Population Pharmacokinetics of Omadacycline Following Intravenous or Oral Administration to Phase 1 Subjects
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• Omadacycline, a novel aminomethylcycline synthesized by chemical modification of minocycline, is active against both Gram-positive and Gram-negative organisms.

Materials and Methods

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• Population Pharmacokinetic Analysis

• Both 2- and 3-compartment (CMT) models with zero-order input and first-order elimination were first evaluated using only IV data.

• The PK analysis population (N = 319) was 81.2% male and 75.2% Caucasian. The mean (SD) age was 32.8 (11.0) years, weight was 75.8 (10.9) kg, and CLcr was 107 (19.6) mL/min/1.73 m² and ranged from 52.8 to 185 mL/min/1.73 m².

Final Population Pharmacokinetic Model

• A 3-CMT model with zero-order IV input, or first-order oral absorption with 2 transit CMTs to provide delayed absorption, best characterized omadacycline PK (Figure 1 and Table 1).

• Observed plasma concentrations agreed well with the population (r²=0.74) and individual post-hoc (r²=0.96) predictions (Figure 2) and PC-VPCs (Figure 3) showed a reasonable fit by formulation.

• Non-renal CL was 5.72 L/hr, while renal CL was linearly related to CLcr (4.62 L/hr at the median of 109 mL/min/1.73 m²) for the range of renal function studied.

• Body size was not predictive of Vc (24.3 L) but steady-state volume of distribution (225 L) indicated extensive tissue distribution.

• Cirrhosis did not impact total CL, although Vc was 74.4% lower relative to healthy subjects.

• F was determined using absolute time of food consumption relative to dosing (AMTIME) via a Hill-type function which estimated F for consuming food exactly at dosing (Fmax) and the AMTIME at which Fmax decreased by 50% (AMTIME½).

• F was more sensitive to food consumption pre-dose (Figure 4: F was <3% when omadacycline was administered just prior to a meal and 27-30% when meals were restricted to 2-4 hours post-dose).

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• A PPK model including significant covariate effects for omadacycline was developed using Phase 1 data. This model provided the basis for recommending food consumption be restricted to at least 4 hours prior to or 2 hours after administration of an oral omadacycline dose.

• Although only a limited range of renal function has been studied to date, this PPK model will be further updated after including additional omadacycline PK from individuals with moderate or severe renal impairment and used to support dosing guidelines for renal impairment.