Omadacycline Pharmacokinetics: Influence of Mortality Risk Score Among Patients with Community-Acquired Bacterial Pneumonia

E.A. Lakota[1], L. Friedrich[2], J.N. Steenbergen[2], P.C. McGovern[2], E. Tzanis[2], S.M. Bhavnani[1], C.M. Rubino[1]
[1]Institute for Clinical Pharmacodynamics, Inc., Schenectady, NY, USA;
[2]Paratek Pharmaceuticals, Inc., King of Prussia, PA, USA

INSTITUTE for CLINICAL PHARMACODYNAMICS

Christopher M. Rubino, Pharm.D.
Institute for Clinical Pharmacodynamics, Inc.
242 Broadway
Schenectady, NY 12305
Telephone: (518) 631-8100
Fax: (518) 631-8199
E-mail: CRubino@ICPD.com

INTRODUCTION

- Omadacycline is a novel aminomethylcycline structurally related to tetracycline agents with *in vitro* activity against Gram-positive and -negative pathogens including tetracycline-resistant pathogens.
- Omadacycline received approval in the U.S. in October 2018 for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) and is available in both intravenous (IV) and oral (PO) formulations [1].

OBJECTIVE

- The objectives of these analyses were to determine if PORT Risk Class and CURB-65 score influence the pharmacokinetics (PK) of omadacycline in patients with CABP.

METHODS

- PK data were available from omadacycline-treated patients with CABP enrolled in the Phase 3 OPTIC Study, which was intended to enroll patients with PORT Risk Class II, III, or IV [2].
- Patients received omadacycline 100 mg IV q12h on Day 1 followed by 100 mg IV q24h. After Day 3, patients could be switched to 300 mg PO q24h if predefined clinical stability criteria were met.
- Four PK samples per patient were collected between Days 2 and 5.
- These data were previously utilized in the development of a population PK model describing the disposition of omadacycline [3].
- Individual post-hoc parameter estimates for patients enrolled in the OPTIC study were utilized to compute total-drug plasma area under the concentration-time curve (AUC) values over 24 hours (AUC_{0-24}) on Day 1 following administration of omadacycline 100 mg IV q12h.
- Differences among these AUC_{0-24} values by PORT Risk Class and CURB-65 score were assessed using a one-way ANOVA.
- Given that females have been shown to have significantly slower clearance than males [3], multivariable analyses was carried out to account for the effect of each of PORT Risk Class and CURB-65, and sex on AUC_{0-24}.

RESULTS

- Summary statistic of baseline subject descriptors for the analysis population are presented in **Table 1**.
- A total of 187 PK samples were available from 50 patients.

Table 1. Summary statistics of subject demographics and clinical laboratory measures for the overall PK analysis population

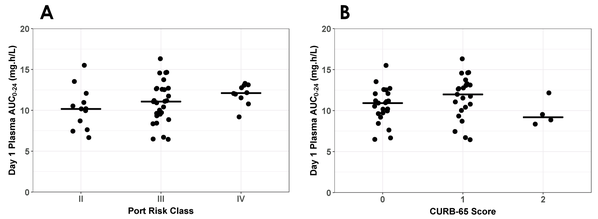
Variable		N (%)	Mean (SD)	Median	Minimum	Maximum
Age (yr)		50 (100)	53.8 (13.4)	54	28	84
Weight (kg)		50 (100)	78.2 (15.8)	77.5	36	127
Height (cm)		50 (100)	172 (10.7)	174	137	192
BSA (m^2)		50 (100)	1.91 (0.219)	1.91	1.25	2.38
BMI (kg/m^2)		50 (100)	26.3 (4.64)	26.2	16	41.5
CLcr (mL/min/1.73 m^2)		50 (100)	86.2 (29.8)	85.2	33.1	162
Albumin (mg/dL)		50 (100)	4.06 (0.526)	4.05	2.7	5.0
Sex	Male	32 (64.0)	—	—	—	—
	Female	18 (36.0)	—	—	—	—
Race	Caucasian	50 (100)	—	—	—	—
	Other	0 (0)	—	—	—	—
PORT Risk Class	I	0 (0)	—	—	—	—
	II	12 (24.0)	—	—	—	—
	III	28 (56.0)	—	—	—	—
	IV	10 (20.0)	—	—	—	—
	V	0 (0)	—	—	—	—
CURB-65 score	0	23 (46.0)	—	—	—	—
	1	23 (46.0)	—	—	—	—
	2	4 (8.00)	—	—	—	—
	≥ 3	0 (0)	—	—	—	—

Note: SD = Standard deviation.

- Distributions of omadacycline total-drug plasma AUC_{0-24} stratified by PORT Risk Class and CURB-65 score are provided in **Figure 1**.
- Results of the univariable comparisons are provided in **Table 2**.
  - Among the patients classified as PORT Risk Class II, III, and IV (n = 12, 28, and 10, respectively), mean Day 1 omadacycline AUC_{0-24} values were 10.3, 11.0, and 12.0 mg•L/h, respectively.
  - Among patients with CURB-65 scores of 0, 1, and 2 (n = 23, 23, and 4, respectively), mean Day 1 omadacycline AUC_{0-24} values were 10.6, 11.6, and 9.72 mg•L/h, respectively.
  - The differences in mean AUC_{0-24} values were not statistically significant among patients by PORT Risk Class (p = 0.248) and CURB-65 score groups (p = 0.745). Moreover, variability was similar across these groups as displayed in **Figure 1**.

RESULTS

Figure 1. Day 1 omadacycline total-drug plasma AUC_{0-24} by PORT Risk Class (A) and CURB-65 score (B)[a]



a. Horizontal line represents the mean total-drug plasma AUC_{0-24} value for each group

Table 2. Mean (SD) omadacycline AUC_{0-24} by PORT Risk Class and CURB-65 score

Stratification Variable		n	Omadacycline AUC_{0-24} (mg•h/L)	p-value[a]
PORT Risk Class	II	12	10.3 (2.57)	
	III	28	11.0 (2.56)	0.248
	IV	10	12.0 (1.26)	
CURB-65 score	0	23	10.6 (2.14)	
	1	23	11.6 (2.62)	0.745
	2	4	9.72 (1.70)	

Note: AUC_{0-24} = Area under the concentration-time curve from time 0 to 24 hours on Day 1; SD = standard deviation.

a. ANOVA.

- The results of multivariable modeling to account for the known effect of sex on omadacycline PK are provided in **Table 3.**
- After accounting for the impact of sex, PORT Risk Class was found to be a significant predictor of omadacycline AUC_{0-24}.
  - Patients with PORT Risk Class IV had a statistically-significant increase in least-squares mean (LSM)AUC_{0-24} of 23.8% (p = 0.0187) compared to the base case of men with PORT Risk Class of II.
  - Patients with PORT Risk Class III had an increase LSM AUC_{0-24} of 8.36%, which was not significant (p = 0.289) compared to the base case of men with PORT Risk Class of II.
  - Interactions between sex and each of PORT Risk Class and CURB-65 score were not significant and thus, not retained in the models presented in **Table 3**.
- CURB-65 score was not predictive of differences in AUC_{0-24}.
- Boxplots showing the distributions of omadacycline total-drug plasma AUC_{0-24} stratified by PORT Risk Class and sex are provided in **Figure 2**.

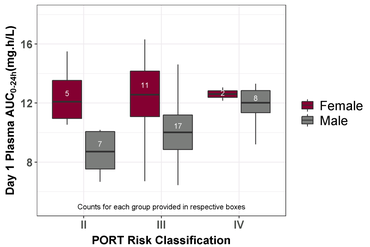
RESULTS

Table 3. Results of multivariable models for AUC_{0-24} accounting for PORT Risk Class/CURB-65 and sex

Category	LSM	90% CI	p-value[a]
Base case (males; PORT Risk Class of II)	9.31	7.99, 10.6	
Covariate effects:			
PORT Risk Class of III	0.778	-0.681, 2.24	0.289
PORT Risk Class of IV	2.22	0.388, 4.05	0.0187
Females	2.32	1.06, 3.58	0.000576
Base case (males; CURB-65 score of 0)	10.0	9.03, 11.0	
Covariate effects:			
CURB-65 score of I	0.804	-0.472, 2.08	0.211
CURB-65 score of 2	-1.34	-3.68, 1.01	0.258
Females	2.09	0.810, 3.37	0.00194

Note: LSM = Least-square mean; CI = Confidence interval for LSM.
a. t-statistic from ANOVA.

Figure 2. Box-and-whisker plots showing the distribution of omadacycline AUC_{0-24}, stratified by PORT Risk Class and sex



CONCLUSIONS

- After adjusting for the impact of sex, omadacycline exposures were higher in patients with PORT Risk Class IV compared to PORT Risk Class II but differences were not seen in patients with PORT Risk Class III or based on CURB-65.
- Given the modest differences seen and the favorable safety profile of omadacycline, dose adjustments based on these classifications are likely not warranted.

REFERENCES

1. Paratek Pharmaceuticals, Inc. NUZYRA (omadacycline)® package insert. Boston, MA; 2019.
2. Stets R *et al.* 2019. Omadacycline for community-acquired bacterial pneumonia. N Engl J Med 380:517-27. DOI:10.1056/NEJMoa1800201.
3. Lakota EA *et al.* 2018. Population Pharmacokinetic Analyses of Omadacycline Using Phase 1 and 3 Data, poster Saturday 628. Abstr American Society for Microbiology Microbe, Atlanta, GA.

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