

A Population Pharmacokinetic Model of Obeldesivir in Healthy Volunteers and Patients With COVID-19

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Conclusions

- A population pharmacokinetic model was developed that was able to adequately describe obeldesivir pharmacokinetic data from Phase 1 studies in healthy volunteers and Phase 3 studies in nonhospitalised participants with COVID-19
- Renal function and disease status were identified as notable, clinically relevant covariates on steady-state obeldesivir exposure
 - The potential impact of these 2 covariates should be considered when applying this model to support dose justifications in special populations and in diseases mediated by other viruses (eg, respiratory syncytial virus or filoviruses)

Plain Language Summary

- Obeldesivir is an oral drug that is being evaluated for the treatment of viral diseases, including COVID-19 and respiratory syncytial virus disease, which are both caused by viruses that affect the lungs and airways
- This analysis used a computer program to show how different characteristics, such as body weight, can change the amount of obeldesivir circulating in the body
- The study found that people with kidney impairment and people with COVID-19 were more likely to have higher obeldesivir concentrations than people without kidney impairment and people without COVID-19, respectively

Introduction

- Obeldesivir (ODV) is an ester prodrug that has potent preclinical antiviral activity against a broad spectrum of RNA viruses, including SARS-CoV-2, filoviruses, and respiratory syncytial virus¹⁻³
- Upon oral administration, ODV is extensively metabolised presystemically to generate GS-441524, which is metabolised within lung cells to the active nucleoside triphosphate, GS-443902
- A population pharmacokinetic (popPK) model for ODV was originally developed based on interim data from a Phase 1, first-in-human study in healthy volunteers and two Phase 3 studies in low-risk and high-risk participants with COVID-19, respectively⁴

Objectives

- To update the interim ODV popPK model with final pharmacokinetic (PK) data from four other Phase 1 studies in healthy volunteers and final PK data from the two Phase 3 studies in participants with COVID-19 in order to characterise the absorption and disposition of ODV following oral administration
- To identify covariates that account for interindividual variability (IIV) in ODV PK

Methods

- Plasma PK data from 7 clinical studies (five Phase 1 studies and two Phase 3 studies) were pooled to inform the popPK model⁵⁻⁹
- Nonlinear mixed-effects modelling with NONMEM® v7.5.0 (ICON plc) was used for model development
- A full covariate modelling approach was used to assess the statistical significance and the clinical relevance of key covariates of interest
- PopPK parameters were estimated using the stochastic approximation expectation maximisation method (with interaction) followed by importance sampling
- Body weight was allometrically scaled to clearance and volume parameters (coefficients of 0.75 and 1.00, respectively)
- The M3 method was used to model data that were below the limit of quantification, which comprised ~19% of samples
- The popPK model was evaluated based on the drop in objective function value, the precision in parameter estimates, visual predictive checks (VPCs), and goodness-of-fit plots
- Data transformation and visualisation were performed in R v4.3.1 (The R Foundation)

Results

- The analysis dataset included 9059 GS-441524 plasma concentration observations from 1444 participants (**Table 1**)

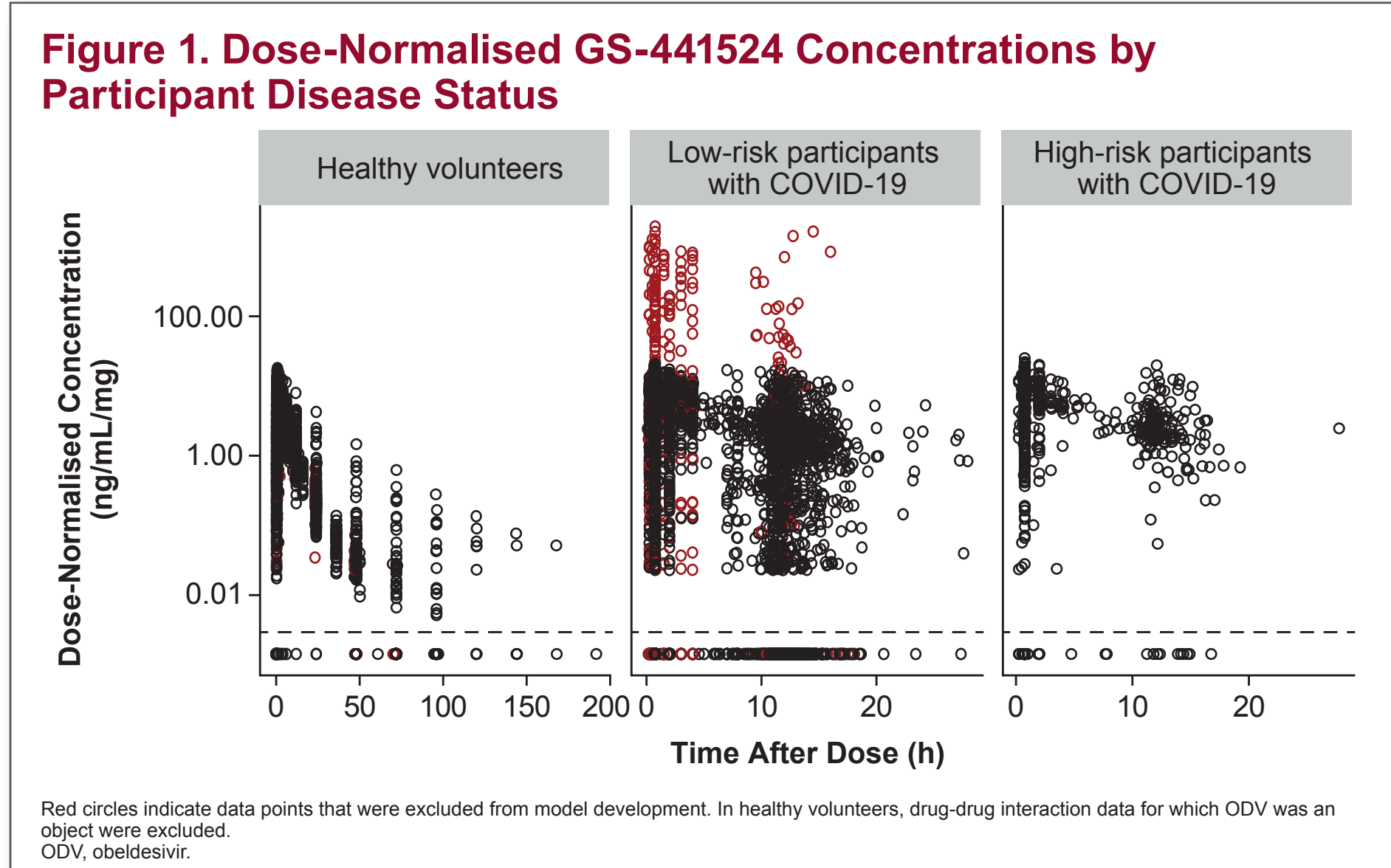
Table 1. Key Covariates in the Analysis Dataset

Covariate, n	Phase 1	Phase 3: GS-US-611-6273 (BIRCH)	Phase 3: GS-US-611-6549 (OAKTREE)
Overall	292	230	922
Disease status			
Healthy volunteers	292	0	0
Low-risk participants with COVID-19	0	0	922
High-risk participants with COVID-19	0	230	0
Baseline eGFR ^a			
≥90 mL/min/1.73 m ²	235	132	739
60 to <90 mL/min/1.73 m ²	40	76	161
30 to <60 mL/min/1.73 m ²	11	18	9
15 to <30 mL/min/1.73 m ²	6	0	0
Missing	0	4	13
Japanese ancestry			
Japanese	20	2	12
Non-Japanese	20	228	910
Missing	252	0	0
Acid-reducing agent coadministration			
Yes	0	47	32
No	292	183	890

^aBaseline eGFR ≥90 mL/min/1.73 m² was considered normal renal function and baseline eGFR of 60 to <90 mL/min/1.73 m², 30 to <60 mL/min/1.73 m², and 15 to <30 mL/min/1.73 m² were considered mild, moderate, and severe renal impairment, respectively.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, glomerular filtration rate estimated using the CKD-EPI Creatinine Equation (2021).

- There was notable variability in dose-normalised GS-441524 concentrations in the Phase 3 GS-US-611-6549 (OAKTREE) study (**Figure 1**)
 - Concentration data from 68 GS-US-611-6549 participants were considered anomalies and excluded from model development



- The final popPK model was a 3-compartment model with linear absorption and elimination (**Figure 2**)
- VPCs and goodness-of-fit plots of GS-441524 observations and predictions confirmed that the final popPK model was able to adequately describe the overall ODV PK data (**Figures 3 and 4**)
 - The model was not able to fully capture delays in absorption, as indicated by some overpredictions at concentrations of 1 to 10 μM

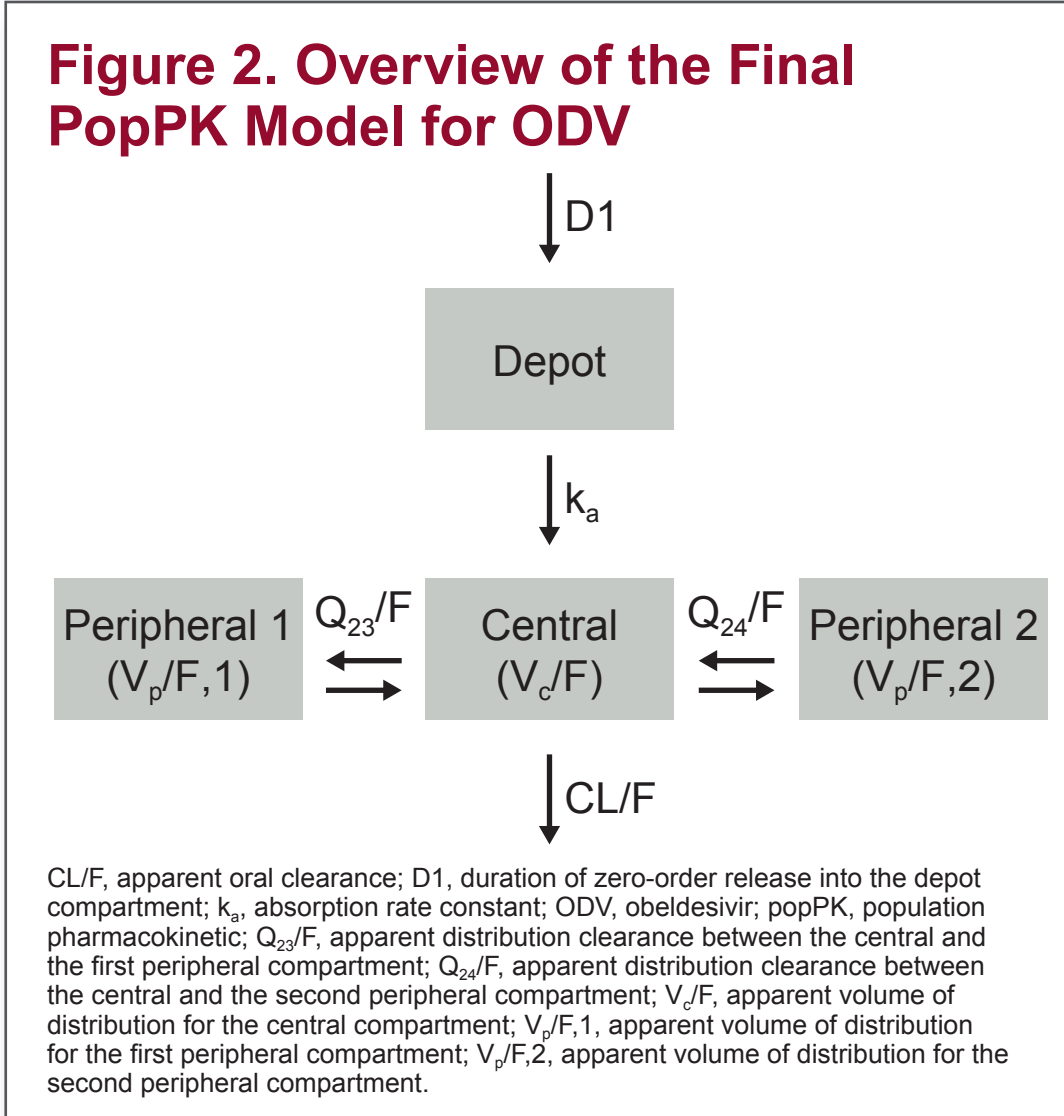


Figure 3. VPC Plot for the Final PopPK Model by Participant Disease Status and Dosing Regimen

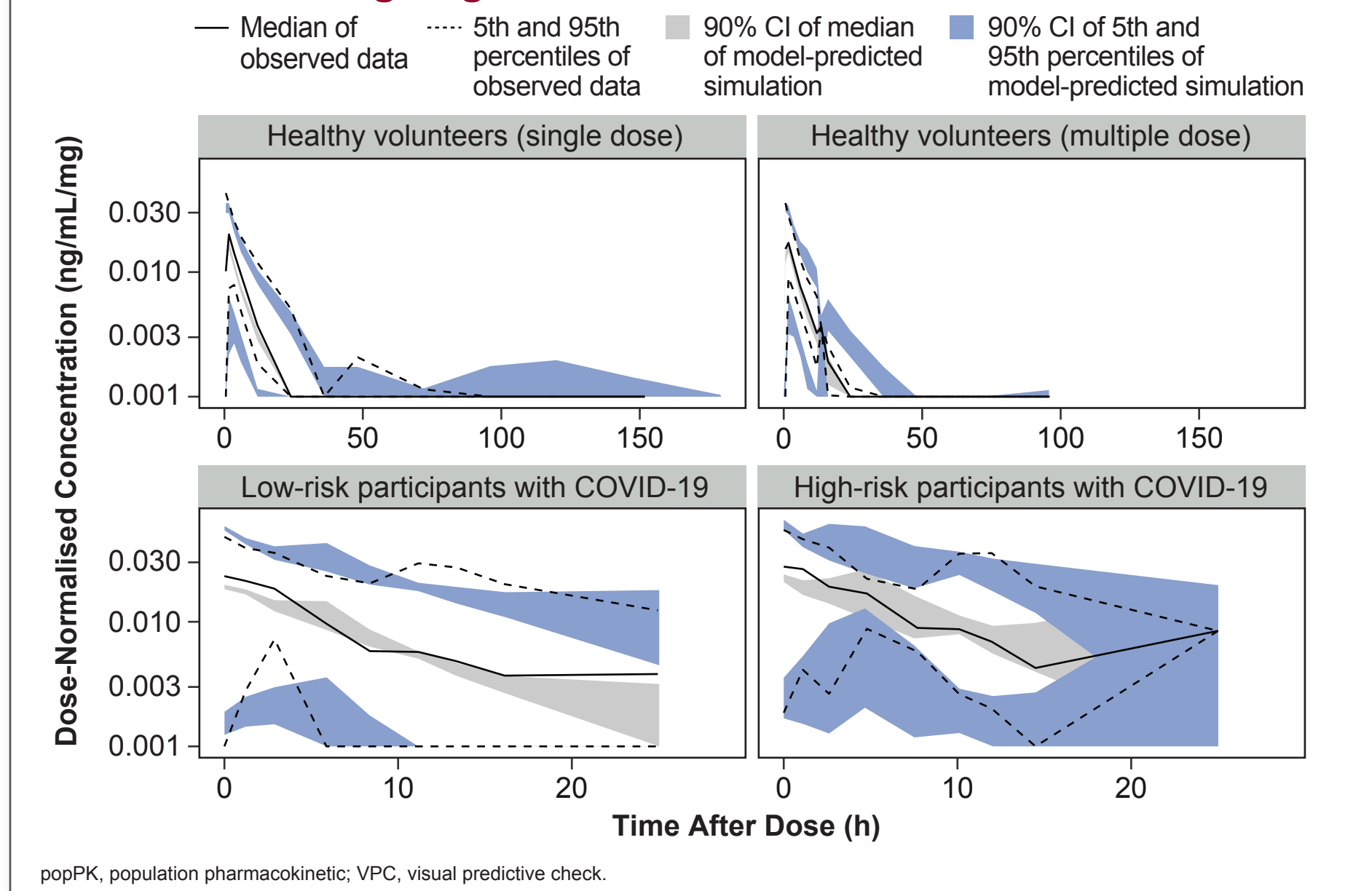
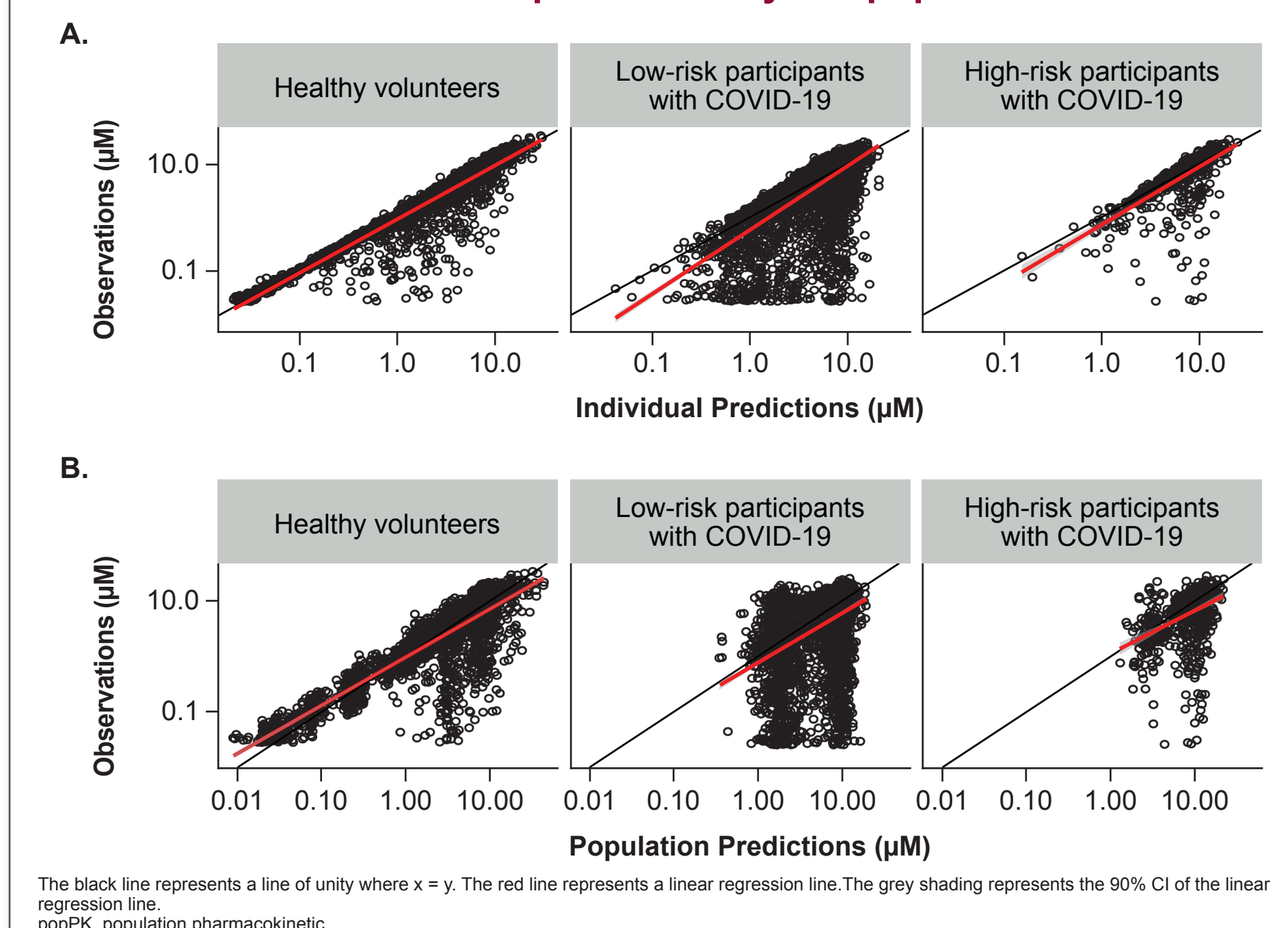


Figure 4. Goodness-of-Fit Plots for (A) Observations Versus Individual Predictions and (B) Observations Versus Population Predictions for the Final PopPK Model by Subpopulation



- The popPK parameter estimates shown in **Table 2** suggest that ODV is rapidly distributed into 1 peripheral compartment (apparent distribution clearance between the central and the first peripheral compartment [Q₂₃/F]), with a slower distribution into a second peripheral compartment (apparent distribution clearance between the central and the second peripheral compartment [Q₂₄/F])

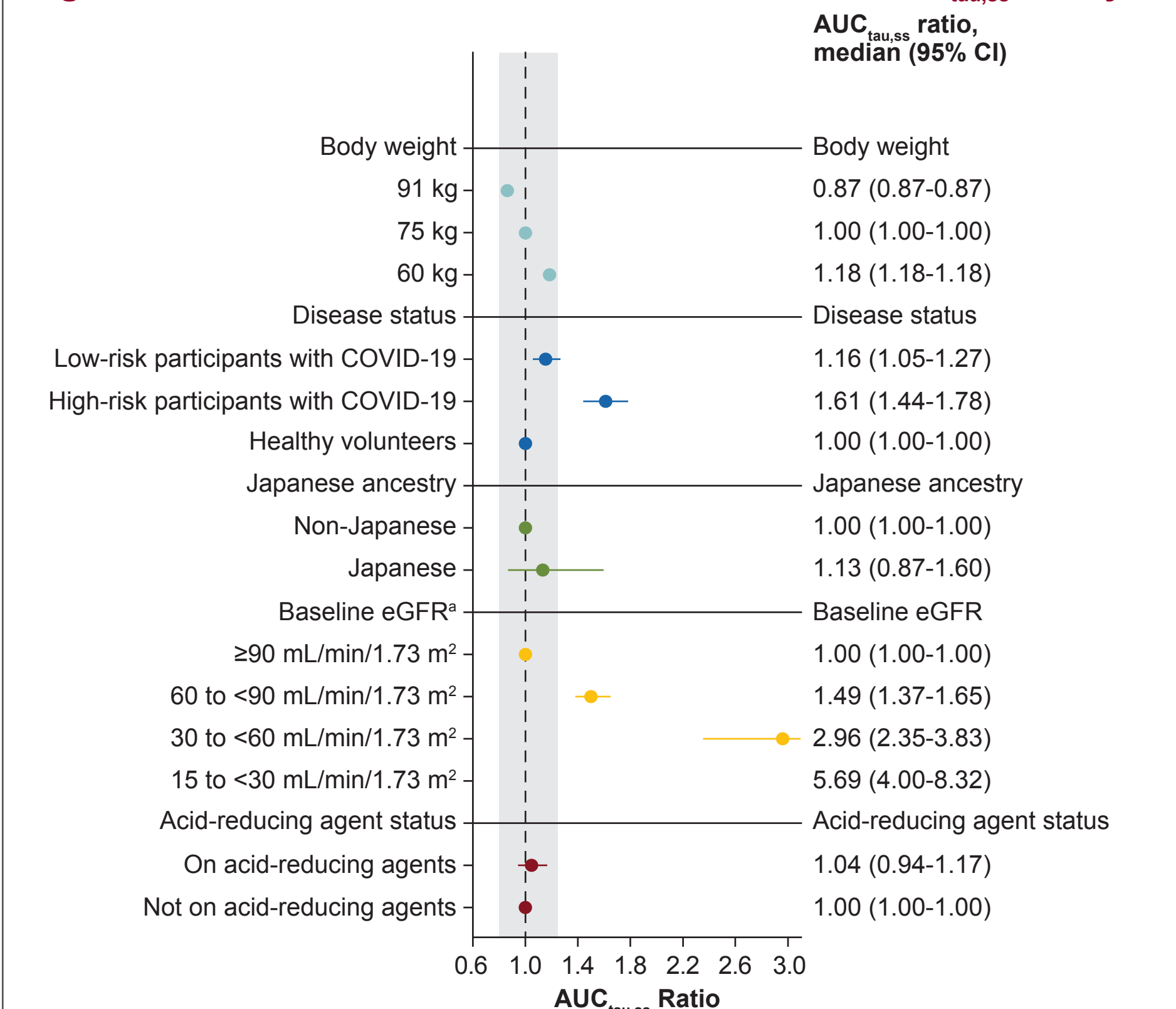
Table 2. PopPK Parameters of the Final Model

Parameter	Estimate	RSE (%)	Shrinkage
D1 (h)	0.595	4.7	—
k ₀ (/h)	0.398	3.6	—
CL/F (L/h)	18.4	1.6	—
V _p /F (L)	1.77	28.9	—
Q ₂₃ /F (L/h)	21.9	5.5	—
V _p /F,1 (L/h)	81.2	3.1	—
Q ₂₄ /F (L/h)	0.631	5.6	—
V _p /F,2 (L/h)	26.4	6.2	—
eGFR on CL	1.00	12.0	—
Healthy volunteer on CL	0.159	33.6	—
Risk factors for severe COVID-19 on CL	−0.279	10.5	—
Japanese ancestry on CL	−0.110	118.2	—
Acid-reducing agent coadministration on CL	−0.0344	166.0	—
Proportional error (Phase 1 studies)	0.308	1.0	—
Proportional error multiplier (GS-US-611-6273)	1.57	3.1	—
Proportional error multiplier (GS-US-611-6549)	2.16	1.5	—
IIV for CL/F (variance)	0.133	5.3	22.2
IIV for V _p /F (variance)	7.88	10.4	37.4

Covariate effects were modelled proportionally. IIV on other structural parameters was fixed to a small value to allow for flexibility in parameter estimation during model run. The IIV %CV was ~40% for D1 and ~15% to 25% for Q₂₃/F, V_p/F,1, Q₂₄/F, V_p/F,2, and k₀. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CL, oral clearance; CL/F, apparent oral clearance; CV, coefficient of variation; D1, duration of zero-order release into the depot compartment; eGFR, glomerular filtration rate estimated using the CKD-EPI Creatinine Equation (2021); IIV, interindividual variability; k₀, absorption rate constant; popPK, population pharmacokinetic; Q₂₃/F, apparent distribution clearance between the central and the first peripheral compartment; Q₂₄/F, apparent distribution clearance between the central and the second peripheral compartment; RSE, relative standard error; V_p/F, apparent volume of distribution for the central compartment; V_p/F,1, apparent volume of distribution for the first peripheral compartment; V_p/F,2, apparent volume of distribution for the second peripheral compartment.

- A full covariate analysis identified the following 2 clinically relevant covariates on GS-441524 area under the concentration-time curve within a dosing interval at steady state (AUC_{tau,ss}; **Figure 5**):
 - Compared with healthy volunteers, low-risk and high-risk participants with COVID-19 were predicted to have AUC_{tau,ss} values that were 16% and 61% higher, respectively
 - Compared to participants with normal renal function, participants with mild, moderate, or severe renal impairment were predicted to have AUC_{tau,ss} values that were approximately 49%, 196%, and 469% higher, respectively

Figure 5. Effect of Select Covariates on GS-441524 AUC_{tau,ss} at Day 5



- Statistically nonsignificant covariates included acid-reducing agent coadministration and Japanese ancestry
- GS-441524 exposures decreased with increasing body weight; this change was not considered clinically relevant

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