Efficacy of Oral Omadacycline versus Linezolid for Treating Adult Subjects with ABSSSI: Analysis by Infection Type and Pathogen in the OASIS-2 Study

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Abstract 4346

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BACKGROUND

- Incidence and severity of acute bacterial skin and skin structure infections (ABSSSI) increased in the early 2000s, in part due to the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA)[1]
- Omadacycline (OMC), an aminomethylcycline antibiotic, is in clinical development as a once-daily oral (po) and intravenous (iv) monotherapy for community-acquired bacterial pneumonia and ABSSSI
- OMC has shown potent *in vitro* activity against the common Gram-positive ABSSSI pathogens, including MRSA, many Gram-negative aerobes, anaerobes, and a number of atypical bacterial pathogens[2-3]
- In the previous OASIS-1 trial, iv OMC, with an optional switch to po OMC, was non-inferior to linezolid (LZD), with high and comparable clinical success rates across all infection types[4]
- OASIS-2 was a Phase 3 randomized (1:1), double-blind, United States multicenter study comparing 7 to 14 day po administration of once-daily OMC to twice-daily LZD for the treatment of adults with ABSSSI that was known or suspected to be caused by Gram-positive pathogen(s)
- In OASIS-2, po OMC was non-inferior to po LZD based on Early Clinical Response (ECR; 48-72 hours after first dose) and investigator's assessment of clinical response at Post Therapy Evaluation (PTE; 7-14 days after last dose)[5]
- Here we report the efficacy results of OASIS-2 by clinical infection type and pathogen

METHODS

- Eligible subjects were ≥ 18 years of age who had qualifying ABSSSI with lesions ≥ 75cm^2, and with evidence of systemic inflammatory response within 24 hours before randomization
- Eligible subjects were randomized 1:1 to receive either OMC 450 mg po once daily for 2 doses followed by 300 mg po once daily, or LZD 600 mg po twice daily
  - Randomization was stratified by type of infection (wound infection, cellulitis/erysipelas, and major abscess [limited to not more than 30% of subjects]), and receipt of a single dose of allowed antibiotic therapy within 72 hours prior to dosing (limited to ≤ 25% of subjects)
- Analysis populations
  - Modified intent-to-treat (mITT): All randomized subjects without a baseline sole Gram-negative ABSSSI pathogen
  - Microbiological modified intent-to-treat (micro-mITT): All mITT subjects with ≥ 1 Gram-positive causative pathogen at baseline
  - Clinically evaluable (CE): All mITT subjects who were administered the treatment and met compliance criteria, had a qualifying ABSSSI, did not have any antibiotic or surgical procedures that could impact the assessment of efficacy, and had an assessment of outcome
  - Microbiologically evaluable (ME): All subjects in the micro-mITT and CE populations
- United States Food and Drug Administration (FDA) primary endpoint: ECR of ≥ 20% reduction in primary lesion size at 48-72 hours after the first dose in the mITT population
- European Medicines Agency (EMA) primary endpoint: Investigator's assessment of clinical response at PTE (7-14 days after last dose), in the mITT and CE populations
- Baseline ABSSSI infection site specimens and blood samples were submitted to the local microbiology laboratory on site for Gram stain and culture
  - Pathogens were identified to genus and species level (verified by the central laboratory)
- Results were summarized by treatment group for the micro-mITT population
- Microbiological responses at end of treatment (EOT; day of last dose) and PTE were classed as favorable (eradication and presumed eradication), unfavorable (persistence, presumed persistence, and indeterminate) or indeterminate for micro-mITT population

RESULTS

- The majority of subjects in both treatment groups were male (63%). Approximately 96% were between the ages of 18 and 64 years (overall mean age: 43.7 years)
- Many subjects had recent history of trauma causing the primary infection (75% OMC group, 72% LZD), and/or recent iv drug use (71% OMC, 67% LZD) (**Table 1**)

Table 1. Subjects reporting ABSSSI relevant medical history at baseline (mITT population)

Characteristics	Omadacycline (N = 360) n (%)	Linezolid (N = 360) n (%)
Subjects reported ABSSSI relevant medical history	309 (85.8)	320 (88.9)
Recent trauma that resulted in the primary infection	270 (75.0)	260 (72.2)
Infection was the result of iv drug abuse	254 (70.6)	240 (66.7)
Subject had a prior ABSSSI	200 (55.6)	198 (55.0)
Hepatitis C	116 (32.2)	125 (34.7)
Concurrent secondary ABSSSI lesions	88 (24.4)	95 (26.4)
Diabetes mellitus	14 (3.9)	31 (8.6)
Relevant surgical procedure that resulted in the primary ABSSSI	2 (0.6)	3 (0.8)
Infection was the result of vascular insufficiency or edema	0	2 (0.6)
Peripheral artery disease	0	1 (0.3)
Infection at the primary ABSSSI was associated with chronic skin lesions	0	0

- Primary infection types were comparable between treatment groups (**Table 2**). The majority (~75% per treatment group) occurred in the extremities

Table 2. Primary ABSSSI infection type at screening (mITT population)

Type of Infection	Omadacycline (N = 360) n (%)	Linezolid (N = 360) n (%)
Wound infection	210 (58.3)	214 (59.4)
Cellulitis/erysipelas	86 (23.9)	84 (23.3)
Major abscess	64 (17.8)	62 (17.2)

- Baseline pathogens were isolated from ABSSSI site or blood sample cultures for 75.0% of OMC subjects and 78.2% of LZD subjects
- Similar numbers of subjects had mono-microbial and poly-microbial Gram-positive or poly-microbial mixed infections across the two groups at baseline (**Table 3**)

Table 3. Subjects with mono- and poly-microbial Gram-positive infection, and with poly-microbial mixed infection (micro-mITT population)

Type of Infection	Omadacycline n (%)	Linezolid n (%)
Overall	276	287
Mono-microbial Gram-positive infection	184 (66.7)	212 (73.9)
Poly-microbial Gram-positive infection	60 (21.7)	37 (12.9)
Poly-microbial mixed infection	32 (11.6)	38 (13.2)

- The incidence and distribution of pathogens were similar between treatment groups and consistent with results observed in prior ABSSSI studies (**Table 4**)
- The most frequently identified pathogens were
  - *S aureus* (80% OMC group, 81% LZD group)
    - of which 38% and 37% were MRSA for the OMC and LZD groups, respectively
  - *Streptococcus anginosus* group (21% OMC, 16% LZD)

RESULTS

Table 4. Baseline pathogenic organisms from the ABSSSI site or blood culture by genus and species in ≥ 1% of the population (micro-mITT population)

Baseline Pathogen	Omadacycline (N = 276) n (%)	Linezolid (N = 287) n (%)
Gram-positive organisms (aerobes)	270 (97.8)	278 (96.9)
Staphylococcus aureus	220 (79.7)	233 (81.2)
MSSA	120 (43.5)	130 (45.3)
MRSA	104 (37.7)	107 (37.3)
Streptococcus anginosus group	57 (20.7)	45 (15.7)
Streptococcus anginosus	27 (9.8)	20 (7.0)
Streptococcus intermedius	23 (8.3)	24 (8.4)
Streptococcus constellatus	9 (3.3)	7 (2.4)
Streptococcus pyogenes	29 (10.5)	16 (5.6)
Enterococcus faecalis (VSE)	7 (2.5)	10 (3.5)
Streptococcus oralis	5 (1.8)	2 (0.7)
Staphylococcus lugdunensis	5 (1.8)	0
Staphylococcus viridans group	3 (1.1)	0
Gram-positive organisms (anaerobes)	17 (6.2)	17 (5.9)
Clostridium perfringens	5 (1.8)	9 (3.1)
Clostridium sporogenes	4 (1.4)	1 (0.3)
Actinomyces odontolyticus	3 (1.1)	1 (0.3)
Finegoldia magna	3 (1.1)	1 (0.3)
Gram-negative organisms (aerobes)	24 (8.7)	30 (10.5)
Gram-negative organisms (anaerobes)	11 (4.0)	12 (4.2)

MSSA = methicillin-susceptible *S aureus*; VSE = vancomycin-susceptible enterococci
Subjects with the same pathogen isolated from multiple specimens or from both blood and ABSSSI cultures were counted only once for that pathogen
MRSA, MSSA, and VSE were considered distinct pathogens
For overall counts of *S aureus*, subjects with both MRSA and MSSA were counted only once

- 2 OMC subjects and 8 LZD subjects had bacteremia at baseline (**Table 5**)

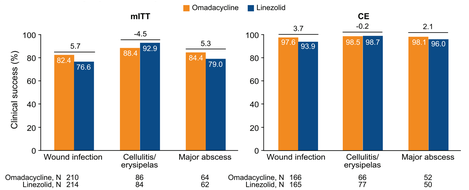
Table 5. Baseline pathogens in subjects with bacteremia (micro-mITT population)

Baseline Pathogen	Omadacycline (N = 276) n (%)	Linezolid (N = 287) n (%)
Subjects with a positive blood culture	2 (0.7)	8 (2.8)
Gram-positive organisms (aerobes)	2 (100.0)	7 (87.5)
Staphylococcus aureus	1 (50.0)	3 (37.5)
MRSA	0	1 (12.5)
MSSA	1 (50.0)	2 (25.0)
Streptococcus pyogenes	0	1 (12.5)
Streptococcus anginosus group	0	1 (12.5)
Streptococcus intermedius	0	1 (12.5)
Granulicatella adiacens	0	1 (12.5)
Rothia dentocariosa	0	1 (12.5)
Streptococcus sanguinis	1 (50.0)	0
Gram-negative organisms (aerobes)	0	1 (12.5)
Moraxella lacunata	0	1 (12.5)

- Comparable clinical success rates were seen across the two treatments at PTE when stratified by infection type (**Figure 1**)

RESULTS

Figure 1. Investigator-assessed clinical success at PTE by infection type (mITT and CE populations)



- Clinical success was similar for each treatment against mono-microbial Gram-positive, poly-microbial Gram-positive, and poly-microbial mixed infections (**Figure 2**), and for each assessed individual pathogen (**Figures 3a, 3b**)

Figure 2. Investigator-assessed clinical success at PTE by mono-microbial and poly-microbial infection (micro-mITT and ME populations)

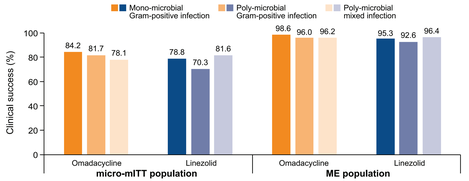


Figure 3a. Investigator-assessed clinical success at PTE by baseline pathogen from the ABSSSI site or blood culture in ≥ 10 subjects (micro-mITT population)

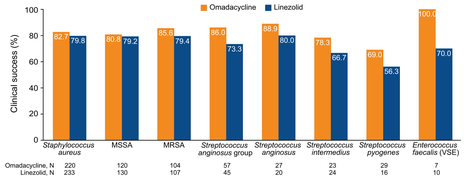
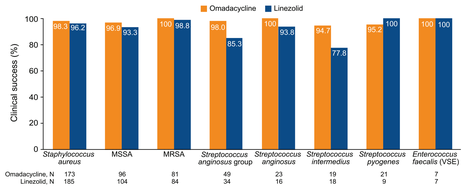


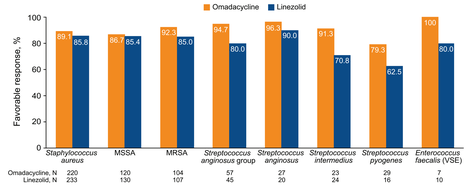
Figure 3b. Investigator-assessed clinical success at PTE by baseline pathogen from the ABSSSI site or blood culture (ME population)



RESULTS

- Favorable microbiological responses were seen for 89.1% OMC subjects and 82.9% LZD subjects at EOT and 83.0% OMC subjects and 78.0% LZD subjects at PTE, with similar responses against individual pathogens across treatment groups (**Figure 4**)
- There was no evidence of decreasing susceptibility to OMC or LZD during therapy, and superinfections and new infections were rare

Figure 4. Microbiological response at EOT by baseline pathogen in ≥ 10 subjects (micro-mITT Population)



CONCLUSIONS

- In the OASIS-2 trial, once-daily monotherapy with po OMC and LZD had high and comparable clinical success rates across all infection types
- OMC po had comparable clinical success to LZD po across the most frequently isolated bacterial pathogens, including MRSA
- Clinical success was comparable between treatments for mono-microbial and poly-microbial infections
- *S aureus* (MSSA and MRSA) and *S anginosus* group were the most common baseline pathogens
- Both treatments led to a favorable microbiological outcome in the majority of subjects, with similar responses against individual pathogens

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