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Safety and efficacy of omadacycline by BMI categories and diabetes history in two Phase III randomized studies of patients with acute bacterial skin and skin structure infections

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Objectives: The objectives of this post-hoc analysis were to examine the safety and efficacy of omadacycline by BMI categories and diabetes history in adults with acute bacterial skin and skin structure infections (ABSSSI) from two pivotal Phase III studies.

Patients and methods: OASIS-1 (ClinicalTrials.gov identifier NCT02378480): patients were randomized 1:1 to IV omadacycline or linezolid for 7–14 days, with optional transition to oral medication. OASIS-2 (ClinicalTrials.gov identifier NCT02877927): patients received once-daily oral omadacycline or twice-daily oral linezolid for 7–14 days. Early clinical response (ECR) was defined as ≥20% reduction in lesion size 48–72 h after the first dose. Clinical success at post-treatment evaluation (PTE; 7–14 days after the last dose) was defined as symptom resolution such that antibacterial therapy was unnecessary. Safety was assessed by treatment-emergent adverse events and laboratory measures. Between-treatment comparisons were made with regard to WHO BMI categories and diabetes history.

Results: Patients were evenly distributed among healthy weight, overweight and obese groups. Clinical success for omadacycline-treated patients at ECR and PTE was similar across BMI categories. Outcomes by diabetes status were similar in omadacycline- and linezolid-treated patients: at ECR, clinical success rates were lower for those with diabetes; at PTE, clinical success was similar between treatment groups regardless of diabetes history. The safety of omadacycline and linezolid was largely similar across BMI groups and by diabetes history.

Conclusions: Omadacycline efficacy in patients with higher BMI and in patients with diabetes was consistent with results from two pivotal Phase III ABSSSI trials. Fixed-dose omadacycline is an appropriate treatment for ABSSSI in adults regardless of BMI.

Introduction

Over the past two decades, the reported incidence of all skin and soft-tissue infections (including those associated with *Staphylococcus aureus*) has increased by approximately 30%.[1] Infections of the skin are more common in obese patients than in patients of other BMI categories. The estimated prevalence of obesity is 13% worldwide and 39% in the USA.[2–5] By 2030, a predicted 49% of adults in the USA will be classified as obese.[6] These statistics necessitate a careful examination of the appropriateness of antibiotic treatment among obese patients with skin and soft-tissue infections.

A large, retrospective study identified obesity as a risk factor for antibiotic treatment failure, potentially due to a 'one size fits all' dosing strategy.[7] In patients with a high BMI, there may be altered pharmacokinetics (PK) of antimicrobial agents.[8,9] Decreased drug exposure occurs with antibiotics that undergo weight-based dosing (e.g. vancomycin),[10,11] as well as with fixed-dose antibiotics (e.g. trimethoprim/sulfamethoxazole) in obesity.[12,13] Increased dosing of antibiotics, to compensate for decreased exposure, may lead to adverse effects.[9] Therapeutic drug monitoring is not available for most antibiotics to guide dose adjustment in obese patients. These dosing uncertainties can increase the overall burden of care and may expose this emerging special population

to a heightened risk of treatment failure, the development of antimicrobial resistance and adverse events.[9]

Omadacycline, an IV and oral aminomethylcycline antibiotic derived from the tetracycline class, is approved by the FDA to treat adults with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia caused by susceptible organisms. As with linezolid, omadacycline is administered at a fixed dose in adults, without regard to body weight or composition. In the Phase III Omadacycline in Acute Skin and Skin Structure Infections Studies (OASIS-1 and OASIS-2), involving adults with ABSSSI, omadacycline was non-inferior to linezolid; omadacycline also demonstrated a similar safety profile to linezolid.[14,15] In this post-hoc analysis of the OASIS-1 and OASIS-2 studies in adults with ABSSSI, we analysed the safety and efficacy of omadacycline in subpopulations of the OASIS-1 and OASIS-2 studies with regard to BMI category and history of diabetes.

Patients and methods

Ethics

The clinical trials were conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki, as previously reported.[14,15] The trials were approved by the Institutional Review Board or Ethics Committee at each participating site and each patient provided written informed consent.

Study designs

The full study designs and methods have been published previously.[14,15] Briefly, OASIS-1 and OASIS-2 (ClinicalTrials.gov identifiers: NCT02378480 and NCT02877927, respectively) were randomized (1:1), double-blind, active comparator-controlled, Phase III studies comparing omadacycline with linezolid for the treatment of adults with ABSSSI.

OASIS-1 initiated patients on either IV omadacycline (100 mg q12h for two doses, then 100 mg q24h for 2 days) or IV linezolid (600 mg q12h), with the option to transition to oral formulations (omadacycline, 300 mg q24h; linezolid, 600 mg q12h) after day 3 if there was evidence of clinical improvement. In OASIS-2, patients received only the oral formulation of omadacycline (450 mg q24h for 2 days, then 300 mg q24h) or the oral formulation of linezolid (600 mg q12h). Treatment was provided for a total of 7–14 days in both studies.

Outcomes

The FDA primary endpoint for both studies was early clinical response (ECR), 48–72 h after treatment onset, defined as the patient being alive, with a reduction from baseline lesion area of ≥20%, and no receipt of rescue antimicrobial therapy. The EMA co-primary endpoint for both studies was investigator-assessed clinical response at post-treatment evaluation (PTE), which occurred 7–14 days after the last dose. Clinical success at PTE was defined as the patient being alive, with resolution of the signs and symptoms of infection to the extent that further antimicrobial treatment was unnecessary.

The analysis population for both primary endpoints was the modified ITT (mITT) population. Additionally, the EMA endpoint was analysed in the clinically evaluable (CE) population.

Analysis of efficacy (at the ECR and PTE timepoints) was also stratified by the presence or absence of history of diabetes in the patients. Clinical success at ECR was also evaluated with respect to baseline serum glucose level.

Infection-site samples and blood specimens were obtained for culture and microbiological testing at baseline, at end of treatment and at PTE.[16] The microbiological mITT population included all patients in the mITT population who had at least one Gram-positive causative pathogen.

Safety was assessed based on adverse events, vital signs, ECG findings and standard clinical laboratory tests. The safety population included all participants who were randomized and received the study drug.

Statistical analyses

Data from OASIS-1 and OASIS-2 were pooled for baseline efficacy and safety analyses by BMI group. Patients were classified on the basis of WHO BMI categories: underweight, BMI <18.5 kg/m^2; healthy 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 ≥30 kg/m^2; obese class I, BMI 30 kg/m^2 to <35 kg/m^2; obese class II, BMI 35 kg/m^2 to <40 kg/m^2; obese class III, BMI ≥40 kg/m^2.

A tipping-point analysis (Markov chain Monte Carlo simulations undertaken with SAS® software; SAS Institute, Inc., Cary, NC, USA) was conducted to determine whether there was a threshold of baseline body weight at which the model determined a probability of change from statistically similar to statistically different outcomes. The objective of the tipping-point analysis was to find the assumption at which conclusions change from favourable for treatment (clinical success) to unfavourable for treatment (clinical failure). This analysis provided probabilities for the assumption that the treatment may switch from a favourable to an unfavourable outcome at a certain baseline weight. The analysis was conducted for patients with body weights between 55 and 120 kg (the 5th and 95th percentile, respectively, for the entire study population).

Logistic regression analyses of clinical success at ECR and PTE were performed, with covariates of BMI at baseline, treatment arm and the interaction between BMI and treatment.

Data sharing

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

Results

The demographics and baseline characteristics of patients in the safety population are included in Table 1. The mean (SD) age in each BMI group was similar to the overall population mean of 45.1 (14.2) years. A small minority of patients (1.6%; 22/1379) was classified as underweight, with BMI ranging from 16.3 to 18.2 kg/m^2 and body weight ranging from 41.7 to 54.9 kg; these patients were not included in the analysis. Rates of hypertension, diabetes and heart disease generally increased with increasing BMI. The most common lesion type across all BMI groups in omadacycline-treated patients was wound infection. There were numerical trends towards increased prevalence of cellulitis/erysipelas and a decrease in wound infections with increasing BMI. The distribution of baseline lesion type was similar in the underweight group compared with the other BMI groups (data not shown).

The baseline pathogens identified are shown in Table 2. *S. aureus* was the most common baseline pathogen in all groups, including similar proportions of MRSA and MSSA; there were modest trends towards an increasing prevalence of MSSA and a decreasing prevalence of MRSA and *Streptococcus* species with increasing BMI.

Clinical success rates at the ECR (Figure 1) and PTE (Figure 2) timepoints were similar in healthy weight, overweight and

Table 1. Patient demographics and baseline characteristics for pooled ABSSSI studies (safety population)

	Healthy weight		Overweight		Obese	
Characteristic	OMC ($n = 252$)	LZD ($n = 231$)	OMC ($n = 221$)	LZD ($n = 243$)	OMC ($n = 210$)	LZD ($n = 200$)
Age (years), mean (SD)	42.3 (14.3)	42.0 (12.5)	44.1 (14.2)	46.7 (14.7)	48.2 (13.5)	48.5 (14.6)
Male, *n* (%)	167 (66.3)	150 (64.9)	159 (71.9)	158 (65.0)	114 (54.3)	122 (61.0)
White, *n* (%)	229 (90.9)	215 (93.1)	199 (90.0)	227 (93.4)	186 (88.6)	185 (92.5)
Weight (kg), mean (SD)	67.2 (9.0)	66.4 (8.4)	81.6 (9.3)	79.2 (9.6)	101.2 (18.0)	103.5 (18.6)
Weight (kg), min, max	45.0, 93.9	48.1, 87.7	61.7, 115.0	58.0, 102.0	63.2, 167.0	65.3, 156.3
BMI (kg/m^2), mean (SD)	22.4 (1.6)	22.6 (1.5)	27.4 (1.3)	27.3 (1.4)	35.6 (5.5)	35.9 (5.6)
BMI (kg/m^2), range	18.5–25.0	18.9–25.0	25.0–29.9	25.0–30.0	30.0–71.3	30.0–54.7
Medical history, *n* (%)						
diabetes	6 (2.4)	10 (4.3)	4 (1.8)	18 (7.4)	28 (13.3)	39 (19.5)
heart disease	2 (0.8)	2 (0.9)	12 (5.4)	9 (3.7)	12 (5.7)	11 (5.5)
hypertension	17 (6.7)	18 (7.8)	32 (14.5)	53 (21.8)	72 (34.3)	67 (33.5)
Baseline lesion type (mITT population)	$n = 248$	$n = 225$	$n = 217$	$n = 241$	$n = 203$	$n = 190$
cellulitis/erysipelas, *n* (%)	49 (19.8)	84 (37.3)	71 (32.7)	72 (29.9)	81 (39.9)	78 (41.1)
major abscess, *n* (%)	64 (25.8)	55 (24.4)	51 (23.5)	59 (24.5)	40 (19.7)	39 (20.5)
wound infection, *n* (%)	135 (54.4)	125 (55.6)	95 (43.8)	110 (45.6)	82 (40.4)	73 (38.4)

LZD, linezolid; OMC, omadacycline.

Table 2. Baseline pathogens found in ≥5% of any group of omadacycline-treated patients (microbiological mITT population)

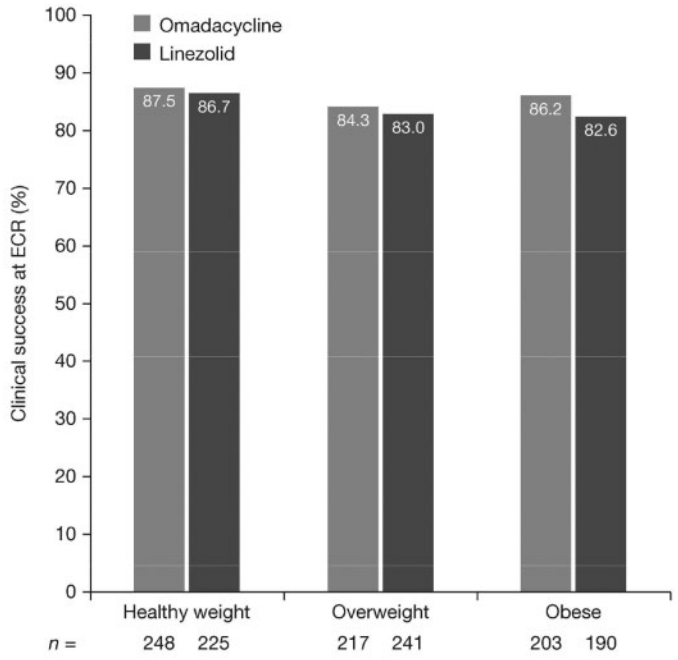
	Healthy weight, *n* (%)		Overweight, *n* (%)		Obese, *n* (%)	
Pathogen	OMC ($n = 201$)	LZD ($n = 184$)	OMC ($n = 167$)	LZD ($n = 182$)	OMC ($n = 129$)	LZD ($n = 136$)
Gram-positive aerobes	197 (98.0)	179 (97.3)	160 (95.8)	177 (97.3)	126 (97.7)	129 (94.9)
S. aureus	148 (73.6)	139 (75.5)	123 (73.7)	141 (77.5)	100 (77.5)	93 (68.4)
MRSA[a]	72 (35.8)	68 (37.0)	61 (36.5)	55 (30.2)	39 (30.2)	29 (21.3)
MSSA[a]	79 (39.3)	72 (39.1)	63 (37.7)	88 (48.4)	62 (48.1)	66 (48.5)
Streptococcus pyogenes	22 (10.9)	18 (9.8)	11 (6.6)	7 (3.8)	7 (5.4)	7 (5.1)
Streptococcus anginosus group	54 (26.9)	35 (19.0)	30 (18.0)	26 (14.3)	17 (13.2)	20 (14.7)
Enterococcus faecalis	6 (3.0)	2 (1.1)	5 (3.0)	11 (6.0)	7 (5.4)	11 (8.1)
Gram-positive anaerobes	13 (6.5)	11 (6.0)	11 (6.6)	11 (6.0)	9 (7.0)	10 (7.4)
Gram-negative aerobes	19 (9.5)	21 (11.4)	16 (9.6)	15 (8.2)	14 (10.9)	13 (9.6)
Gram-negative anaerobes	14 (7.0)	9 (4.9)	10 (6.0)	8 (4.4)	4 (3.1)	7 (5.1)

LZD, linezolid; OMC, omadacycline.
[a]Percentages calculated for MSSA and MRSA are as a proportion of the total number of patients in the group. Eleven patients had both MRSA and MSSA as a baseline pathogen; therefore, numbers may not add up to 100%.

obese patients receiving omadacycline (Table 3). No evidence of the efficacy of omadacycline becoming reduced as BMI increased, including within obese classes I–III, was observed. In the underweight group, clinical success at both ECR and PTE was 100% (eight of eight cases). Similar clinical success results were seen for linezolid in healthy weight, overweight and obese groups, but with slightly higher variability than seen for omadacycline. No significant differences were observed between omadacycline and linezolid for all BMI categories at ECR and PTE. Similar results were observed in the CE population at PTE.

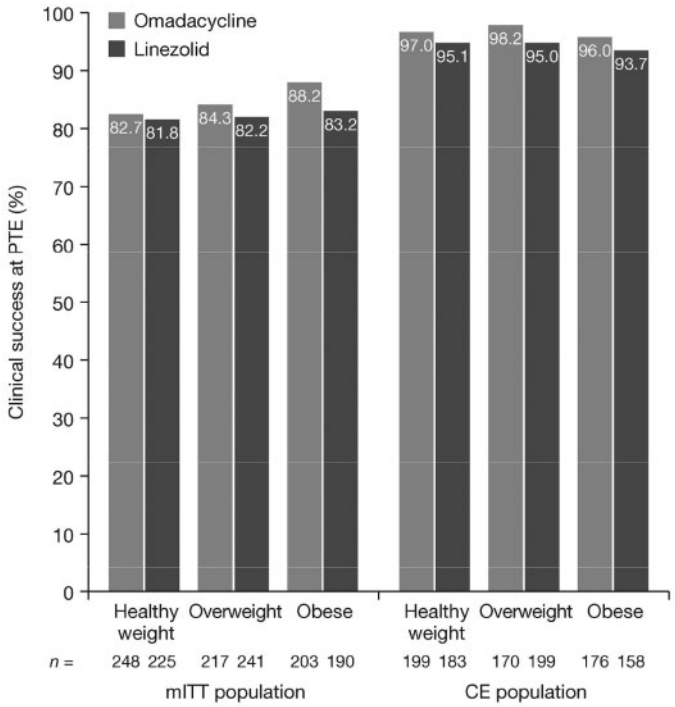
Tipping-point analysis by body weight showed that there was no baseline body weight for which there was a consistent downward trend in the probability of clinical success at ECR or PTE (Figure 3). From the logistic regression analyses of clinical success at ECR and PTE, respectively, there was no significant effect of BMI [0.02 (95% CI: −0.02, 0.06); −0.01 (95% CI: −0.07, 0.04)], treatment [−0.51 (95% CI: −2.23, 1.21); −0.23 (95% CI: −2.32, 1.85)] or the interaction between BMI and treatment [0.02 (95% CI: −0.04, 0.08); 0.02 (95% CI: −0.05, 0.10)].

Analysis of efficacy in ABSSSI patients with and without a history of diabetes demonstrated similar results for omadacycline- and



Clinical success at ECR, mITT population, *n/N* (%)	Omadacycline (*N* = 203)	Linezolid (*N* = 190)
Obese class I	107/123 (87.0)	85/105 (81.0)
Obese class II	39/47 (83.0)	43/47 (91.5)
Obese class III	29/33 (87.9)	29/38 (76.3)

Figure 1. Clinical success at ECR was consistent across BMI categories for patients receiving omadacycline and comparable to outcomes for those receiving linezolid (mITT population). The table shows outcomes by subclasses of the obese group: obese class I, BMI 30 to <35 kg/m^2; obese class II, BMI 35 to <40 kg/m^2; and obese class III, BMI ≥40 kg/m^2.



Clinical success at PTE, *n/N* (%)	mITT population		CE population	
	Omadacycline (*N* = 203)	Linezolid (*N* = 190)	Omadacycline (*N* = 176)	Linezolid (*N* = 158)
Obese class I	108/123 (87.8)	83/105 (79.0)	102/105 (97.1)	75/83 (90.4)
Obese class II	43/47 (91.5)	42/47 (89.4)	40/41 (97.6)	41/42 (97.6)
Obese class III	28/33 (84.8)	33/38 (86.8)	27/30 (90.0)	32/33 (97.0)

Figure 2. Clinical success at PTE was largely similar across BMI categories for patients treated with omadacycline or linezolid. The table shows outcomes by subclasses of the obese group: obese class I, BMI 30 to <35 kg/m^2; obese class II, BMI 35 to <40 kg/m^2; and obese class III, BMI ≥40 kg/m^2.

linezolid-treated patients. At ECR, clinical success rates were lower for patients with than for those without a history of diabetes. At PTE, clinical success rates were similar between treatment groups regardless of diabetes status (Figure 4). No trends in clinical success at ECR were observed in either treatment group across the range of baseline serum glucose levels recorded (4.00–9.38 mmol/L; data not shown).

Safety profiles for omadacycline- and linezolid-treated patients were largely similar across the BMI groups. For the healthy weight, overweight and obese groups, respectively, rates of any treatment-emergent adverse events (TEAEs) for omadacycline-treated patients were 54.0%, 47.5% and 52.4%; rates for linezolid-treated patients were 38.5%, 45.3% and 38.5%. Also, for these groups, rates of severe TEAEs were 2.4%, 1.8% and 0.5%, respectively, for omadacycline-treated patients and 1.7%, 2.9% and 3.0%, respectively, for linezolid-treated patients.

Rates of nausea and vomiting were 2- to 4-fold higher in omadacycline-treated patients compared with linezolid-treated patients (Table 4). No major differences existed between treatment groups with regard to other common TEAEs. There was a numerical trend towards increases in rates of nausea, vomiting and headache with increasing BMI classification, regardless of patient treatment group. Changes in liver enzyme profiles during treatment were infrequent and similar across BMI categories and treatment groups (Table 5).

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 in the Phase III clinical trials. Nausea was reported by 1/6 (16.7%) healthy weight participants. Those with obesity reported diarrhoea (4/28; 14.3%), nausea and vomiting (3/28; 10.7% each), headache, increased ALT and increased AST (2/28; 7.1% each) and subcutaneous abscess (1/28; 3.6%). In the overweight group with a history of diabetes, there were no TEAEs reported with >2% incidence.

Discussion

The prevalence of obesity continues to rise globally, with the staggering prediction that almost half of adults in the USA will be categorized as obese by 2030.[6] Obesity has been independently associated with the development of certain infections and it predisposes patients to comorbidities, such as diabetes, that further influence the prognosis of infectious diseases.[4,17,18] A recent

Table 3. Clinical success at ECR and PTE

	Healthy weight		Overweight		Obese		With diabetes history		No diabetes history	
	OMC	LZD	OMC	LZD	OMC	LZD	OMC	LZD	OMC	LZD
ECR, mITT population	*n* = 248	*n* = 225	*n* = 217	*n* = 241	*n* = 203	*n* = 190	*n* = 33	*n* = 61	*n* = 643	*n* = 610
clinical success, % (*n*)	87.5 (217)	86.7 (195)	84.3 (183)	83.0 (200)	86.2 (175)	82.6 (157)	81.8 (27)	77.0 (47)	86.5 (556)	84.6 (516)
treatment difference (95% CI)	0.8 (−5.3, 7.1)		1.3 (−5.6, 8.1)		3.6 (−3.6, 10.9)		4.8 (−13.9, 20.7)		1.9 (−2.0, 5.8)	
PTE, mITT population	*n* = 248	*n* = 225	*n* = 217	*n* = 241	*n* = 203	*n* = 190	*n* = 33	*n* = 61	*n* = 643	*n* = 610
clinical success, % (*n*)	82.7 (205)	81.8 (184)	84.3 (183)	82.2 (198)	88.2 (179)	83.2 (158)	100 (33)	86.9 (53)	84.3 (542)	81.6 (498)
treatment difference (95% CI)	0.9 (−6.0, 7.9)		2.2 (−4.8, 9.0)		5.0 (−1.9, 12.1)		13.1 (2.1, 23.9)		2.7 (−1.5, 6.8)	
PTE, CE population	*n* = 199	*n* = 183	*n* = 170	*n* = 199	*n* = 176	*n* = 158	*n* = 29	*n* = 51	*n* = 524	*n* = 501
clinical success, % (*n*)	97.0 (193)	95.1 (174)	98.2 (167)	95.0 (189)	96.0 (169)	93.7 (148)	100 (29)	94.1 (48)	96.9 (508)	94.6 (474)
treatment difference (95% CI)	1.9 (−2.2, 6.4)		3.3 (−0.6, 7.5)		2.4 (−2.5, 7.8)		5.9 (−6.2, 16.0)		2.3 (−0.1, 5.0)	

LZD, linezolid; OMC, omadacycline.

epidemiological investigation of 101447 individuals from the Copenhagen General Population Study attempted to disambiguate the relationship between BMI, diabetes status and risk of infections.[5] The analysis incorporated a genetic-based risk scoring system to adjust for lifelong higher BMI and found a linear association between this parameter and risk of ABSSSI. Importantly, a causal link between high BMI and ABSSSI was demonstrated.

Antimicrobial dosing and body size

Some antimicrobials commonly used to treat skin and soft-tissue infections require weight-based dosing, as is the case for daptomycin.[8,9,19] Several antimicrobials are administered on a fixed-dose basis; however, this is largely for pragmatic reasons, such as the number of different oral drug dose formulations that can be developed. In addition, fixed dosing of linezolid in patients with obesity may not attain sufficient antimicrobial activity against MRSA in pneumonia.[20] Research has also shown non-linear relationships between PK parameters and increasing BMI for patients with obesity treated with trimethoprim/sulfamethoxazole, suggesting that body weight and BMI, and possibly body surface area, should be incorporated into dosing calculations.[13] In contrast, the weight-based dosing and drug monitoring of some antimicrobial agents commonly used for ABSSSI treatment may increase the overall burden of care and potentially expose patients with a high BMI to a risk of therapy failure, the development of antimicrobial resistance or adverse events. It is these uncertainties that suggested an analysis of the efficacy of omadacycline in adult patients with ABSSSI and high BMI was warranted.

Omadacycline efficacy by BMI

In two randomized, Phase III clinical trials, omadacycline showed similar efficacy to linezolid in the treatment of ABSSSI.[14,15] Additional analyses presented here demonstrate that omadacycline efficacy in patients with higher BMI (and in patients with a history of diabetes) was consistent with the findings in the full study population of adults with ABSSSI.[14,15] Given that the epidemics of obesity and diabetes continue to increase in prevalence and that they often coexist, the current results—that the fixed dose of omadacycline is appropriate for the treatment of ABSSSI for patients with body weights between 41.7 and 167.0 kg, whether or not they have diabetes—are encouraging. Due to the potential that BMI categorization may not have been sensitive enough to detect outcome differences, we also performed a tipping-point analysis based on body weight. No body weight cut-off value was identified that negatively affected the clinical success for either omadacycline or linezolid; this, therefore, indicates that individuals of higher body weight do not require an increased dosage of omadacycline to treat ABSSSI.

Omadacycline safety by BMI

Adverse events stratified by BMI category were similar to the safety results seen in the two ABSSSI trials, the pooled ABSSSI analysis and the overall Phase III omadacycline clinical development programme.[14–16,21] No new safety signals were observed or concentrated in any BMI category. The small numerical trend in increased nausea and vomiting with increasing BMI classification may require further investigation; however, approximately 50% of patients in each omadacycline BMI group were from the OASIS-2 study, where higher rates of nausea and vomiting compared with

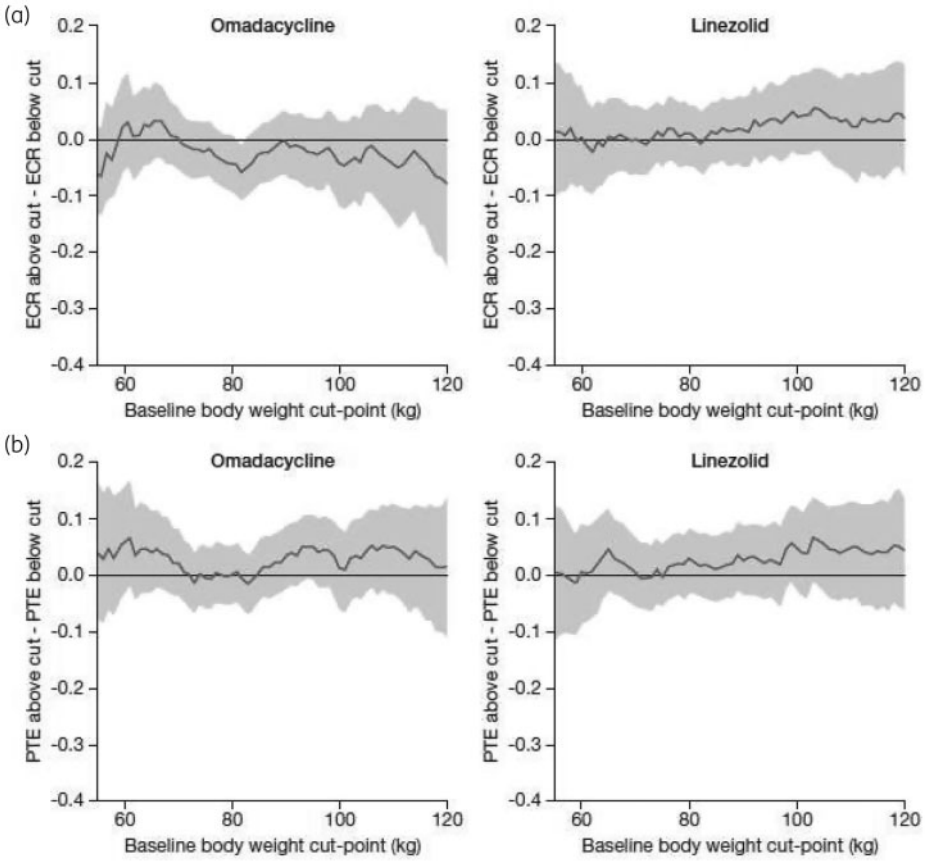


Figure 3. Tipping-point analysis for clinical success at (a) ECR and (b) PTE showed no body weight at which the clinical success of either omadacycline or linezolid was substantially negatively affected. The solid lines represent the difference in probability of clinical success above and below the body weight cut-point and the shaded areas represent the associated 95% CI.

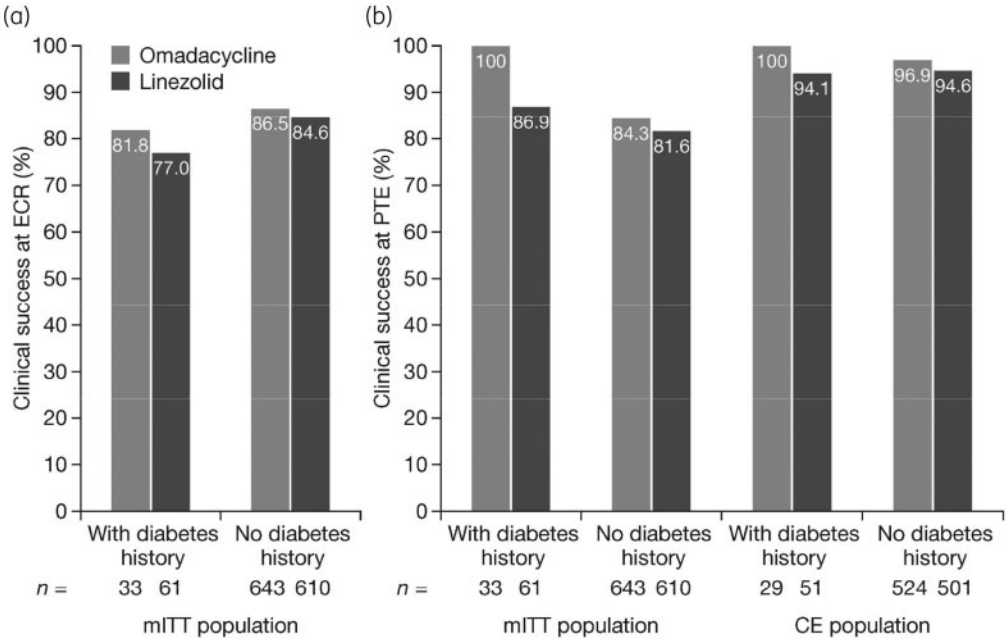


Figure 4. Clinical success was generally similar at (a) ECR and (b) PTE for patients who did and those who did not have a history of diabetes in the omadacycline and linezolid treatment groups.

Table 4. TEAEs occurring in >2% of patients in either treatment group (safety population)

	Healthy weight, *n* (%)		Overweight, *n* (%)		Obese, *n* (%)	
Adverse event	OMC (*n* = 252)	LZD (*n* = 231)	OMC (*n* = 221)	LZD (*n* = 243)	OMC (*n* = 210)	LZD (*n* = 200)
Any TEAE	136 (54.0)	89 (38.5)	105 (47.5)	110 (45.3)	108 (51.4)	77 (38.5)
Nausea	50 (19.8)	22 (9.5)	47 (21.3)	23 (9.5)	51 (24.3)	13 (6.5)
Vomiting	25 (9.9)	11 (4.8)	22 (10.0)	8 (3.3)	32 (15.2)	7 (3.5)
Infusion-site extravasation	14 (5.6)	5 (2.2)	7 (3.2)	12 (4.9)	6 (2.9)	2 (1.0)
Wound infection	14 (5.6)	8 (3.5)	9 (4.1)	8 (3.3)	5 (2.4)	5 (2.5)
Subcutaneous abscess	12 (4.8)	10 (4.3)	5 (2.3)	8 (3.3)	6 (2.9)	7 (3.5)
Increased ALT	10 (4.0)	5 (2.2)	11 (5.0)	11 (4.5)	7 (3.3)	9 (4.5)
Cellulitis	10 (4.0)	5 (2.2)	10 (4.5)	9 (3.7)	7 (3.3)	10 (5.0)
Increased AST	9 (3.6)	3 (1.3)	10 (4.5)	10 (4.1)	6 (2.9)	10 (5.0)
Diarrhoea	5 (2.0)	6 (2.6)	4 (1.8)	6 (2.5)	13 (6.2)	8 (4.0)
Headache	5 (2.0)	6 (2.6)	8 (3.6)	7 (2.9)	10 (4.8)	7 (3.5)

LZD, linezolid; OMC, omadacycline.
TEAEs were adverse events that emerged after treatment initiation and were those with an onset or worsening of severity that occurred at or any time after administration of the first dose of a trial drug through to the final follow-up visit (30–37 days after the first dose of a trial drug).
If a patient had >1 TEAE with the same preferred term, the patient was counted only once for that preferred term.

Table 5. Patients with post-baseline liver chemistry elevations (safety population)

		Healthy weight		Overweight		Obese	
Laboratory parameter	Value	OMC (*n* = 252)	LZD (*n* = 231)	OMC (*n* = 221)	LZD (*n* = 243)	OMC (*n* = 210)	LZD (*n* = 200)
ALT (U/L)	normal at baseline, *n*	184	189	161	196	150	152
	post-baseline observation, *n*	181	185	156	191	146	150
	>3× ULN, *n* (%)	3 (1.7)	5 (2.7)	2 (1.3)	8 (4.2)	1 (0.7)	5 (3.3)
AST (U/L)	normal at baseline, *n*	193	197	177	208	170	158
	post-baseline observation, *n*	190	192	171	203	166	155
	>3× ULN, *n* (%)	4 (2.1)	4 (2.1)	2 (1.2)	5 (2.5)	2 (1.2)	7 (4.5)
Total bilirubin (μmol/L)	normal at baseline, *n*	217	194	187	212	182	180
	post-baseline observation, *n*	215	187	179	207	179	176
	>2× ULN, *n* (%)	3 (1.4)	0	1 (0.6)	1 (0.5)	0	0

LZD, linezolid; OMC, omadacycline; ULN, upper limit of normal.

linezolid were observed due to the oral-only omadacycline loading dose given on days 1 and 2.[16] The review by Opal *et al.*[21] provides a more detailed discussion of nausea and vomiting. Overall, the data suggest there is no altered risk to prescribing omadacycline in patients with higher BMI.

Study limitations

The positive findings of this analysis must be weighed against its limitations. First, this is a secondary post-hoc analysis of two important subpopulations of patients with ABSSSI. The analysis represents the largest number of patients with high BMI or history of diabetes who have been treated with omadacycline to date, but it was not powered for inferential testing. However, the efficacy outcomes with omadacycline were numerically and directionally consistent with the overall results of the two clinical trials. Secondly, PK profiles were not analysed specifically in these subpopulations of patients to account for potential differences in exposure. Previous PK modelling has not identified high BMI or diabetes as covariates of interest, which potentially negates this concern.[22,23] Finally, this analysis was based on well-defined study populations that may not reflect all patient populations that are treated with these antimicrobial agents.

Conclusions

Analysis of omadacycline outcomes in ABSSSI by BMI indicates consistent efficacy and similar safety outcomes across all BMI

categories, thereby demonstrating that the standard fixed dose of omadacycline is an appropriate treatment for ABSSSI in adults regardless of body weight. Omadacycline efficacy outcomes were similar in patients with and those without a history of diabetes.

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Transparency declarations

M.P.P. has received consulting fees from Paratek Pharmaceuticals, Inc. M.H.W. has received consulting fees from Paratek Pharmaceuticals, Inc. S.C. is an employee of Paratek Pharmaceuticals, Inc. P.C.M. was an employee of Paratek Pharmaceuticals, Inc. at the time of the analysis. S.C. and P.C.M. also own Paratek stocks.

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Author contributions

M.P.P., M.H.W., S.C. and P.C.M. designed and conceived the study. All authors had roles in acquisition, analysis and/or interpretation of the data. All authors were involved in drafting and/or critically revising the manuscript and all authors approved the final version of the manuscript.

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