### INTRODUCTION
- Omadacycline, an aminomethylcycline structurally related to tetracycline agents, was approved by the US FDA [1] for the following indications:
  - Patients with acute bacterial skin and skin structure infections (intravenous [IV] to oral [PO]) and
  - Adult patients with community-acquired pneumonia (IV-to-PO).
- Tetracyclines have been associated with hepatic injury [2]. For omadacycline, elevations in ALT were only asymptomatic, transient, of low magnitude, resolved following the completion of therapy, and did not result in discontinuation.
- To better understand exposure-related concerns for omadacycline-associated (ALT) increase, pharmacokinetic-pharmacodynamic (PK/PD) relationship for ALT evaluation was conducted using data from omadacycline-treated patients enrolled in three Phase 3 studies (1-3).

### METHODS
- The final dataset for ALT included data from 327 omadacycline-treated patients evaluated in three clinical studies:
  - For the ABSSSI studies [3,4], patients received IV followed by PO doses for one study and PO doses for the second study, for the CAPB study [3], patients received IV followed by PO doses.
  - ABSSSI IV-to-PO Study (OASIS 1): Patients received omadacycline 100 mg every 12 hours (q12h) for 3 days, followed by 50 mg q12h for 7 days (q12h) with the option to continue to 10 days (q24h) after a minimum of 3 days of therapy, for a total duration of 7 to 14 days (q12h).
  - ABSSSI PO Study (OPTIC): Patients received amoxicillin 250 mg PO q6h for 2 doses, followed by 200 mg PO q8h for 2 days, for a total duration of 7 to 14 days.
  - CAPB Study (B3P): Patients received omadacycline 50 mg PO q12h for 2 doses, followed by 100 mg PO q24h for 6 to 14 days.
- Repeated measures multiple linear regression was used to evaluate factors predictive of ALT, including different omadacycline total-drug area under the concentration curve (AUC) measures prior to each ALT, with interactions and covariates selected stepwise.
- Using a final AICke Information Criterion-optimized model, predicted percent probabilities of ALT elevations in 1, 3, 5, 7, 10, and 15 days were estimated from the model.
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- Analyses of ALT elevation 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.

### RESULTS
- Using final models, predicted percent probabilities of achieving ALT elevations were calculated for simulated subjects after the following FDA-approved omadacycline IV and IV-PO dosing regimens: 100 mg IV at 72-hr following 100 mg IV q24h on Day 1, with a PO switch to 300 mg PO q24h on Day 2, followed by 300 mg PO q24h for 2 days.
- Predicted percent probabilities of ALT elevations among patients receiving 100 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 2, followed by 300 mg PO q24h for 2 days.
- Cumulative AUC measurements were estimated at the fixed post-baseline (5 days).

### CONCLUSIONS
- A statistically significant relationship between increase in ALT and increase in omadacycline for males in the presence of other factors was found.
- Increases in predicted ALT elevation endpoints across fixed omadacycline AUC values were observed among simulated patients after administration of omadacycline IV-PO and PO dosing regimens relative to observed patients, were minimal, and are unlikely to be clinically meaningful in omadacycline-treated patients.

### REFERENCES
- Pharamcokinetic-Pharmacodynamic Analyses for Alumina Aminofluranes Using Phase 3 Data From Omadacycline-Treated Patients.
- Pharmacokinetic-Pharmacodynamic Analyses for Alumina Aminofluranes Using Phase 3 Data From Omadacycline-Treated Patients.

### ACKNOWLEDGEMENTS
- Supported by Paratek Pharmaceuticals, Inc., King of Prussia, PA, USA.