Pharmacokinetic-Pharmacodynamic Analyses for Cardiac Endpoints Using Clinical Study Data From Omadacycline-Treated Subjects

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INTRODUCTION

- Omadacycline, an aminomethylcycline structurally related to tetracycline agents, was approved in October 2018 by the US FDA [1] for the following indications:
  - Adult patients with acute bacterial skin and skin structure infections (intravenous (IV) to oral (PO) and PO regimens); and
  - Adult patients with community-acquired bacterial pneumonia (IV-to-PO regimen).
- As described herein, pharmacokinetic-pharmacodynamic (PK-PD) relationships for two cardiac endpoints, heart rate (HR) and systolic blood pressure (SBP), were evaluated using data for omadacycline-treated subjects enrolled in one Phase 1 and three Phase 3 studies.

METHODS

- Repeated measures multiple linear regression was used to evaluate factors predictive of HR and SBP, including various omadacycline exposure measures prior to each HR or SBP measurement, with interactions and covariates selected stepwise.
  - Different measures of omadacycline total-drug area under the concentration-time curve (AUC) and maximum concentration (C_{max}), with varying time windows prior to HR or SBP measurements, were assessed.
- Using final models, predicted percent probabilities of increases and decreases from baseline in HR or SBP at any time post-baseline and up to two days after end of therapy were calculated among analysis subjects for fixed post-baseline omadacycline exposures.
  - Assessments of HR and SBP endpoints across fixed post-baseline omadacycline exposures were also carried out among subsets of the analysis population defined by independent variables included in the final model or other clinically relevant variables.
- Using final models, predicted percent probabilities of HR or SBP endpoints were calculated for simulated subjects after the following omadacycline IV and IV-to-PO dosing regimens:
  - 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; and
  - 450 mg PO q24h on Days 1 and 2, followed by 300 mg PO q24h on Day 3.

RESULTS

Multivariable Model for HR

- The optimal model for HR based on data for 380 subjects included prior cumulative C_{max}.
  - Independent variables for which there was a statistically significant interaction with cumulative C_{max} included baseline atrial fibrillation, age, concomitant use of diltiazem, and time since first dose.
  - Independent variables not interacting with cumulative C_{max}, but which generally were associated with increased HR with statistical significance, included reduced baseline potassium < 3.5 mmol/L and status as a current smoker.

RESULTS

Multivariable Model for SBP

- The optimal model for SBP based on data for 380 subjects included prior 48-hour average AUC.
  - Independent variables for which there was a statistically significant interaction with prior 48-hour average AUC included concomitant spironolactone use, baseline history of coronary artery disease, and baseline history of heart failure.
  - Independent variables not interacting with prior 48-hour average AUC, but which generally were associated with increased SBP with statistical significance, included increased age, increased body mass index, concomitant diuretic use, baseline history of hypertension, male sex, and increased time since first dose.
- Given the presence of interactions in all the models, a single slope estimate that can describe the association between cumulative C_{max} and HR, or between prior 48-hour average AUC and SBP, could not be obtained.
- As shown in **Figure 1** and **Figure 2**, the model-predicted impact of omadacycline across fixed exposure measures on all HR or SBP endpoints was minimal.

Figure 1. Model-predicted percent probabilities of change in HR from baseline (A) and achieving HR thresholds (B) using a model based on cumulative C_{max} among all subjects across a range of omadacycline exposures

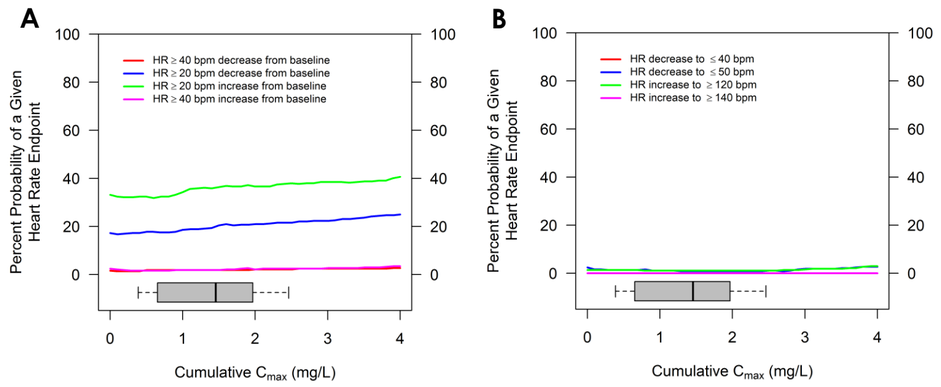
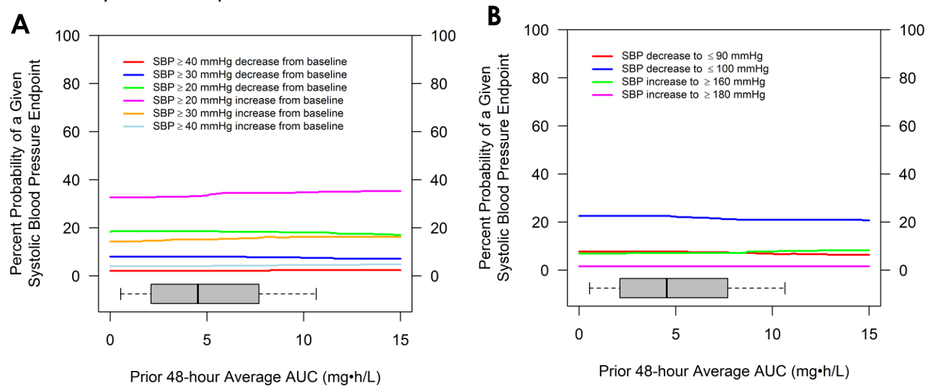


Figure 2. Model-predicted percent probabilities of change in SBP from baseline (A) and achieving SBP thresholds (B) using a model based on prior 48-hour average AUC among all subjects across a range of omadacycline exposures

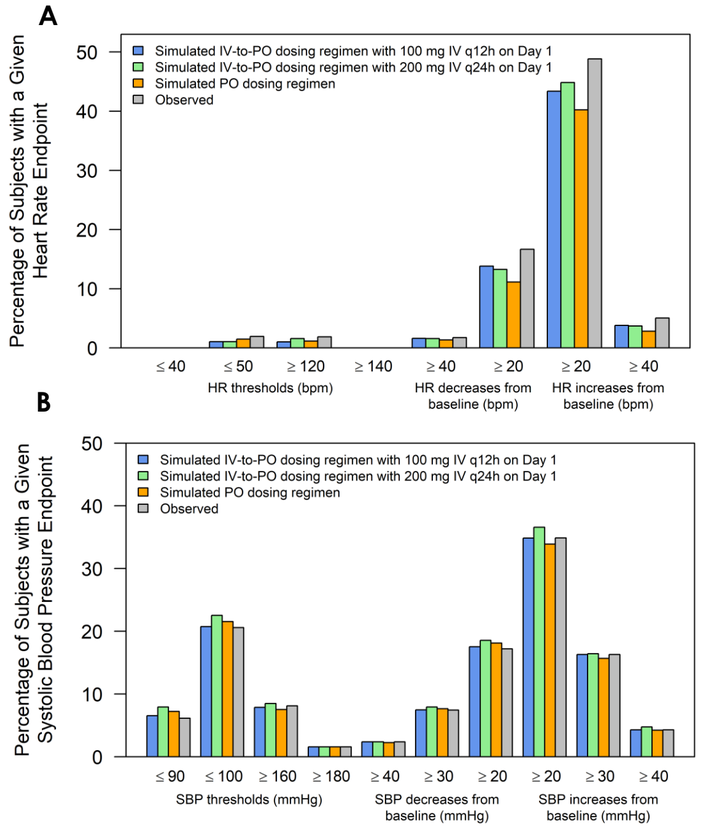


- Among all subjects, the estimated increases in percent probabilities of HR endpoints for the 90th percentile of cumulative C_{max} relative to zero C_{max} were ≤ 4.51%, and the estimated increases in percent probabilities of SBP endpoints for the 90th percentile of prior 48-hour average AUC relative to zero AUC were ≤ 2.12%.
- HR decreases of ≥ 20 beats per minute (bpm) and HR increases of ≥ 20 bpm were the only HR endpoints for which cumulative C_{max} fixed at the 90th percentile yielded a > 1% higher estimate of the event likelihood than zero exposure among any of the investigated subject subsets.
  - For these two endpoints, there was no increase in the estimated event percentage above 7.69% among all subject subsets with at least 20 subjects.

RESULTS

- For endpoints of SBP ≥ 160 mmHg and ≥ 30 mmHg increase in SBP from baseline, the estimated increases in events for the 90th percentile of prior 48-hour average AUC relative to zero exposure did not exceed 2.74 and 4.65%, respectively, among investigated subject subsets, except for the subset of 23 subjects with anemia.
  - For the 23 subjects with anemia, there was an 8.70% increase in the frequency of ≥ 30 mmHg increase in SBP from baseline but this represented only three additional subjects achieving the endpoint.
- Percent probabilities of HR and SBP endpoints were within 8.59 and 2.71%, respectively, when comparing simulated and observed subjects after omadacycline IV-to-PO and PO dosing regimens (**Figure 3A** and **Figure 3B**).

Figure 3. Percentage of HR (A) and SBP (B) endpoints among simulated and observed subjects after administration of omadacycline IV-to-PO and PO dosing regimens



CONCLUSIONS

- Relationships between each of HR and SBP and increases in omadacycline exposure were observed, although the magnitude and direction of relationships was dependent on other covariates through applicable interactions.
- Impacts of relationships on each of HR and SBP endpoints across the range of omadacycline exposure measures associated with recommended dosing regimens were minimal.

REFERENCES

1. Paratek Pharmaceuticals, Inc. NUZYRA (omadacycline)® package insert. Boston, MA; 2019.
2. Lakota EA *et al*. ASM Microbe 2018. Atlanta, GA. June 7-11, 2018. Poster No. Saturday-628.

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