Assessment of Pharmacokinetics-Pharmacodynamics to Support Omadacycline Dosing Regimens for the Treatment of Patients with Acute Bacterial Skin and Skin Structure Infections

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INTRODUCTION

- Omadacycline, an aminomethylcycline that is structurally related to tetracycline agents, demonstrates *in vitro* activity against pathogens commonly associated with acute bacterial skin and skin structure infections (ABSSSI), including *Staphylococcus aureus*, methicillin-resistant isolates, and beta-hemolytic streptococci.
- Omadacycline intravenous (IV) and oral (PO) regimens were recently approved by the US FDA for the treatment of adult patients with ABSSSI.
- Pharmacokinetic-pharmacodynamic (PK-PD) relationships for efficacy were evaluated using data from omadacycline-treated patients with ABSSSI enrolled in two Phase 3 trials.

METHODS

Study Data

- Data from omadacycline-treated patients with ABSSSI were collected from two Phase 3 clinical studies, OASIS-1 and OASIS-2.
  - OASIS-1: Patient received 100 mg IV every 12 hours (q12h) for 2 doses, followed by 100 mg IV every 24 hours (q24h), with the option to switch to 300 mg PO q24h after 3 days.
  - OASIS-2: Patients received 450 mg PO q24h for 2 doses, followed by 300 mg PO q24h for total of 7-14 days.
- Clinical response was evaluated at 48-72 hours (early clinical response; ECR), at end-of-therapy (EOT), and at the post-therapy evaluation (7-14 days after EOT). Lesion size was assessed on Days 2-10.

Pharmacokinetic-Pharmacodynamic Analyses for Efficacy

- Using a population pharmacokinetic (PK) model [1] and PK data from patients, average 24-hour free-drug omadacycline AUC over 0-48 hours was determined.
- Relationships between efficacy endpoints described above and free-drug plasma AUC:MIC ratio were evaluated using the following:
  - Chi-square tests, Fisher's exact tests and/or logistic regression for dichotomous endpoints (clinical and microbiological response and lesion size reduction threshold endpoints);
  - Kruskal-Wallis tests and Spearman correlations for (percent reduction in lesion size by day endpoints); and
  - Log rank tests and Cox proportional hazards regression for time-to-lesion size reduction endpoints.

METHODS

Evaluation of Omadacycline Dosing Regimens

- Using identified clinical PK-PD relationships and non-clinical PK-PD targets for *S. aureus* [2], the population PK model [1], Monte Carlo simulation, and omadacycline minimum inhibitory concentration (MIC) distribution for *S. aureus* [3], mean percent probabilities of response and PK-PD target attainment were evaluated.
- Omadacycline free-drug plasma concentration-time profiles from Days 1-2 were generated for simulated patients with ABSSSI after administration of the dosing regimens described in **Table 1**.
  - Free-drug plasma 24-hour AUC values on Days 1 and 2, which were determined using a free-fraction of 0.79 based on *in vitro* data for human plasma protein binding [4] and numerical integration.

Table 1. Summary of omadacycline dosing regimens evaluated among simulated patients

Route of administration	Omadacycline dosing regimen
IV-to-PO	100 mg IV q12h on Day 1 followed by 100 mg IV q24h on Day 2 with a PO switch to 300 mg PO q24h on Day 3
	200 mg IV q24h on Day 1 followed by 100 mg IV q24h on Day 2 with a PO switch to 300 mg PO q24h on Day 3
PO	450 mg PO q24h on Days 1 and 2, followed by 300 mg PO q24h on Day 3

- Percent probabilities of PK-PD target attainment by MIC were determined using randomly assigned free-drug plasma AUC:MIC ratio targets associated with net bacterial stasis and a 1-$\log_{10}$ colony forming unit (CFU) reduction from baseline for *S. aureus*.
  - Data were obtained from a neutropenic murine-thigh infection model [2]. Median (min, max) free-drug plasma AUC:MIC ratio targets associated with net bacterial stasis and 1-$\log_{10}$ CFU reduction from baseline were 21.9 (13.8, 51.1) and 57.7 (32.2, and 302.5), respectively.
  - Free-drug plasma AUC:MIC ratio targets were randomly assigned for a simulated patient based on an estimated log normal distribution of targets associated with each endpoint. Each distribution was truncated at +/- 2 standard deviations on the log scale.
- Mean percent probabilities of response and percent probabilites of PK-PD target attainnment by MIC were evaluated relative to *S. aureus* MIC distributions for isolates collected from the USA and Europe [3].

RESULTS

- Of patients with *S. aureus* at baseline in the microbiologically evaluable population who had PK and who were evaluable for at least one efficacy endpoint (n=128), significant PK-PD relationships were only identified for clinical response at ECR (**Figure 1**).
- Percent probabilities of clinical success at ECR and PK-PD target attainment by MIC on Days 1-2 for IV-to-PO dosing regimen with 100 IV q12h (A) and 200 IV mg q24h (B) on Day 1 and the PO (C) dosing regimen are shown in **Figure 2**.
  - Percent probabilities of clinical success at ECR for continuous and two-group relationships were 91.9 and 95.6%, 92.1 and 95.7%, and 89.3 and 88.4% at a MIC of 0.5 µg/mL, respectively, for the three dosing regimens.
  - At the MIC_{90} of 0.25 µg/mL, percent probabilities of PK-PD target attainment based on randomly assigned free-drug plasma AUC:MIC ratio targets associated with net bacterial stasis were 91.3, 92.6, and 60.8%, respectively.

Figure 1. Univariable relationships between the percent probability of clinical success at ECR and free-drug AUC:MIC ratio evaluated as continuous (A) and two-group (B) variables based on data from patients with ABSSSI and *S. aureus* isolated at baseline

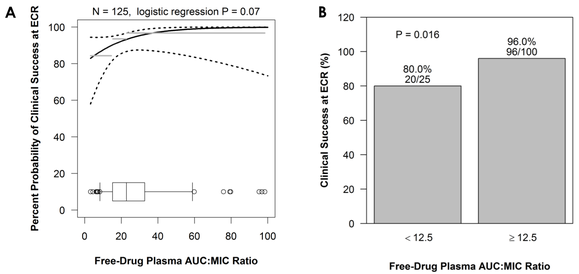
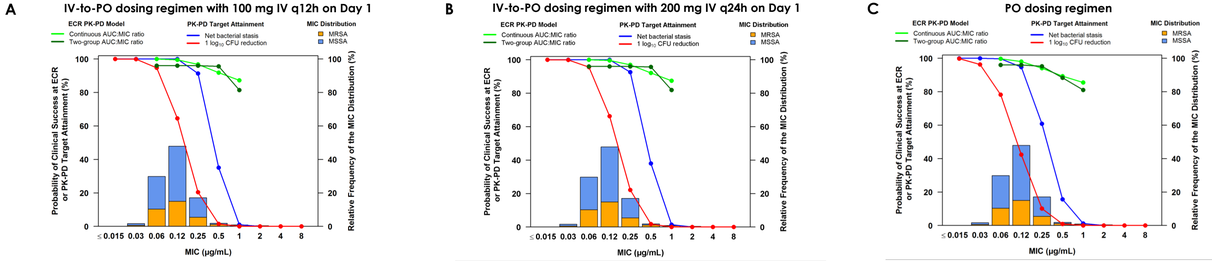


Figure 2. Percent probabilities of clinical success at ECR or PK-PD target attainment by MIC on Days 1-2 among simulated patients after administration of omadacycline IV-to-PO and PO dosing regimens, overlaid on MIC distributions for *S. aureus* isolates from the USA and Europe



CONCLUSIONS

- A PK-PD relationship for clinical response at ECR was identified among omadacycline-treated patients with ABSSSI and *S. aureus* at baseline and was used to assess modeled-predicted clinical success at ECR by MIC.
- Over the common range of MIC values evaluated, model-predicted clinical success at ECR and PK-PD target attainment (based on achieving a plasma AUC:MIC ratio associated with net bacterial stasis) were concordant for MIC values of 0.06 to 0.25 µg/mL but were not concordant at higher MIC values (0.5 or 1 µg/mL).
- These data provide support for omadacycline IV-to-PO and PO regimens for ABSSSI and model-predicted clinical response at ECR data provide support for an omadacycline susceptibility breakpoint of 0.5 µg/mL for *S. aureus*, which covers 98.6% of surveillance isolates.

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