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ORIGINAL RESEARCH ARTICLE

Single-Center Evaluation of the Single-Dose Pharmacokinetics of the Angiotensin II Receptor Antagonist Azilsartan Medoxomil in Renal Impairment

Richard A. Preston · Aziz Karim · Caroline Dudkowski · Zhen Zhao · Dyal Garg · Oliver Lenz · Domenic A. Sica

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Abstract
Background and objective Azilsartan medoxomil (AZL-M) is a potent angiotensin II receptor blocker that decreases blood pressure in a dose-dependent manner. It is a pro-drug and not detected in blood after oral administration because of rapid hydrolysis to the active moiety, azilsartan (AZL). AZL undergoes further metabolism to the major metabolite M-II and minor metabolites. The objective of this study was to determine the effect of renal impairment on the pharmacokinetics of AZL and its major metabolite.
Methods This was a single-center, open-label, phase I parallel-group study which examined the single-dose (40-mg) pharmacokinetics of AZL and M-II in 24 subjects with mild, moderate, or severe renal impairment or end-stage renal disease requiring hemodialysis ($n = 6$ per group), respectively, and healthy matched subjects ($n = 24$).
Results Renal impairment/disease did not cause clinically meaningful increases in exposure to AZL. M-II exposure was higher in all renally impaired subjects and highest in those with severe impairment (approx fivefold higher vs. control). M-II is pharmacologically inactive; increased exposure was not considered important in dose selection for AZL-M in subjects with renal impairment. Hemodialysis did not significantly remove AZL or M-II. Renal impairment had no clinically meaningful effect on the plasma protein binding of AZL or M-II. Single doses of AZL-M 40 mg were well tolerated in all subject groups.
Conclusions Based on the pharmacokinetic and tolerability findings, no dose adjustment of AZL-M is required for subjects with any degree of renal impairment, including end-stage renal disease.

1 Introduction

Blockade of the renin–angiotensin–aldosterone system with either an angiotensin-converting enzyme (ACE)

R. A. Preston (✉) · D. Garg
Clinical Pharmacology Research Unit, Division of Clinical Pharmacology, Department of Medicine, Miller School of Medicine, University of Miami, 1500 NW 12th Avenue 15 West, Miami, FL, USA
e-mail: rpreston@med.miami.edu; rpreston1234@gmail.com

R. A. Preston
Jackson Memorial Hospital, Miami, FL, USA

R. A. Preston
Department of Cellular Biology and Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL, USA

A. Karim
AzK Consulting Inc., Skokie, IL, USA

C. Dudkowski · Z. Zhao
Takeda Global Research & Development Inc., Deerfield, IL, USA

D. Garg
Clinical Research Services, Inc., Boynton Beach, FL, USA

O. Lenz
Division of Nephrology, Department of Medicine, Miller School of Medicine, University of Miami, Miami, FL, USA

D. A. Sica
Division of Nephrology, Department of Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

inhibitor or an angiotensin II receptor blocker (ARB), has emerged as a cornerstone of the modern management of subjects with cardiovascular and kidney diseases [1–14]. ARBs are antihypertensive agents that reduce blood pressure (BP) by direct blockade of the angiotensin II AT_1 receptor [1]. Azilsartan medoxomil (AZL-M) is a potent, long-acting ARB that effectively decreases BP in a dose-dependent manner in subjects with mild to moderate hypertension [15–17].

AZL-M, a potassium salt, is a pro-drug that is rapidly hydrolyzed to the active moiety, azilsartan (AZL). After oral administration of AZL-M, peak plasma concentrations of AZL are reached within 1.5–3 h [18–26]. AZL is highly bound to human plasma proteins (>99 %), mainly serum albumin, and protein binding is constant at AZL plasma concentrations well above the range achieved with recommended doses [18–26]. AZL undergoes further metabolism to AZL M-I (M-I), AZL M-II (M-II), and other minor metabolites [18–26], but neither M-I nor M-II have been shown to have pharmacologically relevant AT_1 receptor binding activity in vitro. The main metabolite of AZL-M, M-II, is formed by *O*-dealkylation of AZL, and the cytochrome P450 2C9 isoform is primarily responsible for this conversion; systemic exposure to M-II is approximately 50 % that of AZL [18–26].

Both renal and hepatic metabolism contribute to the elimination of AZL-M. This was demonstrated in a mass-balance study in which following the oral administration of [^{14}C]-AZL-M 42 % of the total radioactivity was recovered in urine, with 15 and 19 % of the dose identified as AZL and M-II, respectively, and 55 % was recovered in feces where AZL was not detected and AZL M-II was barely detectable (<0.1 % of dose) [19, 20]. The elimination half-life ($t_{½}$) of AZL is approximately 11 h, and renal clearance is approximately 2.3 mL/min [18–26].

The aim of our single-center, open-label, parallel-group study was to determine the effect of graded levels of renal impairment ($n = 24$ subjects) on the single-dose pharmacokinetic profile of AZL and M-II relative to healthy, matched-control subjects ($n = 24$ subjects).

2 Methods

This investigation was a phase 1, open-label, parallel-group, single-dose study conducted at a single academic phase I research center that emphasizes special populations under the direct supervision of a single principal investigator. This investigation was approved by the Human Subjects Protection Committee (Institutional Review Board) of the University of Miami and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained directly from all participants prior to entry into the study and prior to any study procedures.

The study cohort comprised 48 subjects (24 healthy subjects and 24 subjects with various stages of renal impairment). Normal healthy subjects were matched with renal impairment subjects on the basis of race, sex, age (±10 years), weight (±20 %), and smoking status. All subjects were stratified into the following groups based on Cockcroft–Gault estimated creatinine clearance (CL_{CR}):

Group A: 24 normal healthy subjects (CL_{CR} >80 mL/min);
Group B: six subjects with mild renal impairment (CL_{CR} >50–80 mL/min, inclusive);
Group C: six subjects with moderate renal impairment (CL_{CR} 30–50 mL/min, inclusive);
Group D: six subjects with severe renal impairment (CL_{CR} <30 mL/min but not on dialysis);
Group E: six subjects on hemodialysis with end-stage renal disease (ESRD) and no or negligible urine output.

The study consisted of a screening period (days −21 to −2), check-in (day −1), treatment period (days 1 through 6), a return visit (day 8), and a follow-up visit (day 14 ± 1). Subjects reported to the study site on day −1 and remained confined to the site through to the morning of day 6; they returned to the clinic for assessments on days 8 and 14. On day 1, subjects received a single oral 40-mg dose (tablet) of AZL-M following an overnight fast of at least 8 h. Subjects on hemodialysis were required to fast for only 2 h before dosing.

2.1 Selection of Study Participants

To be eligible for study participation, men or nonpregnant, nonlactating women were required to be 18–79 years of age, capable of understanding and complying with the protocol, willing to sign the informed consent form prior to the start of the study-related procedures, at least 50 kg (110 lb) in weight with a body mass index between 18 and 40 kg/m^2, inclusive, and have negative test results for selected substances of abuse, including alcohol, at screening and check-in (day −1).

Subjects were excluded if they had known hypersensitivity to AZL-M or drugs in the ARB class, recent (within 6 months) clinically significant cardiovascular disease, pulmonary dysfunction, acute medical illness within 30 days prior to study initiation, history of alcohol or drug abuse, or clinically significant abnormalities based on the physical examination, laboratory studies, or electrocardiogram (ECG) screening. Subjects were also excluded if they had alanine aminotransferase or aspartate aminotransferase values greater than twofold the upper limit of normal.

Medications for treatment of hypertension, diabetes, or underlying renal impairment were reviewed on a case by case basis for each study subject. For renal-impaired subjects on stable medication regimens (dose unchanged for 28 days prior to check-in/day −1), the following medications were allowed: acetaminophen (≤2,000 mg/day as needed for pain relief), erythropoietin, calcium carbonate, ranitidine, famotidine, misoprostol (cimetidine is prohibited), multivitamins and magnesium supplementation, diuretics, ACE inhibitors, clonidine, calcium channel blockers, beta blockers, and alpha blocking agents. Renal-impaired subjects on additional stable medication regimens were considered for enrollment on a case-by-case basis.

2.2 Bioanalytical Methods

Blood and urine samples were obtained at time points up to 120 h postdose to determine the concentrations of the potassium salt-free form of AZL-M (AZL-M-F), AZL, and M-II; dialysate samples and not urine samples were collected from subjects on hemodialysis. Additional blood samples were collected at approximately the time to reach the maximum plasma concentration (t_{max}) of AZL and M-II to determine plasma protein binding. All blood samples were collected into chilled 6 mL tubes containing potassium ethylene diamine tetraacetic acid (K2EDTA) and centrifuged and the plasma then removed; samples for AZL-M-F analysis were stored at approximately −70 °C or lower and the remaining samples were stored at approximately −20 °C or lower. Urine samples were stored at approximately 4 °C during the collection interval and stirred before the volume was measured; two 10-mL aliquots were then placed in containers and stored frozen at approximately −20 °C or lower. For hemodialysis subjects, dialysate samples were collected while the subjects were on hemodialysis on day 1 at each hour following dosing; two 10-mL aliquots were then placed in containers and stored frozen at approximately −20 °C or lower.

All collected samples were analyzed using liquid chromatography–tandem mass spectrometry (LC-MS/MS). A single internal standard was used for all samples and analytes.

For the determination of AZL-M-F in plasma, the samples were acidified and the internal standard was added. AZL-M-F and the internal standard were then extracted using OASIS® HLB, 96-well solid-phase extraction plates (Waters, Milford, MA, USA). For the determination of AZL and M-II in plasma, 2 % acetic acid in acetonitrile solution with the internal standard was added to the samples for protein precipitation. For the samples for plasma protein binding determination, plasma ultrafiltrate was prepared by adding plasma on the top tube of a Centrifree® YM-30 ultrafiltration device (EMD Millipore, Billerica, MA, USA). Once the samples were centrifuged at room temperature, the ultrafiltrate was collected in the bottom cup. For the determination of AZL and M-II in the ultrafiltrate, 0.1 % acetic acid in acetonitrile with the internal standard was added to the samples. After centrifugation, 0.1 % acetic acid in water was added to the samples for a 2:3 dilution.

For the determination of AZL and M-II in urine, 0.1 % acetic acid in methanol with the internal standard was added to the samples for a 1:6 dilution. After mixing, another aliquot of 0.1 % acetic acid in methanol was added to the samples. For the determination of AZL and M-II in dialysate, 0.1 % acetic acid in acetonitrile with the internal standard was added to the samples for a 1:3 dilution. After mixing and centrifuging, 0.1 % acetic acid in water was added to the supernatants for a 2:3 dilution.

For AZL-M-F in plasma, LC separation was obtained using an Xterra® RP18 column (Waters; 250 × 2.1 mm, 5 μm). The mobile phase consisted of an acetonitrile:water:acetic acid gradient (60:40:0.05, v:v:v)/acetonitrile and was pumped through the column at a flow rate of 0.2 mL/min. For AZL and M-II in the other samples, LC separation was obtained using a Chromolith SpeedROD RP-18e column (EMD Millipore; 50 × 4.6 mm). The mobile phase consisted of a gradient 0.1 % acetic acid in water/0.1 % acetic acid in methanol and was pumped through the column at a flow rate of 2 (plasma and urine) or 1.5 (ultrafiltrate and dialysate) mL/min.

For detection, we used an API 3000 or 4000 mass spectrometer (AB Sciex, Framingham, MA, USA) with positive ion electrospray in multiple reaction monitoring mode. The LC–MS/MS assay range, accuracy, and precision for the samples in this study are shown in Table 1.

2.3 Pharmacokinetics

All subjects were required to fast for at least 8 h predose. Concomitant medications were withheld on day 1 until at least 4 h poststudy medication. Because AZL-M is rapidly and completely converted to AZL and has not been detected in the plasma or urine at any time point after administration of AZL-M at doses up to 320 mg [18–24], the focus of this pharmacokinetic evaluation was on the active moiety AZL and its major metabolite M-II.

Groups A–D comprised healthy subjects and subjects with mild, moderate, or severe renal impairment. For each subject, the following single-dose pharmacokinetic parameters were derived from the total plasma and urine concentrations of the metabolites AZL and M-II unless otherwise noted: area under the plasma concentration–time curve (AUC) from time 0 to the time of last quantifiable concentration (AUC_{last}), AUC from time 0 extrapolated to infinity (AUC_{∞}), AUC from time 0 to 24 h postdose (AUC_{24}), maximum observed plasma concentration (C_{max}), t_{max}, terminal elimination rate constant (λ_z), terminal $t_{½}$,

Table 1 Range, accuracy, and precision of the liquid chromatography–tandem mass spectrometry assay

Matrix	Analyte	Range (ng/mL)	Accuracy[a, b]	Precision[a]
Plasma	AZL-M-F	1.00–2,500	98.7–104.7	4.7–8.5
Plasma	AZL	10.0–5,000	94.0–100.4	3.2–5.9
Plasma	AZL M-II	2.00–1,000	97.3–100.6	5.2–11.1
Plasma ultrafiltrate	AZL	10.0–5,000	99.3–103.2	2.9–5.5
Plasma ultrafiltrate	AZL M-II	2.00–1,000	92.8–96.1	4.7–6.9
Dialysate	AZL	10.0–5,000	100.7–104.0	NA
Dialysate	AZL M-II	2.00–1,000	98.3–118.3	NA
Urine	AZL	50.0–10,000	96.7–97.8	4.0–4.4
Urine	AZL M-II	50.0–10,000	97.5–102.0	3.9–6.7

AZL azilsartan, *AZL-M* AZL medoxomil, *AZL-M-F* potassium salt-free form of AZL-M, *M-I* and *M-II* AZL metabolites, *NA* not available

[a] The statistics may include quality control (QC) values that failed acceptance criteria but the acceptance criteria for each run were met. Acceptance criteria were: (1) if no more than one-fourth of the calibration standards were excluded, and a minimum of six non-zero back-calculated concentrations for calibration standards were within the range of 85–115 % of the theoretical value (80–120 % at the lower limit of quantitation) and (2) if at least one-half of the undiluted QC samples at each concentration and two-thirds of all undiluted QC samples in the curve range were within the range of 85–115 % of the theoretical value

[b] The accuracy is expressed as a percentage of the theoretical concentration

fraction of AZL with molecular weight adjustment from AZL-M excreted in the urine from 0 to 120 h postdose (F_e), total amount of AZL or M-II excreted in urine from 0 to 24 h postdose (Ae_τ), and renal clearance (CL_R; Ae_τ divided by AUC_{24}).

Group E comprised hemodialysis subjects. The following single-dose pharmacokinetic parameters were derived from the plasma concentrations of AZL and M-II for dialysis subjects: AUC_{last}, AUC_∞, AUC_{24}, C_{max}, t_{max}, λ_z, and $t_{½}$. Dialysis subjects were dialyzed at a dialysate flow rate of 800 mL/min using either a BAXTER CT 190 G/105.6 or BAXTER XENIUM 150/82.5 dialysis cartridge. Arterial, venous, and dialysate samples were taken at 1, 2, 3, and 4 h postdose. The amount of AZL or M-II in the dialysate from time 0 to time t [$Ae_{dialysate\ (0–t)}$], hemodialysis clearance [CL_{hem}], and fractions of AZL or M-II recovered in dialysate [$F_{dialysate}$] were calculated, if possible.

The unbound fractions of AZL and M-II were calculated as the concentration in the plasma ultrafiltrate divided by the concentration in the plasma, with the latter representing the total (bound + unbound) concentration.

2.4 Treatment-Emergent Adverse Events

Safety assessments were made at screening, day −1, days 1–6 of inpatient confinement, day 8 (return visit), and day 14 (follow-up). Safety variables included adverse event monitoring, serial safety clinical laboratory testing (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECGs, and physical examination findings.

2.5 Statistical Methods

The sample size chosen for this study was based on precedent set by other pharmacokinetic studies conducted in subjects with renal impairment of a similar nature and not based on statistical considerations. Descriptive statistics (mean, standard deviation, standard error of the mean, % coefficient of variance, median, minimum, and maximum) were used to summarize the plasma, urine, and dialysate pharmacokinetic parameters for AZL and M-II by subject groups. In addition, geometric means were computed for AUC_{last}, AUC_∞, AUC_{24}, and C_{max}.

The 90 % confidence intervals (CI) of the least-squares (LS) mean ratios for subjects with renal impairment versus matched-control subjects (e.g., AUC_{last}, mild/AUC_{last}, control) were provided for AUC_{last}, AUC_∞, and C_{max}. The 90 % CI were obtained by taking the antilog of the 90 % CI for the difference between the LS means on the log scale. The Wilcoxon rank-sum test was performed on t_{max} to compare the renal impairment subject group to the corresponding matched-control group.

All data analyses were performed and graphics were generated using SAS version 8.2 (SAS Institute, Cary, NC, USA). Pharmacokinetic parameters were derived using noncompartmental methods with WinNonlin Professional version 5.2 (Pharsight Corp., Mountain View, CA, USA).

3 Results

A total of 64 potential subjects were evaluated at the single phase I clinical pharmacology center. Forty-eight subjects, including 32 men and 16 women, were enrolled in the study and each received study medication. With the exception of one subject with moderate renal impairment who did not return for the follow-up visit on day 14, all subjects completed all phases of the study. Baseline and demographic characteristics of the 48 enrolled subjects are shown in Table 2.

A detailed listing of the 24 subjects with renal impairment and their concomitant medical conditions and concomitant medications is shown in Table 3. Of the 24

Table 2 Summary of demographic and baseline characteristics

Characteristic	Matched controls ($n = 24$)	Mild renal impairment ($n = 6$)	Moderate renal impairment ($n = 6$)	Severe renal impairment ($n = 6$)	End-stage renal disease ($n = 6$)	Overall ($N = 48$)
Age (years)	60.1 (11.05)	67.0 (8.92)	69.5 (3.27)	61.8 (12.37)	49.0 (10.04)	61.0 (11.36)
Sex (*n*, %)						
Male	16 (66.7)	5 (83.3)	4 (66.7)	4 (66.7)	3 (50.0)	32 (66.7)
Female	8 (33.3)	1 (16.7)	2 (33.3)	2 (33.3)	3 (50.0)	16 (33.3)
Ethnicity (*n*, %)						
Hispanic/Latino	22 (91.7)	3 (50.0)	4 (66.7)	4 (66.7)	1 (16.7)	34 (70.8)
Non-Hispanic or Latino	2 (8.3)	3 (50.0)	2 (33.3)	2 (33.3)	5 (83.3)	14 (29.2)
Race (*n*, %)						
Black/African American	12 (50.0)	3 (50.0)	1 (16.7)	3 (50.0)	5 (83.3)	24 (50.0)
White	12 (50.0)	3 (50.0)	5 (83.3)	3 (50.0)	1 (16.7)	24 (50.0)
Smoking (*n*, %)						
Never smoked	15 (62.5)	4 (66.7)	4 (66.7)	3 (50.0)	4 (66.7)	30 (62.5)
Current smoker			1 (16.7)	1 (16.7)		2 (4.2)
Ex-smoker	9 (37.5)	2 (33.3)	1 (16.7)	2 (33.3)	2 (33.3)	16 (33.3)
Height (cm)	167.7 (8.81)	170.5 (6.16)	164.0 (5.22)	168.2 (8.18)	171.2 (10.68)	168.1 (8.27)
Body weight (kg)	79.7 (11.88)	87.5 (12.11)	74.7 (17.17)	87.6 (16.46)	81.5 (18.04)	81.3 (14.01)
Body mass index (kg/m^2)	28.2 (2.67)	30.1 (4.25)	27.7 (5.69)	30.7 (3.18)	27.6 (4.15)	28.6 (3.60)
Alanine aminotransferase (U/L)	25.6 (12.2)	19.2 (4.7)	21.8 (6.7)	16.3 (7.4)	13.0 (5.0)	21.6 (10.5)
Aspartate aminotransferase (U/L)	25.8 (8.3)	23.5 (3.8)	26.5 (7.2)	23.0 (4.9)	16.7 (4.2)	24.1 (7.4)
Alkaline phosphatase (U/L)	77.4 (22.5)	81.7 (34.1)	67.8 (11.0)	78.0 (25.7)	80.3 (31.1)	77.2 (23.9)
Total bilirubin (mg/dL)	0.5 (0.2)	0.5 (0.2)	0.6 (0.3)	0.3 (0.1)	0.4 (0.3)	0.5 (0.2)
Total protein (g/dL)	7.1 (0.4)	7.1 (0.3)	6.9 (0.3)	6.9 (0.5)	7.2 (0.4)	7.1 (0.4)

Healthy control subjects were generally matched with subjects with renal impairment on the basis of race, sex, age (±10 years), weight (±20 %), and smoking status

Data are presented as mean (standard deviation), unless indicated otherwise

subjects with renal impairment, 24 (100 %) were hypertensive and 10/24 (42 %) had diabetes mellitus.

3.1 Pharmacokinetics

None of the control subjects, subjects with mild, moderate, or severe renal impairment, or subjects with ESRD had detectable concentrations of AZL-M-F in plasma, indicating that renal impairment did not have any effect on the rapid hydrolysis of AZL-M. Because there were no detectable concentrations, pharmacokinetic parameters for this latter analyte were not determined.

Mean AZL and M-II plasma concentrations are given for the 24-h postdose period in Fig. 1. The AZL and M-II plasma-concentrations-over-time profiles were greater among subjects with renal impairment than in the matched controls and appeared to increase with decreasing renal function for subjects with mild, moderate, or severe renal impairment. However, those with ESRD had lower values than subjects with severe renal impairment.

Renal impairment did not have an effect on the extensive metabolism of AZL (Tables 4 and 5). In all of the subject groups, AZL was extensively metabolized (only 8 % of the dose was recovered as AZL in urine in control subjects, and ≤4 % of the dose was recovered as AZL in the urine of patients with mild, moderate, or severe renal impairment). AZL renal clearance and urinary excretion were decreased in subjects with mild, moderate, or severe renal impairment compared with matched-control subjects, although AZL $t_{½}$ values were comparable between subject groups (13 h for control subjects vs. 15–17 h for subjects with renal impairment). Median t_{max} in the renal impairment groups ranged from 2.0 h (moderate group) to 3.52 h (ESRD group) and was comparable to the median t_{max} in the matched-control group (2.25 h).

M-II plasma exposures in subjects with renal impairment were greater than those observed in matched-control subjects. M-II $t_{½}$ was prolonged in the renal impairment groups compared with the control group (25–46 vs. 17 h), and renal clearance and excretion of M-II was decreased

Table 3 Concomitant medical conditions and medications of the 24 subjects with renal impairment

Subject	Subject ID	Category	Hypertension	Diabetes mellitus	ASVD	Hyperlipidemia	Key concomitant medications
1	2001	Mild	X		X	X	Carvedilol, olmesartan, rosuvastatin, clopidogrel, ranitidine
2	2002	Mild	X	X	X	X	Irbesartan, amlodipine, metoprolol, rosuvastatin, metformin, insulin, aspirin
3	2003	Mild	X				Diltiazem, ramipril, carvedilol, colchicine
4	2004	Mild	X	X	X		Rosiglitazone, irbesartan, propranolol, aspirin, fenofibrate
5	2005	Mild	X			X	Metoprolol, nifedipine, atorvastatin, furosemide, colchicine
6	2006	Mild	X				Irbesartan
7	2007	Moderate	X		X	X	Lisinopril, carvedilol, clopidogrel, rosuvastatin, aspirin
8	2008	Moderate	X	X	X	X	Insulin, allopurinol
9	2009	Moderate	X		X	X	Carvedilol, furosemide, lisinopril, allopurinol, clopidogrel, aspirin
10	2010	Moderate	X	X		X	Lisinopril, rosuvastatin, metformin, aspirin
11	2011	Moderate	X		X	X	Carvedilol, nifedipine, HCTZ, clopidogrel, allopurinol, atorvastatin
12	2012	Moderate	X			X	Amlodipine, atorvastatin
13	2013	Severe	X			X	Amlodipine, metoprolol, furosemide, atorvastatin, doxazosin, aspirin
14	2014	Severe	X				Amlodipine, levothyroxine
15	2015	Severe	X	X	X	X	Nifedipine, olmesartan, atorvastatin, HCTZ, insulin
16	2016	Severe	X				Lisinopril, erythropoietin
17	2017	Severe	X	X	X	X	Nifedipine, metoprolol, insulin
18	2018	Severe	X	X	X	X	Valsartan, minoxidil, atenolol, furosemide, glyburide, simvastatin, aspirin
19	2019	ESRD	X	X			Lisinopril, fenofibrate, simvastatin, sevelamer, insulin, cinacalcet
20	2020	ESRD	X	X			Nifedipine, lisinopril, metoprolol, calcium acetate, cinacalcet
21	2021	ESRD	X			X	Candesartan, rosuvastatin, calcium acetate, cinacalcet, erythropoietin
22	2022	ESRD	X				Clonidine, sevelamer, cinacalcet
23	2023	ESRD	X	X			Fosinopril, minoxidil, insulin, cinacalcet,
24	2024	ESRD	X				Nifedipine, hydralazine, valsartan, atenolol, sevelamer, calcium acetate, cinacalcet

ASVD atherosclerotic vascular disease (coronary artery, peripheral or cerebrovascular disease or history of myocardial infarction, stroke or coronary artery bypass graft), *ESRD* end-stage renal disease, *HCTZ* hydrochlorothiazide, *X* indicates presence of the medical condition

among subjects with mild, moderate, or severe renal impairment. In addition, M-II median t_{max} tended to occur later in the moderate and severe renal impairment groups and in the ESRD group (11.0–13.0 h) compared with the mild renal impairment (5.5 h) and control groups (5.0 h). The relationships between CL_{CR} and AUC_{last} for AZL and M-II are shown in Figs. 2 and 3, respectively.

3.2 Mild Renal Impairment

Relative to matched controls, AZL AUC_{last} and AUC_{∞} increased by 30 % and C_{max} increased by 9 % in the mild impairment group (CL_{CR} >50–80 mL/min, inclusive) following a single dose of AZL-M. The M-II AUC_{∞} increased by 103 % and the C_{max} increased by 26 %. Median t_{max} values for AZL and M-II were not significantly different between the mild impairment and control subject groups.

3.3 Moderate Renal Impairment

Relative to healthy matched control subjects, the AZL AUC_{last} and AUC_{∞} each increased by 25 %, and the C_{max} decreased by 5 % in the moderate impairment group (CL_{CR} 30–50 mL/min, inclusive) following a single dose of

Table 4 Comparison of pharmacokinetic parameters of azilsartan and M-II

Parameter	*n*	LS mean[a] test	*n*	LS mean[a] control	Ratio (test/control) × 100[b]	90 % CI for ratio[c]	*p* value[d]
Mild renal impairment (test) vs. healthy match control (control)							
Azilsartan							
AUC_{last} (ng·h/mL)	6	26,605.9	6	20,500.6	129.78	(93.26, 180.61)	0.192
AUC_{∞} (ng·h/mL)	6	27,041.4	6	20,830.5	129.82	(93.68, 179.89)	0.186
C_{max} (ng/mL)	6	2,438.1	6	2,240.7	108.81	(81.07, 146.04)	0.631
$t_{½}$ (h)[f]	6	14.72	24	12.51	n/a	n/a	n/a
t_{max} (h)[g]	6	2.50	6	2.25	n/a	n/a	0.688
M-II							
AUC_{last} (ng·h/mL)	6	21,437.4	6	10,527.6	203.63	(143.28, 289.41)	0.002
AUC_{∞} (ng·h/mL)	6	21,713.3	5	10,676.7	203.37	(141.14, 293.05)	0.002
C_{max} (ng/mL)	6	485.0	6	383.6	126.4	(88.74, 180.20)	0.271
$t_{½}$ (h)[e]	6	25.25	22	17.32	n/a	n/a	n/a
t_{max} (h)[f]	6	5.50	6	5.50	n/a	n/a	0.529
Moderate renal impairment (test) vs. healthy match control (control)							
Azilsartan							
AUC_{last} (ng·h/mL)	6	34,417.8	6	27,461.6	125.33	(90.06, 174.41)	0.257
AUC_{∞} (ng·h/mL)	6	34,781.6	6	27,800.4	125.11	(90.29, 173.37)	0.254
C_{max} (ng/mL)	6	2,740.2	6	2,884.1	95.01	(70.79, 127.51)	0.771
$t_{½}$ (h)[e]	6	16.74	24	12.51	n/a	n/a	n/a
t_{max} (h)[f]	6	2.00	6	2.50	n/a	n/a	1.000
M-II							
AUC_{last} (ng·h/mL)	6	29,779.6	6	12,761.2	233.36	(164.20, 331.65)	<0.001
AUC_{∞} (ng·h/mL)	6	30,293.5	5	11,611.4	260.89	(181.14, 375.77)	<0.001
C_{max} (ng/mL)	6	521.4	6	442.9	117.71	(82.61, 167.73)	0.443
$t_{½}$ (h)[e]	6	27.98	22	17.32	n/a	n/a	n/a
t_{max} (h)[f]	6	11.00	6	5.00	n/a	n/a	0.392
Severe renal impairment (test) vs. healthy match control (control)							
Azilsartan							
AUC_{last} (ng·h/mL)	6	33,881.0	6	17,296.2	195.89	(140.51, 273.08)	0.002
AUC_{∞} (ng·h/mL)	6	34,296.5	6	17,552.4	195.40	(140.76, 271.23)	0.001
C_{max} (ng/mL)	6	2,620.4	6	1,959.09	133.76	(99.50, 179.80)	0.106
$t_{½}$ (h)[e]	6	17.16	24	12.51	n/a	n/a	n/a
t_{max} (h)[f]	6	2.50	6	2.25	n/a	n/a	0.560
M-II							
AUC_{last} (ng·h/mL)	6	51,494.4	6	10,800.1	476.79	(334.86, 678.90)	<0.001
AUC_{∞} (ng·h/mL)	6	52,729.5	6	10,906.4	483.47	(340.62, 686.24)	<0.001
C_{max} (ng/mL)	6	523.4	6	449.9	116.32	(81.48, 166.07)	0.479
$t_{½}$ (h)[e]	6	45.68	22	17.32	n/a	n/a	n/a
t_{max} (h)[f]	6	11.00	6	5.50	n/a	n/a	0.051
ESRD (test) vs. healthy match control (control)							
Azilsartan							
AUC_{last} (ng·h/mL)	6	19,213.0	6	18,316.8	104.89	(75.23, 146.26)	0.81
AUC_{∞} (ng·h/mL)	6	19,467.5	6	18,699.4	104.11	(74.98, 144.55)	0.837
C_{max} (ng/mL)	6	2,135.1	6	2,488.2	85.81	(63.82, 115.37)	0.389
$t_{½}$ (h)[e]	6	10.99	24	12.51	n/a	n/a	n/a
t_{max} (h)[f]	6	3.52	6	2.00	n/a	n/a	0.246

Table 4 continued

Parameter	*n*	LS mean[a] test	*n*	LS mean[a] control	Ratio (test/control) × 100[b]	90 % CI for ratio[c]	*p* value[d]
M-II							
AUC_{last} (ng·h/mL)	6	33,576.6	6	10,874.2	308.77	(216.80, 439.75)	<0.001
AUC_{∞} (ng·h/mL)	6	34,247.2	6	10,900.3	314.19	(221.30, 446.06)	<0.001
C_{max} (ng/mL)	6	471.1	6	553.2	85.15	(59.63, 121.60)	0.452
$t_{½}$ (h)[e]	6	37.75	22	17.32	n/a	n/a	n/a
t_{max} (h)[f]	6	13.00	6	5.00	n/a	n/a	0.060

Due to insufficient data, statistical analysis for metabolite M-I was not performed

Statistical analysis was based on an analysis of covariance (ANCOVA) model with fixed effect for group and body weight as covariate for natural logarithms of AUC_{last}, AUC_{∞}, and C_{max}. Analysis of t_{max} was based on the Wilcoxon rank-sum test

λ_z terminal elimination rate constant, *AUC* area under the plasma concentration–time curve, AUC_{∞} AUC from time 0 extrapolated to infinity, AUC_{last} AUC from time 0 to the time of last quantifiable concentration, *AZL-M* azilsartan medoxomil, *CI* confidence interval, C_{max} maximum observed plasma concentration, *ESRD* end-stage renal disease, *LS* least square, *n/a* not applicable, $t_{½}$ elimination half-life, t_{max} time to C_{max}

[a] Means for AUC_{last}, AUC_{∞}, and C_{max} were obtained by taking the antilogarithm of the LS mean from log-transformed values

[b] Obtained by taking the antilogarithm of the difference between LS means on the natural logarithmic scale, expressed as a percentage

[c] Obtained by taking the antilogarithm of the 90 % CI of the difference between LS means on the natural logarithmic scale, expressed as a percentage

[d] *P* value was based on ANCOVA with fixed effect for subject group and body weight as covariate for AUC_{last}, AUC_{∞}, C_{max}, and Wilcoxon rank sum test for t_{max}

[e] Arithmetic mean for $t_{½}$ and all healthy matched control subjects were pooled together

[f] Median for t_{max}

Table 5 Summary of urine pharmacokinetic parameters

Compound	Healthy controls[a] ($n = 24$)	Mild renal impairment ($n = 6$)	Moderate renal impairment ($n = 6$)	Severe renal impairment ($n = 6$)
Azilsartan				
F_e (%)	8.1 (2.90)	3.3 (1.93)	3.8 (3.26)	1.1 (1.21)
Ae_{τ} (mg)	2.2 (0.80)	0.9 (0.50)	0.9 (0.91)	0.3 (0.25)
CL_R (mL/h)	122.8 (47.17)	43.7 (23.64)	33.2 (31.77)	10.7 (8.07)
M-II				
Ae_{τ} (mg)	2.8 (0.91)	2.1 (1.02)	1.4 (0.89)	0.5 (0.27)
CL_R (mL/h)	393.3 (92.13)	221.5 (88.93)	137.3 (71.68)	54.9 (41.02)

Data are presented as mean (standard deviation)

Urine samples not collected in end-stage renal disease patients

Ae_{τ} total amount of azilsartan or M-II excreted in urine from 0 to 24 h postdose, CL_R renal clearance, F_e fraction of azilsartan with molecular weight adjustment from azilsartan medoxomil excreted in the urine from 0 to 120 h postdose

[a] Healthy subjects with normal renal function were generally matched with subjects with renal impairment on the basis of race, gender, age (±10 years), weight (±20 %), and smoking status

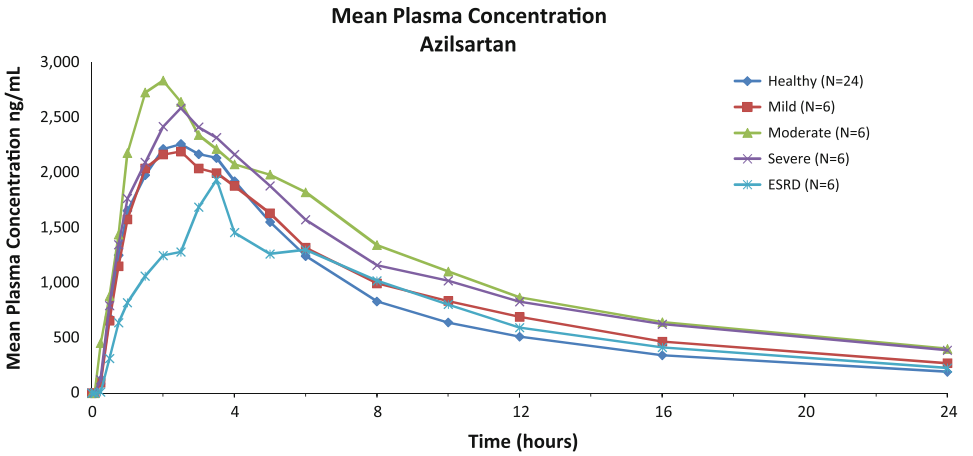
AZL-M. The M-II AUC_{∞} increased by 161 %, and the C_{max} increased by 18 %. Median t_{max} values for AZL and M-II were not significantly different between the moderate impairment and control subject groups.

3.4 Severe Renal Impairment

Relative to healthy matched control subjects, increases in AZL AUC_{∞} (95 %) and C_{max} (34 %) were observed in the severe renal impairment group (CL_{CR} <30 mL/min but not on dialysis) following a single dose of AZL-M, with a greater effect noted for M-II (increase of 383 % in AUC_{∞} and 16 % in C_{max}). Median AZL and M-II t_{max} values were not significantly different between the severe impairment and control groups.

3.5 End-Stage Renal Disease

Relative to healthy matched control subjects, AZL AUC_{last} increased by 5 %, AUC_{∞} increased by 4 %, and C_{max} decreased by 14 % in the ESRD group; the M-II AUC_{∞}



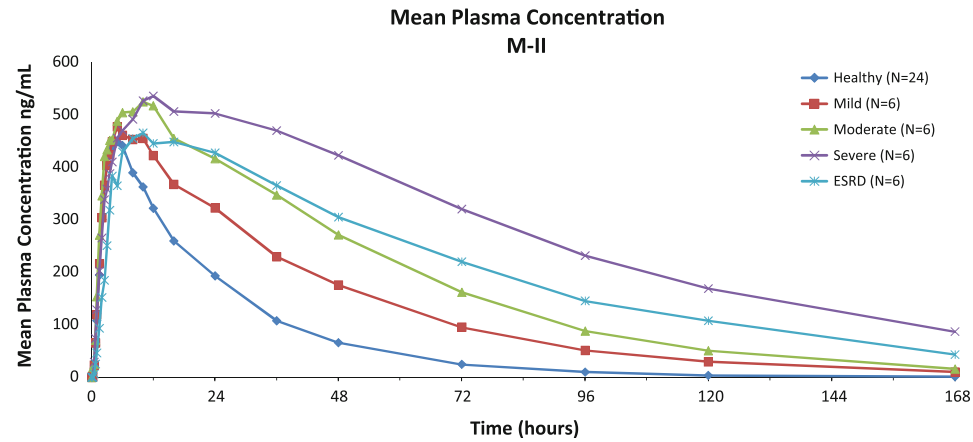


Fig. 1 Mean plasma concentration vs. time curves of azilsartan (AZL; *top*) and metabolite M-II (*bottom*) following a single 40-mg oral dose of AZL medoxomil (AZL-M) given to healthy subjects, patients with mild, moderate or severe renal impairment, and patients with end-stage renal disease (ESRD)

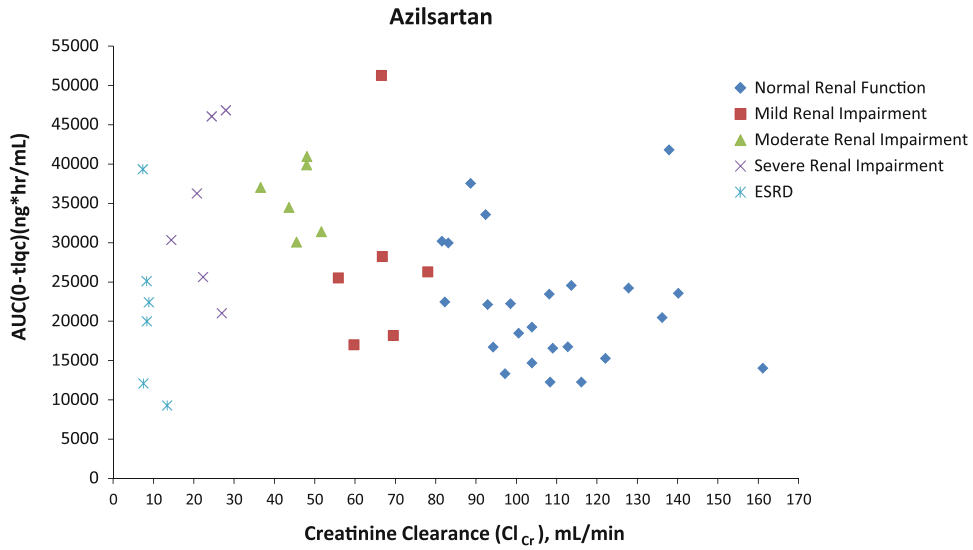


Fig. 2 Relationship between creatinine clearance (CL_{CR}) and the area under the azilsartan time–concentration curve from time 0 to time of last quantifiable concentration [AUC(0-tlqc)] in patients with varying degrees of renal impairment following a single 40-mg oral dose of azilsartan medoxomil

increased by 214 %, and C_{max} decreased by 14 %. AZL and M-II plasma concentrations in arterial and venous samples were comparable, and dialysate concentrations were below the limit of quantification for both analytes, indicating that hemodialysis was not responsible for the decreased plasma exposures. Median AZL and M-II t_{max} values were not significantly different between the ESRD and control subject groups.

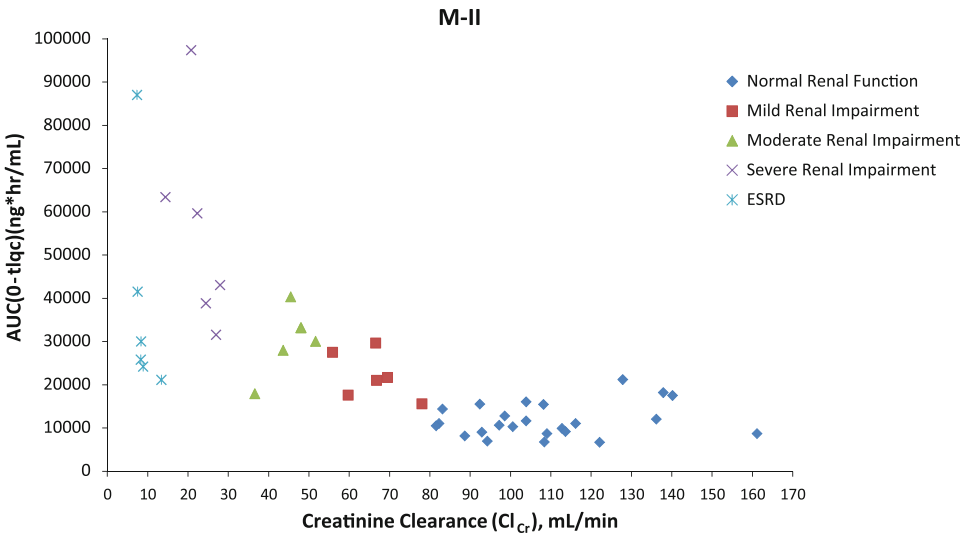


Fig. 3 Relationship between creatinine clearance (CL_{CR}) and M-II area under the AZL time–concentration curve from time 0 to time of last quantifiable concentration [AUC(0-tlqc)] in patients with varying degrees of renal impairment following a single 40-mg oral dose of azilsartan medoxomil. *ESRD* end-stage renal disease

3.6 Effect of Renal Impairment on Protein Binding

Renal impairment did not have a clinically meaningful effect on the plasma protein binding of AZL or M-II compared with healthy subjects. There did not appear to be a direct correlation between the renal function group and the unbound fraction of AZL or M-II in plasma. Overall, the unbound fraction of AZL ranged from 6 to 11 % in control subjects and from 3 to 17 % in subjects with renal impairment; for M-II, the unbound AZL fraction ranged from 5 to 9 % in control subjects and from 2 to 21 % in subjects with renal impairment.

3.7 Treatment-Emergent Adverse Events

The administration of single doses of AZL-M 40 mg was well tolerated in healthy subjects and in subjects with varying degrees of renal impairment. Four subjects (two with moderate renal impairment and two controls) experienced a total of four adverse events (Table 6). Headache and hypotension were reported in the matched-control group, and dizziness and hypotension were reported in the moderate renal impairment group. All of these events were mild in intensity and were considered to have a probable attribution to the study medication. There were no clinically important findings noted in the mean vital sign data, or in individual clinical laboratory values or ECG data. No adverse events causing withdrawal, serious adverse events, or death occurred during the study.

4 Discussion

Randomized clinical trials have consistently demonstrated that ARBs can substantially reduce cardiovascular endpoints in high-risk subjects [1–14]. ARBs can also ameliorate the progression of kidney disease in comparison to more traditional antihypertensive medication regimens, and it has been proposed that angiotensin II receptor antagonists confer target organ protection beyond their effects on BP control [12–14]. Accordingly, these compounds are increasingly used in clinical practice. In that regard, AZL-M is a recently approved ARB that is indicated for the treatment of mild to moderate hypertension [15–17]. The pharmacokinetics of AZL derived from the AZL-M prodrug have been studied in several special populations, including elderly subjects (65–85 years) versus young subjects (18–45 years), women versus men, and white versus black subjects. These studies revealed no clinically significant differences in AZL exposure for these populations [18–26]. The study of age, sex, and racial variations in drug handling for AZL did not, however, offer any meaningful insight into the effect on its handling in renal impairment. Mass-balance studies have shown that 42 % of total radioactivity resulting from an oral radiolabeled dose of [^{14}C] AZL-M was recovered in urine and that its elimination characteristics could possibly be modified in subjects with various stages of chronic kidney disease [19–21].

In this single-center, open-label, parallel-group study in 48 subjects with various levels of renal impairment, we studied the single-dose pharmacokinetic profile of AZL and its metabolite M-II. Subjects with mild, moderate, and severe renal impairment and ESRD did have increases in plasma exposure to AZL in comparison with healthy matched subjects with normal renal function. Although the percentage difference between the severe impairment group and its control group, 95 %, appeared higher in comparison to the mild (30 %) and moderate (25 %) impairment groups, the LS mean AUC_{∞} value for subjects with severe

Table 6 Incidence of treatment-emergent adverse events

System Organ Class preferred term[a]	Matched controls[b] ($n = 24$)	Mild renal impairment ($n = 6$)	Moderate renal impairment ($n = 6$)	Severe renal impairment ($n = 6$)	ESRD ($n = 6$)
Subjects with any event	2 (8.3)	0	2 (33.3)	0	0
Nervous system disorders					
Dizziness	0	0	1 (16.7)	0	0
Headache	1 (4.2)	0	0	0	0
Vascular disorders					
Hypotension	1 (4.2)	0	1 (16.7)	0	0

Data are presented as n (%)

ESRD end-stage renal disease

[a] A subject who reported two or more adverse events within the same preferred term was counted only once for that term

[b] Healthy control subjects were generally matched with renal-impairment subjects on the basis of race, gender, age (±10 years), weight (±20 %), and smoking status

impairment (34,297 ng·h/mL) was similar to the LS mean values for subjects with mild and moderate renal impairment (27,041 and 34,782 ng·h/mL, respectively). LS mean AUC values for the ESRD subjects were approximately 4 % higher than those of the control group. Although the percentage increase in AUC for subjects with ESRD was not as pronounced as that for subjects with mild, moderate, or severe renal impairment, it did not appear that hemodialysis was responsible for this difference. Overall, AZL-M has a wide safety margin, as similar tolerability profiles have been observed in clinical studies with the 40-mg and 80-mg doses; therefore, the increases in exposure in subjects with renal impairment and ESRD are not considered to be clinically meaningful and are consistent with the mechanism of action of AZL (antagonism of the AT_1 receptor) and its effect on intraglomerular pressure [26]. As expected, our subjects with mild, moderate, and severe renal impairment had decreased renal clearance and urinary excretion of AZL and M-II compared with matched control subjects.

In all of the renal impairment groups, the overall plasma exposures (AUC) to the inactive metabolite M-II were markedly increased (two- to fivefold) relative to that in matched controls following a single dose of AZL-M 40 mg. AZL and M-II median t_{max} values were not statistically different between any of the renal impairment groups and their respective control groups. This increased exposure and the delayed clearance of the M-II metabolite is unlikely to be clinically relevant because this metabolite has no pharmacologically significant activity. In addition, based on simulation of single-dose data to predict steady-state exposure of M-II in severe renal impairment, the predicted steady-state exposure has been observed in the multiple-dose rising phase I study at 320 mg once daily for 7 days of AZL-M [18–24]. Exposure in healthy subjects who received multiple 320-mg doses was substantially higher than the exposure predicted in renal impairment, yet this high dose was well tolerated.

Our plasma protein binding results are noticeably different from previous in vitro and ex vivo protein binding results (>99 %) and were highly variable [18–26]. It is unclear why these ex vivo results differ from those of another study with ex vivo protein binding, as both studies were conducted by the same investigator at the same clinical site, and the same analytical methodology was used [21]. Therefore, the protein binding results from this study are not considered to be precise; however, because protein binding between healthy subjects and subjects with renal impairment was similar, it can be concluded that this disease state did not alter the protein binding of AZL or M-II. Hemodialysis did not remove AZL or M-II in a meaningful manner from the systemic circulation, as might have been expected based on the high protein binding of AZL. The administration of single doses of AZL-M 40 mg was well tolerated in control subjects and in subjects with varying degrees of renal impairment.

5 Conclusion

Based on our study, we conclude that no starting dose adjustment for AZL-M is necessary in subjects with mild to severe renal impairment, including ESRD subjects receiving hemodialysis.

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