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Original Research

Safety and efficacy of omadacycline by body mass index in patients with community-acquired bacterial pneumonia: Subanalysis from a randomized controlled trial

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ABSTRACT

Objectives: To examine the safety and efficacy of omadacycline by body mass index (BMI) in adults with community-acquired bacterial pneumonia (CABP) from a Phase III trial.
Methods: Patients hospitalized for suspected CABP were randomized 1:1 to receive intravenous omadacycline or moxifloxacin, with an optional transition to oral, for a total of 7–14 days. Early clinical response (ECR) was assessed 72–120 h after receipt of the first dose, and clinical success was assessed 5–10 days after the last dose (post-treatment evaluation [PTE]). ECR was defined as improvement in at least two CABP symptoms with no worsening of other symptoms or use of rescue antibacterial treatment; success at PTE was defined as resolution of signs and symptoms to the extent that further antibacterial therapy was unnecessary. Safety evaluations included treatment-emergent adverse events and laboratory measures. Between-treatment comparisons were made by World Health Organization BMI categories and by diabetes history.
Results: Distribution of patients in the normal weight, overweight, and obese subgroups was fairly even. Clinical success for omadacycline-treated patients at ECR were similar across ascending BMI groups (OMC: 82.9%, 80.5%, 76.9%; MOX: 88.6%, 80.7%, 76.9%). Outcomes by diabetes status were generally similar in omadacycline- and moxifloxacin-treated patients. Patients who had clinical success or clinical stability at ECR generally showed continued clinical success at PTE. Safety profiles for omadacycline and moxifloxacin were largely similar across BMI subgroups and by diabetes history.
Conclusion: The omadacycline fixed-dosing strategy showed consistent safety and efficacy in patients with CABP of different body sizes.

1. Introduction

Recent estimates from the United States show an age-adjusted prevalence of obesity (body mass index [BMI] $\geq$30 kg/m^2) in adults of 42.4% [1]. Severe obesity (BMI $\geq$40 kg/m^2) occurs in 9.2% of the US adult population. Over the past two decades, there has been a significant upward trend in obesity and severe obesity.

While obesity confers additional risks in some diseases, it presents an interesting paradox in community-acquired pneumonia (CAP). A recent meta-analysis of six randomized controlled trials in community-acquired bacterial pneumonia (CABP), which included 4645 patients in total, demonstrated that obesity was associated with late endpoint success among early endpoint responders [2]. Individuals who had a late failure after an early endpoint response were less likely to be obese.

Other studies have noted a similar association between elevated BMI and more favorable outcomes. A retrospective, single-center study of 266 adults hospitalized for CAP reported decreasing 30-day mortality (odds ratio [OR]: 0.88; 95% confidence interval [CI]: 0.81 to 0.96) with increasing BMI values [3]. From a prospective study of over 1000 patients hospitalized for CAP, patients with obesity had significantly reduced odds of 30-day mortality (OR: 0.53; 95% CI: 0.29 to 0.98) compared to those without obesity [4].

These prior analyses yield intriguing findings but rely on pooled data from multiple antimicrobial drug classes. Whether or not these positive outcomes in patients with obesity are dependent on the antimicrobial is

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Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CABP	community-acquired bacterial pneumonia
CAP	community-acquired pneumonia
CE	clinically evaluable
CI	confidence interval
ECR	early clinical response
ITT	intent-to-treat
IV	intravenous
Micro-ITT	microbiologic intent-to-treat
MOX	moxifloxacin
MSSA	methicillin-susceptible *Staphylococcus aureus*
OMC	omadacycline
OPTIC	Omadacycline for Pneumonia Treatment In the Community study
OR	odds ratio
PSSP	penicillin-susceptible *Streptococcus pneumoniae*
PTE	post-treatment evaluation
q12	every 12 h
q24	every 24 h
SD	standard deviation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

one question that remains unanswered. In theory, inadequate systemic antimicrobial exposures could occur in patients with obesity who are treated with a fixed dose (ie, not adjusted for body size), and could negatively affect outcomes [5]. Omadacycline and moxifloxacin are administered at a fixed dose in adults, without regard to body weight. In a Phase III clinical trial involving adults with CABP (Omadacycline for Pneumonia Treatment In the Community [OPTIC] study), omadacycline was non-inferior to moxifloxacin; it also demonstrated a similar safety profile to moxifloxacin [6]. Here, we examine the safety and efficacy of omadacycline and moxifloxacin by BMI categories in adult patients with CABP from the OPTIC trial, in order to examine the appropriateness of a fixed omadacycline dose in these patients, and to further investigate the "obesity paradox."

2. Methods

The full study design and methods have been published previously [6]. Briefly, OPTIC was a randomized (1:1), double-blind, active comparator-controlled, Phase III study comparing omadacycline with moxifloxacin for the treatment of adults with CABP. Patients were initiated on intravenous (IV) omadacycline (100 mg IV every 12 h for two doses, then 100 mg IV every 24 h [q24 h] for 2 days), or moxifloxacin (400 mg IV q24 h), with the option to transition to oral formulations (omadacycline, 300 mg q24 h; moxifloxacin, 400 mg q24 h) after Day 3 if there was evidence of clinical improvement. Treatment continued for a total of 7–14 days.

The primary efficacy endpoint was early clinical response (ECR), assessed 72–120 h after receipt of the first dose, defined as survival and an improvement in at least two CABP symptoms with no worsening of other symptoms or use of rescue antibacterial treatment. The co-primary efficacy endpoint was clinical success assessed 5–10 days after the last dose of study drug (post-treatment evaluation; PTE). Success at PTE was defined as survival and resolution of signs and symptoms to the extent that further antibacterial therapy was not necessary. Clinical stability was defined as achieving all of the following criteria: (i) temperature $\leq$37.8 °C (100 °F); (ii) heart rate $\leq$100 beats/minute; (iii) respiratory rate $\leq$24 breaths/minute; (iv) systolic blood pressure $\geq$90 mmHg; and (v) arterial oxygen saturation $\geq$90% or partial pressure of oxygen $\geq$60 mmHg while breathing room air. Safety was assessed on the basis of adverse events, vital signs, electrocardiogram findings, and standard clinical laboratory tests through 30–37 days after the first dose of study drug (laboratory tests were conducted at baseline; at Days 4, 7, and 10; and at end of therapy [Days 7–14], PTE [Days 12–24], and final follow-up [Days 30–37]).

The analysis population for both primary efficacy endpoints was the intent-to-treat (ITT) population (all randomized patients). Additionally, clinical success at PTE was assessed in the clinically evaluable (CE) population (all ITT patients who received study drug, had CABP, an assessment of outcome, and met all other evaluability criteria detailed in the Statistical Analysis Plan) [6]. The microbiologic ITT (micro-ITT) population included all randomized patients who had at least one causative bacterial pathogen identified at baseline from culture of a respiratory specimen or blood, or via a culture-independent method (urinary antigen test, serological test).

Efficacy and safety analyses were conducted by BMI subgroup. Patients were classified according to World Health Organization BMI categories: underweight, BMI <18.5 kg/m^2; normal weight, BMI 18.5 kg/m^2 to <25 kg/m^2; overweight, BMI 25 kg/m^2 to <30 kg/m^2; obese, BMI $\geq$30 kg/m^2; obese class I, 30 kg/m^2 to <35 kg/m^2; obese class II, 35 kg/m^2 to <40 kg/m^2; obese class III, BMI $\geq$40 kg/m^2.

A logistic regression analysis was performed, with covariates of BMI at baseline, treatment arm, and the interaction between BMI and treatment. A tipping point analysis was conducted for clinical success at ECR and PTE, to determine if there was a threshold of body weight at which there was a statistically different efficacy outcome; body weight was selected as the model variable as BMI had a slightly skewed distribution due to very few patients in the underweight category. The objective of the tipping point analysis was to find the assumption at which conclusions change from favorable for treatment (clinical success) to unfavorable for treatment (clinical failure). This analysis provided probabilities for the assumption that the treatment may switch from a favorable to an unfavorable outcome at a certain baseline weight. The analysis was conducted for patients with body weights between 50 kg and 110 kg (the 5th percentile and 95th percentile, respectively, for the entire study population).

3. Results

Demographic and baseline clinical characteristics are shown in Table 1. Approximately two-thirds of patients included in OPTIC were overweight (omadacycline, 34.3%; moxifloxacin, 34.8%) or obese (omadacycline, 27.2%; moxifloxacin, 27.8%). A small minority of patients were classified as underweight (14/770 [1.8%]); due to the small size of this group, the data were not plotted in the graphical presentations of efficacy and safety by BMI subgroup.

Baseline diabetes, heart disease, and hypertension prevalence increased with increasing BMI. Diabetes was present in 7.6%, 17.3%, and 31.1% of normal weight, overweight, and obese patients, respectively. Hypertension was present in 35.3%, 50.8%, and 70.3% of normal weight, overweight, and obese patients, respectively.

Baseline pathogens were generally similar in normal weight, overweight, and obese patients, with the most common being *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Haemophilus influenzae* (Table 2). Patients in normal weight and overweight groups had more *H. influenzae* than similar moxifloxacin patients in the same weight categories.

Clinical success rates at ECR (Fig. 1) and PTE (Fig. 2) were similar across the treatment groups, with no effect of increasing BMI on clinical

Table 1
Demographics and baseline characteristics (safety population).

	Normal weight		Overweight		Obese	
	OMC (n = 138)	MOX (n = 140)	OMC (n = 131)	MOX (n = 135)	OMC (n = 104)	MOX (n = 108)
Age, years; mean (SD)	57.4 (15.5)	59.7 (18.2)	63.7 (14.9)	64.3 (13.5)	62.3 (14.2)	62.8 (12.3)
Male, n (%)	72 (52.2)	78 (55.7)	78 (59.5)	81 (60.0)	48 (46.2)	58 (53.7)
Race, n (%)						
White	123 (89.1)	124 (88.6)	124 (94.7)	130 (96.3)	98 (94.2)	100 (92.6)
BMI, kg/m^2; mean (SD)	22.3 (1.7)	22.4 (1.9)	27.3 (1.4)	27.2 (1.4)	34.7 (4.4)	34.7 (4.6)
Body weight, kg; mean (min, max)	63.2 (38.7, 93.0)	63.9 (45.0, 96.8)	79.5 (56.1, 112.0)	79.1 (55.0, 103.0)	96.8 (58.5, 147.0)	96.6 (58.0, 145.2)
Medical history, n (%)						
Diabetes	9 (6.5)	12 (8.6)	20 (15.3)	26 (19.3)	33 (31.7)	33 (30.6)
Heart disease[a]	17 (12.3)	24 (17.1)	41 (31.3)	35 (25.9)	40 (38.5)	37 (34.3)
Hypertension	45 (32.6)	53 (37.9)	69 (52.7)	66 (48.9)	74 (71.2)	75 (69.4)
Liver disease[a]	2 (1.4)	2 (1.4)	2 (1.5)	3 (2.2)	4 (3.8)	5 (4.6)
Asthma/ COPD	29 (21.0)	30 (21.4)	24 (18.3)	25 (18.5)	28 (26.9)	19 (17.6)
Creatinine clearance, n (%)[b]						
>89 mL/min	65 (47.1)	63 (45.0)	67 (51.1)	70 (51.9)	67 (64.4)	73 (67.6)
60–89 mL/ min	37 (26.8)	39 (27.9)	36 (27.5)	44 (32.6)	19 (18.3)	18 (16.7)
30–59 mL/ min	36 (26.1)	38 (27.1)	28 (21.4)	21 (15.6)	18 (17.3)	17 (15.7)
PORT risk class (actual)						
I (0 ≤ PORT score ≤ 50)	0	2 (1.4)	2 (1.5)	0	0	0
II (51 ≤ PORT score ≤ 70)[c]	22 (15.9)	18 (12.9)	16 (12.2)	21 (15.6)	16 (15.4)	15 (13.9)
III (71 ≤ PORT score ≤ 90)	83 (60.1)	76 (54.3)	75 (57.3)	72 (53.3)	61 (58.7)	63 (58.3)
IV (91 ≤ PORT score ≤ 130)	33 (23.9)	44 (31.4)	38 (29.0)	41 (30.4)	27 (26.0)	30 (27.8)
V (PORT score ≥ 131)	0	0	0	1 (0.7)	0	0

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ITT, intent-to-treat; MOX, moxifloxacin; OMC, omadacycline; PORT, Pneumonia Outcomes Research Team; SD, standard deviation.

[a] Heart disease was defined as coronary artery disorders, coronary artery bypass, coronary angioplasty, percutaneous coronary intervention, cardiomegaly, cardiomyopathy, congestive cardiomyopathy, cytotoxic cardiomyopathy, hypertensive cardiomyopathy, hypertensive heart disease, ischemic cardiomyopathy, left ventricular failure, left ventricular hypertrophy, or myocardial fibrosis. Liver disease was defined as alcoholic liver disease, hepatitis B infection (acute or chronic), hepatitis C infection (acute or chronic), hepatic steatosis, hepatic cirrhosis, hepatic failure, or non-alcoholic steatohepatitis. Patients with end-state liver disease (eg, ascites, hepatic encephalopathy), alanine aminotransferase, or aspartate aminotransferase ≥2 × upper limit of normal, or total bilirubin >1.5 × upper limit of normal, were excluded from the trial.

[b] Creatinine clearance was estimated using the Cockcroft–Gault equation. Patients with severe baseline renal impairment (CrCl <30 mL/min) were excluded from the trial.

[c] PORT risk class II was capped at 15% of total population by protocol design.

Table 2
Baseline pathogens found in ≥5% of any subgroup of omadacycline-treated participants (micro-ITT population).

	Normal weight		Overweight		Obese	
n (%)	OMC (n = 69)	MOX (n = 69)	OMC (n = 71)	MOX (n = 61)	OMC (n = 58)	MOX (n = 48)
Gram-positive aerobes	21 (30.4)	21 (30.4)	22 (31.0)	16 (26.2)	17 (29.3)	16 (33.3)
Streptococcus pneumoniae	17 (24.6)	12 (17.4)	13 (18.3)	10 (16.4)	12 (20.7)	12 (25.0)
PSSP	10 (14.5)	8 (11.6)	9 (12.7)	7 (11.5)	7 (12.1)	7 (14.6)
Macrolide-resistant	3 (4.3)	2 (2.9)	3 (4.2)	2 (3.3)	4 (6.9)	1 (2.1)
Staphylococcus aureus (MSSA)	1 (1.4)	5 (7.2)	7 (9.9)	2 (3.3)	3 (5.2)	3 (6.3)
Gram-negative aerobes	28 (40.6)	27 (39.1)	29 (40.8)	19 (31.1)	20 (34.5)	22 (45.8)
Haemophilus influenzae	13 (18.8)	4 (5.8)	13 (18.3)	5 (8.2)	6 (10.3)	6 (12.5)
Haemophilus parainfluenzae	6 (8.7)	6 (8.7)	6 (8.5)	3 (4.9)	6 (10.3)	8 (16.7)
Klebsiella pneumoniae	7 (10.1)	6 (8.7)	2 (2.8)	3 (4.9)	3 (5.2)	4 (8.3)
Atypical pathogens	39 (56.5)	40 (58.0)	42 (59.2)	40 (65.6)	32 (55.2)	24 (50.0)
Mycoplasma pneumoniae	25 (36.2)	26 (37.7)	20 (28.2)	18 (29.5)	21 (36.2)	11 (22.9)
Legionella pneumophila	14 (20.3)	14 (20.3)	15 (21.1)	15 (24.6)	7 (12.1)	8 (16.7)
Chlamydophila pneumoniae	7 (10.1)	7 (10.1)	12 (16.9)	14 (23.0)	8 (13.8)	7 (14.6)

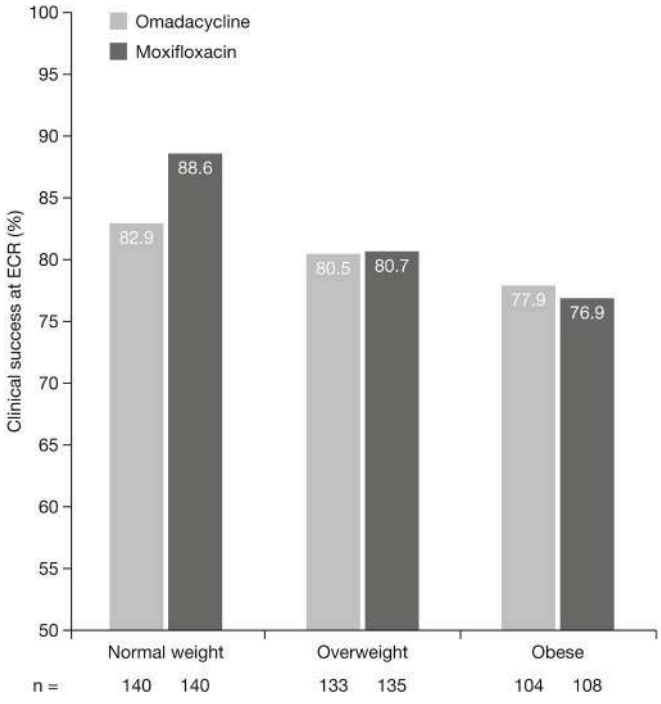
micro-ITT, microbiologic intent-to-treat; MOX, moxifloxacin; MSSA, methicillin-susceptible *Staphylococcus aureus*; OMC, omadacycline; PSSP, penicillin-susceptible *Streptococcus pneumoniae*.

success of omadacycline (Table 3). In the underweight population, clinical success at ECR was 100% for the omadacycline (9/9) and moxifloxacin (5/5) treatment arms. Likewise, clinical success at PTE in the underweight group was 100% for omadacycline-treated patients for both the ITT and CE analysis populations. Clinical success at PTE for moxifloxacin-treated patients was 80.0% (4/5; both ITT and CE populations).

The tipping point analysis by body weight did not reveal a body weight at which a statistically significant difference was found in clinical success at ECR or PTE, though there was a slight downward trend for omadacycline-treated patients at PTE (Fig. 3). From the logistic regression of clinical success at ECR and PTE, respectively, there was no significant effect of BMI (0.04 [95% CI: −0.005 to 0.09]; 0.01 [95% CI: −0.05 to 0.07]), treatment (−0.63 [95% CI: −2.65 to 1.37]; 0.40 [95% CI: −1.93 to 2.74]), or the interaction (BMI*Treatment; 0.2 [95% CI: −0.05 to 0.09]; −0.004 [95% CI: −0.09 to 0.08]) on clinical outcomes.

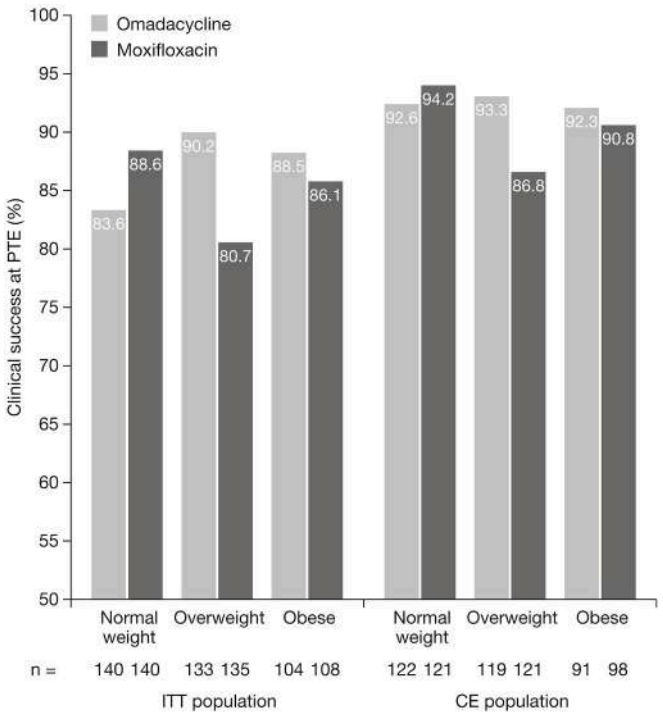
In patients with diabetes, clinical success was statistically similar between omadacycline and moxifloxacin treatment arms for all endpoints and BMI groups, except for ECR in the overweight group (treatment difference −27.3 [95% CI: −50.8, −4.1]) (Fig. 4), though the sample size was small and the upper bound of the 95% CI interval was close to 0. For patients in the overweight group with diabetes, a significant treatment difference was no longer observed at PTE due to patients who had clinical failure at ECR who then met clinical success criteria at PTE.

Clinical success at ECR generally resulted in clinical success at PTE for omadacycline- and moxifloxacin-treated patients (Table 4). In the omadacycline treatment arm, ≥92% of patients in each BMI subgroup who demonstrated clinical success at ECR went on to maintain clinical success at PTE. Similar findings were seen with moxifloxacin. Clinical failure at PTE after clinical success at ECR occurred in ≤5.2% of



Clinical success at ECR, ITT population (%)	Omadacycline (N = 104)	Moxifloxacin (N = 108)
Obese class I	50/64 (78.1)	56/70 (80.0)
Obese class II	21/25 (84.0)	18/26 (69.2)
Obese class III	10/15 (66.7)	9/12 (75.0)

Fig. 1. Clinical success at early clinical response. Clinical success was consistent across BMI subgroups in patients treated with omadacycline, and was comparable to outcomes for those receiving moxifloxacin (ITT population). The table shows outcomes by subclasses of the obese group: obese class I (BMI 30–34.9 kg/m^2), obese class II (BMI 35–39.9 kg/m^2), and obese class III (BMI ≥40 kg/m^2). BMI, body mass index; ECR, early clinical response; ITT, intent-to-treat.



Clinical success at PTE (%)	ITT population		CE population	
	Omadacycline (N = 104)	Moxifloxacin (N = 108)	Omadacycline (N = 91)	Moxifloxacin (N = 98)
Obese class I	58/64 (90.6)	61/70 (87.1)	51/56 (91.1)	59/66 (89.4)
Obese class II	22/25 (88.0)	22/26 (84.6)	22/22 (100)	20/20 (100)
Obese class III	12/15 (80.0)	10/12 (83.3)	11/13 (84.6)	10/12 (83.3)

Fig. 2. Clinical success at post-treatment evaluation (PTE). Clinical success at PTE was similar across BMI subgroups in both the ITT and CE populations of the omadacycline treatment arm. The table shows outcomes by subclasses of the obese group: obese class I (BMI 30–34.9 kg/m^2), obese class II (BMI 35–39.9 kg/m^2), and obese class III (BMI ≥40 kg/m^2). BMI, body mass index; CE, clinically evaluable; ITT, intent-to-treat.

omadacycline-treated patients in each BMI subgroup. There was a small trend for lower rates of clinical failures at PTE after clinical success at ECR in patients with increasing BMI in both treatment arms. Clinical stability at ECR was also associated with high rates of clinical success at PTE in both treatment arms across BMI subgroups.

The safety profiles of omadacycline- and moxifloxacin-treated patients were similar across BMI subgroups. Rates of any treatment-emergent adverse events (TEAEs) in omadacycline-treated patients were, by increasing BMI subgroup (normal weight, overweight, obese), 43.5%, 42.0%, and 36.5%; rates for moxifloxacin-treated patients were 48.6%, 45.2%, and 52.8%. Rates of any TEAE in the underweight subgroup were 44.4% and 40.0% for omadacycline- and moxifloxacin-treated patients, respectively. There were no severe or serious TEAEs reported in the underweight subgroup. Severe TEAEs were reported by 6.5%, 6.9%, and 6.7% of omadacycline- and 7.9%, 5.9%, and 6.5% of moxifloxacin-treated patients, by increasing BMI subgroup. Deaths in the omadacycline and moxifloxacin treatment arms, respectively occurred in 0 and 0 patients in the underweight group, 2.2% (3/138) and 0.7% (1/140) of patients in the normal weight group, 3.1% (4/131) and 1.5% (2/135) of patients in the overweight group, and 1.0% (1/104) and 0.9% (1/108) of patients in the obese group.

The most commonly reported TEAEs were alanine aminotransferase increased, nausea, and vomiting, with no trends seen by BMI subgroup (Table 5). Changes in liver chemistry values were similar across BMI categories and were infrequent (Table 6). The most common TEAEs (>2% incidence) in patients with a history of diabetes who were receiving omadacycline were similar to those seen for all patients: constipation was reported by 2/21 (9.5%) and vomiting by 1/21 (4.8%) in the overweight subgroup; headache, hypertension, insomnia, nausea, and vomiting were each reported by 1/33 (3.0%) in the obese subgroup. In the normal weight subgroup with diabetes, there were no TEAEs reported with >2% incidence.

4. Discussion

IV to once-daily omadacycline showed similar efficacy in obese, overweight, normal weight, and underweight patients with CABP, compared to moxifloxacin. The results of the current post-hoc analysis are consistent with the overall results of the OPTIC trial, which demonstrated similar success at ECR and durable clinical success at PTE. The tipping point analysis revealed no body weight at which there was a change in clinical success/failure outcomes at ECR or PTE. These results suggest that the omadacycline fixed-dosing strategy is appropriate in patients regardless of weight (normal, overweight, or obese). Similarly, clinical success at ECR and PTE for moxifloxacin-treated patients were consistent across BMI subgroups and consistent with previous reports [7, 8]. While there were several comorbidities that were common across BMI subgroups and treatment arms, previous omadacycline analyses have not shown differences in outcomes from the OPTIC trial in patients

Table 3
Clinical success at ECR and PTE (ITT population).

% (n)	Normal weight		Overweight		Obese		With diabetes history		No diabetes history	
	OMC	MOX	OMC	MOX	OMC	MOX	OMC	MOX	OMC	MOX
ECR, ITT population	(n = 140)	(n = 140)	(n = 133)	(n = 135)	(n = 104)	(n = 108)	(n = 62)	(n = 71)	(n = 315)	(n = 312)
Clinical success	82.9 (116)	88.6 (124)	80.5 (107)	80.7 (109)	77.9 (81)	76.9 (83)	75.8 (47)	85.9 (61)	81.6 (257)	81.7 (255)
Treatment difference [95% CI]	−5.7 [−14.1, 2.6]		−0.3 [−9.9, 9.3]		1.0 [−10.4, 12.3]		−10.1 (−24.0, 3.3)		−0.1 (−6.2, 6.0)	
PTE, ITT population	(n = 140)	(n = 140)	(n = 133)	(n = 135)	(n = 104)	(n = 108)	(n = 62)	(n = 71)	(n = 315)	(n = 312)
Clinical success	83.6 (117)	88.6 (124)	90.2 (120)	80.7 (109)	88.5 (92)	86.1 (93)	85.5 (53)	87.3 (62)	87.6 (276)	84.6 (264)
Treatment difference [95% CI]	−5.0 [−13.3, 3.2]		9.5 [1.1, 18.1]		2.4 [−6.9, 11.6]		−1.8 (−14.4, 10.1)		3.0 (−2.4, 8.5)	
PTE, CE population	(n = 122)	(n = 121)	(n = 119)	(n = 121)	(n = 91)	(n = 98)	(n = 53)	(n = 62)	(n = 279)	(n = 278)
Clinical success	92.6 (113)	94.2 (114)	93.3 (111)	86.8 (105)	92.3 (84)	90.8 (89)	90.6 (48)	91.9 (57)	93.2 (260)	90.3 (251)
Treatment difference [95% CI]	−1.6 [−8.4, 5.1]		6.5 [−1.2, 14.6]		1.5 [−7.1, 10.0]		−1.4 (−13.2, 9.7)		2.9 (−1.7, 7.7)	

BMI, body mass index; CE, clinically evaluable; CI, confidence interval; ECR, early clinical response; ITT, intent-to-treat; MOX, moxifloxacin; PTE, post-treatment evaluation; OMC, omadacycline.

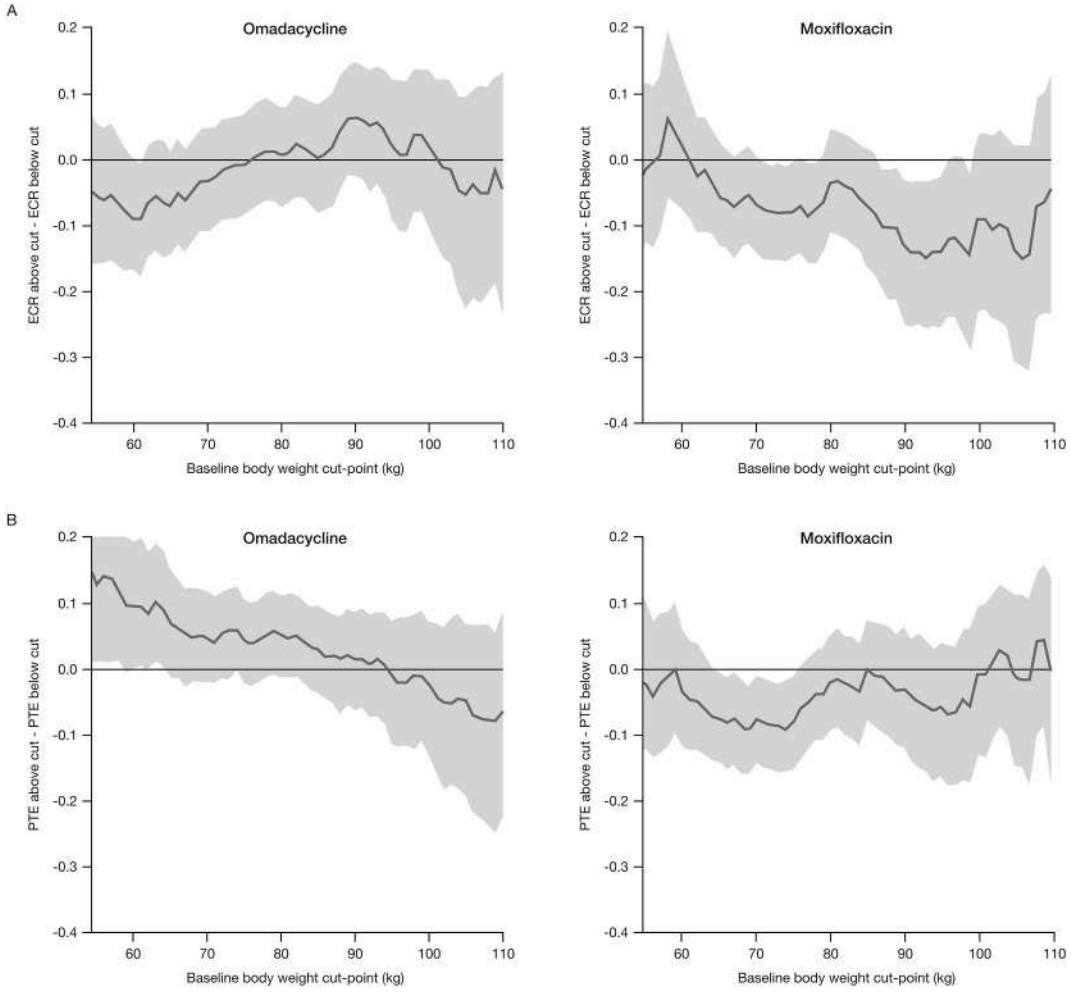


Fig. 3. Tipping point analysis. Tipping point analysis for clinical success at (A) ECR and (B) PTE did not reveal a body weight at which point a statistically significant difference was observed. The solid lines represent the difference in probability of clinical success above and below the weight cut-point, and the shaded areas represent the 95% confidence interval of the difference. ECR, early clinical response; PTE, post-treatment evaluation.

with baseline renal impairment, disease severity, older age, or comorbidities [9,10].

Within BMI strata, clinical success at ECR appears to serve as a prognostic marker of sustained clinical success at PTE. The vast majority of patients in both omadacycline and moxifloxacin treatment arms achieved clinical success at PTE after demonstrating clinical success or clinical stability at ECR, similar to the overall OPTIC trial population [11]. Among early clinical responders in both treatment arms, there was a small trend for fewer clinical failures as BMI increased. These results are consistent with the recent pooled analysis of six randomized controlled CABP trials by the US Food and Drug Administration that included the OPTIC trial where the obesity paradox was observed [2]. While concordance between success at ECR and PTE was high, approximately half of the patients who did not have clinical success at ECR, or clinical stability by the time of ECR assessment, continued to improve and had clinical success at end of treatment and PTE [11].

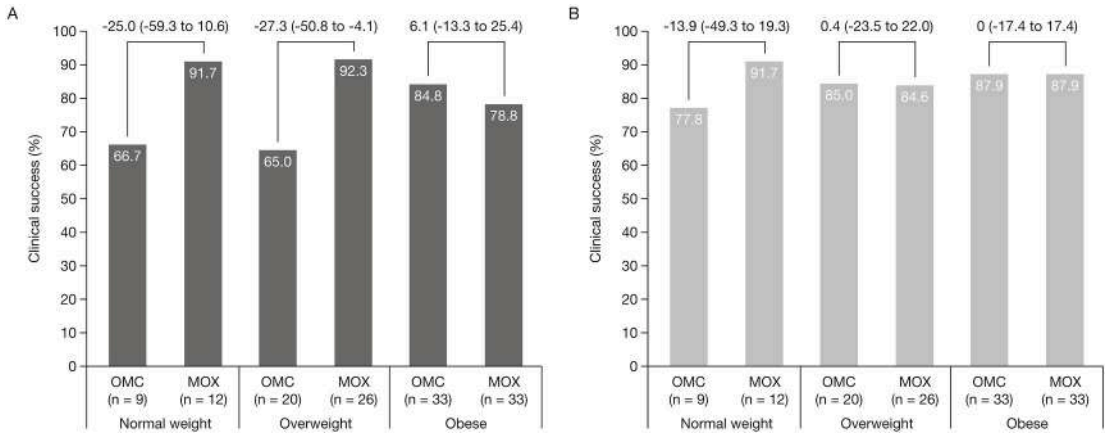


Fig. 4. Clinical success in participants with a history of diabetes. (A) Dark-shaded bars represent clinical success at early clinical response. (B) Light-shaded bars represent clinical success at post-treatment evaluation. ITT population. Treatment difference [95% CI] is shown above the bars. ITT, intent-to-treat; MOX, moxifloxacin; OMC, omadacycline.

Table 4
PTE outcomes following clinical success or clinical stability at ECR (ITT population).

	Normal weight		Overweight		Obese	
n (%)	OMC	MOX	OMC	MOX	OMC	MOX
	(n = 140)	(n = 140)	(n = 133)	(n = 135)	(n = 104)	(n = 108)
Clinical response at ECR	116 (82.9)	124 (88.6)	107 (80.5)	109 (80.7)	81 (77.9)	83 (76.9)
Success at PTE	107 (92.2)	113 (91.1)	104 (97.2)	99 (90.8)	78 (96.3)	79 (95.2)
Failure at PTE	6 (5.2)	8 (6.5)	2 (1.9)	6 (5.5)	1 (1.2)	2 (2.4)
Indeterminate at PTE	3 (2.6)	3 (2.4)	1 (0.9)	4 (3.7)	2 (2.5)	2 (2.4)
Clinical stability at ECR	101 (72.1)	102 (72.9)	65 (48.9)	79 (58.5)	99 (95.2)	98 (90.2)
Stable at PTE	94 (93.1)	98 (96.1)	64 (98.5)	76 (96.2)	95 (96.0)	96 (98.0)
Not stable at PTE	7 (6.9)	4 (3.9)	1 (1.5)	3 (3.8)	4 (4.0)	2 (2.0)

ECR, early clinical response; ITT, intent-to-treat; MOX, moxifloxacin; OMC, omadacycline; PTE, post-treatment evaluation.
Percentages for outcomes at ECR are calculated as a proportion of the entire ITT cohort. Percentages for outcomes at PTE are calculated as a proportion of the patients with clinical success or symptom stability, respectively, at ECR.

Table 5
Treatment-emergent adverse events occurring in ≥2% of omadacycline-treated participants (safety population).

	Normal weight		Overweight		Obese	
n (%)	OMC	MOX	OMC	MOX	OMC	MOX
	(n = 138)	(n = 140)	(n = 131)	(n = 135)	(n = 104)	(n = 108)
Patients with ≥1 TEAE	60 (43.5)	68 (48.6)	55 (42.0)	61 (45.2)	38 (36.5)	57 (52.8)
Alanine aminotransferase increased	4 (2.9)	6 (4.3)	9 (6.9)	5 (3.7)	1 (1.0)	7 (6.5)
Aspartate aminotransferase increased	2 (1.4)	5 (3.6)	5 (3.8)	4 (3.0)	1 (1.0)	5 (4.6)
Constipation	5 (3.6)	4 (2.9)	4 (3.1)	1 (0.7)	0	1 (0.9)
Gamma-glutamyltransferase increased	4 (2.9)	3 (2.1)	4 (3.1)	3 (2.2)	2 (1.9)	2 (1.9)
Headache	3 (2.2)	0	3 (2.3)	2 (1.5)	1 (1.0)	2 (1.9)
Hypertension	3 (2.2)	6 (4.3)	6 (4.6)	3 (2.2)	4 (3.8)	2 (1.9)
Insomnia	6 (4.3)	2 (1.4)	0	3 (2.2)	3 (2.9)	3 (2.8)
Nausea	5 (3.6)	9 (6.4)	3 (2.3)	5 (3.7)	1 (1.0)	7 (6.5)
Vomiting	5 (3.6)	2 (1.4)	2 (1.5)	0	1 (1.0)	4 (3.7)

MOX, moxifloxacin; OMC, omadacycline; TEAE, treatment-emergent adverse event.

Similar safety results for omadacycline were observed for normal weight, overweight, and obese patients with CABP. No safety outcome observed in the overall study was disproportionately observed in any BMI subgroup or as BMI increased [6]. These findings imply that body size is unlikely to influence the omadacycline exposure and safety profiles. A comprehensive population pharmacokinetic analysis of Phase I to Phase III studies has been performed in a sample of 613 adults with a median [min, max] BMI of 25.6 [16.0, 49.3] kg/m^2 [12]. The coefficient of variation for omadacycline clearance was low (22.3%) and body size was not identified as a significant covariate. The body weight range (36–148 kg) was wide in that sample, which gives confidence in this finding.

The results of this study are encouraging, but they should be interpreted with caution due to the limitations of any post-hoc analysis. Subgroup sizes were generally robust, except for the underweight group and in the subgroup with diabetes where any conclusions about efficacy or safety are limited. This post-hoc subanalysis was not prespecified, and not powered nor intended to compare these BMI subgroups. Mortality was low in the trial (n = 12 [1.6%] in entire trial) which precluded a separate examination with regards to the obesity paradox. Additional observational data and future studies of omadacycline in CABP among a larger population of patients with diabetes may be helpful.

5. Conclusion

The omadacycline fixed-dosing strategy was not associated with safety or efficacy differences across adults with different body sizes in patients with CABP, when compared with moxifloxacin.

Declaration of competing interest

Manjunath P. Pai has received consulting fees from Paratek Pharmaceuticals, Inc. Mark Wilcox has received consulting fees from Paratek Pharmaceuticals, Inc. Surya Chitra is a consultant to Paratek Pharmaceuticals, Inc. Paul C. McGovern was an employee of Paratek

Table 6
Patients with post-baseline liver chemistry elevations (safety population).

Laboratory parameter (SI unit), % (*n*)	Normal weight		Overweight		Obese	
	OMC (n = 138)	MOX (n = 140)	OMC (n = 131)	MOX (n = 135)	OMC (n = 104)	MOX (n = 108)
ALT >3 × ULN (U/L)	2.0 (2/100)	3.5 (4/114)	2.3 (2/88)	3.3 (3/90)	3.4 (3/88)	4.5 (4/88)
AST >3 × ULN (U/L)	1.7 (2/115)	1.6 (2/125)	0.9 (1/108)	1.0 (1/104)	2.1 (2/95)	2.1 (2/95)
Total bilirubin >2 × ULN (μmol/L)	0	0.9 (1/117)	0.9 (1/115)	0.8 (1/120)	0	2.0 (2/102)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MOX, moxifloxacin; OMC, omadacycline; ULN, upper limit of normal.

Pharmaceuticals, Inc. at the time of this analysis.

Data availability

Paratek Pharmaceuticals has a commitment to ensure that access to clinical trial data is available to regulators, researchers, and trial patients, when permitted, feasible and appropriate. Requests for de-identified patient-level data may be submitted to medinfo@paratekpharma.com for review.

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CRediT authorship contribution statement

Manjunath P. Pai: Conceptualization, Methodology, Investigation, Writing – review & editing. **Mark Wilcox:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Surya Chitra:** Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing – review & editing. **Paul McGovern:** Conceptualization, Methodology, Investigation, Writing – review & editing.

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