



# Omadacycline Oral Dosing and Pharmacokinetics in Community-Acquired Bacterial Pneumonia and Acute Bacterial Skin and Skin Structure Infection

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## Abstract

Omadacycline, a first-in-class aminomethylcycline antibiotic, is approved in the USA as intravenous (IV) and/or oral therapy for treatment of adults with community-acquired bacterial pneumonia (CABP) or acute bacterial skin and skin structure infections (ABSSSI). Phase 1 and 3 studies indicate that omadacycline dose adjustments are not required for any patient group based on age, sex, race, weight, renal impairment, end-stage renal disease, or hepatic impairment. Equivalency of exposure has also been demonstrated for 300 mg oral and 100 mg IV doses. Using an oral loading-dose regimen results in drug exposures exceeding established efficacy targets against the most common CABP and ABSSSI pathogens by Day 2 of treatment, and omadacycline has demonstrated clinical efficacy and is well tolerated. The oral-only dosing regimens provide the potential for treatment of CABP and ABSSSI either within a hospital setting or in the community, which could support earlier hospital discharge and reduced treatment costs.

## Key Points

Clinical studies of omadacycline indicate that no dose adjustments are needed for any particular group of patients, including those with renal or hepatic impairment.

By the second day of treatment, levels of omadacycline were above efficacy targets needed for bacterial load reduction or stasis for common bacterial pathogens causing community-acquired bacterial pneumonia (CABP; e.g., *Streptococcus pneumoniae*) and acute bacterial skin and skin structure infections (ABSSSI; e.g., *Staphylococcus aureus*).

The oral-only formulation of omadacycline allows the treatment of CABP and ABSSSI in the community, potentially reducing hospital admissions, hospital stays, and associated costs.

## 1 Introduction

Omadacycline is a first-in-class aminomethylcycline antibiotic, approved in the USA for the treatment of adults with community-acquired bacterial pneumonia (CABP) [1] or acute bacterial skin and skin structure infections (ABSSSI) [2, 3]. Studies demonstrate that omadacycline treatment does not require dose adjustment for any patient population [4–6]. Omadacycline treatment for CABP and ABSSSI uses different oral loading dose regimens, so there is a need for clarity regarding these different regimens. This short communication aims to provide background on variations in the oral loading dose for omadacycline, expanding on information in the prescribing information [7]. The article also discusses outcomes from pharmacokinetic and Phase 3 registrational studies investigating omadacycline for CABP and ABSSSI.

## 2 Background on Omadacycline Oral Regimens

Omadacycline is currently approved by the US Food and Drug Administration (FDA) for the treatment of CABP and ABSSSI in adults. Preclinical and clinical data support both indications for intravenous (IV)-to-oral or oral-only dosing regimens [7]. The oral-only dosing regimens include the recent extension to the CABP indication (Table 1).

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**Table 1** Omadacycline dosing regimens for adult patients with CABP or ABSSSI [7]

Infection	Mode of administration	Loading dose	Maintenance dose
CABP	IV	Day 1: 200 mg over 60 min, or 100 mg over 30 min bid	100 mg over 30 min qd
	Oral	Day 1: 300 mg bid	300 mg qd
ABSSSI	IV	Day 1: 200 mg over 60 min, or 100 mg over 30 min bid	100 mg over 30 min qd
	Oral	Days 1 and 2: 450 mg qd	300 mg qd

ABSSSI acute bacterial skin and skin structure infection, *bid* twice daily, CABP community-acquired bacterial pneumonia, IV intravenous, *qd* once daily

Oral antibiotic options can decrease the need for patients to undergo hospitalization and IV therapy, shorten hospital stays, and therefore decrease the overall economic burden of their infectious disease [8, 9]. Omadacycline loading doses vary by indication, as a result of the study designs used to generate data. The ABSSSI oral loading-dose regimen of 450 mg daily on Days 1 and 2 was FDA approved based on safety and efficacy from a Phase 3 registrational study in patients with ABSSSI, while the CABP loading-dose regimen (300 mg twice on Day 1) was approved based on a pharmacokinetic study demonstrating bioequivalence between IV and oral dosing for patients with CABP [10].

The recently completed oral-only pharmacokinetic study of omadacycline in patients with CABP (ClinicalTrials.gov identifier NCT04160260) supported the FDA's recent approval of oral-only omadacycline therapy for CABP. This study included 18 participants (in total and in the safety population) who received omadacycline; 14 were included in the pharmacokinetic population after excluding two patients with emesis and two with outlying pharmacokinetic values. All participants received a loading dose of omadacycline (300 mg orally twice on Day 1), followed by maintenance treatment of 300 mg orally once daily (qd), for a total treatment duration of 7–10 days [10]. The loading dose was selected to closely match the reference IV regimen for bioequivalence: 100 mg IV given twice on Day 1, the FDA-approved IV loading dose for both CABP and ABSSSI [1, 2, 7, 10, 11].

Using the Day 1 plasma concentration profile of 100 mg IV dosing, twice-daily (bid) dosing on Day 1 and qd dosing on Day 2 was simulated using the superposition principle.

The analysis showed that oral omadacycline 300 mg provided 100.8% of the total exposure, as measured by area under the concentration-time curve (AUC), achieved with omadacycline 100 mg IV (log geometric mean ratio of  $AUC_{0-24}$ : 100.8% [90% confidence interval (CI) 88.0–115.5; Table 2]) [10]. All study participants achieved clinical success for overall clinical response. Furthermore, omadacycline was safe and well tolerated by all participants. Consistent with the established safety profile for omadacycline, the most frequent treatment-emergent adverse events (TEAEs), nausea and vomiting, were mild to moderate in nature, and were not treatment limiting [10]. The study was terminated early because of the COVID-19 pandemic and, therefore, achieved lower enrollment than expected. Results of this study supported the expanded FDA label to include an oral-only regimen for CABP.

### 3 Pharmacokinetics of Omadacycline

Pharmacokinetics of omadacycline include peak concentrations ( $C_{max}$ ) that increase proportionally to dose administered, over a certain range ( $C_{max}$  ranges from 548 ng/mL after a single oral dose of 300 mg omadacycline to 1077 ng/mL at steady state [Day 5] of 450 mg qd) [7]. Regardless of the omadacycline dose (300 or 450 mg orally), the median time to maximum plasma concentration ( $T_{max}$ ) is 2.5–3.0 h [11] and the half-life is 15.5–16.8 h [12–14]. Omadacycline absorption is rapid, with peak radioactivity between 1 and 4 h in plasma or blood. Steady-state AUC with 300 mg oral omadacycline is 11,156 ng × h/mL. Omadacycline exhibits high clearance ( $CL/F$ , 34.6 L/h for a single dose of 300 mg oral omadacycline) and volume of distribution ( $V_z/F$  794 L for a single dose of 300 mg oral omadacycline), with no plasma metabolites [7]. Previous studies have shown that there was no significant interaction of omadacycline with a broad range of membrane transporters, suggesting that drug–drug interactions based on the inhibition or induction of human drug transporter activity are unlikely with omadacycline when given at therapeutic concentrations [7, 14]. The bioavailability of oral omadacycline is 34.5%; omadacycline is not metabolized, and oral omadacycline is primarily eliminated in the feces [4, 7, 11, 15]. Previous Phase 1 and Phase 3 studies of omadacycline showed that no dose adjustments are necessary for any patient group, such as people with hepatic or renal impairment, including end-stage renal disease (ESRD) and those receiving dialysis [4, 6, 13]; dose adjustments are also unnecessary by body mass index [13, 16, 17] or older age [1].

General pharmacokinetic principles suggest that drug concentrations reach steady state within 4–5 half-lives. Given that the half-life for omadacycline is ~ 16 h, one may estimate that, without a loading dose, steady state would be

**Table 2** Simulated plasma pharmacokinetic parameters of omadacycline 300 mg oral loading dose followed by 300 mg oral daily versus reference regimen 100 mg IV twice on Day 1, followed by 100 mg IV daily

	Loading dose (Day 1): 300 mg bid Maintenance dose: 300 mg qd		Reference regimen: loading dose (Day 1): 100 mg IV bid Maintenance dose: 100 mg IV qd	
	Day 1	Day 2	Day 1	Day 2
Total AUC <sub>0-24</sub> , ng × h/mL <sup>a</sup>	10.9 (2.8)	9.0 (2.4)	10.7 (2.0)	11.2 (2.4)
Free AUC <sub>0-24</sub> , ng × h/mL <sup>a</sup>	8.8 (2.2)	7.2 (1.9)	8.5 (1.6)	9.0 (1.9)

Data are presented as geometric mean (SD)

Using the superposition principle, the omadacycline concentration data of a single 300 mg oral dose on Day 1 for 26 healthy subjects (from Phase 1 study [12]) was used to develop the concentration profiles and evaluate the AUC<sub>0-24</sub> of the omadacycline oral dosing regimen (bid on Day 1 followed by qd on Day 2) for each day and each subject. Then the PK parameters ( $C_{max}$ ,  $T_{max}$ , and AUC<sub>0-24</sub>) were summarized. Similarly the omadacycline concentration data of a single 100 mg IV dose on Day 1 for 63 subjects (from six Phase 1 studies [7]) were used to develop the concentration profiles and evaluate the AUC<sub>0-24</sub> of the omadacycline IV dosing regimen (bid on Day 1 followed by qd on Day 2) for each day and each subject

AUC<sub>0-24</sub> area under the plasma concentration–time curve from time 0 to 24 h after dosing, *bid* twice daily,  $C_{max}$  maximum serum concentration, *IV* intravenous, *PK* pharmacokinetic, *qd* once daily, *SD* standard deviation,  $T_{max}$  time of maximum serum concentration

<sup>a</sup>Total and free AUC are similar, as protein binding of omadacycline is ~ 20%

achieved on Days 3–4 [13]. In an effort to achieve therapeutic concentration by Day 2, loading doses of omadacycline were utilized in the clinical development program.

#### 4 Pharmacodynamics of Omadacycline

The pharmacodynamic measurement most associated with the antibacterial effect of omadacycline is total exposure (time × concentration) above the minimum inhibitory concentration (MIC) for the bacteria [7, 13, 18]. Omadacycline oral-only dosing can achieve and exceed the necessary exposure needed for common pathogens in CABP and ABSSSI regardless of the loading-dose regimen used [19–21] (Tables 2 and 3). The dose justification for omadacycline is supported by a robust population pharmacokinetic model developed using data obtained throughout the omadacycline clinical development program and incorporates key pathogens' MIC distributions from surveillance studies [22], non-clinical exposure targets for efficacy [23, 24], and clinical outcomes from patients [19, 20]. For example, given MIC<sub>90</sub> values of 0.12 and 0.25 mg/L for omadacycline

**Table 3** Simulated plasma pharmacokinetic parameters of omadacycline 450 mg oral loading dose followed by 300 mg oral daily versus reference regimen 100 mg IV twice on Day 1, followed by 100 mg IV daily

	Loading dose (Days 1, 2): 450 mg qd Maintenance dose: 300 mg qd		Reference regimen: loading dose (Day 1): 100 mg IV bid Maintenance dose: 100 mg IV qd	
	Day 1	Day 2	Day 1	Day 2
Total AUC <sub>0-24</sub> , ng × h/mL <sup>a</sup>	12.1 (3.2)	12.5 (3.3)	10.7 (2.0)	11.2 (2.4)
Free AUC <sub>0-24</sub> , ng × h/mL <sup>a</sup>	9.7 (2.5)	10.0 (2.6)	8.5 (1.6)	9.0 (1.9)

Data are presented as geometric mean (SD)

Using the superposition principle, the omadacycline concentration data of a single 450 mg oral dose on Day 1 for 24 healthy subjects (from Phase 1 study [12]) was used to evaluate the AUC<sub>0-24</sub> of the omadacycline oral dosing regimen 450 mg (qd on Days 1 and 2) for each day and each subject. Similarly the omadacycline concentration data of a single 100 mg IV dose on Day 1 for 63 subjects (from six Phase 1 studies [7]) were used to develop the concentration profiles and evaluate the AUC<sub>0-24</sub> of the omadacycline IV dosing regimen (bid on Day 1 followed by qd on Day 2) for each day and each subject AUC<sub>0-24</sub> area under the plasma concentration–time curve from time 0 to 24 h after dosing, *bid* twice daily,  $C_{max}$  maximum serum concentration, *IV* intravenous, *PK* pharmacokinetic, *qd* once daily, *SD* standard deviation,  $T_{max}$  time of maximum serum concentration

<sup>a</sup>Total and free AUC are similar, as protein binding of omadacycline is ~ 20%

against *Streptococcus pneumoniae* and *Staphylococcus aureus*, respectively, including drug-resistant strains, the omadacycline exposure achieved with an approved oral-only regimen (AUC<sub>0-24h</sub> ~ 11,000 ng × h/mL) would exceed established efficacy targets (*S. pneumoniae*: median target for 1-log<sub>10</sub> reduction = 17.4; *S. aureus*: median target for stasis = 21.9) [22–24]. The favorable pharmacodynamic parameters combined with the low MIC<sub>90</sub> values of bacteria that commonly cause CABP and ABSSSI make target concentrations of omadacycline easily achievable when using it to treat patients, whether it is given orally or IV.

#### 5 Omadacycline Oral Loading Dose Exposures (AUC) Profiles

As shown in Tables 2 and 3, either loading-dose regimen provides similar exposure to the reference IV loading dose used in the Phase 3 registration trials for CABP and ABSSSI [1–3, 7, 10]. The most common TEAEs across Phase 3 clinical trials were nausea and vomiting. These most frequently occurred when patients received 450 mg orally, and resolved or were seen at similar rates to comparators when patients transitioned to a 300 mg maintenance dose [2, 3, 25].

A notable difference between the two oral loading-dose regimens is the need to fast twice on Day 1 when 300 mg bid is utilized, versus fasting once when 450 mg qd is administered (fasting, per label instructions, is defined as no food or drink [except for water] for 4 h before and 2 h after oral dosing).

## 6 Clinical Relevance

The clinical results from Phase 3 studies of omadacycline bore out the expectations, based on pharmacokinetic and pharmacodynamic data for omadacycline, in treating both CABP and ABSSSI. Clinical efficacy (investigator-assessed clinical response at post-treatment evaluation) was 87.6% for omadacycline versus 85.1% for moxifloxacin in CABP ( $p = \text{NS}$ ) [1], 86.1% for omadacycline versus 83.6% for linezolid in one study of ABSSSI ( $p = \text{NS}$ ) [2], and 84.2% for omadacycline versus 80.8% for linezolid in a second study of ABSSSI ( $p = \text{NS}$ ) [3].

## 7 Conclusions

The results of several Phase 1 and Phase 3 studies indicate that omadacycline treatment met the expectations in treating both CABP and ABSSSI, with omadacycline demonstrating more than 80% clinical efficacy in all Phase 3 studies. Furthermore, omadacycline does not require any dose adjustments for patients based on age, sex, race, weight, renal impairment, ESRD, or hepatic impairment. In all three Phase 3 studies, adverse events seen with omadacycline were generally tolerable, and similar in frequency and severity to those seen with comparator antibiotics. Additionally, the available oral loading-dose regimens provide drug exposures by Day 2 that exceed established efficacy targets for the most common pathogens for CABP and ABSSSI and are efficacious and well tolerated [25]. The availability of an efficacious oral-only antibiotic for CABP and ABSSSI provides an additional therapeutic option, regardless of whether a patient needs to be treated in a hospital or in the community. This could also facilitate IV-to-oral transition, potentially enabling outpatient therapy or earlier hospital discharge, thus reducing hospitalization and overall costs [8, 26].

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