Pharmacokinetic-Pharmacodynamic Target Attainment Analyses Evaluating Omadacycline Dosing Regimens for the Treatment of Patients With Community-Acquired Bacterial Pneumonia for *Streptococcus pneumoniae* and *Haemophilus influenzae*

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INTRODUCTION

- Omadacycline is a novel aminomethylcycline with *in vitro* activity against Gram-positive and -negative organisms, including *Streptococcus pneumoniae* and *Haemophilus influenzae*.
- Given this activity, omadacycline is being developed to treat patients with community–acquired bacterial pneumonia (CABP).
- Collection of pharmacokinetic (PK) data from omadacycline-treated patients with CABP allowed for refinement of a previously–described population PK model developed based on Phase 1 data [1, 2].
- As described herein, the above–described population PK model [2], non-clinical pharmacokinetics-pharmacodynamics (PK-PD) targets for efficacy [3, 4], *in vitro* surveillance data [5], and Monte Carlo simulation, were used to evaluate intravenous (IV) to oral (PO) and PO omadacycline dosing regimens for patients with CABP and interpretive criteria for the *in vitro* susceptibility testing of omadacycline against *S. pneumoniae* and *H. influenzae*.

METHODS

Population Pharmacokinetic Model

- A linear, three-compartment model with epithelial lining fluid (ELF) as a sub-compartment of peripheral compartment 1 and IV input or 1st-order delayed absorption after PO doses was utilized to simulate IV and PO omadacycline concentration-time profiles [2].

Monte Carlo Simulations

- Using the above-described omadacycline population PK model [2], total-drug plasma and ELF concentration-time profiles from 0 to 120 hours were generated for 5,000 simulated patients following two omadacycline dosing regimens:

IV to PO Dosing Regimen	100 mg IV q12h on Day 1, followed by 100 mg IV q24h on Day 2 and 300 mg PO q24h on Days 3-5
PO Dosing Regimen	450 mg PO q24h on Days 1-2, followed by 300 mg PO q24h on Days 3-5

- 24-hour total-drug ELF and plasma area under the concentration time curve (AUC) values were then calculated for each simulated patient.
- Total-drug plasma AUC values were adjusted to free-drug plasma AUC values using a free-fraction of 0.79 based on *in vitro* data for human plasma protein binding [5].
- AUC values were divided by the minimum inhibitory concentration (MIC) to calculate the ratio of the AUC to MIC (AUC:MIC ratio), the PK-PD index of interest for omadacycline.

Non-Clinical Pharmacokinetic-Pharmacodynamic Targets for Efficacy

- Non-clinical total-drug ELF AUC:MIC ratio targets from neutropenic murine-lung and one-compartment *in vitro* infection models for *S. pneumoniae* [3] and *H. influenzae* [4], respectively, as shown in **Table 1**, were evaluated.

METHODS

Table 1. Omadacycline total-drug ELF AUC:MIC ratio targets for *S. pneumoniae* and *H. influenzae* efficacy based on data from neutropenic murine-lung [3] and one-compartment *in vitro* [4] infection models, respectively

Pathogen (infection model)	Isolate	MIC value (µg/mL)	AUC:MIC ratio targets by efficacy endpoint	
			1-$\log_{10}$ CFU reduction from baseline	2-$\log_{10}$ CFU reduction from baseline
S. pneumoniae (neutropenic murine-lung infection model)	1293[a]	0.06	200.6	—
	10813	0.06	17.6	23.2
	140	0.125	6.00	17.3
	49619	0.03	13.3	47.3
	Mean (SD)	—	59.4 (94.3)	—
	Mean without 1293 (SD)	—	12.3 (5.86)	29.3 (15.9)
	Median	—	15.5	—
	Median without 1293	—	13.3	23.2
H. Influenzae (one-compartment *in vitro* infection model)	437	1	8.91	11.1
	10929	1	9.73	12.9
	2696	2	5.44	6.72
	49247	2	11.6	15.5
	543	2	5.78	7.45
	Mean (SD)	—	8.30 (2.64)	10.7 (3.69)
	Median	—	8.91	11.1

a. The AUC:MIC ratio target for a 1-$\log_{10}$ colony forming units (CFU) reduction from baseline for *S. pneumoniae* 1293 was not considered given the greatly dissimilar magnitude of the target relative to targets derived for the other *S. pneumoniae* isolates.

PK-PD Target Attainment Analyses

- Percent probabilities of PK-PD target attainment by MIC and weighted over omadacycline MIC distributions for each pathogen based on average 24-hour AUC values on Days 1 to 2 and the 24-hour AUC on Day 3 (the day of PO switch) were determined for simulated patients after administration of each omadacycline dosing regimen.
  - The AUC:MIC ratio target for a simulated patient was randomly assigned based on an estimated log normal distribution of targets associated with a given endpoint for that pathogen. The distribution was truncated at +/- 2 standard deviations on the log scale.
  - PK-PD target attainment results were interpreted relative to *in vitro* surveillance data for 605 *S. pneumoniae* and 445 *H. influenzae* clinical isolates that were collected during 2016 from North American medical centers as part of the SENTRY Antimicrobial Surveillance Program [5].
    - The MIC values at which 50%/90% of isolates were inhibited ($MIC_{50/90}$) were 0.06/0.06 and 1/1 µg/mL for *S. pneumoniae* and *H. influenzae* isolates, respectively.
    - The subsets of the penicillin-susceptible, -intermediate, and -resistant *S. pneumoniae* isolates (n= 389, 142, and 74, respectively) and β-lactamase-positive and –negative *H. influenzae* isolates (n=141 and 304, respectively) were also evaluated.
- Emphasis was placed on the PK-PD target attainment results based on total-drug ELF AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline.

RESULTS

PK-PD Target Attainment Analyses

- **Table 2** shows the percent probabilities of PK-PD target attainment by MIC based on randomly assigned total-drug ELF AUC:MIC ratio targets associated with 1-$\log_{10}$ CFU reductions from baseline for *S. pneumoniae* and *H. influenzae* among simulated patients after administration of the omadacycline IV to PO and PO dosing regimens.
  - After administration of the omadacycline IV to PO dosing regimen, percent probabilities of PK-PD target attainment on Days 1 to 2 and Day 3 exceeded 90.0% at MIC values of 0.5 µg/mL for *S. pneumoniae* (i.e., one dilution higher than the MIC_{100}) and 1 µg/mL for *H. influenzae* (i.e., the MIC_{90}).
    - At the same MIC values, percent probabilities of PK-PD target attainment based on free-drug plasma AUC:MIC ratio targets were 75.4 and 59.9%, respectively, for *S. pneumoniae* and 67.0 and 42.0%, respectively, for *H. influenzae* (data not shown).
  - After administration of the PO dosing regimen, percent probabilities of PK-PD target attainment on Days 1 to 2 were 89.5% at an MIC of 0.5 µg/mL for *S. pneumoniae* and 82.7% at an MIC of 1 µg/mL for *H. influenzae*.
    - At the same MIC values, percent probabilities of PK-PD target attainment based on free-drug plasma AUC:MIC ratio targets were 53.0 and 35.0% for *S. pneumoniae* and *H. influenzae*, respectively (data not shown).
- **Figure 1** and **Figure 2** show percent probabilities of PK-PD target attainment by MIC on Days 1 to 2 based on randomly assigned total-drug ELF AUC:MIC ratio targets associated with 1- and 2-$\log_{10}$ CFU reductions from baseline for *S. pneumoniae* and *H. influenzae*, respectively, overlaid on the MIC distributions for each pathogen.

Table 2. Percent probabilities of PK-PD target attainment by MIC based on total-drug ELF AUC:MIC ratio targets associated with 1-$\log_{10}$ CFU reductions from baseline for *S. pneumoniae* or *H. influenzae* among simulated patients after administration of IV to PO and PO omadacycline dosing regimens

Pathogen	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC		
		IV to PO dosing regimen		PO dosing regimen
		Days 1 to 2[a]	Day 3[b]	Days 1 to 2[a]
S. pneumoniae	0.12	100	100	100
	0.25	100	99.9	98.9
	0.5	99.3	95.5	89.5
	1	82.9	67.9	59.5
	Overall[c]	100	100	100
H. influenzae	0.25	100	100	100
	0.5	100	99.9	98.7
	1	99.5	93.0	82.7
	2	68.8	45.3	36.5
	Overall[c]	96.6	91.2	84.9

Note: Shaded cells indicate percent probabilities of PK-PD target attainment ≥90%.
a. Based on the assessment of average 24-hour total-drug ELF AUC on Days 1 and 2.
b. Based on the assessment of 24-hour total-drug ELF AUC on Day 3, after the PO switch.
c. Represents the weighted percent probability of PK-PD target attainment over the omadacycline MIC distribution.

RESULTS

Figure 1. Percent probabilities of attaining randomly assigned total–drug ELF AUC:MIC ratio targets for *S. pneumoniae* by MIC on Days 1 to 2 among simulated patients after administration of the IV to PO (A) and PO (B) omadacycline dosing regimens, overlaid on the MIC distributions for *S. pneumoniae*

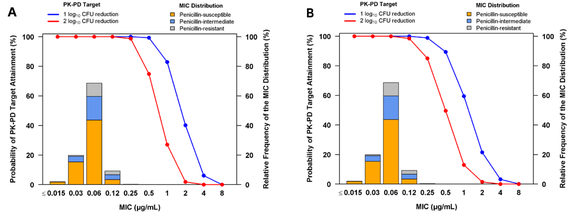
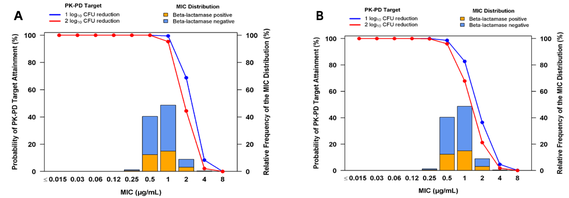


Figure 2. Percent probabilities of attaining randomly assigned total–drug ELF AUC:MIC ratio targets for *H. influenzae* by MIC on Days 1 to 2 among simulated patients after administration of the IV to PO (A) and PO (B) omadacycline dosing regimens, overlaid on the MIC distributions for *H. influenzae*



CONCLUSIONS

- These data provide support for proposed omadacycline dosing regimens and the evaluation of omadacycline susceptibility breakpoints against *S. pneumoniae* and *H. influenzae*.

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