



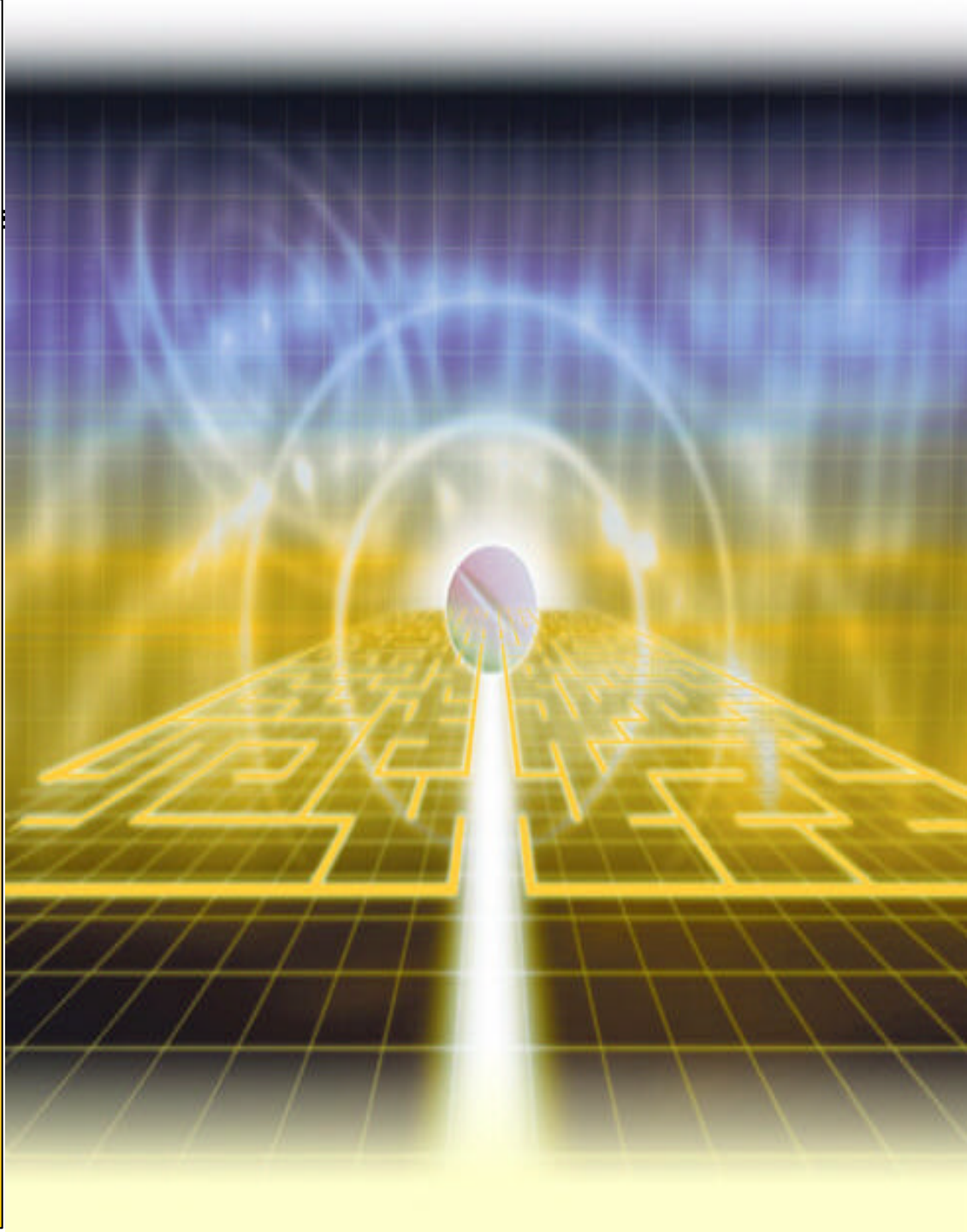
## Population Pharmacokinetic Case Study

*Population pharmacokinetics of  
olmesartan after Administration  
of its prodrug olmesartan  
medoxomil in healthy volunteers  
and hypertensive patients*

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# Objectives\*

- Olmesartan medoxomil is a orally active angiotensin II receptor antagonist that is highly selective for the subtype AT<sub>1</sub> receptor and used as an effective antihypertensive agent.
- Olmesartan medoxomil is a prodrug that is rapidly and completely de-esterified to the active metabolite olmesartan (OLM) by both arylesterase and albumin during gastrointestinal absorption.
- The objectives of this study were to model a population PK of OLM using pooled population of healthy volunteers and a diverse, ambulatory population of hypertensive patients from 12 phase I to III trials conducted in the USA, Europe and Japan, and to evaluate covariate effects on the apparent oral clearance (CL) of OLM, with particular emphasis on the effect of race.

\* This work was published in the following reference:

**Population Pharmacokinetics of Olmesartan Following Oral Administration of its Prodrug, Olmesartan Medoxomil: In Healthy Volunteers and Hypertensive Patients**

Authors: Yoshihara, Kazutaka; Gao, Yuying; Shiga, Hiroshi; Wada, D. Russell; Hisaoka, Masafumi

Source: Clinical Pharmacokinetics, Volume 44, Number 12, 2005, pp. 1329-1342(14)

# Data

- A total of 7911 sample concentration data of OLM from 472 participants (=89 healthy volunteers and 383 patients with mild to moderate hypertension) were examined in this study.
- The doses of olmesartan medoxomil administered comprised a single oral dose of 10 mg (2 trials), multiple oral doses 2.5 to 80 mg once daily for 1 to 12 weeks (9 trials), and titratable oral doses of 5 to 40 mg once daily for 1 year (1 trial).
- Five to 29 plasma samples were serially drawn per participant over a period of 3 to 96 hours after either a single dose, after the last dose of a multiple dose regimen, or at the time assumed to represent the steady state.

Trial no.	Phase	n	Participant Description <sup>a</sup>	Doses (mg) and treatment period	Number and relative time of plasma samplings
1	II	23	W; patients (young/elderly)	80 (10 days)	28 (0-240 hr)
2	III	211	W; patients	2.5, 5, 10 (12 weeks)	7 (Week 8: 0-24 hr)
3	II	33	W; patients (young/elderly)	10 (14 days)	27 (0-408 hr)
4	I	34	W; patients (renal impairment) and volunteers	10 (7 days)	29 (0-240 hr)
5	I	30	W; volunteers (5-way crossover design)	2.5, 5, 10, 20, 40 (7 days)	15 (Day 7: 0-60 hr)
6	I	24	W; patients (hepatic impairment) and volunteers	10 (single dose)	13 (0-96 hr)
7	II	21	J; patients	5, 10, 20, 40 (1 year titration)	5 (Month 6: 0-3 hr)
8	II	8	J; patients (renal impairment)	5 (7 days)	17 (0-240 hr)
9	III	27	J; volunteers	10, 20, 40 (7 days)	28 (0-240 hr)
10	III	39	J; patients	10, 20 (14 days)	7 (Day 14: 0-24 hr)
11	III	12	J; volunteers (young/elderly)	10 (single dose)	10 (0-24 hr)
12	III	10	J; patients	40 (7 days)	7 (Day 7: 0-24 hr)

a. W = Westerner, J = Japanese; patients = hypertensive patients, volunteers = healthy volunteers.  
n = number of participants.

# Participant demographics

Characteristic	Healthy volunteers	Hypertensive patients		
		Hypertension	+ Renal impairment	+ Hepatic impairment
Participants <sup>a</sup>	209 <sup>d</sup>	337	34	12
Plasma samples <sup>a</sup>	3426	3449	881	155
Race <sup>a</sup> (W/J) <sup>b</sup>	170 <sup>d</sup> /39	267/70	26/8	12/0
Gender <sup>a</sup> (F/M) <sup>c</sup>	0/209	140/197	16/18	0/12
Age (yr)	30.6 ± 11.8	54.2 ± 12.2	54.6 ± 11.8	53.9 ± 6.7
Body weight (kg)	70.4 ± 9.5	77.8 ± 15.6	70.3 ± 11.3	86.1 ± 14.6
SCr (μmol/L)	83.6 ± 12.2	80.1 ± 14.4	232.2 ± 153.8	62.4 ± 9.7
ALT (U/L)	27.2 ± 12.0	25.5 ± 16.7	17.3 ± 7.2	58.2 ± 79.1
AST (U/L)	25.3 ± 8.4	24.1 ± 12.2	20.4 ± 6.8	67.3 ± 65.4
ALP (U/L)	172.7 ± 61.1	170.9 ± 53.1	208.5 ± 80.3	94.0 ± 36.8
BIL (U/L)	13.4 ± 4.0	13.1 ± 3.5	11.6 ± 4.4	21.4 ± 11.9
GGT (U/L)	24.0 ± 16.6	28.4 ± 27.8	23.8 ± 10.4	106.9 ± 100.6

a Values represent the number.

b W = Westerner, J = Japanese.

c F = female, M = male.

d 30 male Westerner volunteers were enrolled in a 5-way crossover study (trial no.5) and treated as separate individuals.

**ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **ALP** = alkaline phosphatase; **BIL** = bilirubin; **SCr** = serum creatinine; **GGT** = gamma glutamyl transferase; **NA** = not available.

# Covariates

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- A total of 11 covariates were evaluated for their impact of the IIV of OLM CL, which were age, body weight, gender, race (Westerners/Japanese), patient status (Healthy volunteers/hypertensive patients), serum creatinine concentration (SCr) as an index of renal function, and serum chemistry data (ALT, AST, ALP, BIL and GGT) as indices of hepatic function.
- In this study, Westerner participants comprised Caucasians (N=338) and Hispanics (N=17). Caucasians and Hispanic population were pooled and handled as one racial category (i.e. Westerners).

# Pharmacokinetic model

- The prodrug olmesartan medoxomil was assumed to be completely converted to OLM during its absorption from intestinal tract, and the PK calculation were based on the concentration data of OLM.
- NONMEM version V was used for model building.
- Structural model: 2-compartment linear model with first-order absorption along with a lag-time.  
(ADVAN4, TRANS1 with reparameterization to get CL by  $V2=CL/K$ )
- Interindividual variability (IIV): exponential error model  $\theta_i = \theta_T \times \exp(\eta)$
- Residual variability: exponential error model  $Y = \text{LOG}(F) + \text{EPS}(1)$ , where DV were log-transformed.
- The final population model retained age, body weight, gender, race, patient status, and SCr as covariates for CL as shown below:

$$\text{CL} = \text{CL}_{\text{typ}} \cdot (\text{Age}/50)^{K_{\text{AGE}}} \cdot (\text{Body weight}/70)^{K_{\text{WT}}} \cdot (\text{SCr}/80)^{K_{\text{SCr}}} \\ \cdot \exp(\text{Gender} \cdot K_{\text{GENDER}}) \cdot \exp(\text{Patient status} \cdot K_{\text{PV}}) \cdot \exp(\text{Race} \cdot K_{\text{RACE}}) \cdot \exp(\eta_{\text{CL}})$$

Where: Age (yr); Body weight (kg); SCr ( $\mu\text{mol/L}$ );  
Race = 0 (Westerner), 1 (Japanese);  
Gender = 0 (female), 1 (male);  
Patient status = 0 (healthy volunteers), 1 (hypertensive patients)

# Population pharmacokinetic model building

- Covariates were screened using a linear regression modeling and selected using a backward-elimination approach. Statistical significance of each covariates was assessed with the use of a likelihood ratio test. The level of significant level was set at  $\alpha=0.05$  ( $\alpha=0.01$  for liver enzymes).
- Both the first order (FO) estimation method and the first order with conditional estimation (FOCE) method were assessed during the model development process. However, the models did not converge successfully using FOCE method, so the estimation with FO method was employed finally.

Model no.	Model	Data set <sup>b</sup>	OBJ	Reference model	P-value	Comments
1	Basic model (no covariate)	A	-7984.241	-	-	Basic model (data set A)
2	#1 + all 11 covariates on CL	A	-8208.313	#1	<0.01 *	Full model
3	#2 – ALT, AST, and Race	A	-8208.267	#2	1	ALT, AST and Race are not important factors on CL.
4	#3 – ALP	A	-8202.749	#3	0.02	OBJ is not statistically different at $\alpha=0.01$ .
5	#4 –GGT	A	-8197.017	#4	0.02	OBJ is not statistically different at $\alpha=0.01$ .
6	#5 – BIL	A	-8192.557	#5	0.03	OBJ is not statistically different at $\alpha=0.01$ .
7	#6 – Age	A	-8189.096	#6	0.06	Age is not an important factor on CL ( $\alpha=0.05$ ).
8	#7 – Gender	A	-8178.559	#7	<0.01 *	Gender is an important factor on CL.
9	#8 – SCr	A	-8138.595	#8	<0.01 *	SCr is an important factor on CL.
10	#9 – Patient Status (= #1 + Body Weight on CL)	A	-7987.976	#9	<0.01 *	Patient Status is an important factor on CL.
11	#1 + SCr, Gender, and Patient Status on CL	A	-8175.273	#1	<0.01 *	Body Weight is not an important factor on CL ( $\alpha=0.05$ ).
12	#11 + Race on CL	A	-8178.881	#11	0.06	Race is not an important factor on CL.
13	Basic model (no covariate)	B	-8621.531	-	-	Basic model (data set B)
14	#13 + SCr, Gender, and Patient Status on CL	B	-8794.453	#13	<0.01 *	SCr, Gender, and Patient Status are important factors.
15	#14 + Body Weight on CL	B	-8809.325	#14	<0.01 *	Body Weight is an important factor on CL.
16	#15 + Age on CL	B	-8813.942	#15	0.03 *	Age is an important factor on CL.
17 <sup>a</sup>	#16 + Race on CL	B	-8814.474	#16	0.48	Race is not an important factor on CL.

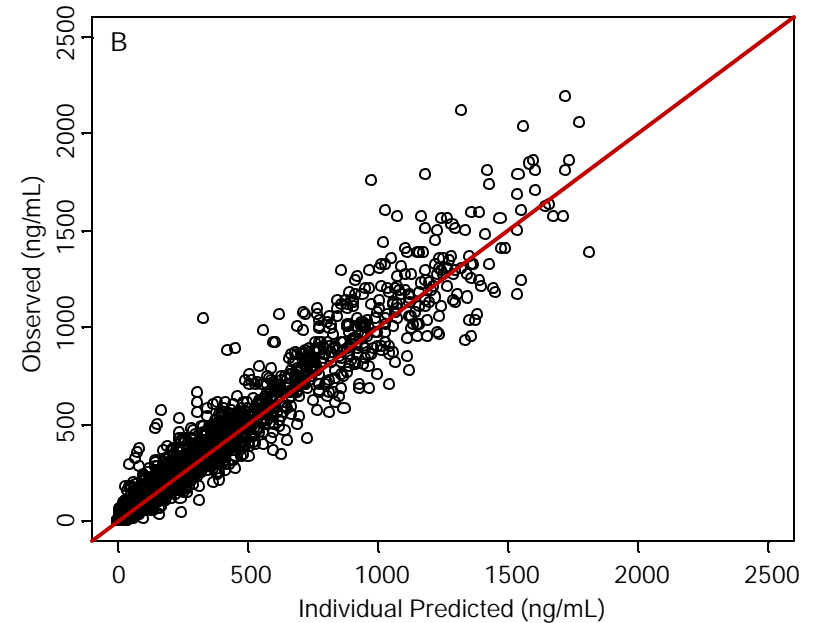
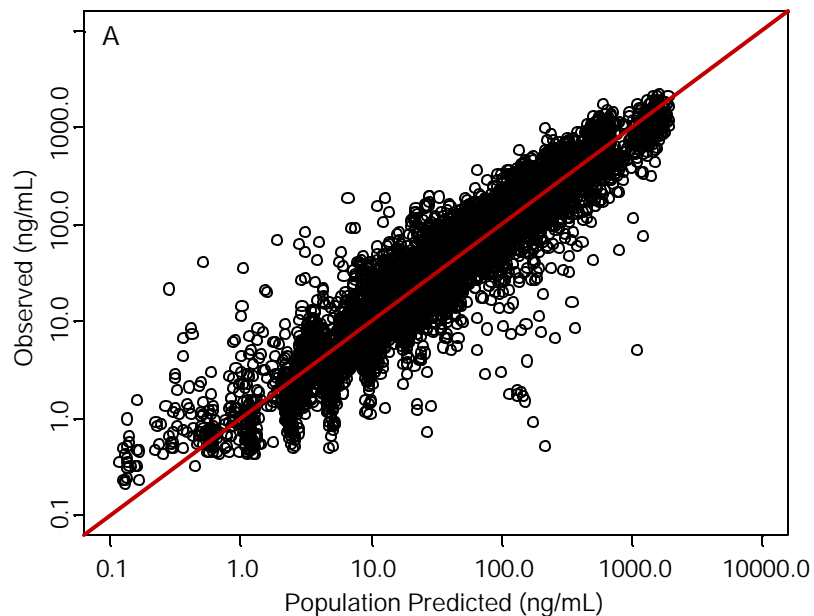
a. The final model.

b. Participants in one of the 12 trials received the highest dose (80 mg) but showed the lowest dosenormalized AUC; therefore, the population PK

model was initially built from 11 trials, and then the trial was added in. (Data set A = 11 trials data; Data set B = 12 trials data)

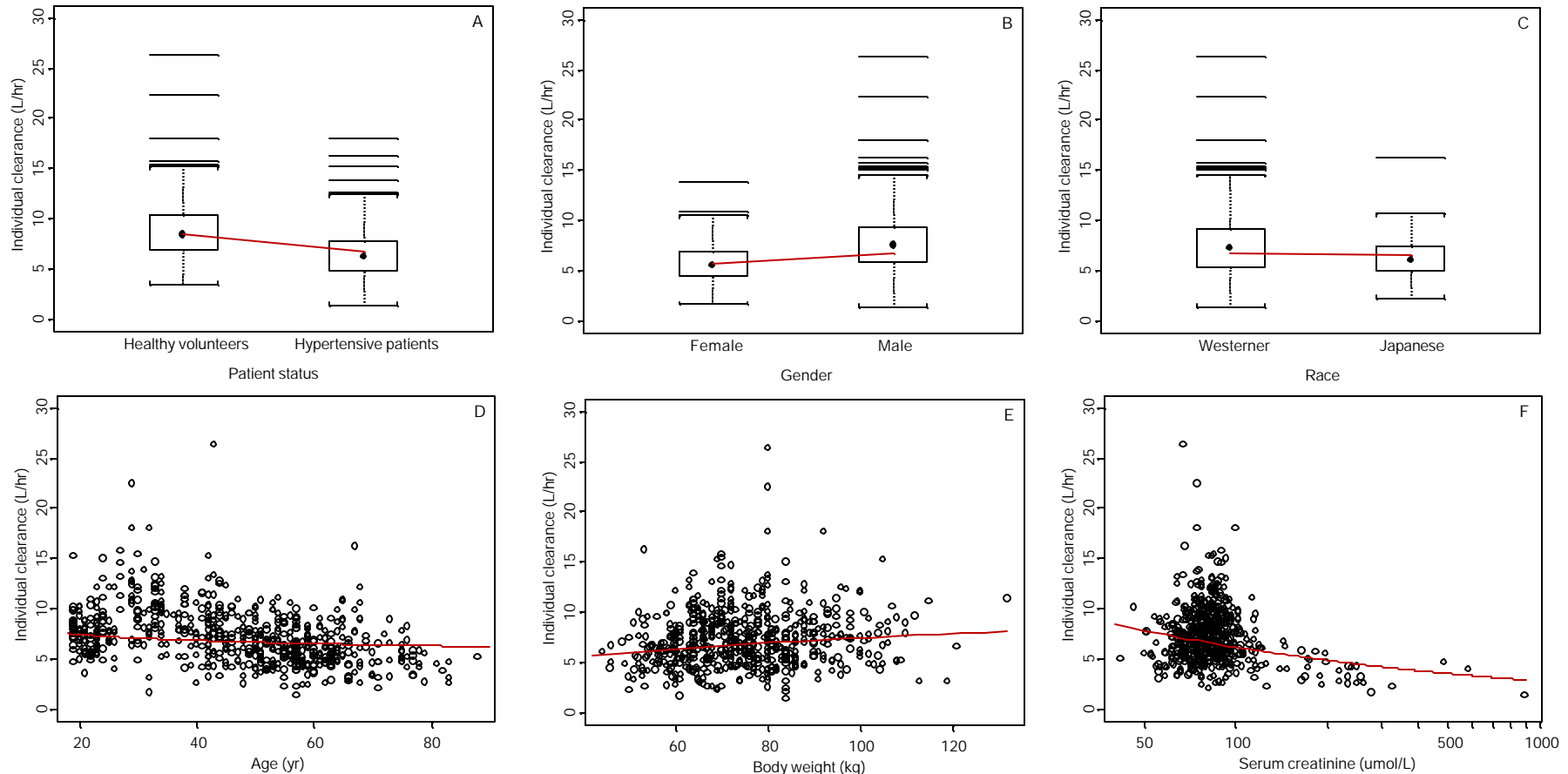
\* Statistically significant at  $\alpha=0.05$ , except liver parameters for which  $\alpha=0.01$ .

The OLM PK were well described by a 2-compartment linear model with first-order absorption and a lag-time



Scatter plot of the observed vs. the population predicted (**A**) and individual post hoc predicted (**B**) plasma concentration of OLM from the final model. The solid lines are the line of unity.

# The covariate model well described the relationship between individual *post hoc* parameter estimates and important covariates



Distribution of the individual post hoc estimates of CL of OLM for the final model plotted against the covariates. **(A-C)** The individual CL vs. patient status, gender, and race. **(D-F)** The individual CL vs. age, body weight, and SCr. Solid lines represent the population model equation for CL in a 50-year-old, 70-kg, male Westerner hypertensive patient with a SCr of 80  $\mu\text{mol/L}$  except where indicated in the horizontal axes.

# Model evaluation: bootstrapping

- Pharmacokinetic parameter estimates and the results of bootstrapping (B=200) for the final model. Mean values of the bootstrapping were very similar to the parameter estimates of the original data set and the 95% CIs overlapped with those, indicating that the final population model was stable.

Parameters (units)	NONMEM	Results of Bootstrapping ( B=200)		Bootstrap mean / NONMEM estimate ( %)
	Estimates ( %CV)	Mean	95%CI <sup>c</sup>	
<b>Fixed effects</b>				
CL (L/h) <sup>a</sup>	7.320 (6)	7.309	[6.575, 8.087]	99.8
K (1/h)	0.193 (2)	0.193	[0.186, 0.199]	100.0
K <sub>23</sub> (1/h)	0.061 (3)	0.061	[0.057, 0.064]	100.0
K <sub>32</sub> (1/h)	0.079 (2)	0.079	[0.076, 0.082]	100.0
KA (1/h)	1.460 (6)	1.493	[1.331, 1.739]	102.3
ALAG <sub>1</sub> (h)	0.427 (2)	0.426	[0.410, 0.453]	99.8
<b>Covariables</b>				
K <sub>AGE</sub>	-0.117 (52)	-0.121	[-0.228, -0.004]	103.4
K <sub>WT</sub>	0.310 (33)	0.307	[0.103, 0.490]	99.0
K <sub>SCR</sub>	-0.344 (14)	-0.342	[-0.437, -0.254]	99.4
K <sub>GENDER</sub>	0.145 (26)	0.146	[0.081, 0.218]	100.7
K <sub>PV</sub>	-0.239 (23)	-0.235	[-0.353, -0.127]	98.3
K <sub>RACE</sub> <sup>b</sup>	-0.030 (131)	-0.031	[-0.103, 0.049]	103.3
<b>Random effects</b>				
$\omega_{CL/F}^2$	0.116 (7)	0.116	[0.099, 0.133]	100.0
$\omega_K^2$	0.066 (13)	0.066	[0.050, 0.081]	100.0
$\omega_{K23}^2$	0.110 (24)	0.108	[0.062, 0.164]	98.2
$\omega_{K32}^2$	0.062 (15)	0.062	[0.045, 0.079]	100.0
$\omega_{KA}^2$	1.640 (19)	1.715	[1.166, 2.365]	104.6
$\omega_{ALAG1}^2$	0.011 (30)	0.011	[0.004, 0.020]	100.0
$\sigma^2$	0.058 (10)	0.058	[0.048, 0.070]	100.0

a. The final population model:

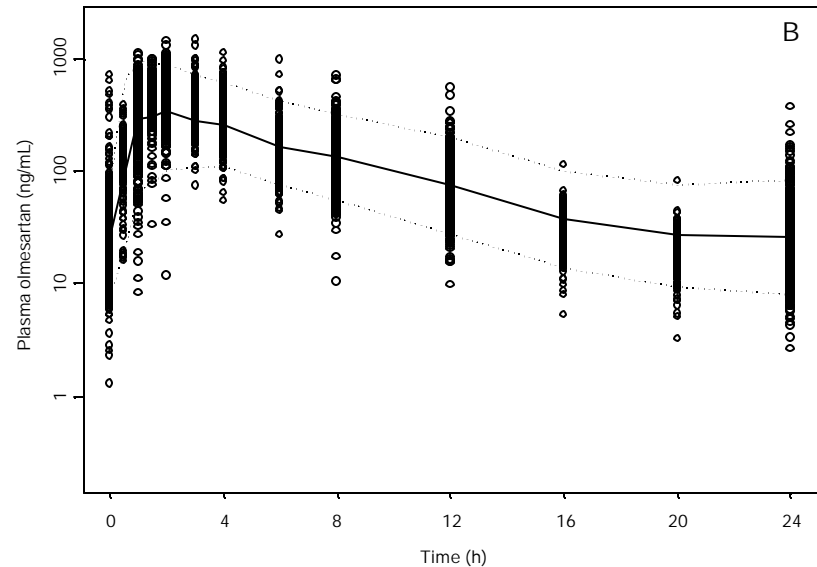
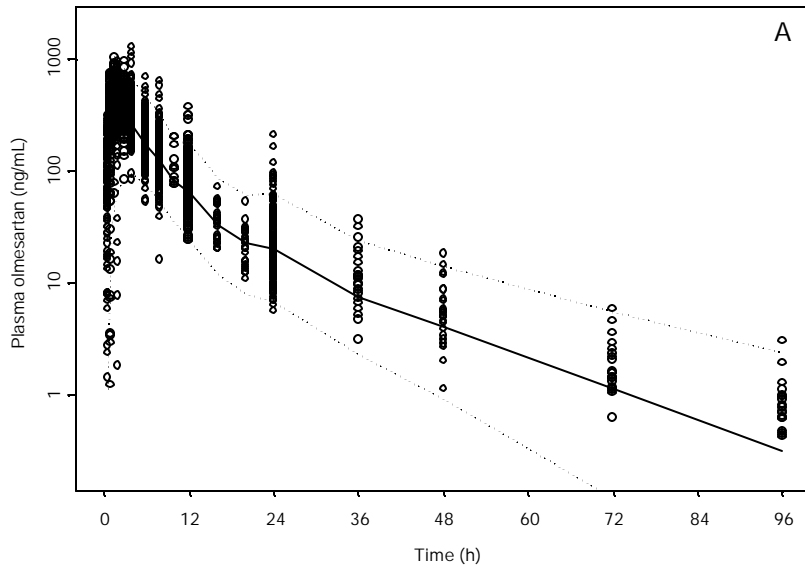
$$CL = CL_{typ} \cdot (Age/50)^{K_{AGE}} \cdot (Weight/70)^{K_{WT}} \cdot (SCR/80)^{K_{SCR}} \cdot \exp(Gender \cdot K_{GENDER}) \cdot \exp(Patient\ status \cdot K_{PV}) \cdot \exp(Race \cdot K_{RACE})$$

\* Age (yr); Weight (kg); SCR (μmol/L); Race = 0 ( Westerner) ,1( Japanese) ; Gender = 0 ( female) ,1( male) ; Patient status = 0( healthy volunteers) ,1( hypertensive patients) .

b. Not statistically significant at α=0.05 level. ; c. Bootstrap percentile method

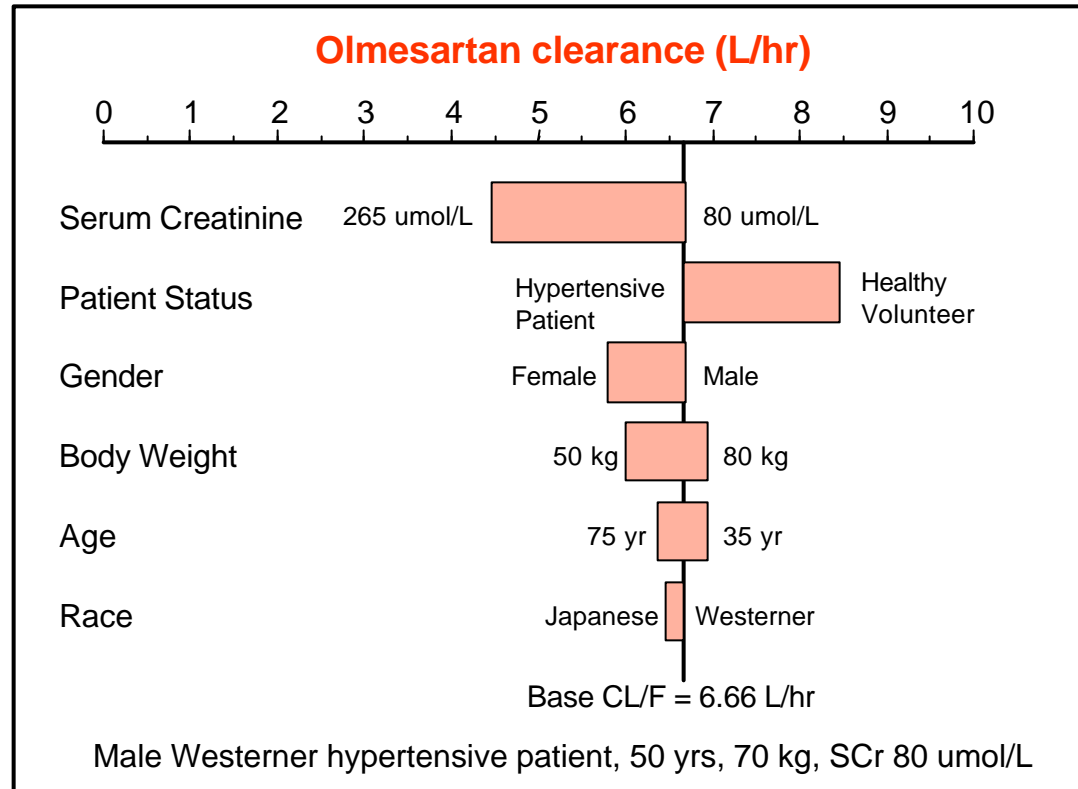
# Model evaluation: predictive check

- The majority of observed OLM data fell within the boundaries of the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the simulated data, suggesting that the final model accurately described the observed data



Predictive check of the final population model after single dosing (**A**) and at steady state (**B**). Simulated data (lines; median and 95% prediction interval) are compared to the observed data (symbols) that are dose-normalized to 20 mg.

A sensitivity analysis is performed to compare the relative impact of different covariates on apparent oral clearance of OLM



Sensitivity plot comparing the effect of covariates on apparent oral clearance of OLM. The solid vertical line is the clearance in a typical male Westerner patient (value of  $\eta$  set to zero). The label at each end of the bar represents the participant characteristic. The length of each bar describes the clearance changes for typical individuals with specified demographics.

# Conclusions

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- The parameter estimates with the final population model were stable.
- Severe renal impairment ( $\text{SCr} > 265 \mu\text{mol/L}$ , roughly 3 mg/dL) could cause a clearance decrease of 30% or more.
  - No initial dosage adjustment was considered to be clinically required in patients with renal impairment; however, careful observation and subsequent dosage adjustment based on clinical response might be required.
- Older age, lower body weight, and being female were determinants of lower clearance, but their effects were relatively small (within 20%).
- No statistically significant difference in clearance was found between Westerners and Japanese.