Efficacy of Oral and IV Omadacycline vs Linezolid for Treating Adult Subjects With ABSSSI: Analyses by Infection Type and Pathogen in the OASIS Study

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INTRODUCTION

- Omadacycline (OMC) is the first antibiotic in a new class of compounds, the aminomethylcyclines, which are semi-synthetic antibiotics related to the tetracyclines^{1,2}
- Modifications in the chemical structure of OMC allow it to overcome the two main mechanisms of tetracycline resistance: efflux pumps and ribosomal protection^{3,4}
- OMC demonstrates potent, broad-spectrum in vitro activity against common Gram-positive aerobes (including methicillin- and penicillin-resistant strains), Gram-negative aerobes, anaerobes, and atypical bacterial pathogens^{4,5}
- OMC is in clinical development as a once-daily oral and intravenous (IV) monotherapy for acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia
- Oral and IV formulations have demonstrated bioequivalence (300 mg oral = 100 mg IV)⁶ and are well-tolerated in healthy subjects, special populations, and subjects with skin infections^{1,}
- OASIS was a global randomized (1:1) double-blind multi-center phase 3 study comparing OMC and linezolid (LZD) for treatment of adults with ABSSSI known or suspected to be caused by a Gram-positive pathogen(s)⁸
- Results of the OASIS trial demonstrated that OMC was well-tolerated and statistically noninferior to LZD for United States Food and Drug Administration (US FDA)- and European Medicines Agency (EMA)-specified efficacy endpoints
- Here we report efficacy (EMA endpoints) and microbiological outcomes by infection type, which was a randomization stratification factor, by causative pathogen, and for monomicrobial versus polymicrobial infections

METHODS

- Trial eligibility: adults \geq 18 years of age with qualifying ABSSSI severe enough to require \geq 3 days' IV treatment and evidence of systemic inflammatory response during the 24 hours before randomization. Subjects were excluded for use of any systemic or topical antibacterial treatment within 72 hours before the first dose of study drug
- Eligible subjects were randomized 1:1 to receive OMC 100 mg IV q12h × 2 doses then 100 mg IV q24h, or LZD 600 mg IV q12h. After \geq 3 days' IV therapy, subjects could transition to oral OMC 300 mg q24h or oral LZD 600 mg q12h based on investigator assessment. Total treatment duration was 7 to 14 days
- Randomization was stratified by type of infection (wound infection, cellulitis/erysipelas, and major abscess [limited to not more than 30% of subjects]) and geographic region (North America, Latin America, Eastern Europe, and Western Europe)
- Analysis populations included
- **ITT**: intent-to-treat; all randomized subjects
- **mITT**: modified intent-to-treat; all randomized subjects without a sole Gram-negative causative pathogen at screening
- CE: clinically evaluable; all mITT subjects who received study drug, had qualifying ABSSSI, had an assessment of outcome, and met all other criteria for evaluation
- **micro-mITT**: microbiological mITT; all mITT subjects with ≥ 1 Gram-positive causative pathogen at screening
- ME: microbiologically evaluable; subjects that were in both the CE and micro-mITT populations
- Pathogen recovery: Baseline infection site specimens and blood samples were submitted to the site's local microbiology lab for Gram stain and culture, with identification of pathogens to the level of genus and species (subsequently verified at a central lab)
- Primary efficacy endpoints:
- **FDA-specified**: Early Clinical Response (ECR) in mITT population based on $\geq 20\%$ reduction in primary lesion size 48 to 72 hours after first dose without administration of a rescue antibiotic
- **EMA-specified**: Investigator-assessed Clinical Response (IACR; sufficient resolution of infection such that further antibacterial therapy not needed) in mITT and CE populations at Post-Treatment Evaluation (PTE) 7 to 14 days after last dose
- Microbiological responses at End of Treatment (EOT) and PTE: Classified as "favorable" (eradication or presumed eradication), "unfavorable" (persistence or presumed persistence) or "indeterminate." Subjects who were a clinical success and had no post-therapy specimen for culture were scored as "favorable" due to presumed eradication

RESULTS

Table 1. Primary ABSSSI Infection Type at Screening (mITT Population)				
Type of Infection	Omadacycline, n (%) (N = 316)	Linezolid, n (%) (N = 311)		
Wound infection	102 (32.3)	104 (33.4)		
Cellulitis/erysipelas	123 (38.9)	118 (37.9)		
Major abscess	91 (28.8)	89 (28.6)		
Per study protocol, randomization was stratified by type of infection and the number of subjects with major				

abscess was limited to $\leq 30\%$ of randomized subjects. The majority of primary infections of all types (~80%) occurred in extremities

Figure 1a. mITT population.

Omadacycline, n(N = 316)Linezolid. n(N = 311)

Figure 1b. CE population.

10
8
6
Z
4

Omadacycline, n (N = 269) Linezolid. n(N = 260)

(micro-mITT Population)

Baseline Patho Gram-positive org Staphylococc MSSA **MRSA** Streptococcus S. conste S. intermed S. anginos Streptococcus Enterococcus VSE Staphylococcu Streptococcus Streptococcu Streptococcus Streptococcus Streptococcu Gram-positive org Finegoldia mag Clostridium s Clostridium pe Gram-negative or Gram-negative or VSE, vancomvcin-susceptible enterococci. with both MRSA and MSSA were only counted once.

RESULTS



Table 2. Incidence of Baseline Pathogenic Organisms Isolated From ABSSSI Site or Blood Culture by Genus and Species in \geq 1% of the Population

n	Omadacycline, n (%) (N = 228)	Linezolid, n (%) (N = 227)
ganisms (aerobes)	220 (96.5)	219 (96.5)
is aureus	156 (68.4)	151 (66.5)
	88 (38.6)	102 (44.9)
	69 (30.3)	50 (22.0)
<i>anginosus</i> group	47 (20.6)	37 (16.3)
atus	25 (11.0)	14 (6.2)
dius	12 (5.3)	18 (7.9)
us	8 (3.5)	7 (3.1)
pyogenes	11 (4.8)	18 (7.9)
faecalis	10 (4.4)	13 (5.7)
	10 (4.4)	13 (5.7)
is lugdunensis	6 (2.6)	3 (1.3)
mitis	6 (2.6)	4 (1.8)
Group C	4 (1.8)	1 (0.4)
<i>viridan</i> s group	3 (1.3)	5 (2.2)
sanguinis	2 (0.9)	6 (2.6)
Group F	1 (0.4)	4 (1.8)
ganisms (anaerobes)	16 (7.0)	15 (6.6)
gna	4 (1.8)	5 (2.2)
ecies	3 (1.3)	2 (0.9)
rfringens	1 (0.4)	5 (2.2)
ganisms (aerobes)	28 (12.3)	23 (10.1)
ganisms (anaerobes)	17 (7.5)	13 (5.7)

MRSA. methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*;

Subjects with the same pathogen isolated from multiple specimens or from both blood and ABSSSI site

cultures were only counted once for that pathogen. MRSA and MSSA were considered distinct pathogens; however, for overall count of S. aureus, subjects

Subjects with only Gram-negative infections were excluded from the mITT population; thus, Gram-negative organisms are from subjects with polymicrobial mixed Gram-positive/-negative infections.

Baseline pathogens were isolated from ABSSSI site specimen or blood sample cultures for approximately 72% of subjects in the mITT population

The incidence and distribution of identified pathogens was similar between treatment groups; the majority of subjects had aerobic Gram-positive pathogens (96.5% in each treatment group) including Staphylococcus aureus (MRSA and MSSA; 68.4% OMC, 66.5% LZD) and Streptococcus anginosus group species (20.6% OMC, 16.3% LZD)

MRSA was slightly more frequent in the OMC group (30.3% OMC, 22.0% LZD), while MSSA was slightly less frequent (38.6% OMC, 44.9% LZD)

RESULTS

Baseline Pathogen	Omadacycline, n (%) (N = 228)	Linezolid, n (%) (N = 227)
Subjects with a positive blood culture	11	9
Gram-positive organisms (aerobes)	11 (100.0)	9 (100.0)
Staphylococcus aureus	6 (54.5)	6 (66.7)
MRSA	3 (27.3)	2 (22.2)
MSSA	3 (27.3)	4 (44.4)
Streptococcus pyogenes	2 (18.2)	2 (22.2)
Streptococcus anginosus group ^a	1 (9.1)	0
Streptococcus anginosus ^a	1 (9.1)	0
Enterococcus faecalis (VSE)	0	1 (11.1)
Streptococcus dysgalactiae	1 (9.1)	0
Streptococcus viridans group	1 (9.1)	1 (11.1)
MRSA, methicillin-resistant <i>S. aureus</i> ; MSSA, ^a S. anginosus (along with <i>S. constellatus</i> and S	methicillin-susceptible <i>S. aureus</i> . <i>S. intermedius</i>) comprises the <i>S. a</i> .	<i>nginosus</i> group.

- LZD) and all involved Gram-positive pathogens, primarily MRSA, MSSA, and Streptococcus pyogenes
- The majority of subjects with bacteremia had a favorable microbiological response at PTE (90.9% OMC, 100% LZD) (data not shown)

Figure 2. Investigator-assessed clinical response at PTE by baseline pathogen recovered from blood or ABSSSI site specimen cultures (for pathogens in \geq 10 subjects in either treatment arm).

Figure 2a. Clinical success in subjects with *S. aureus* infections.



Figure 2b. Clinical success in subjects with the most common non-S. aureus infections.



• Clinical success rates (IACR at PTE) were generally high and comparable between subgroups of OMC and LZD subjects with the most common ABSSSI pathogens

• By-pathogen microbiological responses at end of treatment (EOT) closely mirrored clinical responses (data not shown). For example, favorable microbiological responses for between OMC and LZD groups for MRSA and MSSA strains

*S. constellatus and S. intermedius (along with S. anginosus) comprise the S. anginosus group.

Staphylococcus aureus, the most common ABSSSI pathogen, were observed in 87.8% of OMC subjects and 86.1% LZD subjects. Favorable microbiological response rates were also similar

RESULTS

Figure 3. Microbiological response at end of treatment (EOT) by pathogen class (Gram-positive/-negative, aerobic/anaerobic) (micro-mITT population).



• The rate of favorable microbiological responses at EOT (and PTE, data not shown) was high and generally comparable between subgroups of OMC and LZD subjects with different classes of pathogen infection (Gram-positive/-negative, aerobic/anaerobic)

Table 4. Frequency of Monomicrobial Gram-Positive and Polymicrobial Gram-Positive or Mixed Gram-Positive/-Negative Infections at Baseline (micro-mITT Population)

Mono- vs Polymicrobial Infection	Omadacycline, n (%) (N = 228)	Linezolid, n (%) (N = 227)
Monomicrobial Gram-positive	156 (68.4)	171 (75.3)
Polymicrobial Gram-positive	31 (13.6)	27 (11.9)
Polymicrobial mixed	41 (18.0)	29 (12.8)

Irrespective of treatment group, monomicrobial Gram-positive infections were most common (72% overall), followed by polymicrobial Gram-positive (13%) and mixed Gram-positive/ -negative infections (15%)

Figure 4. Clinical success by Mono- vs Polymicrobial infection.



• OMC and LZD led to high and comparable rates of clinical success and favorable microbiological response (data not shown) in polymicrobial Gram-positive infections, mixed infections, and monomicrobial Gram-positive infections

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CONCLUSIONS

- In the OASIS trial, omadacycline (OMC) and linezolid (LZD) treatment led to high and comparable clinical success rates across all infection types
- The spectrum and incidence of baseline pathogens were similar between OMC and LZD groups, with aerobic Gram-positive species (e.g., Staphylococcus aureus [MSSA and MRSA] and Streptococcus anginosus group) being most common
- By-pathogen clinical success rates and microbiological responses were generally high and comparable between OMC and LZD groups
- For S. aureus infections, including MSSA and MRSA, the rate of clinical response at post-treatment evaluation (PTE) was 82.4% to 100%
- OMC and LZD led to favorable microbiological outcome in the majority of subjects with bacteremia, although small sample sizes limited this assessment
- OMC and LZD showed strong and comparable efficacy against polymicrobial Grampositive infections, mixed infections, and monomicrobial Gram-positive infections
- Overall, in the Phase 3 OASIS trial, once-daily monotherapy with IV/oral omadacycline was effective in adult ABSSSI subjects across all infection types present in the subject population and across the most frequently isolated pathogens, including MRSA

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