Efficacy of Omadacycline Versus Linezolid in Treating ABSSSI Patients From Different Geographic Regions (OASIS Trial)

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Abstract 4114

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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 (CABP)
- Oral and IV formulations have demonstrated bioequivalence[6] and are well-tolerated in healthy subjects, special populations, and subjects with skin infections[1,7]
- OASIS was a global, randomized (1:1), double-blind, multicenter, 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]
- Overall, OMC was well-tolerated and statistically noninferior to LZD for United States Food and Drug Administration (US FDA)- and European Medicines Agency (EMA)-specified primary efficacy endpoints
- Here we report efficacy outcomes by geographic region (North America, Western Europe, Eastern Europe, Latin America), which was a randomization stratification factor

METHODS

- Trial eligibility: adults ≥ 18 years of age with qualifying ABSSSI severe enough to require ≥ 3 days' IV treatment, a primary lesion ≥ 75 cm^2 in total surface area of contiguous involved tissue, 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 ≥ 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 ≤ 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
- 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)
- ABSSSI lesion area: calculated as maximum length (head-to-toe) × maximum width (perpendicular to maximum length) inclusive of contiguous involvement (erythema, edema, and/or induration) as measured by a standardized ruler
- Efficacy evaluations:
  - **FDA-specified**: Early Clinical Response (ECR) in mITT population based on ≥ 20% reduction in 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 is not needed) in mITT and CE populations at Post-Treatment Evaluation (PTE) 7 to 14 days after last dose

RESULTS

Table 1. Subject Population by Geographic Region and Country (ITT population)

Region	Country	Omadacycline, n (%)	Linezolid, n (%)	All Subjects, n (%)
Overall	**Overall**	**329**	**326**	**655**
North America	**USA**	**208 (63.2)[a]**	**207 (63.5)**	**415 (63.4)**
Eastern Europe	**Overall**	**92 (28)**	**92 (28.2)**	**184 (28.1)**
	Bulgaria	22 (23.9)[b]	27 (29.3)	49 (26.6)
	Latvia	14 (15.2)	17 (18.5)	31 (16.8)
	Romania	28 (30.4)	21 (22.8)	49 (26.6)
	Ukraine	28 (30.4)	27 (29.3)	55 (29.9)
Western Europe	**Overall**	**24 (7.3)**	**23 (7.1)**	**47 (7.2)**
	Greece	2 (8.3)	6 (26.1)	8 (17.0)
	Croatia	11 (45.8)	7 (30.4)	18 (38.3)
	Hungary	4 (16.7)	8 (34.8)	12 (25.5)
	Poland	4 (16.7)	2 (8.7)	6 (12.8)
	Turkey	1 (4.2)	0	1 (2.1)
	South Africa	2 (8.3)	0	2 (4.3)
Latin America	**Peru**	**5 (1.5)**	**4 (1.2)**	**9 (1.4)**

[a]Percentage of overall (all regions) population.
[b]Percentage of regional population.

Table 2. Baseline Area (cm^2) of Primary ABSSSI Lesion by Geographic Region (mITT population)

Geographic Region	Omadacycline (N=316)	Linezolid (N=311)	*P* Value[a]
North America			
n	207	202	
Mean (SD)	423.45 (324.183)	456.99 (551.714)	0.501
Median	300.76	314.25	
Min, Max	80.0, 2050.6	95.0, 6739.2	
Eastern Europe			
n	81	84	
Mean (SD)	375.28 (329.876)	512.52 (717.806)	0.475
Median	270.00	263.50	
Min, Max	100.0, 2562.0	88.0, 4331.0	
Western Europe			
n	23	21	
Mean (SD)	939.14 (1,039.503)	736.57 (693.382)	0.972
Median	360.00	528.00	
Min, Max	77.0, 4100.0	91.0, 3120.0	
Latin America			
n	5	4	
Mean (SD)	811.40 (477.097)	1,038.50 (758.136)	0.903
Median	952.00	1039.25	
Min, Max	180.0, 1420.0	115.5, 1960.0	

SD, standard deviation.
[a]*P* values for differences between treatment groups by Wilcoxon Rank Sum test.

- At baseline, the size of primary ABSSSI lesions was generally similar between OMC and LZD groups within a given geographic region
- In all geographic regions, median baseline lesion area was well above that required by protocol (75 cm^2)

RESULTS

Table 3a. Pathogen Recovery by Geographic Region (mITT population)

	micro-mITT/mITT, n/N (%)[b]		
Geographic Region[a]	OMC	LZD	All Subjects
North America	173/207 (83.6%)	166/202 (82.2%)	339/409 (82.9%)
Eastern Europe	48/81 (59.3%)	56/84 (66.7%)	104/165 (63.0%)
Western Europe	7/23 (30.4%)	4/21 (19.0%)	11/44 (25.0%)

[a]Latin America not shown because of small sample size (≤ 5 subjects/group).
[b]Percentage of mITT population for which at least 1 Gram-positive causative pathogen was identified through culture of a baseline infection site specimen or blood sample.

Table 3b. Baseline Infection Type by Geographic Region (mITT population)

	Infection type					
	Cellulitis/erysipelas n (%)		Major Abscess n (%)		Wound Infection n (%)	
Geographic Region[a]	OMC	LZD	OMC	LZD	OMC	LZD
North America	53 (25.6)	49 (24.26)	67 (32.37)	66 (32.67)	87 (42.03)	87 (43.07)
Eastern Europe	43 (53.09)	45 (53.57)	23 (28.4)	23 (27.38)	15 (18.52)	16 (19.05)
Western Europe	22 (95.65)	20 (95.24)	1 (4.35)	–	–	1 (4.76)

[a]Latin America not shown because of small sample size (≤ 5 subjects/group).

- The frequency of pathogen recovery from baseline infection site specimens or blood samples was generally similar between OMC and LZD groups within a given geographic region
- Pathogen recovery was more successful in North America (82.9% recovery) than in Eastern Europe (63%) and, particularly, Western Europe (25%); however, this assessment is limited by the small number of mITT subjects enrolled in Western Europe
- Pathogen recovery was inversely related to the incidence of cellulitis/erysipelas at baseline (~95% in Western Europe, ~53% in Eastern Europe, ~25% in North America)
- Rates of bacteremia were low in all geographic regions: North America, 9/409 (2.2%); Eastern Europe, 7/165 (4.2%); Western Europe, 4/44 (9.1%); Latin America, 0/9 (within the mITT population, OMC and LZD together). Again, the small size of the mITT population in Western Europe limits assessment of data from that region

Table 4. Baseline Pathogenic Organisms by Region (micro-mITT Population)

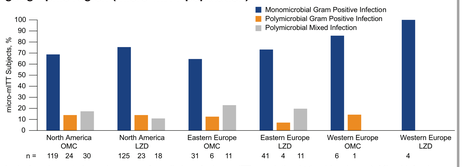
	North America			Eastern Europe			Western Europe		
Baseline Pathogen[a]	OMC N=173 n (%)	LZD N=166 n (%)	Overall N=339 n (%)	OMC N=48 n (%)	LZD N=56 n (%)	Overall N=104 n (%)	OMC N=7 n (%)	LZD N=4 n (%)	Overall N=11 n (%)
Gram-positive organisms (aerobes)	**168 (97.1)**	**162 (97.6)**	**330 (97.3)**	**45 (93.8)**	**52 (92.9)**	**97 (93.3)**	**7 (100)**	**4 (100)**	**11 (100)**
Staphylococcus aureus[b]	123 (71.1)	117 (70.5)	240 (70.8)	30 (62.5)	30 (53.6)	60 (57.7)	3 (42.9)	3 (75.0)	6 (54.5)
MRSA	58 (33.5)	47 (28.3)	105 (31.0)	11 (22.9)	3 (5.4)	14 (13.5)	0	0	0)
MSSA	65 (37.6)	71 (42.8)	136 (40.1)	20 (41.7)	27 (48.2)	47 (45.2)	3 (42.9)	3 (75.0)	6 (54.5)
Streptococcus pyogenes	7 (4.0)	12 (7.2)	19 (5.6)	1 (2.1)	6 (10.7)	7 (6.7)	3 (42.9)	0	3 (27.3)
Streptococcus anginosus group[c]	44 (25.4)	33 (19.9)	77 (22.7)	3 (6.3)	4 (7.1)	7 (6.7)	0	0	0
Enterococcus faecalis	1 (0.6)	1 (0.6)	2 (0.6)	8 (16.7)	12 (21.4)	20 (19.2)	1 (14.3)	0	1 (9)
Gram-positive organisms (anaerobes)	**9 (5.2)**	**9 (5.4)**	**18 (5.5)**	**7 (14.6)**	**6 (10.7)**	**13 (12.5)**	**0**	**0**	**0**
Gram-negative organisms (aerobes)[d]	**21 (12.1)**	**13 (7.8)**	**34 (10.0)**	**7 (14.6)**	**10 (17.9)**	**17 (16.3)**	**0**	**0**	**0**
Gram-negative organisms (anaerobes)[d]	**12 (6.9)**	**9 (5.4)**	**21 (6.2)**	**5 (10.4)**	**4 (7.1)**	**9 (8.7)**	**0**	**0**	**0**

[a]Baseline pathogen isolated from ABSSSI site sample or blood culture.
[b]*S. aureus* subjects with both MRSA and MSSA were counted only once.
[c]*S. anginosus* group consists of *S. anginosus*, *S. intermedius*, and *S. constellatus*.
[d]Subjects with only Gram-negative infections were excluded from the mITT population; thus, Gram-negative organisms shown here were from subjects with polymicrobial mixed Gram-positive and -negative infections.

- In all geographic regions, *Staphylococcus aureus* was the most commonly identified pathogen among subjects with at least 1 Gram-positive pathogen. However, the percentage of subjects with methicillin-resistant *S. aureus* (MRSA) varied (North America, 31.0%; Eastern Europe, 13.5%; Western Europe, 0)

RESULTS

Figure 1. Frequency of monomicrobial Gram-positive and polymicrobial Gram-positive or mixed Gram-positive/-negative infections at baseline by geographic region (micro-mITT population).



Latin America not shown because of small size of micro-mITT population (≤ 1 subject/group); Mixed infection = Gram-positive and Gram-negative.

- In all geographic regions, monomicrobial Gram-positive infections were most common. In regions where larger subject populations allowed assessment (North America and Eastern Europe), monomicrobial Gram-positive infections accounted for 65% to 75% of micro-mITT subjects, polymicrobial Gram-positive 7% to 14%, and polymicrobial mixed Gram-positive and -negative infections 11% to 23% (depending on region and treatment group)

Figure 2. Primary efficacy endpoints for clinical response by geographic region.
Figure 2a. Early clinical response at 48 to 72 hours (mITT population).

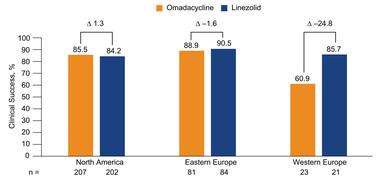


Figure 2b. Investigator-assessed clinical response at post-treatment evaluation (mITT population).

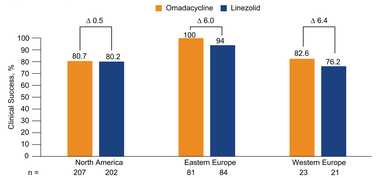
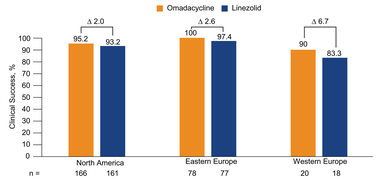


Figure 2c. Investigator-assessed clinical response at post-treatment evaluation (CE population).



Latin America not shown because of small sample size (≤ 5 subjects/group).

RESULTS

- Rates of clinical success with OMC treatment and LZD treatment were generally high and similar within each geographic region and across geographic regions for both the FDA endpoint of ECR and the EMA endpoint of IACR at PTE
- Although a larger difference in ECR was observed between OMC (60.9%) and LZD (85.7%) among subjects from Western Europe (**Figure 2a**), this comparison is limited by the small number of mITT subjects enrolled from this region. In addition, a higher number of OMC subjects enrolled in Western Europe had indeterminate responses at the early time point (21.7% OMC vs 4.8% LZD, data not shown)

CONCLUSIONS

- For all geographic regions assessed in the OASIS trial, the OMC and LZD arms were similar in terms of baseline lesion size and the spectrum and incidence of baseline pathogens
- *Staphylococcus aureus* was the most commonly identified pathogen in all geographic regions, but MRSA was more prevalent in North America (31.0% of the micro-mITT population) than in Eastern Europe (13.5%), and particularly, Western Europe (0)
- Despite small sample sizes in Western Europe and Latin America, the efficacy of OMC in treating ABSSSI was generally comparable to that of LZD across the geographic regions studied in the OASIS trial

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