Demonstrating Similarity of Denosumab Biosimilar SB16 to Reference Denosumab Using Population PK-PD Modeling

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Introduction/Objectives

- Denosumab is a fully human monoclonal IgG2 antibody that binds with high affinity and specificity to receptor activator of nuclear factor kappa-B ligand (RANKL), a critical mediator of osteoclast formation, function, and survival. By inhibiting RANKL–RANK interaction, denosumab suppresses osteoclast activity and bone resorption, thereby increasing bone mineral density (BMD) and reducing fracture risk [1].
- Obodence™ (SB16) is a biosimilar to Prolia (reference denosumab, DEN), approved for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, as well as for bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, or with long-term systemic glucocorticoid therapy in adults [2].
- This study aimed to characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of denosumab in healthy men and postmenopausal women with osteoporosis.
- A PK-PD modeling approach was employed to evaluate the relationship between denosumab exposure and lumbar spine BMD response, and the PK/PD similarities between SB16 and the DEN.

Methods

- Data from a Phase I study in healthy men and a Phase III study in postmenopausal women with osteoporosis were used to construct population PK and PK-PD models. A total of 6,583 serum denosumab concentrations (SB16, EU-sourced DEN, US-sourced DEN) from 615 subjects and 1,716 lumbar spine BMD measurements (SB16, EU-sourced DEN) from 456 subjects were analyzed.
- A sequential modeling approach (PPP&D method) was used: the population PK model was first developed using observed PK data, and the resulting population PK parameters were fixed in the subsequent PK-PD modeling, which incorporated both observed PK and BMD data.
- Model selection and evaluation were based on likelihood ratio tests (p = 0.05) and diagnostic goodness-of-fit plots.
- Covariate effects (body weight, age, race) were assessed, and PK comparability between SB16 and DEN (EU- and US-sourced) was evaluated by testing treatment group effects on PK parameters using Wald tests and hierarchical likelihood ratio tests.
- The final PK-PD model was validated using visual predictive checks (VPC).
- Monte-Carlo simulations (n = 1,000/group) were performed using Simulx to compare PK and BMD profiles by treatment and covariates.
- Simulations were performed to compare steady-state maximum concentration (C_{max}), area under the concentration-time curve over a dosing interval (τ) at steady state ($AUC_{\tau,ss}$), and lumbar spine BMD between SB16 and DEN.
- Modeling was conducted using Monolix with data processing and graphical outputs generated using R software (v4.3.2).
- An overview of the full modeling and simulation workflow is provided in Figure 1.

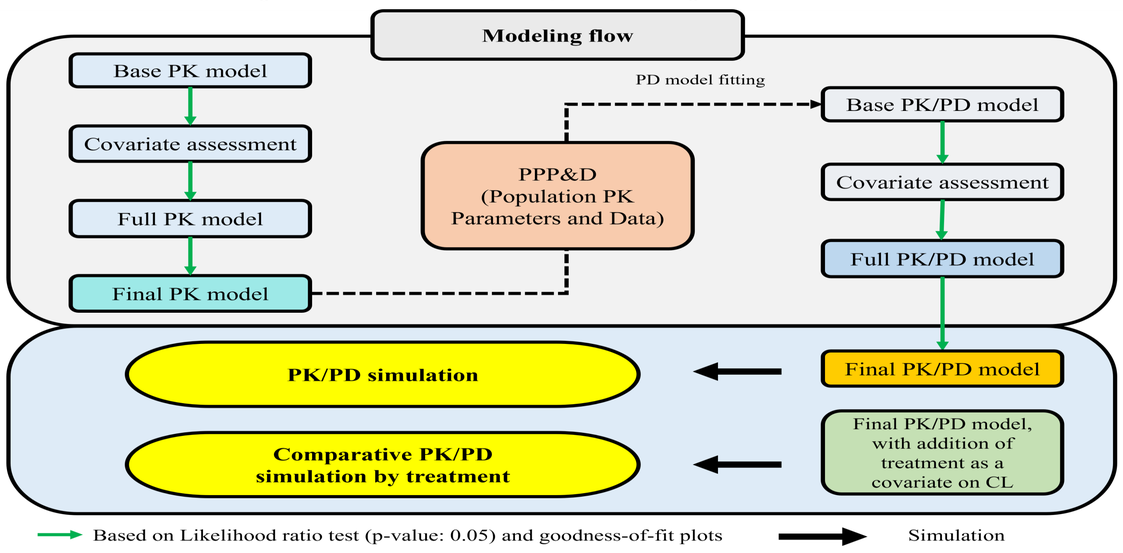


Figure 1. Workflow for PK/PD model and prediction of PK/PD profiles of denosumab

Results

- A two-compartment Target Mediated Drug Disposition (TMDD) model with quasi-steady state (QSS) approximation and an indirect response model with maximal inhibitory function adequately described the PK and PD profiles of denosumab (Figure 2).
- The final model parameter estimates are summarized in Table 1. Model performance was acceptable, as demonstrated by goodness-of-fit plots (Figure 3) and prediction-corrected visual predictive checks (Figure 4), indicating good agreement between observed and predicted values.
- Covariate effects, including study population, age, and race showed no clinically meaningful impact on treatment outcomes. Treatment group (SB16 vs. DEN) was not identified as a significant covariate.
- Simulation results based on a model incorporating treatment group as a covariate on clearance (CL) showed comparable PK parameters and BMD between SB16 and the DEN (Table 2, Figure 5).

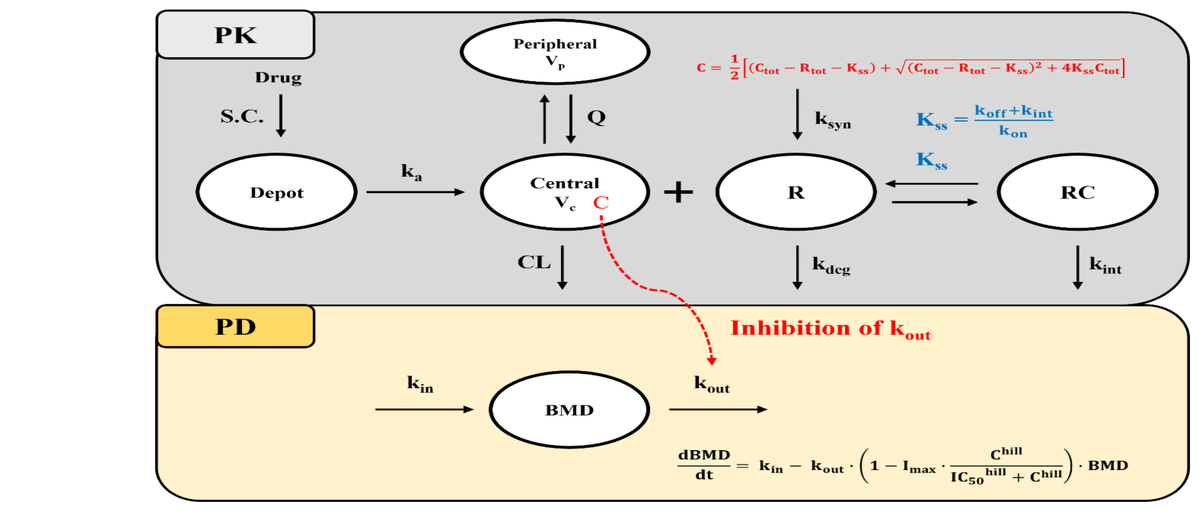


Figure 2. Schematic diagram of the QSS TMDD model and turnover model with inhibitory effect on k_{out}

Conclusion

- The TMDD-QSS model with an indirect response component adequately described the PK/PD of denosumab.
- While some covariates influenced PK profiles, they had no clinically meaningful impact on treatment effect, and SB16 demonstrated comparable PK/PD profiles to DEN.

Reference

1. Hanley DA, Adachi JD, Bell A, Brown V. Denosumab: mechanism of action and clinical outcomes. *Int J Clin Pract*. 2012;66(12):1139–1146. https://doi.org/10.1111/ijcp.12022
2. European Medicines Agency. Obnodence: EPAR – Product information [Internet]. Amsterdam (NL): EMA; 2024 [cited 2025 May 22]. Available from: https://www.ema.europa.eu/en/documents/product-information/obodence-epar-product-information_en.pdf

Parameter (units)	Definition	Estimate [%RSE]	Inter-individual Variability (CV%) [%RSE]
	Final Pharmacokinetic parameter estimate		
k_a (1/h)	Absorption rate constant for healthy subjects	0.014 [4.56]	56.57 [5.05]
k_a_PMO (1/h)	Absorption rate constant for PMO patients	0.0078 [4.96]	
V_C/F (L)	Apparent volume of central compartment	1.58 [4.30]	61.69 [5.68]
Covariate effect (θ) of body weight on V_C/F	Covariate effect (θ) in the power model described as $(V_C/F) \times WT^{\theta}$	1.50 [13.78]	-
V_P/F (L)	Apparent volume of peripheral compartment	6.06 [1.20]	15.55[6.65]
Covariate effect (θ) of body weight on V_P/F	Covariate effect (θ) in the power model described as $(V_P/F) \times WT^{\theta}$	0.52 [11.25]	-
k_{int} (1/h)	Denosumab-target complex internalization rate constant	0.022 [1.71]	7.88 [13.46]
K_{SS} (nmol/L)	Quasi-steady state equilibrium constant	1.56 [12.41]	58.12 [23.07]
k_{syn} (1/h)	target (RANKL) synthesis rate constant	0.01 [2.86]	22.46 [11.92]
R_0 (nmol/L)	Baseline target (RANKL) for HV	0.98 [24.33]	158.3 [7.14]
R_0_PMO (nmol/L)	Baseline target (RANKL) for PMO	15.23 [12.78]	
CL/F in Caucasian (L/h)	Apparent clearance for Caucasian	0.006 [1.46]	
CL/F on Black (L/h)	Apparent clearance for Black	0.0069 [4.15]	26.39 [3.67]
CL/F on Asian (L/h)	Apparent clearance for Asian	0.0074 [3.96]	
Covariate effect (θ) of body weight on CL/F	Covariate effect (θ) in the power model described as $(CL/F) \times WT^{\theta}$	0.93 [7.98]	-
Q/F (L/h)	Apparent inter-compartment clearance for HV	1.13[15.57]	295.99 [6.97]
Q/F_PMO (L/h)	Apparent inter-compartment clearance for PMO	0.20[20.22]	
	Correlation		
$CORR_{Vp/F-CL/F}$	Correlation between IIV of CL/F and IIV of Vp/F	0.43 [12.35]	
	Residual error		
ε_{add} (nmol/L)	Additional error	0.72 [4.05]	-
ε_{prop}	Proportional error	0.07 [3.74]	-
	Final Pharmacodynamic parameter estimate		
BMD_0 (g/cm²)	Baseline Lumbar spine BMD	0.76 [0.46]	59.85 [3.37]
k_{out} (1/h)	Rate constant for the elimination of Lumbar spine BMD; $\frac{dBMD}{dt} = k_{in} - k_{out} \cdot BMD \cdot \frac{I_{max} \cdot C^{hill}}{IC_{50}{}^{hill} + C^{hill}}$	0.00018 [9.5]	-
I_{max}F	Logit-transformed fractional maximum inhibitory effect	-1.75 [3.02]	-
IC_{50} (nmol/L)	Inhibition effect achieving 50% of Imax	6.92 [11.65]	9.52 [17.45]
HILL	Hill coefficient	0.17 [4.9]	-
	Residual error		
ε_{add} (g/cm²)	Additional error	0.02 [2.06]	-

Inter-individual variability (IIV) is expressed as coefficient of variation (CV %); RSE: relative standard error

Table 1. Final population pharmacokinetic and pharmacodynamic parameter estimates of denosumab

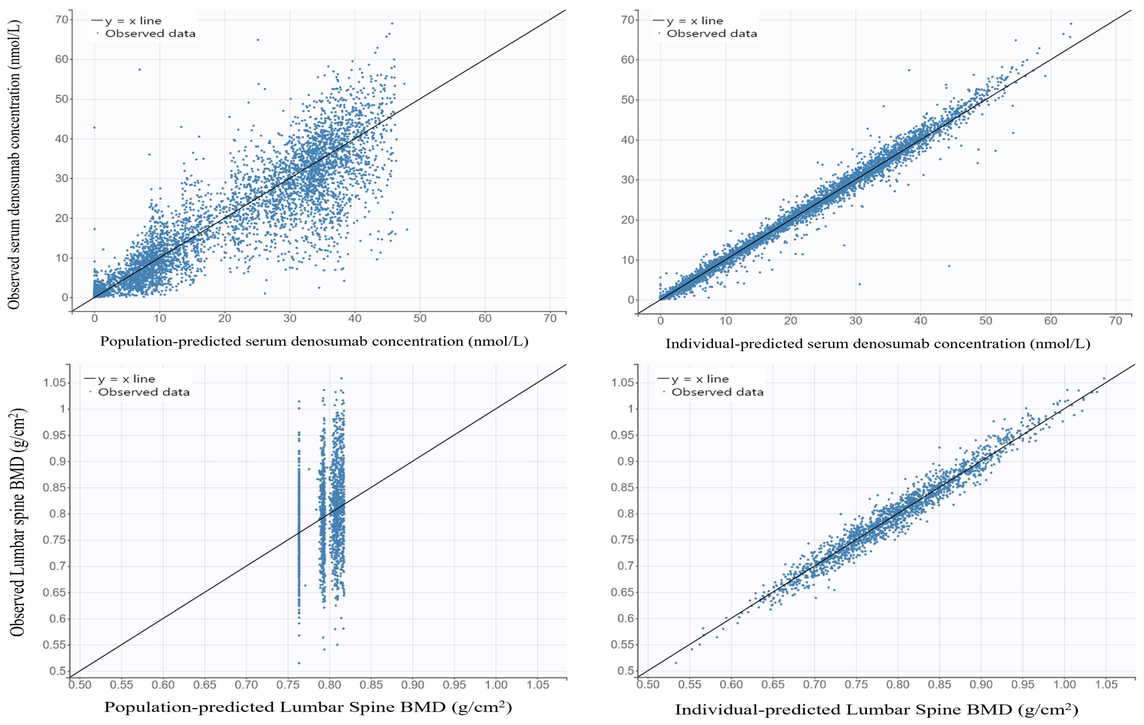


Figure 3. Basic goodness-of-fit plots of the final pharmacokinetic model and pharmacodynamics models

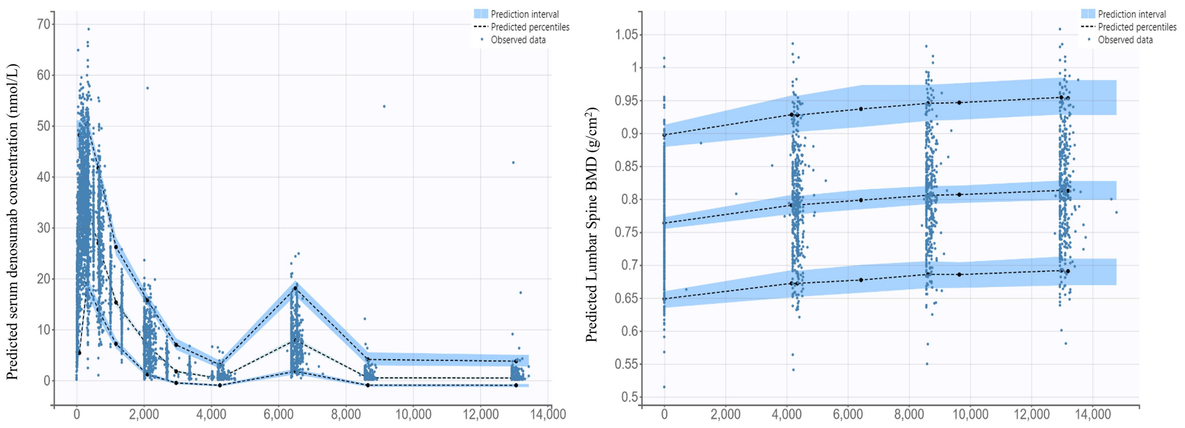


Figure 4. Visual predictive check for the final pharmacokinetic model and pharmacodynamics models

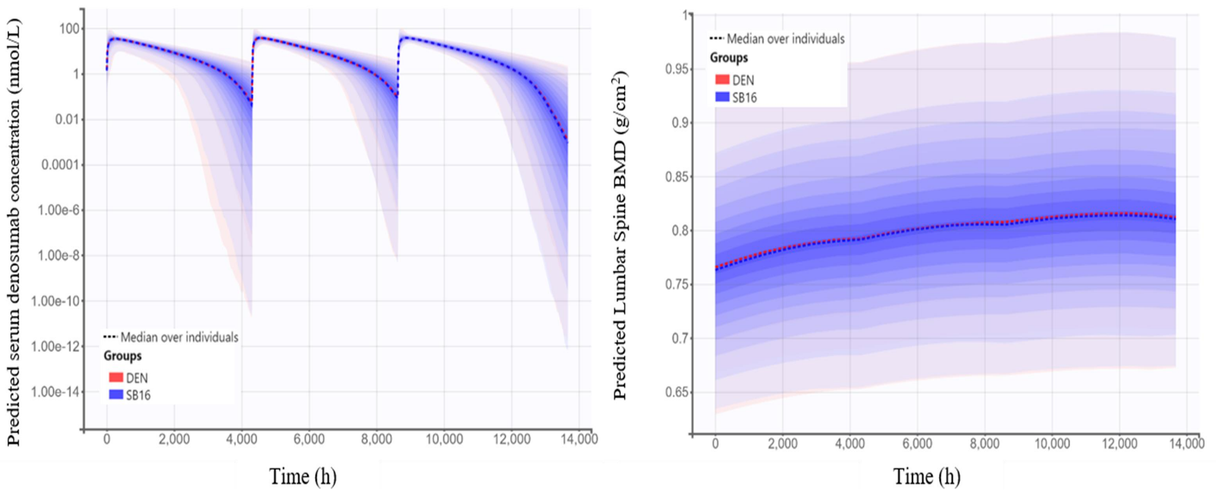


Figure 5. Simulated time profiles comparing SB16 and DEN after three subcutaneous administrations of 60 mg denosumab at 6-month intervals

Parameters (units)	SB16	DEN
	Median (90% Prediction Interval)	
C_{max} (nmol/L)	40.66 (26.90 – 77.50)	40.29 (26.04 – 80.45)
T_{max} (h)	259 (52 – 530)	267 (59 – 505)
$AUC_{\tau,ss}$ (nmol/L/h)	55040 (33625 – 85011)	53731 (33706 – 87790)
Change from baseline in lumbar spine BMD (%)	6.59 (4.90 – 7.52)	6.59 (4.96 – 7.58)

Table 2. Comparison of simulated PK and PD results between SB16 and DEN