Pharmacokinetics of Omarigliptin (Mk-3102), A Once-Weekly Dipeptidyl Peptidase-IV (DPP-4) Inhibitor, in Patients With Renal Impairment

Daniel Tatosian,[1] Shirley Glasgow,[1] Maria Caceres,[1] Julie Grenier,[2] Bruce DeGroot,[2] Thelma Ward,[2] Amy Johnson-Levonas,[1] Laura George,[1] Kenneth C. Lasseter,[3] Thomas C. Marbury,[4] Eunkyung Kauh[1]

[1]Merck & Co., Inc., Whitehouse Station, NJ; [2]Celerion, Lincoln, NE; [3]Clinical Pharmacology of Miami, Inc., Miami, FL; [4]Orlando Clinical Research Center, Orlando, FL

Abstract

Background: Omarigliptin is a potent, long-acting DPP-4 inhibitor currently in Phase 3 development as a once-weekly treatment for type 2 diabetes. This study evaluated the pharmacokinetics (PK) and urinary excretion of omarigliptin in patients with varying degrees of renal impairment (RI).

Methods: In this open-label study, men and women, age 18-75 yrs, with varying degrees of RI based on estimated glomerular filtration rate (mild: ≥60 to <80, moderate: ≥30 to <60, severe: <30 mL/min/1.73 m^2 not on dialysis), patients with end-stage renal disease (ESRD), and healthy control subjects (≥80 mL/min/1.73 m^2 matched by age, gender, race, and body mass index) received a single 3-mg dose of omarigliptin. Plasma and urine samples were collected to characterize omarigliptin PK in RI or ESRD patients vs. healthy controls.

Results: The geometric mean ratios for plasma exposure ($AUC_{0-\infty}$) were 0.94, 1.34, 1.56, and 1.97 in patients with mild, moderate, severe impairment and ESRD vs. healthy control subjects, respectively. C_{max} was generally similar among patients with mild, moderate, severe RI and healthy subjects but was approximately 20% lower in patients with ESRD vs. healthy subjects. In ESRD patients, PK exposures were comparable regardless of dialysis schedule. Renal clearance of omarigliptin decreased with worsening renal function in a linear manner. Omarigliptin 3 mg was generally well tolerated in all patients.

Conclusions: AUC was not meaningfully altered by mild or moderate RI compared with healthy matched control subjects. AUC increased by ~56% and 97% in patients with severe RI and ESRD, respectively, vs. healthy matched controls. Omarigliptin may be administered without dosage adjustment in mild and moderate RI patients and without regard to timing of hemodialysis in ESRD patients.

Introduction

- Incretin hormones, including glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), are released by the neuroendocrine cells of the intestine in response to a meal and lower blood glucose concentrations by increasing insulin (for GLP-1 and GIP) and decreasing glucagon levels (for GLP-1) in a glucose-dependent manner.
- Incretins are rapidly degraded in the blood stream by the enzyme dipeptidyl peptidase-4 (DPP-4).
- DPP-4 inhibitors are oral anti-hyperglycemic agents used for the treatment of type 2 diabetes (T2DM) that act by augmenting the action of incretin hormones thereby lowering blood glucose by increasing insulin (GLP-1 and GIP) and decreasing glucagon levels (GLP-1) in a glucose-dependent manner.
- Omarigliptin (MK-3102) is a long-acting, oral DPP-4 inhibitor currently in Phase III development for the treatment of T2DM as a once-weekly dosing regimen.
- Omarigliptin is primarily eliminated as unchanged parent drug in urine.

Objectives

- To compare the single-dose pharmacokinetics (PK), pharmacodynamics (PD) and urinary excretion of omarigliptin (administered as a 3-mg dose) in patients with mild, moderate and severe RI as well as in patients with end-stage renal disease (ESRD) requiring hemodialysis versus healthy, matched control subjects.
- To evaluate the safety and tolerability of a single oral dose of 3-mg omarigliptin in patients with varying degrees of RI as well as ESRD requiring hemodialysis.

Methods

Study Design

- This was an open-label, 2-part, 8-panel study in which a single, oral 3-mg dose of omarigliptin was administered to healthy subjects and patients with varying degrees of RI or ESRD requiring hemodialysis.
- In Part I, 3 panels of 6 patients each, were enrolled with varying degrees of renal disease based on their estimated glomerular filtration rate (eGFR) as calculated by the Modification of Diet in Renal Disease (MDRD) study equation. Each of the 3 panels (Panels A, C, E, respectively) of patients with renal disease was matched with a corresponding panel (Panels B, D, F, respectively) consisting of an equal number of healthy matched control subjects (age, gender, race, and BMI).
- In Part II, 1 panel (Panel G) of 6 patients with ESRD who required hemodialysis was enrolled. An equal number of healthy matched control subjects (age, gender, race, and BMI) were enrolled in a separate panel (Panel H). ESRD patients in Panel G only participated in two treatment periods: a single 3-mg dose of omarigliptin was administered immediately following their normally scheduled hemodialysis in Period 1, and a single 3-mg dose of omarigliptin was administered 2 hours prior to their normally scheduled demodialysis in Period 2.

Subjects:

- Men and women
- Ages 18-75 yrs
- Body mass index ≤40 kg/m^2
- Patients with varying degrees of RI based on estimated glomerular filtration rate (eGFR; mild: ≥60 to <80, moderate: ≥30 to <60, severe: <30 mL/min/1.73 m^2 not on dialysis) with or without T2DM
- Patients with end-stage renal disease (ESRD) requiring hemodialysis with or without T2DM
- Healthy control subjects without T2DM (eGFR ≥80 mL/min/1.73 m^2 matched to patients by age, gender, race, and body mass index)

Table 1. Summary of renal function enrollment criteria for patients and healthy subjects

Part	Panel	n	Description	eGFR† (mL/min/1.73 m^2)
I	A	6	Mildly decreased eGFR	≥60 to <80
	B	6	Control subjects to match Panel A	≥80
	C	6	Moderately decreased eGFR	≥30 to < 60
	D	6	Control subjects to match Panel C	≥80
	E	6	Severely decreased eGFR	<30 not on dialysis
	F	6	Control subjects to match Panel E	≥80
II	G	6	ESRD requiring hemodialysis	Requiring hemodialysis
	H	6	Control subjects to match Panel G	≥80

†eGFR = Estimated glomerular filtration rate (calculated according to the Modification of Diet in Renal Disease [MDRD] study equation).

Pharmacokinetic and Pharmacodynamic Assessments:

- Omarigliptin blood, urine, and dialysate concentrations
- Ex vivo measurement of plasma protein binding
- DPP-4 enzyme activity assay (uncorrected for dilution)

Safety and Tolerability Assessments:

- Safety and tolerability were evaluated by clinical assessment of adverse events, physical examinations, vital signs, 12-lead electrocardiograms (ECG), and laboratory safety measurements.
- Investigators evaluated all clinical adverse events in terms of intensity (mild, moderate, or severe), duration, severity, outcome, and relationship to study drug.

Results

Demographics and Baseline Characteristics:

- This study enrolled 18 patients with RI, 6 patients with ESRD, and 25 healthy, matched control subjects

Table 2. Baseline demographics of study population

Panel	N	Description	Age† (y)	Female (n/N; %)	BMI† (kg/m^2)	eGFR†‡ (mL/min/1.73 m^2)
A	6	Mild RI	71 (67-75)	4/6 (66.7%)	27.3 (21.2-31.7)	71.8 (60-77)
B	6	Healthy control subjects to match Panel A	68 (64-74)	4/6 (66.7%)	25.7 (22.2-28.6)	106.8 (83-124)
C	6	Moderate RI	62 (50-74)	2/6 (33.3%)	28.1 (23.2-34.3)	48.5 (43-56)
D	6	Healthy control subjects to match Panel C	60 (51-74)	2/6 (33.3%)	27.6 (23.9-30.9)	107 (82-133)
E	6	Severe RI	64 (54-72)	2/6 (33.3%)	31.3 (25.4-39.6)	21.5 (18-28)
F	6	Healthy control subjects to match Panel E	60 (51-69)	2/6 (33.3%)	29.2 (25.2-35.6)	99.8 (80-124)
G	6	ESRD requiring hemodialysis	46 (30-60)	2/6 (33.3%)	30.5 (22.2-37.6)	--
H	7¡	Healthy control subjects to match Panel G	43 (33-57)	3/7 (42.9%)	28.0 (24.6-33.5)	113.6 (89-165)

†eGFR = Estimated glomerular filtration rate (calculated according to the Modification of Diet in Renal Disease [MDRD] study equation).
‡Expressed as mean (range)
¡One subject in Panel H withdrew consent for study participation on Day 15 and was replaced by another subject who completed the study.

Pharmacokinetics:

Figure 1. Semi-log plot of mean omarigliptin (nM) plasma concentration-time profiles in patients with varying degrees of RI (mild, moderate, or severe) and matched healthy control subjects (left) and patients with ESRD and healthy matched control subjects (right) following the administration of a single oral dose omarigliptin 3 mg. Inlay for patients with ESRD shown in linear scale up to 24 hours to illustrate the concentration of drug detected in the entrance (upper curve) and exit (lower curve) of dialyzer device.

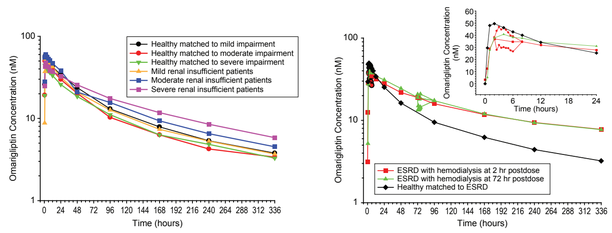


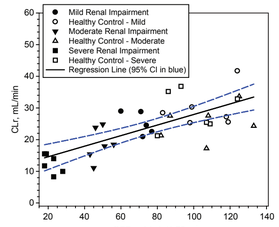
Table 3. Statistical comparisons of plasma $AUC_{0-\infty}$ and C_{max} of omarigliptin following the administration of a single oral 3-mg dose in patients with varying degrees of RI (mild, moderate, or severe) or ESRD as well as healthy matched control subjects.

Panel	N	Description	Geometric Mean (95% CI)	GMR	90% CI	rMSE
$AUC_{0-\infty}$ (nM•hr)						
A	6	Mild RI	4703.2 (4078.2, 5423.9)	0.94	(0.80, 1.11)	0.157
B	6	Healthy control subjects to match Panel A	4983.6 (4231.3, 5747.3)			
C	6	Moderate RI	5785.2 (4950.0, 6761.3)	1.34	(1.12, 1.61)	0.171
D	6	Healthy control subjects to match Panel C	4312.2 (3689.6, 5039.7)			
E	6	Severe RI	6466.7 (5577.3, 7497.8)	1.56	(1.32, 1.85)	0.163
F	6	Healthy control subjects to match Panel E	4142.9 (3573.2, 4803.5)			
G	5	ESRD requiring hemodialysis (Part 2, Period 1)	7257.2 (5595.7, 9411.9)	1.89	(1.40, 2.55)	0.080
H	6	Healthy control subjects to match Panel G (Part 2, Period 1)	3842.6 (2964.8, 4980.4)			
G	6	ESRD requiring hemodialysis (Part 2, Period 2)	7585.9 (5852.9, 9832.1)	1.97	(1.46, 2.66)	0.080
H	6	Healthy control subjects to match Panel G (Part 2, Period 1)	3842.6 (2964.8, 4980.4)			
C_{max} (nM)						
A	6	Mild RI	60.4 (51.8, 70.3)	0.94	(0.79, 1.12)	0.168
B	6	Healthy control subjects to match Panel A	64.0 (55.0, 74.6)			
C	6	Moderate RI	61.4 (50.6, 74.5)	1.13	(0.91, 1.41)	0.212
D	6	Healthy control subjects to match Panel C	54.3 (44.8, 65.9)			
E	6	Severe RI	48.7 (37.3, 63.5)	0.90	(0.66, 1.23)	0.292
F	6	Healthy control subjects to match Panel E	53.9 (41.3, 70.3)			
G	5	ESRD requiring hemodialysis (Part 2, Period 1)	41.4 (32.7, 52.5)	0.74	(0.57, 0.96)	0.038
H	6	Healthy control subjects to match Panel G (Part 2, Period 1)	56.1 (45.0, 69.9)			
G	6	ESRD requiring hemodialysis (Part 2, Period 2)	41.0 (32.3, 52.0)	0.73	(0.56, 0.95)	0.038
H	6	Healthy control subjects to match Panel G (Part 2, Period 1)	56.1 (45.0, 69.9)			

rMSE: Square root of conditional mean squared error (residual error) from the ANOVA model.
rMSE*100% approximates the %CV on the raw scale.
‡Back-transformed least-squares mean and confidence interval from linear fixed effect model performed on natural log-transformed values. For Part 2, back-transformed least-squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values.
GMR = Geometric mean ratio; CI = Confidence interval.
For ESRD, N=5 in cases where one patient did not have estimable parameters.
For Healthy Matched Control, N=7 in cases where both Subject AN 0044 (who dropped from the study) and Subject AN 0144 (who replaced Subject AN 0044) are included in the summary statistics.

- Omarigliptin plasma exposure ($AUC_{0-\infty}$) increased with increasing degrees of RI.
- Omarigliptin plasma exposure was approximately 2-fold higher in patients with ESRD versus healthy matched control subjects.
- C_{max} values were similar in patients with mild, moderate and severe RI whereas C_{max} was approximately 20% lower in patients with ESRD.
- In ESRD patients, both $AUC_{0-\infty}$ and C_{max} were similar in Periods 1 and 2 demonstrating equivalent pharmacokinetic exposure irrespective of dialysis schedule.
- The in vitro concentration-dependent plasma protein binding of omarigliptin was similar between patients with varying degrees of RI and healthy control subjects (data not shown).

Figure 2. Individual CLr values plotted by eGFR values following the administration of a single oral 3-mg dose in patients with varying degrees of RI (mild, moderate or severe) or ESRD as well as healthy matched control subjects.



Predicted value = Intercept + Slope * eGFR
Slope = 0.166865 Intercept = 11.257325 R^2=0.4729

- Omarigliptin renal clearance (CLr) decreased with increasing degree of RI.
- The mean CLr values were similar between patients with mild renal impairment versus their healthy matched controls whereas CLr values were lower in patients with moderate and severe renal impairment versus their respective healthy matched controls.
- The GMRs for CLr were 0.93, 0.73, and 0.42 in patients with mild, moderate, and severe RI, respectively.

Table 4. Omarigliptin plasma and dialysate pharmacokinetic parameters following the administration of a single oral 3-mg dose in patients with ESRD.

Parameters	ESRD (Period 1) N	ESRD (Period 1) Mean ± SD	ESRD (Period 2) N	ESRD (Period 2) Mean ± SD
CLD, plasma (mL/min)	6	83.8 ± 17.5	6	104.5 ± 11.2
AD (mg)	6	0.153 ± 0.042	6	0.433 ± 0.071
CLD, dialysate (mL/min)	6	96.7 ± 31.0	6	105.7 ± 12.1

CLD, plasma= dialysis clearance based on plasma
CLD, dialysate= dialysis clearance based on dialysate
SD= standard deviation

- The mean omarigliptin concentration recovered from the dialysate around the time of C_{max} in Period 2 was marginally higher as compared with the dialysate recovered at 3 days post C_{max} in Period 1 (0.433 mg versus 0.153, respectively).
- The dialysis clearance rates calculated from plasma and dialysate measurements were comparable at both dialysis times (i.e., Periods 1 and 2), with mean values ranging from 84 to 106 mL/min.

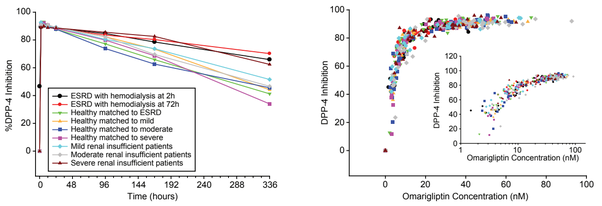
Pharmacodynamics

Table 5. Statistical comparison of percent inhibition of DPP-4 activity at trough (168 h postdose) uncorrected for dilution following the administration of a single oral 3-mg dose in patients with varying degrees of RI (mild, moderate, or severe) or ESRD as well as healthy matched control subjects.

Parameter	Renal Impairment N	Renal Impairment GM	Renal Impairment 95% CI	Healthy Matched Control N	Healthy Matched Control GM	Healthy Matched Control 95% CI	Patients With Renal Impairment Healthy Matched Control Diff	Patients With Renal Impairment Healthy Matched Control 90% CI	Patients With Renal Impairment Healthy Matched Control rMSE†	Inter-subject Variance
Mild Renal Impairment										
% DPP-4 Inhibition‡	6	73.60	(66.70, 81.22)	6	73.14	(66.28, 80.71)	0.46	(-7.56, 8.48)	0.054	
Moderate Renal Impairment										
% DPP-4 Inhibition‡	6	69.46	(62.94, 76.65)	6	62.23	(56.40, 68.68)	7.23	(0.04, 14.43)	0.054	
Severe Renal Impairment§										
% DPP-4 Inhibition‡	5	82.49	(74.06, 91.89)	5	68.50	(61.49, 76.30)	14.00	(4.98, 23.06)	0.054	
ESRD (Part 2, Period 1)¶										
% DPP-4 Inhibition‡	6	80.17	(72.65, 88.47)	7	65.21	(59.52, 71.43)	14.96	(7.33, 22.63)	0.054	0.006
ESRD (Part 2, Period 2)¶										
% DPP-4 Inhibition‡	6	78.37	(71.02, 86.49)	7	65.21	(59.52, 71.43)	13.16	(5.63, 20.74)	0.054	0.006

†rMSE*100% approximates the %CV on the raw scale.
‡Back-transformed least-squares mean and the CI from linear mixed effects model performed on natural log-transformed values.
§Patient AN 0029 was excluded from the Severe Renal Impairment summary statistics due to anomalous predose value. Subject AN 0031 was excluded from the Severe – Healthy Matched Control summary statistics due to missing predose value.
¶For Healthy Matched Control, N=7 in cases where both Subject AN 0044 (who dropped from the Study) and Subject AN 0144 (who replaced Subject AN 0044) were included in the summary statistics.
rMSE = square root of conditional mean squared error (residual error) from the ANOVA model; ESRD = end-stage renal disease; GM = geometric mean; CI = confidence interval

Figure 3. Mean DPP-4 inhibition profiles (left) and DPP-4 inhibition vs. drug concentration plot (right) uncorrected for dilution colored by same subgroup, plotted on linear concentration scale and semi-log concentration (right, inlay).



- Trough DPP-4 inhibition uncorrected for dilution was elevated in patients with increasing degrees of RI following treatment with single doses of 3 mg omarigliptin.
- Assessment of DPP-4 inhibition versus plasma drug concentrations supports the conclusion that the observed shift in DPP-4 inhibition is entirely due to an increase plasma concentration profile due to RI.

Safety and tolerability:

- Single oral doses of omarigliptin 3-mg were generally safe and well-tolerated in healthy subjects and patients with varying degrees of RI or ESRD.
- There were no deaths or serious adverse experiences reported in this study.
- No patients or subjects discontinued from the study due to adverse experiences.
- Ten (10) of the 49 patients and subjects had a total of 11 clinical adverse experiences which all were rated as mild in severity by the study investigator.
- There were no reports of hypoglycemia or low blood sugar in this study.
- There were no consistent treatment-related trends in the incidences of adverse experiences or changes in laboratory, vital signs, or ECG safety parameters. Out-of-range laboratory values were generally consistent with the patients' disease state of RI or ESRD requiring dialysis and did not worsen following administration of omarigliptin.

Conclusions

- The $AUC_{0-\infty}$ of omarigliptin increased with increasing severity of RI, such that there was no change in patients with mild impairment whereas the GMRs (90% CIs) in patients with moderate and severe RI and ESRD versus healthy control subjects were 1.34 (1.12. 1.61), 1.56 (1.32, 1.85), and up to 1.97 (1.46, 2.66), respectively.
- The comparable PK exposures regardless of dialysis schedule indicate that omarigliptin can be administered in ESRD patients without regard to timing of hemodialysis.
- A single 3-mg dose of omarigliptin was generally well tolerated in patients with mild, moderate, and severe RI as well as in patients with ESRD requiring hemodialysis.
- Renal clearance [CLr] decreased with increasing degree of RI, such that the GMRs (90% CIs) in patients with mild, moderate, and severe RI vs. healthy control subjects were 0.93 (0.74, 1.18), 0.73 (0.55, 0.96), and 0.42 (0.33, 0.54), respectively.
- RI (uremia) did not alter the plasma protein binding of omarigliptin as assessed by in vitro assays of patient/subject plasma samples.
- The percent inhibition of DPP-4 activity uncorrected for dilution at 168 hours post-dose following administration of a single 3-mg oral omarigliptin increased with increasing severity of RI. The mean differences between patients with RI and their healthy matched control subjects were less than 15% overall.