Treatment of wound infection using omadacycline versus linezolid: Pooled results from Phase 3 randomized, double-blind, multicenter studies (OASIS-1 and -2)

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Disclosures

- Kelly Wright, Dina Besece, and Amy Manley are Paratek Pharmaceuticals, Inc. employees and shareholders
- Surya Chitra is a consultant to Paratek Pharmaceuticals, Inc

Background (1)

- Skin and skin structure infections place a considerable burden on healthcare systems[1,2]
- Acute bacterial skin and skin structure infections (ABSSSI) account for more than 800,000 hospitalizations annually in the United States and Europe[3]

1. Russo A, et al. *Clin Microbiol Infect*. 2016;22(suppl 2):S27–36; 2. Kaye KS, et al. *PLoS One*. 2015;10:e0143276;
3. Edelsberg J, et al. *Emerg Infect Dis*. 2009;15:1516–18.

Background (2)

- Omadacycline is a novel aminomethylcycline antibiotic approved in the United States for community-acquired bacterial pneumonia and ABSSSI in adults[1]
  - Intravenous and oral formulations
  - Designed to overcome the two main mechanisms of tetracycline resistance: efflux pumps and ribosomal protection[2,3]
- Omadacycline has in vitro and in vivo activity against key pathogens, including *Staphylococcus aureus* (MRSA and MSSA) and *Streptococcus pyogenes*[3,4]

ABSSSI, acute bacterial skin and skin structure infection; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus.*

1. NUZYRA® (omadacycline) Prescribing Information. May 2021. https://www.nuzyra.com/nuzyra-pi.pdf; 2. Draper MP, et al. *Antimicrob Agents Chemother*. 2014;58:1279–83; 3. Macone AB, et al. *Antimicrob Agents Chemother*. 2014;58:1127–35; 4. Russo A, et al. *Clin Microbiol Infect*. 2016;22(suppl 2):S27–36.

Objective

To report results of a pooled post-hoc analysis of data from the OASIS-1 and -2 phase 3 clinical program for ABSSSI[1,2] in patients who had wound infection and were not PWID

ABSSSI, acute bacterial skin and skin structure infection; OASIS, Omadacycline in Acute Skin and Skin Structure Infections Study; PWID, persons who inject drugs.

1. O'Riordan W, et al. *N Engl J Med*. 2019;380:528–38; 2. O'Riordan W, et al. *Lancet Infect Dis*. 2019;19:1080–90.

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OASIS-1 and OASIS-2: Eligibility criteria and treatment duration

- Methodology for OASIS-1 (NCT02378480) and OASIS-2 (NCT02877927) has been previously described[1,2]

- In both studies, eligible patients were ≥18 years of age and had qualifying ABSSSI with lesion size measuring ≥75 cm^2 within 24 hours before randomization[1,2]

- Planned duration of therapy for both studies was 7–14 days[1,2]

ABSSSI, acute bacterial skin and skin structure infection; OASIS, Omadacycline in Acute Skin and Skin Structure Infections Study.

1. O'Riordan W, et al. *Lancet Infect Dis*. 2019;19:1080–90; 2. O'Riordan W, et al. *N Engl J Med*. 2019;380:528–38.

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Treatment regimens used in OASIS trials

- OASIS-1 (NCT02378480) patients received
  - IV to oral omadacycline or linezolid[1]
  - Possible transition to oral regimens after ≥3 days of IV therapy (omadacycline: 300 mg q24h; linezolid: 600 mg q12h)
  - Eligible for transition to oral therapy with evidence of local and systemic improvement:
    - Temperature ≤100°F
    - Return of white blood cell count and differential toward normal range
    - No increase in lesion area compared to baseline
    - Decrease in extent and intensity of ≥1 inflammatory finding
- OASIS-2 (NCT02877927) patients received
  - Oral-only omadacycline or linezolid[2]
  - Omadacycline (Day 1, 2: 450 mg q24h; Day 3+: 300 mg q24h) versus linezolid (600 mg q12h)

IV, intravenous; OASIS, Omadacycline in Acute Skin and Skin Structure Infections Study.

1. O'Riordan W, et al. *N Engl J Med*. 2019;380:528–38; 2. O'Riordan W, et al. *Lancet Infect Dis*. 2019;19:1080–90.

Efficacy and safety endpoints

- Primary efficacy endpoint: ECR (mITT population), defined as survival with a reduction in lesion size of ≥20% at 48–72 hours after the first dose without rescue antibacterial therapy
- Key secondary efficacy endpoint: survival with resolution or improvement in signs and symptoms of infection (to the extent that further antibacterial therapy was unnecessary) at the PTE (7–14 days after the last dose), mITT population
- Safety: adverse events, vital signs, ECGs, and laboratory results

ABSSSI, acute bacterial skin and skin structure infection; ECGs, electrocardiograms; ECR, early clinical response; mITT, modified intent-to-treat; OASIS, Omadacycline in Acute Skin and Skin Structure Infections Study; PTE, post-treatment evaluation.

Statistical analysis populations

- Patient populations included
  - modified intent-to-treat (mITT; comprising all randomized patients without a sole Gram-negative ABSSSI pathogen, as the comparator linezolid does not provide Gram-negative pathogen coverage), and
  - micro-mITT (all mITT patients who had ≥1 Gram-positive causative pathogen identified from the ABSSSI site or blood culture)

ABSSSI, acute bacterial skin and skin structure infection; mITT, modified intent-to-treat; OASIS, Omadacycline in Acute Skin and Skin Structure Infections Study.

Baseline characteristics

- In the pooled mITT population, 87 patients had wound infection
  - 37 were treated with omadacycline
  - 50 were treated with linezolid
- For omadacycline- and linezolid-treated patients with wound infection, 67.6% and 48.0% were male, mean age was 47.3 and 52.0 years, and mean body mass index was 28.9 and 29.4 kg/m^2, respectively

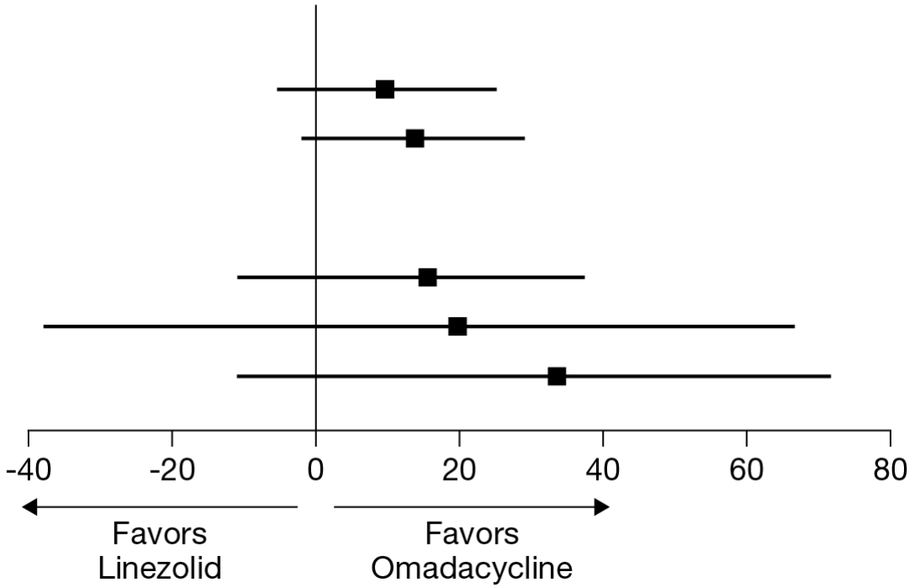
	Omadacycline (N=37)	Linezolid (N=50)
Source of wound infection (mITT), n/N (%)		
Recent trauma	29/37 (78.4)	33/50 (66.0)
Surgical procedure	7/37 (18.9)	3/50 (6.0)
Baseline pathogen (micro-mITT), n/N (%)	N=26	N=37
Gram-positive (aerobes)	25/26 (96.2)	37/37 (100)
Staphylococcus aureus	16/26 (61.5)	26/37 (70.3)
MRSA	6/26 (23.1)	12/37 (32.5)
MSSA	10/26 (38.5)	14/37 (37.8)
Streptococcus pyogenes	2/26 (7.7)	10/37 (27.0)
Enterococcus faecalis	5/26 (19.2)	5/37 (13.5)

mITT, modified intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

Clinical success in patients with wound infection

- Omadacycline and linezolid demonstrated comparable ECR and clinical success at PTE in patients with wound infection
  - Observed for monomicrobial Gram-positive, polymicrobial Gram-positive, and polymicrobial mixed pathogens

	Omadacycline	Linezolid	Percentage-point difference (95% CI)
Patients with wound infection in mITT population			
Early clinical response	34/37 (91.9%)	41/50 (82.0%)	9.9 (-5.6 to 24.3)
Post-treatment evaluation	34/37 (91.9%)	39/50 (78.0%)	13.9 (-2.1 to 28.8)
Patients with wound infection in micro-mITT population (PTE)			
Monomicrobial Gram-positive	13/14 (92.9%)	20/26 (76.9%)	15.9 (-11.7 to 37.1)
Polymicrobial Gram-positive	4/5 (80.0%)	3/5 (60.0%)	20.0 (-38.0 to 67.0)
Polymicrobial mixed (Gram-positive and Gram-negative)	7/7 (100.0%)	4/6 (66.7%)	33.3 (-11.1 to 71.1)



A two-sided 95% CI was calculated for the difference in the proportion of patients achieving ECR, as well as at PTE, using the unadjusted Miettinen–Nurminen method[1] without stratification.

CI, confidence interval; ECR, early clinical response; mITT, modified intent-to-treat; PTE, post-treatment evaluation.

1. Miettinen O, Nurminen M. *Stat Med*. 1985;4:213–26.

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Investigator-assessed clinical success at PTE according to baseline pathogen (micro-mITT)

- Clinical success at PTE was comparable according to baseline pathogen
- This was consistent with the overall finding for the trials

	Omadacycline (N=26)	Linezolid (N=37)
Baseline pathogen, n/N (%)		
S. aureus	15/16 (93.8)	19/26 (73.1)
MRSA	6/6 (100)	9/12 (75.0)
MSSA	9/10 (90.0)	10/14 (71.4)
S. pyogenes	1/2 (50.0)	7/10 (70.0)
E. faecalis	5/5 (100)	3/5 (60.0)

mITT, modified intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PTE, post-treatment evaluation.

Adverse events (safety population)

- No new safety signals were identified for omadacycline and linezolid
  - No patients from either arm discontinued treatment due to serious treatment-emergent adverse events

	Omadacycline (N=40)	Linezolid (N=51)
Total number of TEAEs	53	30
Patients reporting, n (%)		
TEAE	16 (40.0)	18 (35.3)
Serious TEAE	1 (2.5)	2 (3.9)
Serious TEAE leading to treatment discontinuation	0	0
Most common TEAEs occurring in ≥5% of patients, n (%)		
Nausea	8 (20.0)	3 (5.9)
Infusion site extravasation	3 (7.5)	1 (2.0)
ALT increase	3 (7.5)	0
Diarrhea	2 (5.0)	2 (3.9)
AST increase	2 (5.0)	0
Headache	2 (5.0)	0
Vomiting	2 (5.0)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Conclusions

- In adults with wound infection not related to injection drug use, omadacycline was an effective treatment, with clinical efficacy for the most frequently isolated bacterial pathogens, including MRSA
- Omadacycline offers a treatment option to address wound infections, including those resulting from drug-resistant organisms
  - In vitro and in vivo activity against many pathogens, including pathogens of interest such as *Acinetobacter baumannii* and *Klebsiella pneumoniae*
  - Ability to overcome the most common tetracycline resistance mechanisms
  - Flexible administration options

MRSA, methicillin-resistant *Staphylococcus aureus*.

Acknowledgments

- We wish to thank all the patients and investigators from the OASIS studies

Thank you