Omadacycline Pharmacokinetics: Impact of Comorbidities

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INTRODUCTION

- Omadacycline, a novel aminomethylcycline antibiotic with activity against many Gram-positive, Gram-negative, anaerobic, and atypical pathogens, was recently approved in the U.S. for the treatment of adults with community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections.
- During drug development, robust population PK analyses based on Phase 1, 2, and 3 data were undertaken to characterize the disposition of omadacycline [1].

OBJECTIVES

- The objective of this analysis was to evaluate differences in omadacycline clearance among subjects stratified by comorbidities not previously evaluated.

METHODS

- The population PK model has previously been shown to be a linear, three-compartment model with zero-order IV input and first-order absorption using transit compartments to account for a delay in oral absorption following administration of the tablet or capsule formulations [1].
  - During model development, potential covariates evaluated included age, body size measures, renal function (calculated CrCl), albumin, sex, race, and presence of infection (various types). Sex was the only significant covariate identified.
  - This model was used in the current analysis to evaluate the effect of certain comorbidities in the same PK analysis population.
- Individual post-hoc clearance estimates were computed in NONMEM for all subjects in the original model development (n=613) and validation dataset (n=202) (total n=815). Since clearance drives area under the concentration-time curve (AUC) and omadacycline's efficacy is associated with AUC:MIC ratio, clearance was the focus of these analyses.
- Differences in clearance by smoking status or history of diabetes mellitus, chronic lung disease (COPD, asthma, emphysema, or chronic bronchitis), hypertension, heart failure, or coronary artery disease were evaluated using a Welch two-sample t-test.
- In addition, potential imbalances in patient sex in the various groups were controlled for using an ANOVA approach.
- Subjects missing information for any of these covariates were removed from the respective analysis.

RESULTS

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

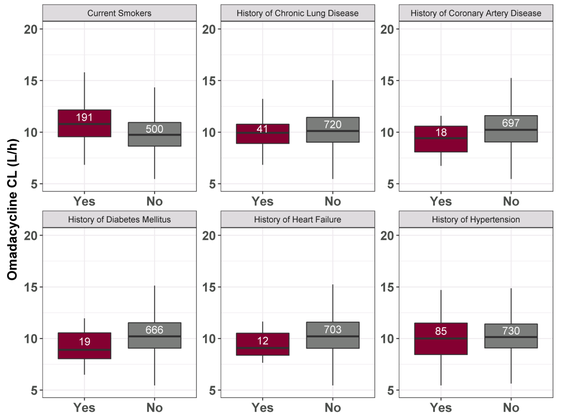
Variable		N (%)	Mean (SD)	Median	Minimum	Maximum
Age (yr)		815	39.8 (14.1)	38	18	88
Weight (kg)		815	79.2 (15.6)	78	36	167
Height (cm)		815	173 (9.19)	173	137	201
BSA (m^2)		815	1.92 (0.196)	1.92	1.25	2.73
BMI (kg/m^2)		815	26.5 (5.13)	25.8	16	71.3
CLcr ($mL/min/1.73\ m^2$)		815	101 (29.5)	101	5.53	214
Albumin (mg/dL)		815	4.25 (0.458)	4.3	2.2	5.3
Sex	Male	574 (70.4)	—	—	—	—
	Female	241 (29.6)	—	—	—	—
Current smokers	No	500 (72.4)	—	—	—	—
	Yes	191 (27.6)	—	—	—	—
History of CLD	No	720 (94.6)	—	—	—	—
	Yes	41 (5.39)	—	—	—	—
History of CAD	No	697 (97.5)	—	—	—	—
	Yes	18 (2.52)	—	—	—	—
History of diabetes	No	666 (97.2)	—	—	—	—
	Yes	19 (2.77)	—	—	—	—
History of heart failure	No	703 (98.3)	—	—	—	—
	Yes	12 (1.68)	—	—	—	—
History of hypertension	No	730 (89.6)	—	—	—	—
	Yes	85 (10.4)	—	—	—	—

Note: SD = Standard deviation; CLD = Chronic lung disease; CAD = Coronary artery disease.

- Summary statistics of baseline subject descriptors for the analysis population are presented in **Table 1**.
- Distributions of omadacycline clearance by the comorbidity are provided in **Figure 1**.
- Mean omadacycline clearance estimates by comorbidity along with corresponding p-values are presented in **Table 2**.
  - Mean clearance was statistically significantly higher in current smokers, and lower in patients with a history of heart failure or coronary heart disease.
  - Mean clearance was not significantly different in patients with a history of diabetes, chronic lung disease, or hypertension.
- Least-square mean differences between groups after correcting for patient sex, which was the only statistically significant covariate from the population PK analysis [1], are presented in **Table 3**.
  - Smoking was the only comorbidity that remained statistically significant after correcting for patient sex. Distributions of omadacycline clearance by sex and smoking status are provided in **Figure 2.**
  - The least-square mean difference of 1.13 represents an increase of < 15% in clearance in smokers, suggesting that the effect of smoking is not clinically relevant.

RESULTS

Figure 1. Box-and-whisker plots showing the distribution of omadacycline clearance, stratified by various comorbidities



Note: Counts for each group are provided in respective boxes

Table 2. Mean omadacycline clearance estimates by presence or absence of comorbidities

Comorbidity		Omadacycline CL (L/h)	p-value[a]
Current smokers	Yes	11.2	< 0.001
(n = 691)	No	10.0	
History of chronic lung disease	Yes	9.9	0.084
(n = 761)	No	10.3	
History of coronary artery disease	Yes	9.25	0.005
(n = 715)	No	10.4	
History of diabetes mellitus	Yes	9.9	0.467
(n = 685)	No	10.4	
History of heart failure	Yes	9.07	0.0293
(n = 715)	No	10.4	
History of hypertension	Yes	10.3	0.898
(n = 815)	No	10.4	

Note: CL = Clearance.
a. Welch two-sample t-test

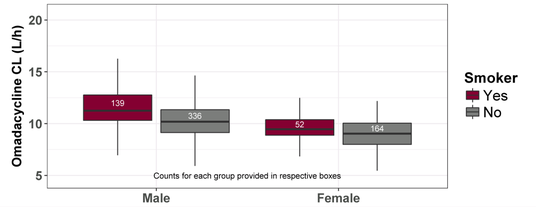
RESULTS

Table 3. Results of ANOVA comparisons of omadacycline clearance based on various comorbidities, correcting for sex

Comorbidity	LSM	90% CI	p-value[a]
Current smokers	1.13	0.802, 1.45	< 0.0001
History of chronic lung disease	-0.0394	-0.665, 0.586	0.902
History of coronary artery disease	-0.932	-1.87, 0.00734	0.0518
History of diabetes mellitus	0.0635	-0.863, 0.990	0.893
History of heart failure	-0.849	-2.00, 0.300	0.147
History of hypertension	0.189	-0.247, 0.626	0.395

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 clearance, stratified by smoking status and sex



CONCLUSIONS

- A history of diabetes, chronic lung disease, coronary artery disease, or hypertension did not impact clearance. Omadacycline dose adjustments based on these covariates are likely not warranted.
- Although current smokers had statistically significant increases in omadacycline clearance compared to non-smokers after accounting for the effect of sex, the difference was < 15% and, thus, is unlikely to be clinically relevant.

REFERENCES

1. Lakota EA, Van Wart SA, Tzanis E, Bhavnani SM, Ambrose PG, Rubino CM. 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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