90% prediction interval for the 5th and 95th percentiles of the prediction-corrected simulated values.

KEY FINDINGS

Using serum samples from participants enrolled in phase 1 and phase 2/3 studies, a PPK model was developed that provided a precise and unbiased fit to observed adintrevimab concentration-time data

Adintrevimab PK was impacted by body weight, age, and race, but the relationship between body weight and clearance suggested that there was no need for a dose adjustment

There was no apparent impact of baseline viral load or age on adintrevimab clearance

Adintrevimab demonstrated high IM bioavailability (90.5%) and a median terminal elimination half-life of 118 to 152 days

CONCLUSIONS

- The PPK model provided a precise and unbiased fit to the observed adintrevimab concentration-time data
- A single dose of adintrevimab at 300 mg by IM administration demonstrated high IM bioavailability and an extended half-life
- The PPK model will be useful for future PK-pharmacodynamic analyses

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