• Data were fit using noncompartmental methods
• The following dose regimens were simulated using actual PK profiles

METHODS
Pharmacokinetics
• Pharmacokinetic (PK) data from two studies in healthy volunteers were used:
  – One study investigated IV OM administration (N = 20)
  – One investigated oral OM administration (N = 28)
• Extension PK sampling was performed (13) samples collected over 24 hours in each group
• Data were fit using noncompartmental methods
• Area under the concentration–time curve (AUC) was calculated using the linear trapezoidal rule
• PK profiles were simulated on Days 2, 5, and 10; and AUCs were calculated
• The following dose regimens were simulated using actual PK profiles from clinical studies:
  – IV load: 100 mg/kg IV on Day 1, followed by 100 mg/kg IV every 12 hours on Days 2-5
  – IV no load: 100 mg/kg IV on Days 1-5
  – Oral load: 450 mg q4h on Days 1 and 2, then 300 mg q4h on Days 3-5
  – Oral no load: 300 mg q8h on Days 1-5
• AUCs calculated for each subject were corrected for protein binding (97%); 17% free ALA, and subsequently used in all analyses
• 95% confidence intervals (CIs) generated around the mean PK profile were used in subsequent analysis to evaluate the PK/PD target attainment

RESULTS
• Microbiology
  – 2018 SENTRY surveillance program: OM daily minimum inhibitory concentration (MIC) data obtained for S. pneumoniae and S. aureus, tested against clinical isolates from in the United States and Europe, were used
  – Since OM activity is not impacted by classical tetacycline resistance mechanisms nor by resistance mechanisms to other classes of antibiotics (e.g., cefoxitin), MIC values were used for analysis
• Pharmacodynamics
  – The PK parameter associated with efficacy for OM is AUC/MIC
• Pharmacokinetics
  – AUC is calculated using the linear trapezoidal rule

RESULTS
• For S. pneumoniae, load and no-load regimens exceeded the states AUC and AUC/MIC thresholds at MIC50 and MIC90 (Table 3 and Fig. 4)
• For S. aureus, the AUC/MIC ratio threshold was exceeded for the load and no-load regimens on Days 2 and 5 (Table 3 and Fig. 4)
• However, both oral load and oral no-load regimens on Days 2 and 5 or exceeded the AUC/MIC threshold associated with clinical success identified from the Phase 3 ABOSS studies (12.5 µg*h/mL) with both MICs up to 0.25 µg/mL and MICs ≥0.50 µg/mL
• For S. aureus, AUC and AUC/MIC in the load and no-load regimens were essentially the same as those for loading dose, for both MIC (0.06 µg/mL) and MIC (0.50 µg/mL)

REFERENCES
6. Omadacycline (NUZYRA), Paratek Pharmaceuticals, Inc. Medical editorial assistance, funded by Paratek Pharmaceuticals, Inc. at the time of the reported research. This study was sponsored by Paratek Pharmaceuticals, Inc.

CONCLUSIONS
• OM exposure assessed as observed by AUC was lower early on in therapy (Day 2) for oral and IV regimens when a loading dose was not used. However, exposures on Day 5 were not different and thus were not impacted by the absence of a loading dose
• Despite lower exposures on Day 2 without a loading dose, omadacycline would be expected to meet or exceed PK/PD thresholds associated with success for both S. pneumoniae and S. aureus. The 1 log kill threshold was met or exceeded regardless of the use of a loading dose for S. aureus; however, for S. pneumoniae, the 1 log kill threshold was met or exceeded only at MICs ≥0.50 µg/mL

Figure 2. Correlation Between AUC/MIC and Clinical Success

Figure 3. MIC Distribution of Omadacycline vs. Susceptible Clinical Isolates Collected From United States and Europe (2018 Surveillance)