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Pharmacokinetics and Safety of the Aminomethylcycline Antibiotic Omadacycline in Subjects With Impaired Renal Function

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ABSTRACT

Background: Omadacycline (OMC) is an aminomethylcycline antibiotic in the tetracycline family that is currently in phase 3 clinical development as a once daily intravenous (IV) and oral monotherapy for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections. Numerous antibiotics and other medications require dose adjustment for patients with renal function impairment. To determine whether such adjustment would be necessary for OMC, this phase 1 study evaluated the pharmacokinetics (PK) and safety of IV OMC in subjects with end-stage renal disease (ESRD) on hemodialysis (HD).

Methods: This open-label study enrolled adult subjects with ESRD who were on a stable HD regimen and healthy subjects matched with the ESRD subjects based on sex, age, and weight. The ESRD subjects received a single dose of OMC 100 mg IV in 2 treatment periods: just after the end of HD and just prior to HD (periods were separated by a 10- to 20-day washout period). Healthy subjects received a single dose of OMC 100 mg IV. Blood samples were collected for PK analyses at specified times up to ~72 hours post-dose. Standard safety assessments were performed.

Results: Sixteen subjects (8 ESRD, 8 healthy) were enrolled and treated; 75% male, median age 59 years, median weight 89 kg, median body mass index (BMI) 29 kg/m^2. Following a 100-mg IV dose, OMC plasma-time concentration profiles in ESRD (both before and after HD) and healthy subjects were similar: plasma area under the curve from time zero to infinity (AUC_{0-inf}) (geometric mean µg•h/mL) was 10.0 in ESRD before HD, 10.1 in ESRD after HD, and 9.6 in healthy subjects. Treatment-emergent adverse events (TEAEs) related to OMC occurred in only 1 ESRD subject (mild dizziness and mild rash). There were no serious TEAEs and no study discontinuations due to TEAEs.

Conclusion: Pharmacokinetic and safety profiles of OMC were similar in healthy subjects and in ESRD patients on hemodialysis; thus, OMC does not require dose adjustment in patients with renal impairment.

INTRODUCTION

- Omadacycline (OMC) is the first antibiotic in a new class of compounds, the aminomethylcyclines, which are semi-synthetic antibiotics related to the tetracyclines[1,2]
- Modifications in the chemical structure of OMC overcome the two main mechanisms of tetracycline resistance: efflux pumps and ribosomal protection[3,4]
- OMC shows potent, broad-spectrum in vitro activity against common Gram-positive aerobes (including methicillin- and penicillin-resistant strains), Gram-negative aerobes, anaerobes, and atypical bacterial pathogens[4,5]
- OMC is in late-stage clinical development as an intravenous (IV) and once-daily oral monotherapy for
  - Acute bacterial skin and skin structure infections (ABSSSI; completed phase 3 OASIS trial with IV-to-oral transition demonstrated non-inferiority to linezolid and similar safety/tolerability)[6]
  - Community-acquired bacterial pneumonia (CABP; completed phase 3 OPTIC trial with IV-to-oral transition demonstrated non-inferiority to moxifloxacin, to be submitted in future scientific conferences)
- In prior studies, IV-administered OMC demonstrated a rapid initial distribution phase, dose-linear PK, high volume of distribution (Vz; 300 to 640 L), a terminal elimination half-life in plasma ($t_{1/2}$) of ~18 hours, and total systemic clearance (CL) of 10 to 21 L/hour[4]

METHODS

- This phase 1 study evaluated the pharmacokinetics (PK) and safety of IV OMC in subjects with end-stage renal disease (ESRD) on hemodialysis (HD) in order to determine whether OMC dosing should be adjusted in subjects with impaired renal function
- Phase 1, open-label, two period, single-dose, parallel group study performed at 2 US clinical research centers
- Enrolled adults with ESRD and on a stable HD regimen (n = 8) and healthy subjects (n = 8) matched with ESRD subjects by sex, age (± 5 years), and weight (± 10 kg)
- Objectives:
  - Primary: Compare OMC PK in subjects with ESRD and on HD vs matched healthy subjects
  - Secondary: (i) Evaluate the safety and tolerability of single IV doses of OMC administered to subjects with ESRD and on HD; (ii) Determine the amount of OMC removed by hemodialysis; and (iii) Determine urine concentrations of IV-administered OMC in healthy subjects

METHODS

Key inclusion criteria

- *Healthy subjects*:
  - In good health based on medical history, physical exam, lab tests, vital signs and ECG at screening
  - Creatinine clearance by Cockcroft-Gault formula at least 90 mL/min
- *ESRD subjects*:
  - On a stable HD program (defined as showing urea clearance by time divided by urea volume [Kt/V] above 1.2 within the past 4 weeks without significant change in the past 3 months)
  - Stable ECG findings
  - No evidence of hepatic decompensation, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN) or bilirubin ≤ 1.5 times the ULN

Key exclusion criteria

- *Healthy subjects*:
  - History of clinically significant cardiac rhythm abnormalities; lab tests indicating liver disease or injury; history or presence of impaired renal function; signs of urinary obstruction/difficulty voiding at screening
- *ESRD subjects*:
  - History or evidence of congestive heart failure, significant coronary artery disease, or unstable angina
- All doses: 100 mg OMC IV infused over 30-45 minutes (100 mg is the daily IV dose used in studies of ABSSSI and CABP)
- ESRD subjects received two doses, with a 10- to 20-day washout period between doses
  - Period 1: Single dose 0-2 hr after end of HD
  - Period 2: Single dose 1-1.5 hr before next HD
  - In both Periods 1 and 2, blood samples collected at specified times through ~68 hr post-dose (up to next HD session); dialysate samples collected at specified times during Period 2
- Healthy subjects received one dose
  - Blood and urine samples collected at specified times through ~72 hr post-dose
- OMC concentrations in blood, urine and dialysate samples determined using a validated LC-MS/MS method
- Standard safety assessments performed: physical examinations, electrocardiograms (ECGs), vital signs, and clinical laboratory evaluations (hematology, chemistry, coagulation, urinalysis [healthy subjects]), pregnancy tests, and adverse event [AE] monitoring
- Analysis populations:
  - Safety population = all subjects that received any dose of test article
  - PK population = subjects that received the intended dose of test article for a given treatment period and for whom PK parameters could be calculated
  - All 16 subjects (100%) were included in both the Safety and PK analysis populations

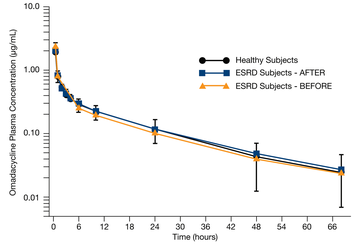
RESULTS

Table 1. Demographics—Safety Population

	ESRD subjects		
	ESRD subjects (n = 8)	Healthy subjects (n = 8)	All subjects (N = 16)
Gender, n (%)			
Female	2 (25.0)	2 (25.0)	4 (25.0)
Male	6 (75.0)	6 (75.0)	12 (75.0)
Age, years			
Median (range)	58.5 (43-70)	56.5 (45-67)	58.5 (43-70)
Race, n (%)			
White	4 (50.0)	7 (87.5)	11 (68.8)
Black/African American	3 (37.5)	1 (12.5)	4 (25.0)
Other	1 (12.5)	0	1 (6.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (12.5)	1 (12.5)	2 (12.5)
Not Hispanic or Latino	7 (87.5)	7 (87.5)	14 (87.5)
Weight, kg			
Median (range)	87.5 (52.9-129.7)	91.7 (61.2-129.3)	88.9 (52.9-129.7)
BMI, kg/m^2			
Median (range)	28.0 (21.5-39.2)	28.5 (20.9-41.7)	28.5 (20.9-41.7)

RESULTS

Figure 1. Mean (±SD) plasma concentrations of OMC in ESRD and healthy subjects after IV dosing—PK population.



- Following a 100-mg IV dose, OMC plasma-time concentration profiles in ESRD subjects (whether dosed after or before HD) and healthy subjects were similar
- In all cohorts, OMC distributed rapidly in plasma (median T_{max} values ≤ 1 hour) and OMC plasma concentrations declined in a biphasic manner

Table 2. Summary of OMC Plasma PK Parameters in ESRD and Healthy Subjects—PK Population

Cohort	AUC_{0-last} (h•µg/mL)	AUC_{0-inf} (h•µg/mL)	C_{max} (µg/mL)	T_{max} (h)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
ESRD Period 1 (after HD) n = 8	9.40 (2.10)	10.30 (2.35)	1.88 (0.74)	0.58 (0.58-1.08)	18.6 (5.21)	10.1 (2.24)	214 (56.1)
ESRD Period 2 (before HD) n = 8	9.25 (1.80)	10.20 (1.99)	2.33 (1.02)	0.59 (0.58, 0.77)	18.9 (6.34)	10.1 (2.05)	194 (69.2)
Healthy controls n = 8	9.08 (1.86)	9.76 (1.77)	1.92 (0.41)	0.58 (0.58, 0.68)	17.1 (2.60)	10.6 (1.99)	204 (47.6)

Arithmetic mean (SD) is shown for all parameters except T_{max}, where median and range (minimum, maximum) are shown.
AUC, area under the concentration-time curve; C_{max}, maximum observed concentration of OMC in plasma; CL, total body clearance; ESRD, end-stage renal disease; HD, hemodialysis; PK, pharmacokinetics; $t_{1/2}$, terminal elimination half-life in plasma; T_{max}, time of maximum observed plasma concentration; Vss, volume of distribution at steady state.

- All PK parameters were similar in ESRD subjects (whether dosed after or before HD) and healthy subjects

Table 3. Statistical Comparison of OMC Plasma PK Parameters in ESRD Subjects vs Healthy Subjects—PK Population

Parameter (Unit)	Cohort	Geometric Mean	Ratio of Geometric Mean	90% CI for Ratio
AUC_{0-last} (µg•h/mL)	ESRD[a]	9.21	1.03	0.86 – 1.24
	Healthy[b]	8.91		
AUC_{0-inf} (µg•h/mL)	ESRD	10.10	1.05	0.87 – 1.26
	Healthy	9.61		
C_{max} (µg/mL)	ESRD	1.78	0.94	0.72 – 1.23
	Healthy	1.88		
CL (L/h)	ESRD	9.91	0.95	0.79 – 1.14
	Healthy	10.40		

[a]ESRD subjects dosed in Period 1 (after HD); served as test cohort for this analysis.
[b]Healthy subjects served as reference cohort for this analysis.
ANOVA model with log-transformed PK parameters as response variable, fixed effect term as ESRD status and matched pair as random effect.
AUC, area under the concentration-time curve; C_{max}, maximum observed concentration of OMC in plasma; CL, total body clearance; CI, confidence interval; ESRD, end-stage renal disease.

- Renal impairment did not affect overall exposure (AUC_{0-last} and AUC_{0-inf}) or CL and had minimal effect on C_{max}

RESULTS

Table 4. Statistical Comparison of OMC Plasma PK Parameters in ESRD Subjects Dosed Before or After Hemodialysis—PK Population

Parameter (Unit)	Cohort	Geometric Mean	Ratio of Geometric Mean	90% CI for Ratio
AUC_{0-last} (µg•h/mL)	ESRD dosed before HD	9.09	0.988	0.95 – 1.03
	ESRD dosed after HD	9.21		
AUC_{0-inf} (µg•h/mL)	ESRD dosed before HD	10.00	0.995	0.96 – 1.03
	ESRD dosed after HD	10.10		
C_{max} (µg/mL)	ESRD dosed before HD	2.18	1.23	0.98 – 1.54
	ESRD dosed after HD	1.78		
CL (L/h)	ESRD dosed before HD	9.95	1.00	0.97 – 1.04
	ESRD dosed after HD	9.91		

ESRD subjects dosed in Period 2 (before HD) served as the test cohort and ESRD subjects dosed in Period 1 (after HD) served as the reference cohort for this analysis.
ANOVA model with log-transformed PK parameters as response variable, fixed effect term as period and weight at baseline, age and gender as covariates and subject as random effect.
AUC, area under the concentration-time curve; C_{max}, maximum observed concentration of OMC in plasma; CL, total body clearance; ESRD, end-stage renal disease; HD, hemodialysis; PK, pharmacokinetics.

- HD did not substantially affect overall exposure (AUC_{0-last} and AUC_{0-inf}) or CL
- Increased C_{max} seen in subjects given OMC before HD was not due to HD since T_{max} (time of C_{max}) was before the start of HD

Summary of OMC PK Parameters in Urine (Healthy Subjects) and Dialysate (ESRD Subjects)—PK Population

- PK of OMC in urine was analyzed in healthy control subjects after 100 mg IV dosing, n = 8 (mean ± SD)
  - Cumulative amount of OMC excreted in urine (Ae) = 27.0 ± 3.49 mg
  - Fraction of total OMC dose excreted in urine (Fe_u, calculated as Ae/AUC_{0-last}) = 27 ± 3.49%
  - Renal clearance (CL_R) = 3.06 ± 0.694 L/h
- PK of OMC in dialysate was analyzed in ESRD subjects after 100 mg IV dosing in Period 2 (before HD), n = 8
  - Mean percentage of OMC dose cleared by HD compared to total clearance was 47.8%
  - 7.89 mg (7.89%) of OMC was recovered in the dialysate during the dialysis period

Table 5. Safety of IV OMC in ESRD and Healthy Subjects—Safety Population

	ESRD subjects			
Omadacycline 100-mg single dose IV	Period 1 (post-HD dosing) (n = 8)	Period 2 (pre-HD dosing) (n = 8)	Healthy subjects (n = 8)	Total (N = 16)
Subjects with at least one, n (%)				
TEAE	3 (37.5)	2 (25.0)	1 (12.5)	5 (31.3)
Drug-related TEAE	1 (12.5)	0	0	1 (6.3)
Types of TEAEs observed, n (%)				
Upper respiratory tract infection (RTI)	2 (25.0)	0	0	2 (12.5)
Viral upper RTI	1 (12.5)	0	0	1 (6.3)
Dizziness	1 (12.5)	0	0	1 (6.3)
Headache	0	1 (12.5)	0	1 (6.3)
Infusion site erythema	0	0	1 (12.5)	1 (6.3)
Bronchospasm	0	1 (12.5)	0	1 (6.3)
Rash papular	1 (12.5)	0	0	1 (6.3)

RESULTS

- Only a single subject in the study experienced drug-related TEAEs (mild dizziness and mild rash)
- There were no severe or serious TEAEs, TEAEs leading to study discontinuation, or deaths
- All cohorts showed transient heart rate (HR) increase peaking within 2 h post-dose (maximum median increase 9.5 bpm). Transient increase in blood pressure was seen in ESRD pre-HD cohort around the time of HD initiation. No changes in vital signs were considered TEAEs
- There were no clinically relevant changes in hematology, clinical chemistry or ECGs

CONCLUSIONS

- Intravenous (IV) administration of a single 100-mg dose of omadacycline as a 30-minute infusion produced a similar plasma concentration-time profile and pharmacokinetic parameters in end-stage renal disease (ESRD) subjects on stable hemodialysis and matched healthy subjects
- Hemodialysis did not significantly impact omadacycline plasma pharmacokinetics after IV dosing
  - Only 7.89% of the OMC dose (7.89 mg) was recovered in the dialysate during the dialysis period. This is due to the low total systemic clearance (10.1 to 10.6 L/h) and large volume of distribution (194 to 214 L) for omadacycline
- Despite 27% of the IV-administered omadacycline dose being eliminated in the urine of healthy subjects, overall clearance and volume of distribution were similar in ESRD subjects and healthy subjects
- PK findings from this study were generally consistent with those observed in previous studies with healthy subjects[4]
- The 100 mg IV dose of omadacycline was generally safe and well-tolerated in ESRD subjects and healthy subjects; TEAEs were infrequent and only mild or moderate in both groups
- Overall, these results show that omadacycline dose adjustment is not required for subjects with renal impairment or those on hemodialysis

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