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MAJOR ARTICLE

Efficacy and Safety of Eravacycline in Obese Patients: A Post Hoc Analysis of Pooled Data From the IGNITE1 and IGNITE4 Clinical Trials

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Background. The increasing prevalence of obesity worldwide merits an examination of the efficacy and safety profiles of agents dosed by weight.

Methods. Data for patients (n = 1037) were obtained from the pooled IGNITE1 and IGNITE4 randomized double-blind trials in which patients with complicated intra-abdominal infections received eravacycline 1 mg/kg (actual body weight [ABW]) every 12 hours or comparator (ertapenem 1 g every 24 hours or meropenem 1 g every 8 hours) intravenously. This post hoc analysis evaluated clinical cure rates, adverse events, and drug discontinuation rates stratified by body mass index (BMI) categories of BMI >40 kg/m^2 (Obese, Class III), BMI 35–39.9 kg/m^2 (Obese, Class II), BMI 30–34.9 kg/m^2 (Obese, Class I), BMI 25–29.9 kg/m^2 (Overweight), BMI 18.5–24.9 kg/m^2 (Healthy weight), and BMI <18.5 kg/m^2 (Underweight).

Results. Clinical cure rates were high across BMI categories and ranged from 82% to 94% in the eravacycline group and 88.5%–100% in the comparator group. Similar cure rates were observed among eravacycline-treated healthy weight (126/134; 94%), overweight (127/146; 87%), and obese (BMI ≥30 kg/m^2; 110/129; 85.3%) patients. In the comparator group, a similar proportion of patients demonstrated clinical response (healthy weight [132/145; 91%], overweight [130/144; 90.3%], and obese [115/129; 89.1%]). Of the treatment-emergent adverse events that occurred in eravacycline-treated obese patients, a larger proportion were gastrointestinal-related (ie, nausea and vomiting); however, discontinuation rates were low and similar between eravacycline and carbapenems.

Conclusions. This post hoc analysis demonstrates the therapeutic utility and acceptable safety profile of eravacycline dosed by ABW in obese patients (BMI ≥30 kg/m^2).

Keywords. obesity; BMI; eravacycline; multidrug resistance; complicated intra-abdominal infection.

Antimicrobial therapy in obese patients can represent a clinical challenge due to physiological changes in cardiac output, volume of distribution, and liver and renal function, ultimately resulting in altered drug pharmacokinetics and the potential for inadequate drug exposures [1–4]. Obesity (body mass index [BMI] ≥30 kg/m^2) is a well-recognized chronic condition associated with morbidity and mortality and an escalating global health issue [5, 6]. In the United States, the age-adjusted prevalence of obesity increased from 30.5% (1999–2000) to 42.4% (2017–2018) [7]. Among European Union countries, 30%–70% of the population is overweight, while obesity affects 10%–30% of adults [8]. This increasingly prevalent comorbid condition warrants examination of the impact of body weight on the efficacy and safety profile of newly registered drugs such as eravacycline, an antimicrobial whose dosing regimen is based upon the patient's actual body weight.

Eravacycline is a broad-spectrum intravenous fluorocycline antibiotic of the tetracycline class that is Food and Drug Administration (FDA)– and European Medicines Agency–approved for the treatment of complicated intra-abdominal infections (cIAIs) in patients 18 years of age or older [9, 10]. As a fully synthetic antibiotic, eravacycline was designed to retain activity against the 2 main tetracycline-specific resistance mechanism mediated by ribosomal protection and drug efflux [11]. Eravacycline has potent in vitro and in vivo activity against gram-positive bacteria (ie, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *enterococci*), as well as the increasingly prevalent extended-spectrum β-lactamase (ESBL)– and carbapenemase-producing gram-negative bacteria [12–16].

In the Investigating Gram-Negative Infections Treated with Eravacycline (IGNITE) Phase 3 clinical trials in adults hospitalized with cIAI, eravacycline was compared with either

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ertapenem (IGNITE1) or meropenem (IGNITE4) as the active comparator for 4–14 days of therapy. An assessment of clinical outcomes demonstrated that eravacycline was noninferior to carbapenems at the test-of-cure visit in all prespecified populations [17, 18]. Complicated intra-abdominal infections encompassed several infections such as appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscesses, and peritonitis.

A major concern with weight-based dosing is effectiveness and tolerability in patients with extreme body weights [19]. Furthermore, while commonly associated with comorbidities such as cardiovascular disease and diabetes, obesity has also emerged as an independent risk factor for infection due to obesity-related immune system dysregulation [20–23]. Based on these concerns, limited pharmacokinetic data in obese patients, and the need to provide guidance to clinicians on the frequent question of the clinical success and risk of toxicity in overweight and obese patients, we conducted a post hoc analysis of the IGNITE1 and IGNITE4 trials. The objective of the current analysis was therefore to examine clinical cure rates, the incidence of adverse events, and drug discontinuation rates by weight categories in patients with cIAI receiving eravacycline vs carbapenem comparator.

Study Design and Population

We performed a post hoc analysis of pooled efficacy and safety data from the IGNITE1 (NCT01844856) and IGNITE4 (NCT02784704) clinical trials, which were conducted in 13 and 11 countries, respectively [17, 18]. Briefly, these phase 3, randomized, double-blind, multicenter noninferiority trials were designed to test the efficacy and safety of eravacycline compared with either ertapenem (IGNITE1; conducted August 2013 to August 2014) or meropenem (IGNITE4; conducted October 2016 to May 2017) in acutely hospitalized patients diagnosed with cIAI [17, 18, 24, 25]. The primary efficacy analysis, as required by the FDA, was conducted using a 10% (IGNITE1) and 12.5% (IGNITE4) noninferiority margin in the microbiological intent-to-treat (micro-ITT) population.

Patients aged ≥18 years who were hospitalized for suspected cIAI and able to provide informed consent were considered for inclusion. Across the 2 studies, patients were randomized to intravenous (IV) eravacycline 1 mg/kg every 12 hours (actual body weight), IV ertapenem 1 g every 24 hours, or IV meropenem 1 g every 8 hours. Randomization was stratified based on the primary site of infection (complicated appendicitis vs all other cIAI diagnoses).

Patient Consent Statement

The institutional review board/independent ethics committee at each study site reviewed and approved the clinical study protocol and all relevant supporting information before study initiation. All patients at each site provided written consent before study enrollment. Each trial was conducted in accordance with Good Clinical Practice and was consistent with the World Medical Assembly Declaration of Helsinki. Given the retrospective nature of this post hoc study, a separate informed consent was not required.

Outcomes

For this analysis, efficacy and safety data from the ertapenem and meropenem treatment arms were pooled and defined as the carbapenem "Comparator group" to compare with the pooled "Eravacycline group." Patients were classified into 6 weight categories based on National Institutes of Health (NIH) BMI categories: BMI >40 kg/m^2 (Obese, Class III), BMI 35–39.9 kg/m^2 (Obese, Class II), BMI 30–34.9 kg/m^2 (Obese, Class I), BMI 25–29.9 kg/m^2 (Overweight), BMI 18.5–24.9 kg/m^2 (Healthy weight), and BMI <18.5 kg/m^2 (Underweight) [26].

The primary end point evaluated across BMI categories was clinical response (cure, failure, indeterminate/missing) at test of cure (TOC), which occurred 25–31 calendar days after the initial dose of the study drug. Treatment-emergent adverse events (TEAEs) occurring in >2% of patients (safety population) in either the eravacycline or comparator group are reported as counts and percentages. The safety population (ie, modified intent-to-treat population) includes all randomized patients who received at least 1 dose of the study drug.

Statistical Analyses

Descriptive statistics were performed using Sigma Plot 14 (Systat Software Inc, San Jose, CA, USA). Any difference in the clinical cure rates in the primary efficacy population at TOC in 3 BMI categories (healthy, overweight, and obese [all classes]) was determined using the χ^2 test, and a prespecified alpha level of .05 was used. For additional sensitivity analysis, efficacy end points were also assessed based on 3 patient weight categories: <70 kg, 70–100 kg, >100 kg.

RESULTS

Demographics and Baseline Characteristics

A total of 842 patients with a recorded BMI from the primary efficacy population (micro-ITT population) in the pooled IGNITE1 and IGNITE4 studies were included in this present analysis; 415 and 427 received eravacycline and a carbapenem, respectively. Complicated appendicitis was the cause of infection in 160 patients (38.6%) and 157 patients (36.8%) in the eravacycline and comparator groups, respectively. In general, baseline characteristics were similar across patients in each BMI category as well as between treatment arms (Table 1). Within the Obese category (BMI ≥30 kg/m^2), a larger proportion of patients in both treatment arms were subclassified as Obese Class I. Patients were evenly distributed between the 3 main BMI categories (Healthy weight: eravacycline [n = 134] vs comparator [n = 145]; Overweight: eravacycline [n = 146] vs comparator [n = 144]; and Obese: eravacycline [n = 129]

Table 1. Demographics and Baseline Characteristics of the Microbiological Intent-to-Treat Population

	Eravacycline Group (Weight Category)							Carbapenem Comparator Group (Weight Category)						
Characteristic	Total (n = 415)	Underweight (n = 6)	Healthy Weight (n = 134)	Overweight (n = 146)	Obese I (n = 89)	Obese II (n = 33)	Obese III (n = 7)	Total (n = 427)	Underweight (n = 9)	Healthy Weight (n = 145)	Overweight (n = 144)	Obese I (n = 96)	Obese II (n = 29)	Obese III (n = 4)
Sex, female	180 (43.4)	4 (66.7)	57 (42.5)	51 (34.9)	35 (39.3)	28 (84.8)	5 (71.4)	194 (45.4)	4 (44.4)	59 (40.7)	54 (37.5)	54 (56.3)	21 (72.4)	2 (50)
Age, y														
<65	297 (71.6)	6 (100)	98 (73.1)	97 (66.4)	62 (69.7)	28 (84.8)	6 (85.7)	304 (71.2)	9 (100)	113 (77.9)	95 (66)	64 (66.7)	20 (69)	3 (75)
≥65	118 (28.4)	0	36 (26.9)	49 (33.6)	27 (30.3)	5 (15.2)	1 (14.3)	127 (29.7)	0	34 (23.4)	51 (35.4)	32 (33.3)	9 (31)	1 (25)
APACHE II score														
0–10	360 (86.7)	6 (100)	121 (90.3)	124 (84.9)	73 (82)	29 (87.9)	7 (100)	356 (83.4)	7 (77.8)	130 (89.7)	121 (84)	74 (77.1)	21 (72.4)	3 (75)
11–14	39 (9.4)	0	8 (6)	19 (13)	8 (9)	4 (12.1)	0	58 (13.6)	2 (22.2)	14 (9.7)	15 (10.4)	20 (20.8)	6 (20.7)	1 (25)
>15	15 (3.6)	0	4 (3)	3 (2.1)	8 (9)	0	0	14 (3.3)	0	2 (1.4)	8 (5.6)	2 (2.1)	2 (6.9)	0
Actual primary disease diagnosis														
Complicated appendicitis	160 (38.6)	4 (66.7)	54 (40.3)	51 (34.9)	36 (40.4)	14 (42.4)	1 (14.3)	157 (36.8)	4 (44.4)	53 (36.6)	59 (41)	33 (34.4)	6 (20.7)	2 (50)
Other complicated intra-abdominal infection	255 (61.4)	2 (33.3)	80 (59.7)	95 (65.1)	53 (59.6)	19 (57.6)	6 (85.7)	274 (64.2)	5 (55.6)	94 (64.8)	87 (60.4)	63 (65.6)	23 (79.3)	2 (50)
Duration of treatment, d														
Mean ± SD	7.61 ± 2.83	6.67 ± 1.21	7.57 ± 2.56	7.88 ± 3.12	7.46 ± 3.06	7.00 ± 1.87	8.29 ± 3.15	7.64 ± 2.73	8.00 ± 3.84	7.65 ± 2.73	7.42 ± 2.41	7.81 ± 3.00	7.90 ± 3.11	8.25 ± 2.63

Data are presented as No. (%) unless otherwise indicated. Underweight: BMI <18.5 kg/m^2; Healthy weight: BMI 18.5–24.9 kg/m^2; Overweight: BMI 25–29.9 kg/m^2; Obese Class I: BMI 30–34.9 kg/m^2; Obese Class II: BMI 35–39.9 kg/m^2; Obese Class III: BMI >40 kg/m^2.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index.

vs comparator [n = 129]) (Figure 1). Duration of antibiotic therapy was similar across obesity classes.

Efficacy

Figure 2 shows the clinical response (cure rate) at the TOC visit in the micro-ITT population stratified by BMI. Clinical cure rates were high across all BMI categories and ranged from 82% to 94% in the eravacycline group and 88.5% to 100% in the comparator group. Importantly, similar cure rates were observed among eravacycline-treated healthy weight (126/134; 94%), overweight (127/146; 87%), and obese (110/129; 85.3%) patients (P = .223). Among the 129 eravacycline-treated obese patients, a 93.9% cure rate in the Obese Class II population suggests that efficacy was not impacted as patient BMI increased.

Concordant observations were made when kilogram-only weight cutoffs were applied to the micro-ITT population: <70 kg (85/92; 92.4%), 70–100 kg (247/281; 87.9%), and >100 kg (36/42; 85.7%; P = .199). In the carbapenem comparator group, a similar proportion of patients demonstrated clinical response utilizing either BMI categories or kilogram-only cutoffs: healthy weight (132/147; 89.8%), overweight (130/146; 89%), and obese (115/129; 89.1%) or <70 kg (87/97; 89.7%), 70–100 kg (260/294; 88.4%), and >100 kg (38/40; 95%).

Eravacycline-treated patients within the Obese category, that is, Obese Class I, II, and III, demonstrated similar cure rates compared with their carbapenem-treated counterparts.

Safety

Overall, TEAEs occurred in 39.6% (206 of 520) of patients in the eravacycline group compared with 29.4% (152 of 517) in the comparator group. The incidence of TEAEs and study drug discontinuation rates were stratified by BMI to elucidate any differences between weight groups (Table 2). Of the TEAEs that occurred in >2% of eravacycline-treated obese patients, a larger proportion were gastrointestinal-related; nausea (11.2%) and vomiting (5.6%) were recorded among eravacycline-treated obese patients, while comparator obese patients experienced 2.1% and 3.4% incidence rates, respectively. Despite this, eravacycline discontinuation rates were low across healthy weight (2/172; 1.2%), overweight (2/180; 1.1%), and obese (4/161; 2.5%) patients and similar to the carbapenem comparator group (healthy weight 2/184 [1.1%], overweight 2/176 [1.1%], and obese 6/145 [4.1%]).

Concordant with BMI analysis, gastrointestinal-related AEs occurred more frequently in eravacycline-treated patients weighing >100 kg (nausea: 9.3%; vomiting: 5.6%) compared with the carbapenem comparator group (nausea: 0%; vomiting: 2.3%); drug discontinuation rates were 0% (eravacycline) and 2.3% (carbapenems) in this patient weight category.

Of the severe TEAEs (n = 37), including life-threatening and fatal events reported among all obese patients, a lower percentage occurred in eravacycline-treated patients (7.5%; 12/161) compared with comparator (17.2%; 25/145). There were 6 deaths among all obese patients (eravacycline group n = 1; carbapenem comparator group n = 5), none of which were determined to be treatment related.

DISCUSSION

With respect to antimicrobial drug development, regulatory agencies have guidelines for establishing dose-exposure-response relationships in special populations and patients deviating from the average patient when applicable. These include pregnant women, children, and patients with renal or hepatic insufficiency, but no such guidance exists for individuals with extreme body weights [22, 27]. As a result, efficacy and safety data for numerous therapeutic agents are limited despite obese patients being frequently encountered

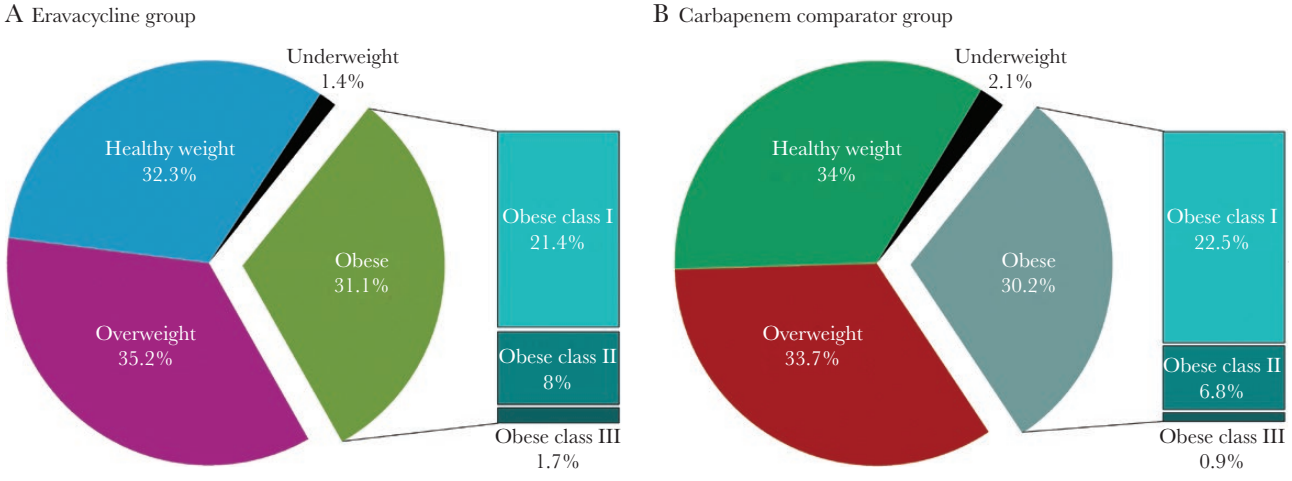

Figure 1. Patient distribution by weight category in the (A) eravacycline (n = 415) and (B) carbapenem comparator (n = 427) microbiological intent-to-treat population at baseline.

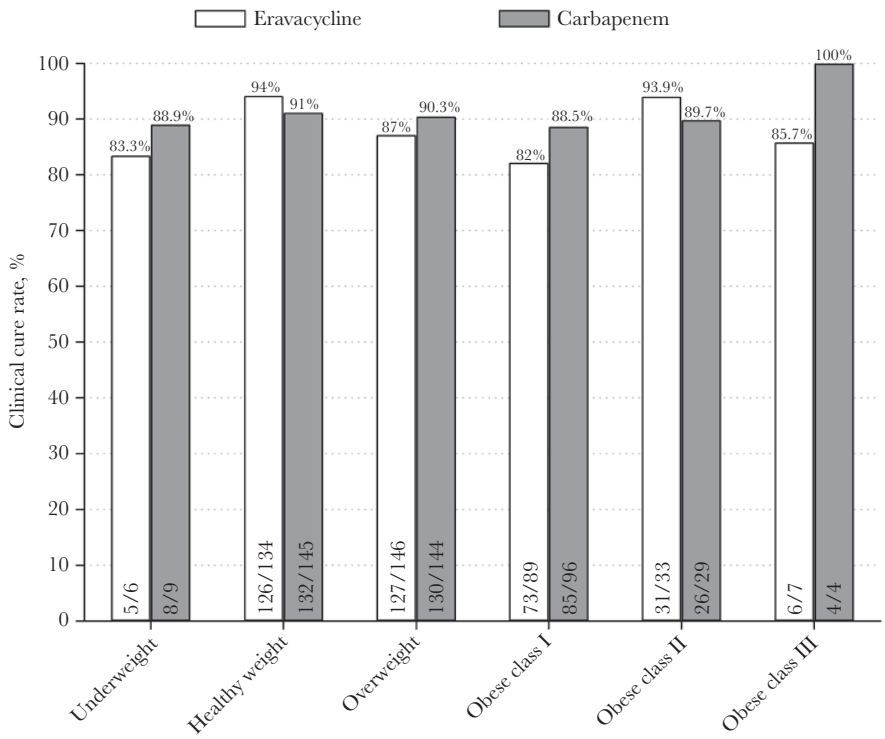

Figure 2. Clinical cure rate analyzed by weight category in the microbiological intent-to-treat population at test of cure.

in the health care system. The IGNITE1 and IGNITE4 clinical trials were pivotal phase 3 studies that demonstrated the noninferiority of eravacycline compared with carbapenems for the treatment of cIAI and that subsequently resulted in drug approval [17, 18]. This post hoc analysis shows that eravacycline, which was dosed using a weight-based regimen, was effective and generally well tolerated, irrespective of BMI. There was no difference in clinical cure rates or drug discontinuation rates among eravacycline-treated obese patients compared with their carbapenem-treated counterparts.

Numerous pathophysiological changes occur in obese patients. Alterations in body composition as a result of accumulating adipose tissue can affect cardiac output, volume of distribution, plasma volume, protein binding, and hepatic and renal clearance [1, 2, 28–31]. These in turn impact drug pharmacokinetics, necessitating an examination of drug parameters or clinical outcomes in obese patients [32, 33]. Furthermore, for weight-based drugs, several indices for dose adjustment exist, such as actual (total), adjusted, ideal, or lean body weight, body surface area, and BMI [22, 34, 35]. However, consistent with its development (ie, PK-PD optimization) and evaluation in clinical trials as an agent dosed by actual body weight [9, 10], eravacycline in this present study demonstrates similar efficacy in obese patients compared with healthy weight patients. It is worth noting that while the heaviest patient in the eravacycline arm of the cIAI clinical trials was 137 kg (enrolled in IGNITE4), corresponding to an eravacycline dose of 137 mg q12h, there is no dose cap restriction, per product labeling [9, 10]. To facilitate administration of a variety of eravacycline doses to patients, preparation of infusion bags only requires making an infusion solution with a target eravacycline concentration (range) of 0.3 (0.2–0.6) mg/mL [9, 10].

Eravacycline had an acceptable safety and tolerability profile across BMI groups. Whereas gastrointestinal-related TEAEs tended to be more frequent in eravacycline-treated patients with higher BMIs, rates of drug discontinuation due to adverse events were low and similar to rates observed in the carbapenem-treated patients.

This study utilizes a pooled data set that is balanced in number of patients and baseline characteristics across treatment groups; however, as a post hoc analysis, this study was not designed or powered to assess for statistical significance between BMI subgroups. Nonetheless, with more than one-third of the US population being classified as obese (BMI ≥30 kg/m^2), this study serves to address a knowledge gap with eravacycline dosing in an increasingly prevalent and challenging patient population. Consistent with previously published phase 3 trials and real-world data [17, 18, 36], this post hoc analysis demonstrates the therapeutic utility and acceptable safety profile of eravacycline in cIAI patients with BMI ≥30 kg/m^2.

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Table 2. Treatment-Emergent Adverse Events Occurring in >2% of Patients in Either Group (Safety Population)

Adverse Event	Eravacycline Group (Weight Category)							Carbapenem Comparator Group (Weight Category)						
	Total (n = 520)	Underweight (n = 7)	Healthy Weight (n = 172)	Overweight (n = 180)	Obese I (n = 106)	Obese II (n = 44)	Obese III (n = 11)	Total (n = 517)	Underweight (n = 12)	Healthy Weight (n = 184)	Overweight (n = 176)	Obese I (n = 110)	Obese II (n = 31)	Obese III (n = 4)
Nausea	34 (6.5)	0	8 (4.7)	8 (4.4)	9 (8.5)	5 (11.4)	4 (36.4)	5 (1.0)	1 (8.3)	1 (0.5)	0	3 (2.7)	0	0
Vomiting	20 (3.8)	0	7 (4.1)	4 (2.2)	5 (4.7)	2 (4.5)	2 (18.2)	15 (2.9)	0	3 (1.6)	7 (4.0)	3 (2.7)	2 (6.5)	0
Wound infection (superficial)	14 (2.7)	0	3 (1.7)	6 (3.3)	2 (1.9)	3 (6.8)	0	6 (1.2)	0	4 (2.2)	0	2 (1.8)	0	0
Infusion site phlebitis	13 (2.5)	0	5 (2.9)	4 (2.2)	4 (3.8)	0	0	1 (0.2)	0	1 (0.5)	0	0	0	0
Diarrhea	12 (2.3)	0	3 (1.7)	4 (2.2)	3 (2.8)	1 (2.3)	1 (9.1)	8 (1.5)	0	2 (1.1)	2 (1.1)	4 (3.6)	0	0
Anemia	10 (1.9)	0	3 (1.7)	3 (1.7)	4 (3.8)	0	0	15 (2.9)	0	6 (3.3)	4 (2.3)	4 (3.6)	1 (3.2)	0
Pyrexia	10 (1.9)	0	4 (2.3)	3 (1.7)	2 (1.9)	0	1 (9.1)	11 (2.1)	0	4 (2.2)	5 (2.8)	2 (1.8)	0	0
Hypertension	6 (1.2)	0	0	3 (1.7)	2 (1.9)	1 (2.3)	0	11 (2.1)	0	1 (0.5)	5 (2.8)	3 (2.7)	2 (6.5)	0
Discontinued because of any adverse event	9 (1.7)	1 (14.3)	2 (1.2)	2 (1.1)	3 (2.8)	1 (2.3)	0	10 (1.9)	0	2 (1.1)	2 (1.1)	6 (5.5)	0	0

Data are presented as No. (%). Underweight: BMI <18.5 kg/m^2; Healthy weight: BMI 18.5–24.9 kg/m^2; Overweight: BMI 25–29.9 kg/m^2; Obese Class I: BMI 30–34.9 kg/m^2; Obese Class II: BMI 35–39.9 kg/m^2; Obese Class III: BMI >40 kg/m^2.

Abbreviation: BMI, body mass index.

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References

1. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy **2007**; 27:1081–91.
2. Smit C, De Hoogd S, Brüggemann RJM, Knibbe CAJ. Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. Expert Opin Drug Metab Toxicol **2018**; 14:275–85.
3. Mazuski JE, Tessier JM, May AK, et al. The surgical infection society revised guidelines on the management of intra-abdominal infection. Surg Infect (Larchmt) **2017**; 18:1–76.
4. Wurtz R, Itokazu G, Rodvold K. Antimicrobial dosing in obese patients. Clin Infect Dis **1997**; 25:112–18.
5. Hurt RT, Kulisek C, Buchanan LA, McClave SA. The obesity epidemic: challenges, health initiatives, and implications for gastroenterologists. Gastroenterol Hepatol (N Y) **2010**; 6:780–92.
6. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann Transl Med **2017**; 5:161.
7. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018 key findings data from the National Health and Nutrition Examination Survey. **2017**. Available at: https://www.cdc.gov/nchs/products/index.htm. Accessed 10 July 2020.
8. WHO/Europe. Obesity—data and statistics. Available at: https://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/data-and-statistics. Accessed 10 July 2020.
9. Xerava (eravacycline) injection, for intravenous use. Prescribing information. Tetraphase Pharmaceuticals, Inc.; **2018**. Available at: www.fda.gov/medwatch. Accessed 14 July 2020.
10. Xerava (eravacycline) injection, for intravenous use. Prescribing information. Tetraphase Pharmaceuticals, Inc.; **2018**. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/xerava. Accessed 14 July 2020.
11. Xiao XY, Hunt DK, Zhou J, et al. Fluorocyclines. 1. 7-fluoro-9-pyrrolidinoacetamido-6-demethyl-6- deoxytetracycline: a potent, broad spectrum antibacterial agent. J Med Chem **2012**; 55:597–605.
12. Sutcliffe JA, O'Brien W, Fyfe C, Grossman TH. Antibacterial activity of eravacycline (TP-434), a novel fluorocycline, against hospital and community pathogens. Antimicrob Agents Chemother **2013**; 57:5548–58.
13. Zhanel GG, Cheung D, Adam H, et al. Review of eravacycline, a novel fluorocycline antibacterial agent. Drugs **2016**; 76:567–88.
14. Monogue ML, Thabit AK, Hamada Y, Nicolau DP. Antibacterial efficacy of eravacycline in vivo against gram-positive and gram-negative organisms. Antimicrob Agents Chemother **2016**; 60:5001–5.
15. Livermore DM, Mushtaq BS, Warner AM, Woodforda AN. In vitro activity of eravacycline against carbapenem-resistant Enterobacteriaceae and *Acinetobacter baumannii*. Antimicrob Agents Chemother **2016**; 60:3840–4.
16. Lutgring JD, Balbuena R, Reese N, et al. Antibiotic Susceptibility of NDM-Producing Enterobacterales Collected in the United States in 2017 and 2018. Antimicrob Agents Chemother. **2020**; 64:e00499–20.
17. Solomkin JS, Gardovskis J, Lawrence K, et al. IGNITE4: Results of a phase 3, randomized, multicenter, prospective trial of eravacycline vs meropenem in the treatment of complicated intraabdominal infections. Clin Infect Dis **2019**; 69:921–9.
18. Solomkin J, Evans D, Slepavicius A, et al. Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the investigating gram-negative infections treated with eravacycline (IGNITE 1) trial a randomized clinical trial. JAMA Surg **2017**; 152:224–32.
19. Barras M, Legg A. Drug dosing in obese adults. Aust Prescr **2017**; 40:189–93.
20. Serrano PE, Khuder SA, Fath JJ. Obesity as a risk factor for nosocomial infections in trauma patients. J Am Coll Surg **2010**; 211:61–7.
21. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes **2013**; 37:333–40.
22. Falagas ME, Karageorgopoulos DE. Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet **2010**; 375:248–51.
23. Francisco V, Pino J, Campos-Cabaleiro V, et al. Obesity, fat mass and immune system: role for leptin. Front Physiol **2018**; 9:640.
24. ClinicalTrials.gov. Efficacy and safety study of eravacycline compared with ertapenem in complicated intra-abdominal infections. **2000**. Available at: https://clinicaltrials.gov/ct2/show/NCT01844856. Accessed 14 July 2020.

25. ClinicalTrials.gov. Efficacy and safety study of eravacycline compared with meropenem in complicated intra-abdominal infections. Available at: https://clinicaltrials.gov/ct2/show/NCT02784704. Accessed 14 July 2020.
26. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. National Institutes of Health. Obes Res **1998**; 6:51S–209S.
27. Peck CC, Cross JT. "Getting the dose right": facts, a blueprint, and encouragements. Clin Pharmacol Ther **2007**; 82:12–4.
28. Janson B, Thursky K. Dosing of antibiotics in obesity. Curr Opin Infect Dis **2012**; 25:634–49.
29. Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther **2014**; 39:584–608.
30. Tucker CE, Lockwood AM, Nguyen NH. Antibiotic dosing in obesity: the search for optimum dosing strategies. Clin Obes **2014**; 4:287–95.
31. Meng L, Mui E, Holubar MK, Deresinski SC. Comprehensive guidance for antibiotic dosing in obese adults. Pharmacotherapy **2017**; 37:1415–31.
32. Bhalodi AA, Papasavas PK, Tishler DS, et al. Pharmacokinetics of intravenous linezolid in moderately to morbidly obese adults. Antimicrob Agents Chemother **2013**; 57:1144–9.
33. Hutton M, Kenney RM, Vazquez JA, Davis SL. Influence of body weight category on outcomes in candidemia patients treated with anidulafungin. J Pharm Pract. **In press**.
34. Erstad BL. Which weight for weight-based dosage regimens in obese patients? Am J Health Syst Pharm **2002**; 59:2105–10.
35. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet **2010**; 49:71–87.
36. Alosaimy S, Molina KC, Claeys KC, et al. Early experience with eravacycline for complicated infections. Open Forum Infectious Diseases **2020**; 7:ofaa071.