

# Population Pharmacokinetic Modeling and Simulation of Lenalidomide in Renally Impaired Patients with Multiple Myeloma

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## INTRODUCTION

Renal impairment (RI) is a common complication in patients with multiple myeloma (MM), often resulting from immunoglobulin-induced kidney damage.

Lenalidomide, a first-line therapy for MM, is primarily excreted through the kidneys and requires dose adjustments based on renal function. Reduced renal clearance can significantly increase lenalidomide exposure, with increase in half-life (up to 3 folds) and area under the concentration-time curve (AUC). In addition, RI can alter plasma protein levels potentially affecting drug-protein binding and thereby influencing drug concentrations.

Considering the high interindividual variability in pharmacokinetic among MM patients with RI, especially for renally excreted drugs like lenalidomide, dosing optimization is crucial to achieve therapeutic benefits and safety. However, population pharmacokinetic (PopPK) modeling of total and unbound lenalidomide with covariate evaluation in MM patients with CKD has not been sufficiently investigated.

This study aimed to characterize the PopPK of total and unbound lenalidomide in MM patients with CKD, identify significant covariates, and propose model-informed precision dosing strategies.

## RESULTS

Table 1. Baseline characteristics of study patients (median (IQR))

| Baseline characteristics  | eGFR < 30 (n=11)  | 30 ≤ eGFR < 60 (n=11) | 60 ≤ eGFR < 90 (n=8) | Overall (n=30)      |
|---------------------------|-------------------|-----------------------|----------------------|---------------------|
| Male, no. of patients (%) | 3 (23)            | 6 (55)                | 3 (37)               | 12 (40)             |
| Age, years                | 67 (47-83)        | 67 (50-77)            | 69.5 (52-84)         | 67.5 (47-84)        |
| eGFR, mL/min              | 25.2 (11.1-28.6)  | 52.1 (31.3-59.9)      | 77.4 (60.5-94.7)     | 38.44 (10.33-83.47) |
| CRCL                      | 21.2 (15.3-25.2)  | 38.9 (28.4-69.8)      | 61.2 (48.6-81.2)     | 31.9 (10.8-65.9)    |
| Height, cm                | 161 (151.4-173.8) | 163 (149-179)         | 160.2 (140-174)      | 161.7 (140-179)     |
| Body weight, kg           | 59 (48-70)        | 62 (51.9-83.7)        | 66.5 (46.7-86)       | 62 (46.7-86)        |
| BMI, kg/m <sup>2</sup>    | 21.3 (18.1-27.4)  | 23.1 (21.6-27.9)      | 24.55 (19.7-32.6)    | 23.15 (18.1-32.6)   |
| BSA, m <sup>2</sup>       | 1.6 (1.49-1.84)   | 1.65 (1.48-2.01)      | 1.75 (1.41-1.91)     | 1.64 (1.41-2.01)    |
| SCR, g/dL                 | 2.3 (1.8-5.9)     | 1.4 (1.0-2.3)         | 0.95 (0.7-1.1)       | 1.57 (0.7-5.9)      |
| CRP, mg/dL                | 0.2 (0-11.7)      | 0.2 (0-5.6)           | 0.1 (0-4.2)          | 0.2 (0-11.7)        |
| PLT, ×10 <sup>9</sup> /L  | 173 (100-379)     | 184 (39-290)          | 151.5 (63-381)       | 171 (39-381)        |
| WBC, ×10 <sup>9</sup> /L  | 6.1 (3.8-8.4)     | 4.7 (3.9-8.2)         | 5.1 (2.8-6.6)        | 5.4 (2.8-8.4)       |
| ANC, ×10 <sup>9</sup> /L  | 3.2 (1.5-6.1)     | 2.8 (2.1-5)           | 2.05 (1.4-3.8)       | 2.95 (1.4-6.1)      |
| PTN, g/dL                 | 7.2 (5.6-8.9)     | 7.1 (5.3-9.3)         | 6.5 (5.5-8.6)        | 6.9 (5.3-9.3)       |
| AST, U/L                  | 18 (2-65)         | 24 (11-51)            | 30.5 (24-43)         | 24.5 (2-65)         |
| ALT, U/L                  | 14.5 (13-90)      | 24 (10-35)            | 49.5 (20-96)         | 23.5 (5-96)         |
| Dose, mg/day              | 7.5 (7.5-10)      | 10 (5-10)             | 10 (5-10)            | 7.5 (5-10)          |

Table 2. Final PopPK model parameters of lenalidomide

| Parameters                         | Estimate (%RSE) | Shrinkage (%) | Bootstrap median (95% CI)      |
|------------------------------------|-----------------|---------------|--------------------------------|
| <b>Fixed effect parameters</b>     |                 |               |                                |
| $\theta_{CL/F}$ (L/h)              | 9.79 (4.12)     | N/A           | 9.64 (8.94 - 10.4)             |
| $\theta_{Vc/F}$ (L)                | 48.6 (10.8)     | N/A           | 48.1 (39.5 - 56.7)             |
| $\theta_{Q/F}$ (L/h)               | 8.11 (27.8)     | N/A           | 8.27 (4.82 - 12.5)             |
| $\theta_{Vp/F}$ (L)                | 21.3 (13.6)     | N/A           | 21.3 (16.1 - 26.1)             |
| $\theta_{ka}$ (1/h)                | 1.16 FIX        | N/A           | 1.16 FIX                       |
| $\theta_{Fu}$                      | 0.614 (1.32)    | N/A           | 0.614 (0.601 - 0.628)          |
| $\theta_{CLBSA}$                   | 0.879 (23.0)    | N/A           | 0.891 (0.474 - 1.23)           |
| $\theta_{CLEGFR}$                  | 0.0134 (10.2)   | N/A           | 0.013 (0.0104 - 0.0155)        |
| $\theta_{CLALT}$                   |                 |               |                                |
| ALT < 26.5                         | 0.0109 (34.7)   | N/A           | 0.0106 (0.00509 - 0.0163)      |
| ALT ≥ 26.5                         | -0.00659 (9.58) | N/A           | -0.00626 (-0.00761 to -0.0042) |
| $\theta_{VcBSA}$                   | 1.16 (26.0)     | N/A           | 1.11 (0.55 - 1.67)             |
| <b>Interindividual variability</b> |                 |               |                                |
| $\omega_{CL/F}$                    | 13.5% (12.2)    | 4             | 12.2% (8.94 - 14.9%)           |
| $\omega_{Vc/F}$                    | 30.4% (24.6)    | 8             | 29.7% (17.9 - 43.8%)           |
| <b>Residual error</b>              |                 |               |                                |
| $\sigma_{unbound-proportional}$    | 0.0158 (33.5)   | 8             | 0.0151 (0.00501 - 0.0244)      |
| $\sigma_{unbound-addictive}$       | 1.22 (51)       | 8             | 1.18 (0.47 - 3.74)             |
| $\sigma_{total-proportional}$      | 0.0157 (32.8)   | 7             | 0.015 (0.00609 - 0.0237)       |
| $\sigma_{total-addictive}$         | 4.7 (50.2)      | 7             | 4.68 (1.69 - 12.5)             |

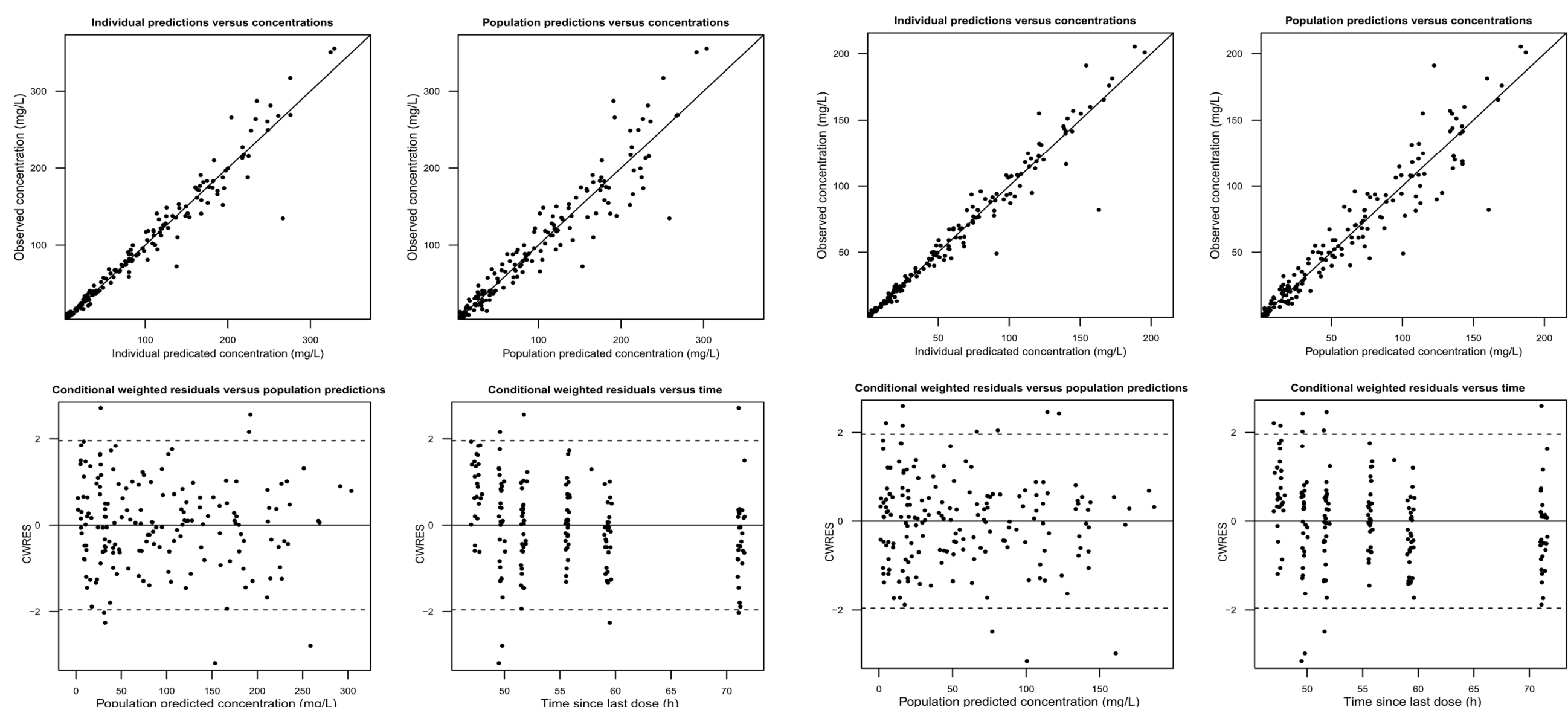


Figure 1. Goodness-of-fit plot (GOF) of the final PopPK model for lenalidomide (left: total, right: unbound concentrations)

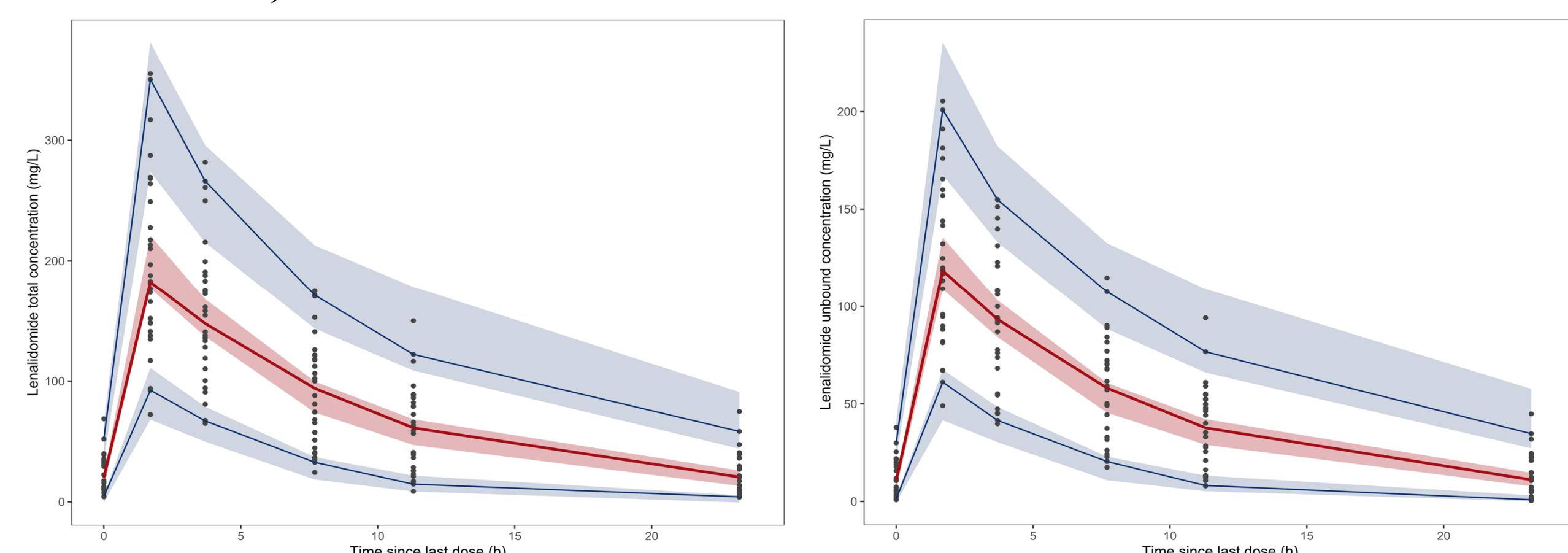


Figure 2. Visual predicted checks (VPC) of the final PopPK model for lenalidomide with 5% and 95% prediction intervals and median simulated concentrations (left: total, right: unbound concentrations)

## METHODS

### [Patients and study design]

A prospective clinical trial was conducted in Korea for MM patients with CKD treated with lenalidomide as maintenance regimen. Upon the discretion of treating clinicians, patients received lenalidomide at doses of 5 mg, 7.5 mg, or 10 mg daily. Serial blood samples were collected on the third day of treatment at pre-dose and 2, 4, 8, 12, and 24 hours after oral administration of the study dose. Total and unbound plasma concentrations of lenalidomide were measured using a previously developed high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method.

### [Population pharmacokinetic analysis]

Pop-PK analysis was performed using NONMEM 7.5.1 (Globomax LLC, Ellicott, MD), incorporating allometric scaling on CL/F and Vd/F. The covariate analysis followed forward inclusions and backward elimination steps, using an OFV difference of >3.84 (P < 0.05) and >6.63 (P < 0.01) for statistical significance, respectively. Covariates of interest including demographics, markers of renal and liver functions, hematological parameters were evaluated in this study. For renal function markers, creatinine clearance (CrCL, estimated using the Cockcroft-Gault equation) and estimated glomerular filtration rate (eGFR, calculated by the CKD-EPI 2021 equation), were evaluated as covariates in the PopPK model. The final PK model was selected based on goodness-of-fit criteria (GOF), including clinical plausibility, successful minimization, objective function value (OFV), relative standard error (RSE), and graphical diagnostics.

### [Dosing simulation]

Monte Carlo simulations (n = 1,200 per model) were performed using the final PopPK models including either CrCL or eGFR as a covariate. For each model, lenalidomide doses were simulated according to FDA-approved labeling based on their estimated renal function; 7.5 mg Q.D. for CrCL or eGFR < 30, 10 mg Q.D. for 30-60, and 25 mg Q.D. for ≥ 60 (mL/min for CrCL; mL/min/1.73 m<sup>2</sup> for eGFR).

Simulated AUCs were compared with reference mean AUC values of 2124 ng·h/mL in Caucasians and 2305 ng·h/mL in Asians, as observed in adult MM patients with normal renal function (CrCL > 60 mL/min) receiving 25 mg Q.D., reported by Chen et al. (2017)

## CONCLUSION

- ❖ The eGFR (estimated by the CKD-EPI 2021)-based PopPK model demonstrated a better fit compared to the CrCL-based model
- ❖ In simulations based on dosing recommendations for impaired renal function, the eGFR-based model also showed relatively better target AUC attainment at doses approved by regulatory agencies in patients with severe RI
- ❖ Notably, patients with moderate RI who received 10 mg once daily showed substantially lower AUC values compared to those with normal renal function, suggesting that the current dosing regimen might be suboptimal
- ❖ Achieving optimal exposure may not only improve treatment outcomes in MM but also contribute to renal function recovery by preventing complication. Therefore, individualized dose adjustment based on eGFR, BSA, and ALT should be considered for lenalidomide therapy in renally impaired MM patients

- A total of 345 plasma concentrations from 30 patients (12 males) were analyzed to develop a PopPK model of lenalidomide; including 11 patients with eGFR < 30 mL/min/1.73 m<sup>2</sup>, 11 patients with eGFR between 30 and 60, and 8 patients with eGFR between 60 and 90.

- A two-compartment PK model with linear protein binding and first-order elimination The absorption rate constant (Ka) was fixed at 1.16 h<sup>-1</sup> based on the NCA analysis. Interindividual variability (IIV, η) of pop-PK parameters was assumed to follow a log-normal distribution, with a mean of zero and variance of ω<sup>2</sup>. IIV was estimated for CL/F and Vc/F. Residual error (ε) was best modelled by the combination form with both proportional and additive terms for total and unbound concentrations.

- Two covariate models were developed using different renal function markers (eGFR and CrCL)

① The CrCL-based model: CL/F was significantly associated with CrCL and alanine aminotransferase (ALT), and Vc/F with BSA (P < 0.05, ΔOFV = -53.05)

② The eGFR-based model: CL/F was significantly associated with body surface area (BSA), eGFR, and ALT, while Vc/F was associated with BSA (P < 0.05, ΔOFV = -67.03)

### Final PopPK Model for lenalidomide

$$CL/F \text{ (L/h)} = \theta_{CL/F} \cdot e^{\eta_{CL/F}} \cdot e^{\theta_{CLEGFR} (eGFR - 46.92)} \cdot e^{\theta_{BSA} (BSA - 1.64)} \cdot (1 + \theta_{ALT} (ALT - 26.5))$$

$$Vc/F \text{ (L)} = \theta_{Vc/F} \cdot e^{\eta_{Vc/F}} \cdot e^{\theta_{VcBSA} (BSA - 1.64)}$$

Figure 3. Boxplots of simulated AUC in CrCL- vs. eGFR-based final models grouped by respective renal function categories. The red line indicates the target AUC range ±10% (1993.05-2435.95 ng·h/mL)

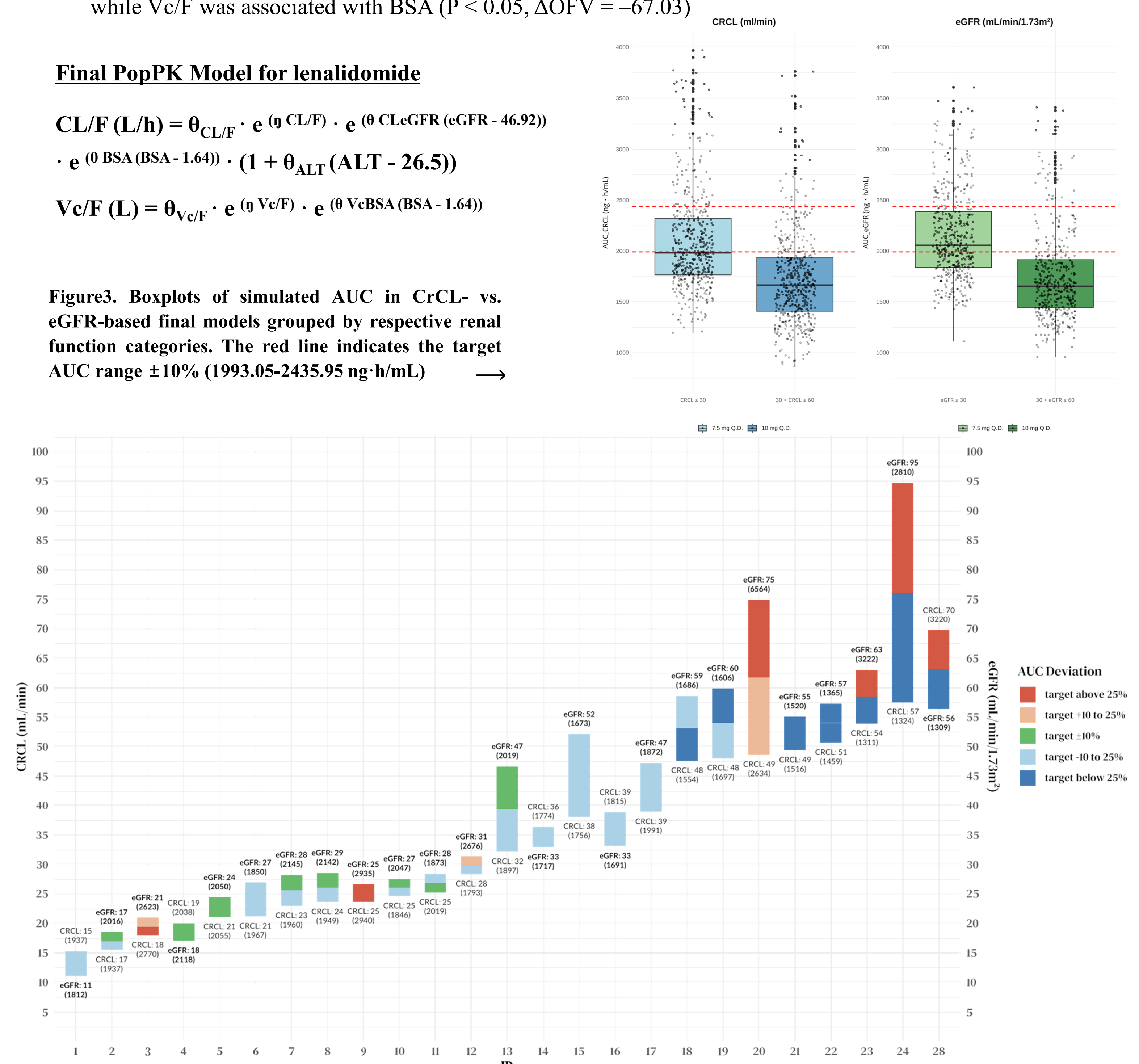


Figure 4. Comparison of simulated AUC from CrCL- vs. eGFR-based covariate models using Monte-Carlo simulation (n=1,200). Renal function values (CrCL and eGFR) and mean simulated AUCs for each patient are shown in parentheses. The degree of deviation from the target AUC range (2104-2305 ng·h/mL) is color-coded

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