Efficacy and Safety of Eravacycline in Obese Patients: a post hoc analysis of pooled data from IGNITE1 and IGNITE4 clinical trials

Tomefa E. Asempa1, Sergey Izmailyan2, Kenneth Lawrence3, and David P. Nicolau1,4

1Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT, 2University of Texas School of Public Health, Dallas, TX, 3Tetraphase Pharmaceuticals, Watertown, MA, 4Division of Infectious Diseases, Hartford Hospital, Hartford, CT

2Formerly of Tetraphase Pharmaceuticals

Summary: This analysis demonstrates the therapeutic utility and acceptable safety profile of eravacycline across the weight spectrum, particularly in obese patients (BMI ≥ 30 kg/m²).

Corresponding Author:
David P. Nicolau, Center for Anti-Infective Research and Development, Hartford Hospital 80 Seymour Street, Hartford, CT 06102; Tel: 860-972-3941; Fax: 860-545-3992; Email: david.nicolau@hhchealth.org

Alternate Corresponding Author:
Tomefa E. Asempa, Center for Anti-Infective Research and Development, Hartford Hospital 80 Seymour Street, Hartford, CT 06102; Tel: 860-972-1109; Fax: 860-545-3992; Email: tomefa.asempa@hhchealth.org

© The Author(s) 2020. Published by Oxford University Press on behalf of Infectious Diseases Society of America.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Abstract

Background. 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 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% - 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 (i.e., 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$^2$).

Key words: Obesity; BMI; eravacycline; multidrug resistance; complicated intra-abdominal infection
Introduction

Antimicrobial therapy in obese patients can represent a clinical challenge due to physiological changes in cardiac output, volume of distribution, liver and renal function, ultimately resulting in altered drug pharmacokinetics and the potential for inadequate drug exposures [1–4]. Obesity (BMI ≥ 30 kg/m²) 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 are overweight while obesity affects 10-30% of adults [8]. This increasingly prevalent comorbid condition warrants examining 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 FDA- and EMA-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 (i.e., 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 ertapenem (IGNITE1) or meropenem (IGNITE4) as the active comparator for 4 to 14 days of therapy. An assessment of clinical outcomes demonstrated that eravacycline was non-inferior
to carbapenems at the test-of-cure visit in all pre-specified 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 is therefore to examine clinical cure rates, incidence of adverse events, and drug discontinuation rates by weight categories in patients with cIAI receiving eravacycline versus carbapenem comparator.

**Study Design and Population**

We performed post hoc analysis of the pooled efficacy and safety data from the IGNITE1 (NCT01844856) and IGNITE4 (NCT02784704) clinical trials that were conducted in 13 and 11 countries respectively [17,18]. Briefly, these phase 3, randomized, double-blind, multicenter non-inferiority 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) non-inferiority 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 versus 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 prior to study initiation. All patients at each site provided a written consent prior to study enrollment. Each trial was conducted in accordance with Good Clinical Practice and 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) Body Mass Index (BMI) categories: BMI > 40 kg/m² (Obese, Class III), BMI: 35-39.9 kg/m² (Obese, Class II), BMI: 30-34.9 kg/m² (Obese, Class I), BMI: 25-29.9 kg/m² (Overweight), BMI: 18.5-24.9 kg/m² (Healthy weight), and BMI < 18.5 kg/m² (Underweight) [26].

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

**Statistical analyses**

Descriptive statistics were performed using Sigma Plot 14 (Systat Software Inc, San Jose, CA). 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 \( \chi^2 \) test and a pre-specified alpha-level of 0.05 was used. For additional sensitivity analysis, efficacy endpoints were also assessed based on 3 patient weight (kg) 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 sub-classified 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 \( n=129 \) 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 \( (p = 0.223) \). Among the 129 eravacycline-treated obese patients, a 93.9% cure rate in the Obese Class II population suggests efficacy was not impacted as patient BMI increased.

Concordant observations were made when kilogram only weight cut-offs were applied to the micro-ITT population: <70 kg \( (85/92; 92.4\%) \), 70 - 100 kg \( (247/281; 87.9\%) \), and >100 kg \( (36/42; 85.7\%) \) \( (p = 0.199) \). In the carbapenem comparator group, a similar proportion of patients demonstrated clinical response utilizing either BMI categories or kilogram only cut-offs: 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, i.e., 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 TEAE and study drug discontinuation rates was stratified by BMI to elucidate any differences by weight groups (Table 2). Of the TEAEs that occurred in more than 2% of eravacycline-treated obese
patients, a larger proportion were gastrointestinal-related; nausea (11.2%) and vomiting (5.6%) was recorded among eravacycline-treated obese patients while comparator obese patients experienced a 2.1% and 3.4% incidence rate, 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%) patients.

Concordant with BMI analysis, gastrointestinal-related AEs occurred more frequently in eravacycline-treated patients weighing over 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) and 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 exist 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 in the healthcare system. The IGNITE1 and IGNITE4 clinical trials were pivotal phase 3 studies...
that demonstrated the non-inferiority of eravacycline compared with carbapenems for the treatment of cIAI subsequently resulting 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 (i.e., 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 of 0.3 mg/mL (range 0.2 to 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 BMI, 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/m²), this study serves to address a knowledge gap with eravacycline dosing in an increasing 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/m².
Notes

Acknowledgments. We thank Stephanie Hughes for contributions to data analysis.

Financial support. This work was supported by Tetraphase Pharmaceuticals Inc.

Potential conflicts of interest. D.P.N has received support from Tetraphase Pharmaceuticals Inc. K. L. is employed by Tetraphase Pharmaceuticals Inc. S.I. is a former employee of Tetraphase Pharmaceuticals Inc. T.E.A has no conflicts of interest to report. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.
Reference

1. Pai MP, Bearden DT. Antimicrobial Dosing Considerations in Obese Adult Patients. Pharmacotherapy 2007; 27:1081–1091. Available at: https://pubmed.ncbi.nlm.nih.gov/17655508/. Accessed 8 July 2020.
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; 14:275–285. Available at: https://pubmed.ncbi.nlm.nih.gov/29431542/. Accessed 8 July 2020.
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. Available at: www.sisna.org. Accessed 8 July 2020.
4. Wurtz R, Itozuka G, Rodvold K. Antimicrobial Dosing in Obese Patients. Clin Infect Dis 1997; 25:112–118. Available at: https://academic.oup.com/cid/article-lookup/doi/10.1086/514505. Accessed 15 July 2020.
5. Hurt RT, Kulisek C, Buchanan LA, McClave SA. The obesity epidemic: Challenges, health initiatives, and implications for gastroenterologists. Gastroenterol. Hepatol. 2010; 6:780–792. Available at: /pmc/articles/PMC3033553/?report=abstract. Accessed 10 July 2020.
6. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann. Transl. Med. 2017; 5. Available at: /pmc/articles/PMC5401682/?report=abstract. Accessed 10 July 2020.
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. FDA. Tetraphase Pharmaceuticals, Inc. Xerava (eravacycline) injection, for intravenous use. Prescribing information. Watertown, MA. Tetraphase, 2018. Available at: www.fda.gov/medwatch. Accessed 14 July 2020.
10. EMA. Tetraphase Pharmaceuticals, Inc. Xerava (eravacycline) injection, for intravenous use. Prescribing information. Watertown, MA. Tetraphase, 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. Available at: https://pubmed.ncbi.nlm.nih.gov/22148514/. Accessed 10 July 2020.
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; 57:5548–5558. Available at: http://aac.asm.org/. Accessed 10 July 2020.
13. Zhanel GG, Cheung D, Adam H, et al. Review of Eravacycline, a Novel Fluorocycline Antibacterial Agent. Drugs. 2016; 76:567–588. Available at: https://pubmed.ncbi.nlm.nih.gov/26863149/. Accessed 10 July 2020.
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; 60:5001–5005. Available at:
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; 60:3840–3844. Available at: https://pubmed.ncbi.nlm.nih.gov/27044556/. Accessed 14 July 2020.

16. Lutgring JD, Balbuena R, Reese N, et al. Antibiotic Susceptibility of NDM-Producing Enterobacteriales Collected in the United States, 2017-2018. Antimicrob Agents Chemother 2020; Available at: https://pubmed.ncbi.nlm.nih.gov/32540972/. Accessed 6 August 2020.

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; 69:921–929. Available at: https://pubmed.ncbi.nlm.nih.gov/30561562/. Accessed 14 July 2020.

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; 152:224–232. Available at: https://pubmed.ncbi.nlm.nih.gov/27851857/. Accessed 14 July 2020.

19. Barras M, Legg A. Drug dosing in obese adults. Aust Prescr 2017; 40:189–193. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5662437/. Accessed 6 August 2020.

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. Available at: https://pubmed.ncbi.nlm.nih.gov/20610250/. Accessed 14 July 2020.

21. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int. J. Obes. 2013; 37:333–340. Available at: www.nature.com/ijo. Accessed 10 July 2020.

22. Falagas ME, Karageorgopoulos DE. Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet 2010; 375:248–251. Available at: www.thelancet.com. Accessed 8 July 2020.

23. Francisco V, Pino J, Campos-Cabaleiro V, et al. Obesity, fat mass and immune system: Role for leptin. Front. Physiol. 2018; 9:640. Available at: www.frontiersin.org. Accessed 10 July 2020.

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 - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02784704. Accessed 14 July 2020.

26. 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 Suppl 2:51S–209S. Available at: https://pubmed.ncbi.nlm.nih.gov/9813653/. Accessed 14 July 2020.

27. Peck CC, Cross JT. “Getting the Dose Right”: Facts, a Blueprint, and Encouragements. Clin Pharmacol Ther 2007; 82:12–14. Available at: http://doi.wiley.com/10.1038/sj.clpt.6100215. Accessed 8 July 2020.

28. Janson B, Thursky K. Dosing of antibiotics in obesity. Curr. Opin. Infect. Dis. 2012; 25:634–649. Available at: https://pubmed.ncbi.nlm.nih.gov/23041773/. Accessed 8 July 2020.

29. Polso AK, Lassiter JL, Nagel Pharmd 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. Available at: https://pubmed.ncbi.nlm.nih.gov/25826157/. Accessed 8 July 2020.

31. Meng L, Mui E, Holubar MK, Deresinski SC. Comprehensive Guidance for Antibiotic Dosing in Obese Adults. Pharmacotherapy. 2017; 37:1415–1431. Available at: https://pubmed.ncbi.nlm.nih.gov/28869666/. Accessed 15 July 2020.

32. Bhalodi AA, Papasavas PK, Tishler DS, Nicolau DP, Kuti JL. Pharmacokinetics of intravenous linezolid in moderately to morbidly obese adults. Antimicrob Agents Chemother 2013; 57:1144–1149. Available at: /pmc/articles/PMC3591894/?report=abstract. Accessed 10 July 2020.

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 2020; :897190020938219. Available at: http://journals.sagepub.com/doi/10.1177/0897190020938219. Accessed 21 August 2020.

34. Erstad BL. COMMENTARIES Weight-based dosage regimens Which weight for weight-based dosage regimens in obese patients? 2002.

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, Claeyss KC, et al. Early Experience With Eravacycline for Complicated Infections. Open forum Infect Dis 2020; 7:ofaa071. Available at: https://pubmed.ncbi.nlm.nih.gov/3241809/. Accessed 18 August 2020.
Table 1. Demographics and Baseline Characteristics of the Microbiological Intent-to-Treat Population (Micro-ITT)

| Characteristic                        | Eravacycline group (Weight Category) | Carabapenem comparator group (Weight Category) |
|---------------------------------------|--------------------------------------|-----------------------------------------------|
|                                       | Total (N=415) | Under weight (n=134) | Healthy weight (n=146) | Over weight (n=114) | Obese I (n=39) | Obese II (n=33) | Obese III (n=7) | Total (N=427) | Under weight (n=145) | Healthy weight (n=144) | Over weight (n=144) | Obese I (n=96) | Obese II (n=29) | Obese III (n=4) |
|                                       |              | Under weight           | Healthy weight           | Over weight         | Obese I        | Obese II       | Obese III      |              | Under weight           | Healthy weight           | Over weight         | Obese I         | Obese II       | Obese III       |
| Sex, female                           | 180 (43.4%)  | 4 (66.7%)              | 51 (34.9%)               | 35 (39.3%)         | 5 (84.8%)      | 28 (71.4%)     |                | 194 (45.4%)  | 4 (44.4%)              | 59 (40.7%)               | 54 (37.5%)         | 54 (56.3%)      | 21 (72.4%)     | 2 (50%)         |
| Age, years                            |              |                        |                         |                   |               |                 |                 |              |                        |                         |                  |                |                |                |
| <65                                   | 297 (71.6%)  | 6 (100%)               | 98 (73.1%)              | 97 (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 (0%)                 | 36 (26.9%)              | 49 (33.6%)        | 27 (30.3%)    | 5 (15.2%)      | 1 (14.3%)      | 127 (29.7%)  | 0 (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 (100%)               | 130 (89.7%)              | 121 (84%)        | 74 (77.1%)      | 21 (72.4%)     | 3 (75%)        |
| 11-14                                 | 39 (9.4%)    | 0 (0%)                 | 8 (6%)                  | 8 (9%)           | 4 (12.1%)     | 0 (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 (0%)                 | 4 (3%)                  | 8 (9%)           | 0 (0%)        |               |               | 14 (3.3%)    | 0 (0%)                 | 2 (1.4%)                | 8 (5.6%)        | 2 (2.1%)        | 0 (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, days          | 7.61 ± 2.83  | 6.67 ± 2.56            | 7.57 ± 3.12             | 7.88 ± 3.06       | 7.46 ± 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    |

APACHE: Acute Physiology and Chronic Health Evaluation

Underweight: BMI < 18.5 kg/m², Healthy weight: BMI 18.5-24.9 kg/m², Overweight: BMI 25-29.9 kg/m², Obese Class I: BMI 30-34.9 kg/m², Obese Class II: BMI 35-39.9 kg/m², Obese Class III: BMI > 40 kg/m²
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) Under weight (n=7)     | Total (N=517) Under weight (n=12) |
|                                | Healthy weight (n=172)               | Healthy weight (n=184) |
|                                | Over weight (n=180)                  | Over weight (n=176) |
|                                | Obese I (n=106)                     | Obese I (n=110) |
|                                | Obese II (n=44)                     | Obese II (n=31) |
|                                | Obese III (n=11)                    | Obese III (n=4) |
| Nausea                         | 34 (6.5%)                           | 5 (1.0%) |
|                                | 0                                  | 1 (8.3%) |
|                                | 8 (4.7%)                            | 1 (0.5%) |
|                                | 8 (4.4%)                            | 0       |
|                                | 9 (8.5%)                            | 0       |
|                                | 5 (11.4%)                           | 4 (2.7%) |
|                                | 4 (36.4%)                           | 0       |
| Vomiting                       | 20 (3.8%)                           | 15 (2.9%) |
|                                | 0                                  | 3 (1.6%) |
|                                | 7 (4.1%)                            | 7 (4.0%) |
|                                | 4 (2.2%)                            | 3 (2.7%) |
|                                | 5 (4.7%)                            | 2 (6.5%) |
|                                | 2 (4.5%)                            | 2       |
|                                | 3 (18.2%)                           | 0       |
| Wound infection (superficial)  | 14 (2.7%)                           | 6 (1.2%) |
|                                | 0                                  | 4 (2.2%) |
|                                | 3 (1.7%)                            | 4 (1.8%) |
|                                | 6 (3.3%)                            | 0       |
|                                | 2 (1.9%)                            | 2       |
|                                | 3 (6.8%)                            | 0       |
|                                | 0                                  | 2       |
| Infusion site phlebitis        | 13 (2.5%)                           | 1 (0.2%) |
|                                | 0                                  | 1 (0.5%) |
|                                | 5 (2.9%)                            | 0       |
|                                | 4 (2.2%)                            | 0       |
|                                | 4 (3.8%)                            | 0       |
|                                | 0                                  | 0       |
| Diarrhea                       | 12 (2.3%)                           | 8 (1.5%) |
|                                | 0                                  | 2 (1.1%) |
|                                | 3 (1.7%)                            | 2 (1.1%) |
|                                | 4 (2.2%)                            | 4       |
|                                | 3 (2.8%)                            | 3 (3.6%) |
|                                | 1 (2.3%)                            | 0       |
|                                | 1 (9.1%)                            | 1 (3.2%) |
| Anemia                         | 10 (1.9%)                           | 15 (2.9%) |
|                                | 0                                  | 6 (3.3%) |
|                                | 3 (1.7%)                            | 4 (2.3%) |
|                                | 3 (1.7%)                            | 4       |
|                                | 4 (3.8%)                            | 4       |
|                                | 0                                  | 1       |
| Pyrexia                        | 10 (1.9%)                           | 11 (2.1%) |
|                                | 0                                  | 4 (2.2%) |
|                                | 4 (2.3%)                            | 5 (2.8%) |
|                                | 3 (1.7%)                            | 2 (1.8%) |
|                                | 2 (1.9%)                            | 0       |
| Hypertension                   | 6 (1.2%)                            | 11 (2.1%) |
|                                | 0                                  | 1 (0.5%) |
|                                | 3 (1.7%)                            | 5 (2.8%) |
|                                | 2 (1.9%)                            | 3 (2.7%) |
|                                | 1 (2.3%)                            | 2       |
|                                | 0                                  | 6       |
| Discontinued because of any    | 9 (1.7%)                            | 10 (1.9%) |
| adverse event                  | 1 (14.3%)                           | 0       |
|                                | 2 (1.2%)                            | 2       |
|                                | 2 (1.1%)                            | 2       |
|                                | 3 (2.8%)                            | 1       |
|                                | 1 (2.3%)                            | 0       |
|                                | 0                                  | 6       |

Underweight: BMI < 18.5 kg/m², Healthy weight: BMI 18.5-24.9 kg/m², Overweight: BMI 25-29.9 kg/m², Obese Class I: BMI 30-34.9 kg/m², Obese Class II: BMI 35-39.9 kg/m², Obese Class III: BMI > 40 kg/m²
Figure Legends

**Figure 1.** Patient distribution by weight category in the (A) eravacycline (N=415) and (B) carbapenem comparator (N=427) micro-ITT population at baseline

**Figure 2.** Clinical cure rate analyzed by weight category in the micro-ITT population at test-of-cure
Figure 1. Patient distribution by weight category in the (A) eravacycline (N=415) and (B) carbapenem comparator (N=427) micro-ITT population at baseline.
Figure 2. Clinical cure rate analyzed by weight category in the micro-ITT population at test-of-cure.