Efficacy and Safety of Omadacycline in Patients With Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and High Body Mass Index or Diabetes: A Subgroup Analysis From the OASIS Trial

Poster 1838

Mark Wilcox, MD[1]; Nancy Cure-Bolt, MD[2]; Surya Chitra, PhD, MBA[2]; Evan Tzanis, BA[2]; Paul McGovern, MD[2]

[1]Leeds Teaching Hospitals, Leeds, UK; [2]Paratek Pharmaceuticals, King of Prussia, PA, USA

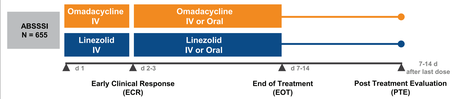
BACKGROUND

- The incidence and severity of acute bacterial skin and skin structure infections (ABSSSI) have increased in recent years, imposing a substantial burden on the healthcare system. ABSSSI include cellulitis, erysipelas, wound infections, and major cutaneous abscesses[1,2]
- The PK of many antibacterial agents, including beta-lactams, aminoglycosides, vancomycin, fluoroquinolones, and daptomycin are altered in obese patients, and dosing adjustments are suggested for this population[3,4]
- Further, recent reports indicate that diabetes is the most common comorbidity among hospitalized SSSI patients[1]
- Omadacycline (OMC), a first-in-class aminomethylcycline antibiotic, is a semisynthetic derivative of the tetracyclines that exhibits activity against Gram-positive and Gram-negative aerobes, anaerobes, and atypical bacteria[5-9]
- In the **O**madacycline in **A**cute **S**kin and Skin Structure **I**nfections **S**tudy (OASIS-1, NCT02378480), intravenous to oral OMC demonstrated non-inferiority to intravenous to oral linezolid (LZD) for the treatment of ABSSSI with comparable safety in the general population.[10] In the OASIS-2 study (NCT02877927), oral-only administration of OMC demonstrated non-inferiority to oral LZD for the treatment of ABSSSI with comparable safety in the general population[11]
- The goal of this work was to determine if body mass index (BMI) or medical history of diabetes mellitus had any effect on the efficacy or safety of OMC relative to LZD in the OASIS-1 study

METHODS

- OASIS-1 was a randomized (1:1), double-blind, active comparator-controlled, phase 3 study comparing OMC with LZD for the treatment of adults with ABSSSI[10]
  - Patients randomized to OMC treatment were administered OMC 100 mg intravenously (IV) every 12 hours (q12h) for 2 doses, followed by 100 mg IV OMC every 24 hours (q24h), for a minimum of 3 days of IV OMC. Patients could then transition to 300 mg OMC administered orally q24h for a total treatment duration of 7 to 14 days
  - Patients randomized to LZD treatment were administered LZD 600 mg IV q12h. After a minimum of 3 days of IV therapy, patients could transition to oral LZD, with 600 mg LZD administered q12h, with a total treatment duration of 7 to 14 days

Figure 1. OASIS-1 Study Design.



- Patients from OASIS-1 were classified on the basis of BMI and medical history of diabetes mellitus:
  - Normal BMI: BMI < 25 kg/m^2
  - High BMI: BMI ≥ 25 kg/m^2
    - Overweight: 25 kg/m^2 ≤ BMI < 30 kg/m^2
    - Obese: BMI ≥ 30 kg/m^2
    - Diabetic: any patient with a medical history of diabetes mellitus, irrespective of BMI
- Study endpoints were
  - Early clinical response (ECR): survival with ≥ 20% reduction in lesion size at 48 to 72 hours after first dose of OMC or LZD
  - Clinical success at post treatment evaluation (PTE) assessed 7-14 days after the last dose of OMC or LZD: survival with resolution of signs and symptoms of the infection such that further antibacterial therapy is not needed
  - Patients whose clinical response to OMC or LZD could not be adequately inferred due to withdrawal of consent, loss to follow-up, or other specified reason were considered indeterminate

METHODS

- Any systemic or topical antibacterial agent with a spectrum that is active against the potential infecting pathogen(s) responsible for the ABSSSI under study was prohibited, except in cases of clinical failure
- Bacterial pathogens were identified from a biopsy of the involved tissue at baseline (Day –1 or 1). For patients with cellulitis/erysipelas, if no infectious material had been obtained or no pathogen identified, a Day 2 or 3 sample was used as baseline.
- Any planned surgical treatments were to be performed within 24 hours and no later than 48 hours after the first dose of OMC or LZD
- Safety was assessed based on adverse events (AEs), vital signs, electrocardiograms (ECGs), and standard clinical laboratory tests
- Populations for analysis:
  - Modified intent-to-treat (mITT): all randomized patients without a baseline sole Gram-negative ABSSSI pathogen
  - Clinically evaluable (CE): patients in the mITT population who received at least 1 dose of OMC or LZD, PTE visit occurred 7 to 14 days after last dose of OMC or LZD, and overall clinical response was not indeterminate at PTE
  - Safety: all randomized patients who received any dose of OMC or LZD
  - micro-mITT: All patients in the mITT population who had at least 1 Gram-positive causative bacterial pathogen identified at baseline

RESULTS

Figure 2. Subgroup Breakdown.

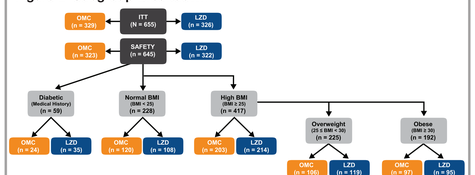
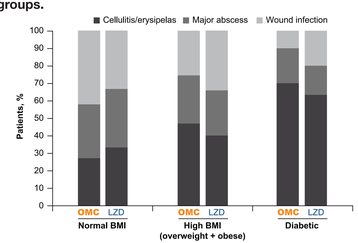


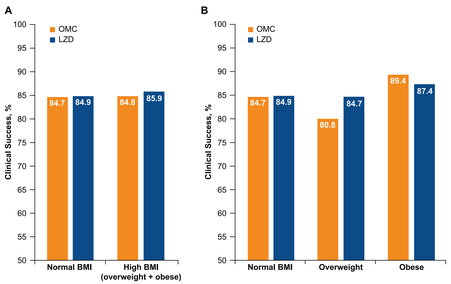
Figure 3. Baseline infections in normal BMI, high BMI, and diabetic subgroups.



- Baseline infections did not differ significantly between the normal BMI and high BMI subgroups, but cellulitis/erysipelas tended to be more frequent in patients with high versus normal BMI (**Figure 3**)
- In the diabetic subgroup, cellulitis/erysipelas was the most common and wound infection was the least common baseline infection (**Figure 3**)
- Baseline pathogens were similar across all subgroups
  - *S. aureus* was the most common baseline pathogen (66% of all patients had *S. aureus*)

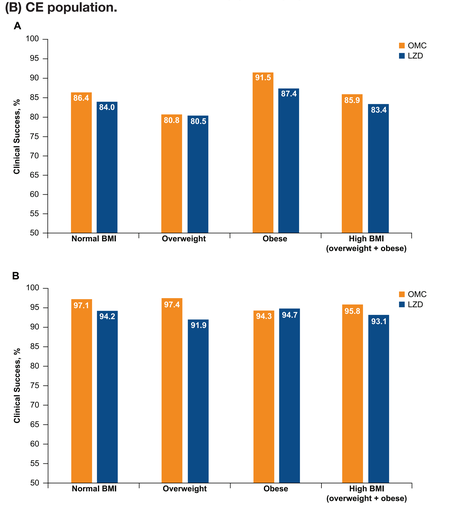
RESULTS

Figure 4. Clinical success at ECR in mITT population.



- Clinical success at ECR was similar between OMC and LZD treatment in both the normal BMI and high BMI subgroups (**Figure 4A**)
  - Within the high BMI group, overweight patients had a higher ECR rate with LZD and obese patients had a higher ECR rate with OMC (**Figure 4B**)
  - No significant differences were observed between OMC- and LZD-treated patients within subgroups

Figure 5. Clinical success at PTE in (A) mITT population and (B) CE population.



RESULTS

- At PTE, in both the mITT and CE populations, OMC-treated patients trended to higher clinical success compared to LZD-treated patients across most BMI subgroups (**Figure 5**)
- At PTE, in both the mITT and CE populations, OMC-treated diabetic patients showed higher clinical success compared to LZD-treated diabetic patients (data not shown)
- No significant differences in clinical success were observed between OMC- and LZD-treated patients within subgroups

Table 1. Overview of Treatment-Emergent Adverse Events

	Normal BMI		High BMI (overweight + obese)		Diabetic	
	OMC N = 120	LZD N = 108	OMC N = 203	LZD N = 214	OMC N = 24	LZD N = 35
Patients with at least 1 TEAE, n (%)	65 (54.17)	53 (49.07)	91 (44.83)	94 (43.93)	11 (45.83)	15 (42.86)
Drug-related TEAEs, n (%)	15 (12.50)	16 (14.81)	24 (11.82)	26 (12.15)	3 (12.50)	3 (8.57)
Severe TEAEs, n (%)	1 (0.83)	1 (0.93)	2 (0.99)	2 (2.80)	0	2 (5.71)
Serious TEAEs, n (%)	0	1 (0.93)	3 (1.48)	3 (1.87)	0	1 (2.86)
Drug-related serious TEAEs, n (%)	0	0	0	0	0	0
TEAEs leading to discontinuation, n (%)	0	1 (0.93)	5 (2.46)	3 (1.40)	0	0
Serious TEAEs leading to death, n (%)	0	1 (0.93)	0	1 (0.47)	0	0

BMI, body mass index; TEAE, treatment-emergent adverse event.

- Overall TEAEs and drug-related TEAEs were comparable among OMC- and LZD-treated patients in all subgroups
- There were very few severe or serious TEAEs and no drug-related serious TEAEs in any subgroups across both OMC and LZD recipients
- There were no statistically significant differences in TEAEs leading to discontinuation

Table 2. Frequency of Gastrointestinal, Liver Chemistry and Infusion Site Extravasation Treatment-Emergent Adverse Events

	Normal BMI		High BMI (overweight + obese)		Diabetic	
	OMC N = 120	LZD N = 108	OMC N = 203	LZD N = 214	OMC N = 24	LZD N = 35
Gastrointestinal TEAEs, n (%)						
Nausea	3 (2.50)	8 (7.41)	5 (2.46)	12 (5.61)	0	1 (2.86)
Diarrhea	2 (1.67)	2 (1.85)	4 (1.97)	6 (2.80)	1 (4.17)	1 (2.86)
Vomiting	2 (1.67)	1 (0.93)	0	1 (0.47)	0	0
Liver Chemistry TEAEs, n (%)						
ALT increased	3 (2.50)	3 (2.78)	4 (1.97)	11 (5.14)	0	0
AST increased	2 (1.67)	0	1 (0.49)	1 (0.47)	0	0
Infusion site extravasation, n (%)	9 (7.50)	3 (2.78)	6 (2.96)	7 (3.27)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; TEAE, treatment-emergent adverse event.

RESULTS

- Overall, gastrointestinal TEAEs were moderate
  - Nausea was less frequent in patients treated with OMC vs LZD
- There were minor variations in liver chemistry between regimens across subgroups
- 79% of patients in each treatment group had ABSSSI considered related to IV drug use. All infusion site extravasation events were mild and typically due to difficulty in finding reliable venous access sites.

CONCLUSIONS

- IV to once-daily oral omadacycline was effective and well tolerated for treating ABSSSI irrespective of BMI or diabetic status
  - No difference in outcomes was observed in OMC-treated patients regardless of BMI or diabetic status
  - No significant differences in efficacy at ECR or PTE were observed between omadacycline and linezolid treatment in any subgroup
  - Overall, TEAEs were comparable between omadacycline and linezolid treatment
  - Gastrointestinal TEAEs were infrequent across both omadacycline and linezolid treatment
- These data show that omadacycline is well tolerated and clinically effective in patients with high BMI or diabetes, with no need for dosage adjustment

REFERENCES

1. Kaye KS, et al. *PLoS One*. 2015;10(11):e0143276.
2. US FDA. Guidance for Industry. Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. 2013.
3. Pai MP, et al. *Pharmacotherapy*. 2007;27(8):1081-1091.
4. Tucker CE, et al. *Clin Obes*. 2014;4(6):287-295.
5. Villano S, et al. *Future Microbiol*. 2016;11:1421-1434.
6. Honeyman L, et al. *Antimicrob Agents Chemother*. 2015;59(11):7044-7053.
7. Draper MP, et al. *Antimicrob Agents Chemother*. 2014;58(3):1279-1283.
8. Tanaka SK, et al. *Bioorg Med Chem*. 2016;24(24):6409-6419.
9. Macone AB, et al. *Antimicrob Agents Chemother*. 2014;58(2):1127-1135.
10. O'Riordan W, et al. Presented at ECCMID. 24 April 2017; Vienna, Austria. Abstract 630.
11. Paratek Pharmaceuticals [press release]. Boston, MA; July 17, 2017.

FUNDING AND DISCLOSURES

This work was funded by Paratek Pharmaceuticals, Inc.

ACKNOWLEDGMENTS

Medical editorial assistance, funded by Paratek Pharmaceuticals, Inc., was provided by Healthcare Consultancy Group.

Presented at: IDWeek 2017; October 4-8, 2017; San Diego, CA