# INTEGRATED POPULATION PHARMACOKINETIC-PHARMACODYNAMIC-EFFICACY ANALYSIS OF ENAVOGLIFLOZIN: LINKING EXPOSURE, GLUCOSURIA, AND HBA1C REDUCTION IN TYPE 2 DIABETES

Yang E[1,2] , Kim Y[1] , Kang J[1] , Yoon S[3] , Park C[3] , Lee S[1]

1 Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea
2 Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco CA, United States of America
3 Daewoong Pharmaceutical, Seoul, Republic of Korea

## OBJECTIVES

- **Enavogliflozin is a sodium-glucose cotransporter 2 inhibitor approved in the Republic of Korea for the treatment of type 2 diabetes (T2D) with 0.3 mg once-daily regimen.**
- **Here, we aimed to quantitatively characterize the exposure-response relationship of enavogliflozin for its glucosuric and HbA1c-lowering effects, provide model-informed evidence to support its use across varying degrees of renal function, and explore the potential influence of ethnicity on its exposure and response.**

## METHODS

- **We integrated data from ten enavogliflozin clinical trials in Korean participants (five phase 1 studies in 203 healthy volunteers and five phase 1/2/3 studies in 221 patients with T2D). We sequentially developed and linked population pharmacokinetic (PK), population PK-pharmacodynamic (PD), and population PD-efficacy models (Figure 1). Steady-state PK, PD, and efficacy profiles were simulated across renal function categories, using individual baseline data from the 221 patients with T2D.**
- **We then incorporated data from an additional phase 3 study in 151 Chinese patients with T2D, extended the PK and PD-efficacy models, and assessed the influence of ethnicity.**
- **Model development and simulation were performed using a nonlinear mixed-effects modeling approach with NONMEM v7.4.4 through PsN v5.3.0. All models were qualified by goodness-of-fit diagnostics and visual predictive checks.**

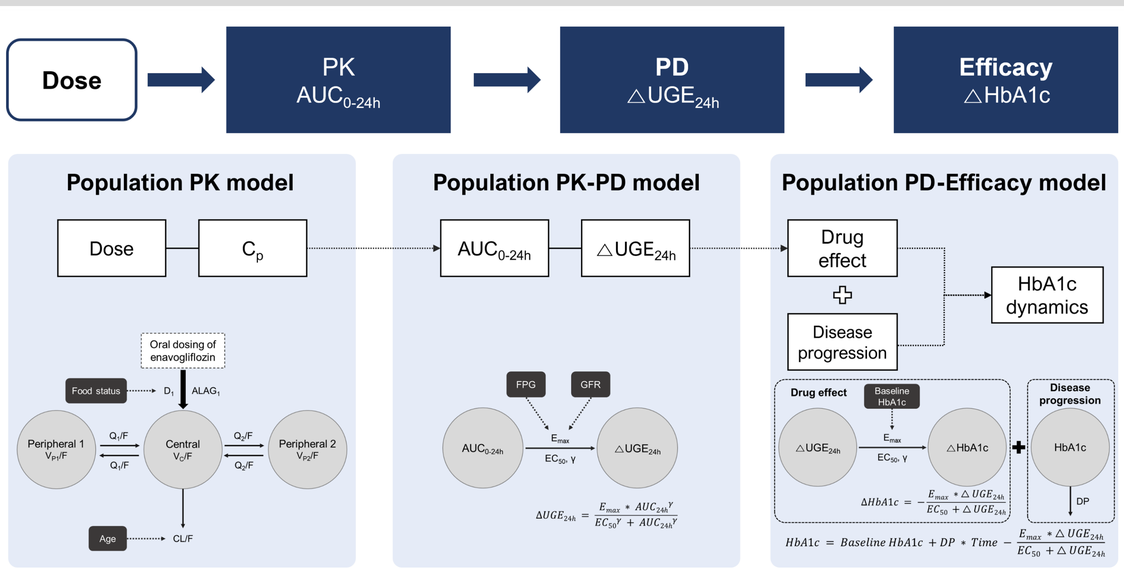


**Figure 1. Analysis workflow and structural overview of the integrated population PK-PD-efficacy models of enavogliflozin**

**Abbreviations** △HbA1c, change in HbA1c from baseline; $\triangle UGE_{24h}$, change in urinary glucose excretion over 24 hours from baseline; $ALAG_1$, absorption lag-time; $AUC_{0\text{-}24h}$, area under the concentration-time curve from 0 to 24 h post-dose; CL/F, apparent clearance; $C_p$, plasma concentration; $D_1$, duration of zero-order absorption; DP, disease progression slope for HbA1c increase; $EC_{50}$, exposure (or $\triangle UGE_{24h}$) producing half-maximal effect; $E_{max}$, maximum effect; FPG, fasting plasma glucose; GFR, glomerular filtration rate; γ, hill coefficient; PK, pharmacokinetics; PD, pharmacodynamics; $Q_1$/F, apparent inter-compartmental clearance between central and peripheral 1 compartment; $Q_2$/F, apparent inter-compartmental clearance between central and peripheral 2 compartment; $V_C$/F, apparent central volume of distribution; $V_{P1}$/F, apparent peripheral 1 volume of distribution; $V_{P2}$/F, apparent peripheral 2 volume of distribution

## RESULTS

- **A total of 424 Korean participants were included in the analysis. They were mostly male (78.1%), and most had normal renal function (65.3%), with 30.9% having mild, 2.6% moderate, and 1.2% severe renal impairment. The median age was higher in patients (62 years) than in healthy volunteers (30 years). Additional 151 Chinese patients had comparable baseline characteristics (Table 1).**

**Table 1. Baseline characteristics of participants**

| Parameter (unit) | Korean | | | Chinese |
|---|---|---|---|---|
| | Total (n = 424) | Healthy volunteers (n = 203) | T2D patients (n = 221) | T2D patients (n = 151) |
| Age (years) | 46 (19 - 81) | 30 (19 - 58) | 62 (23 - 81) | 62 (23 - 80) |
| Male sex, n (%) | 331 (78.1) | 203 (100.0) | 128 (57.9) | 103 (68.2) |
| Weight (kg) | 69.5 (49.0 - 99.8) | 71.2 (54.2 - 98.0) | 66.0 (49.0 - 99.8) | 66.0 (49.0 - 99.8) |
| BMI (kg/m²) | 24.3 (18.7 - 37.5) | 23.9 (18.7 - 29.1) | 25.1 (20.1 - 37.5) | 25.1 (20.2 - 37.5) |
| eGFR (mL/min/1.73 m²) | 95.6 (17.7 - 154.6) | 103.8 (77.0 - 150.0) | 84.4 (17.7 - 154.6) | 85.8 (55.4 - 154.6) |
| Renal function, n (%) | | | | |
| Normal | 277 (65.3) | 198 (97.5) | 79 (35.7) | 122 (80.8) |
| Mild | 131 (30.9) | 5 (2.5) | 126 (57.0) | 27 (17.9) |
| Moderate | 11 (2.6) | - | 11 (5.0) | 2 (1.3) |
| Severe | 5 (1.2) | - | 5 (2.3) | - |

Data are expressed as median (range) for continuous variables and as number of participants (%) for categorical variables.

**Abbreviations** BMI, body mass index; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes

- **Enavogliflozin PK was best characterized by a three-compartment model with zero-order absorption and first-order elimination (Figure 1, Table 2).**
- **The PD data were well described by a sigmoid maximum effect ($E_{max}$) model characterizing change in urinary glucose excretion over 24 hours from baseline ($\triangle UGE_{24h}$) as a function of area under the concentration-time curve from 0 to 24 h post-dose ($AUC_{0\text{-}24h}$), where the maximum reachable glucosuric effect was dependent on both fasting plasma glucose and renal function (Figure 1, Table 3).**
- **The efficacy data were adequately captured by a model combining a linear disease progression component with a drug effect component. This drug effect linked $\triangle UGE_{24h}$ to change in HbA1c from baseline (△HbA1c) through an $E_{max}$ relationship, where baseline HbA1c was negatively correlated with the maximum glycemic reduction (Figure 1, Table 4).**

**Table 2. Parameter estimates for the population PK models**

| Parameter (unit) | Final model Estimates (RSE%) | Extended model Estimates (RSE%) |
|---|---|---|
| $D_1$ (h)[a] | 0.919 FIX | 0.919 FIX |
| Effect of food intake | 9.34 FIX | 9.34 FIX |
| $ALAG_1$ (h) | 0.204 FIX | 0.204 FIX |
| CL/F (L/h)[b] | 7.04 (1.4) | 7.18 (1.2) |
| Effect of age | -0.222 (12.2) | -0.202 (12.0) |
| $V_C$/F (L) | 46.4 (2.5) | 46.9 (2.5) |
| $Q_1$/F (L/h) | 1.12 FIX | 1.12 FIX |
| $V_{P1}$/F (L) | 25.9 FIX | 25.9 FIX |
| $Q_2$/F (L/h) | 6.97 FIX | 6.97 FIX |
| $V_{P2}$/F (L) | 46.8 FIX | 46.8 FIX |
| IIV $ALAG_1$ (CV%) | 40.9 FIX | 40.9 FIX |
| IIV CL/F (CV%) | 25.6 (4.7) | 25.3 (4.2) |
| IIV $V_C$/F (CV%) | 38.2 (5.0) | 38.3 (5.1) |
| Correlation IIV CL/F-$V_c$/F | 73.3 (10.3*) | 74.3 (10.1*) |
| IIV $V_{P2}$/F (CV%) | 39.4 FIX | 39.4 FIX |
| Additive residual error for full PK data (μg/L) | 0.276 (5.1) | 0.276 (5.0) |
| Additive residual error for trough PK data (μg/L) | 0.428 (7.6) | 0.416 (5.8) |

Abbreviations not defined in Figure 1: CV, coefficient of variation; IIV, inter-individual variability; RSE, relative standard error.
*Relative measure derived from covariance matrix (not a direct RSE for correlation)

[a] $D_1$ (h) = 0.919 * (1 + 9.34 * FOOD); FOOD=0 (fasted) or 1 (fed)
[b] CL/F (L/h) = 7.04 * (Age / 47)$^{(-0.222)}$ (Final model); 7.18 * (Age / 47)$^{(-0.202)}$ (Extended model)

**Table 3. Parameter estimates for the population PK-PD model**

| Parameter (unit) | Final model Estimates (RSE%) |
|---|---|
| $E_{max}$ (g)[a] | 48.9 (4.0) |
| Effect of FPG | 0.827 (20.9) |
| Effect of GFR | 0.759 (16.9) |
| $EC_{50}$ (μg·h/L) | 20.7 (14.5) |
| Hill coefficient | 2.41 (14.9) |
| IIV $E_{max}$ (CV%) | 26.0 (11.8) |
| Additive residual error | 11.5 (5.7) |

Abbreviations not defined in Figure 1: CV, coefficient of variation; IIV, inter-individual variability; RSE, relative standard error.

[a] $E_{max}$ (g) = 48.9 * (FPG / 100)$^{(0.827)}$ * (GFR / 90)$^{(0.759)}$

**Table 4. Parameter estimates for the population PD-efficacy models**

| Parameter (unit) | Final model Estimates (RSE%) | Extended model Estimates (RSE%) |
|---|---|---|
| $E_{max}$ (%)[a] | 1.37 (5.1) | 3.16 (12.3) |
| Effect of baseline HbA1c | 4.43 (9.3) | 2.01 (13.8) |
| $EC_{50}$ (g) | 24.9 (14.2) | 47.7 (10.4) |
| Disease progression (%/week) | 0.0035 FIX | 0.0446 (15.7) |
| IIV $EC_{50}$ (CV%) | 247.0 (7.9) | 81.9 (8.2) |
| Proportional residual error (%) | 2.77 (4.0) | 3.01 (3.5) |

Abbreviations not defined in Figure 1: CV, coefficient of variation; IIV, inter-individual variability; RSE, relative standard error.

[a] $E_{max}$ (%) = 1.37 * (Baseline HbA1c / 7.7)$^{(4.43)}$ (Final model); 3.16 * (Baseline HbA1c / 7.7)$^{(2.01)}$ (Extended model)

- **At the approved 0.3 mg dose, median $\triangle UGE_{24h}$ and ΔHbA1c at week 24 in patients with T2D were predicted to be 61.8 g and −0.79%, respectively.**
- **Compared with patients with normal renal function, median $\triangle UGE_{24h}$ at a 0.3 mg dose was predicted to decline by 22% and 39% in patients with mild and moderate renal impairment, respectively (Figure 2a). The resulting ΔHbA1c at week 24 was predicted to be −0.75% and −0.63%, respectively, indicating that the reduction in HbA1c was less pronounced than the reduction in glucosuria as renal function declined (Figure 2b).**
- **No apparent ethnic differences were observed in PK or efficacy parameters; marginal variations in the extended PD-efficacy model were likely confounded by higher baseline HbA1c levels in Chinese patients and imbalances in treatment regimens.**

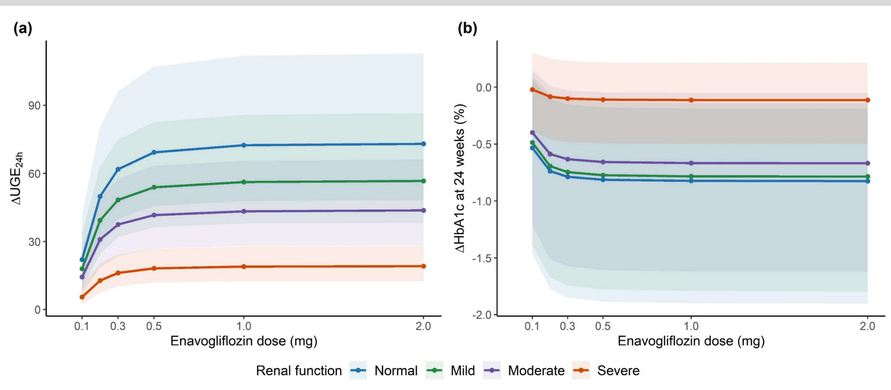


**Figure 2. Simulated enavogliflozin response in patients by renal function.**

(a) Dose vs. $\triangle UGE_{24h}$ at steady state. (b) Dose vs. △HbA1c at week 24 after enavogliflozin initiation. Solid lines represent the medians and the shaded areas represent the 10th and 90th percentiles of the predicted data.

## CONCLUSION

- **We established the first integrated framework linking enavogliflozin dose, systemic exposure, glucosuria, and HbA1c dynamics, providing a quantitative rationale for its clinical use in patients with T2D.**
- **This framework supports the appropriate use of enavogliflozin across varying degrees of renal function. Comparable PK and efficacy between Korean and Chinese patients suggest no dose adjustment is required for Chinese patients.**

**This study is supported by Daewoong Pharmaceutical Co., Ltd., Seoul, Republic of Korea.**