Effects of IV/Oral Omadacycline Versus IV/Oral Linezolid on Lesion Size and Local Signs of ABSSSI in the Phase 3 OASIS Trial

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Abstract 4089

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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 IV monotherapy for acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia
- Oral and IV formulations have demonstrated bioequivalence[6] (300 mg oral = 100 mg IV) 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]
- The OASIS trial demonstrated that OMC was well-tolerated and statistically noninferior to LZD for US Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-specified efficacy endpoints
- Here we provide trial data for treatment effects on lesion size and specific local and systemic clinical signs of ABSSSI

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 prior to 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: 7 to 14 days
- Analysis populations included the mITT (modified intent-to-treat) population, defined as all randomized subjects without a sole Gram-negative causative pathogen at screening
- Primary efficacy endpoints: Early Clinical Response (≥ 20% reduction in lesion size 48 to 72 hours after first dose) [United States Food and Drug Administration (FDA)-specified] and investigator-assessed Clinical Response (resolution of infection such that further antibacterial therapy is not needed) at post therapy evaluation (PTE) 7 to 14 days after last dose [European Medicines Agencies (EMA)-specified]
- Clinical assessment of the primary lesion site (including scoring of local signs of infection), lesion measurement, and physical examination were performed at screening, on Days 2 to 10 and at end of treatment (EOT, within 2 days of last dose) and PTE visits. White blood cell counts were determined at screening, Days 4, 7, and 10, EOT, and PTE. Exceptions to these schedules were that the Day 6 visit was not required for subjects that had transitioned to oral treatment and were discharged from the hospital setting and the Day 10 visit was not required for subjects that ended treatment on Day 9 or earlier or when the Day 10 visit would coincide with the EOT visit
- Lesion area was calculated as maximum length (head-to-toe) multiplied by maximum width (perpendicular to maximum length) inclusive of contiguous involvement (erythema, edema and/or induration) as measured by a standardized ruler
- Local signs of infection (tenderness, edema, erythema, and induration) were scored on a semi-quantitative scale (none, mild, moderate, severe). Drainage was recorded as serous/serosanguineous, seropurulent, or purulent

RESULTS

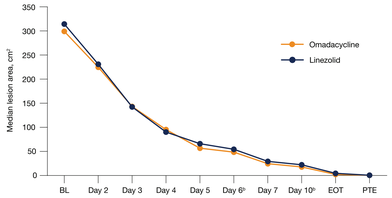
Table 1. Calculated Lesion Area (cm^2) at Baseline: mITT Population Overall and by Type of Infection

	OMC	LZD	*P* Value[a]
Overall			
n	316	311	
Mean (SD)	454.77 (442.88)	498.34 (616.99)	
min, max	77.0, 4100.0	88.0, 6739.2	0.562
Wound infection			
n	102	104	
Mean (SD)	467.71 (348.38)	453.22 (383.45)	
Median	343.75	310.75	
Min, Max	117.0, 2050.6	126.0, 2200.0	0.308
Cellulitis/erysipelas			
n	123	118	
Mean (SD)	556.83 (591.45)	667.45 (897.0)	
Min, Max	77.0, 4100.0	88.0, 6739.2	0.536
Major abscess			
n	91	89	
Mean (SD)	302.32 (195.41)	326.87 (169.32)	
Min, Max	100.0, 1395.0	110.0, 882.0	0.086

[a]*P* value for differences between treatment groups by Wilcoxon Rank Sum test.
LZD, linezolid; mITT, modified intent-to-treat; OMC, omadacycline; SD, standard deviation.

- Baseline lesion sizes were comparable between OMC and LZD groups for the mITT population overall and by infection type, with median lesion areas well above the inclusion criterion of ≥75 cm^2

Figure 1. Effect of OMC and LZD treatment on primary ABSSSI lesion size (mITT population).



[a] Number of subjects (n) evaluated at the indicated visit
[b] Visits on Day 6 and Day 10 were not required for all subjects (see Methods)
ABSSSI, acute bacterial skin and skin structure infection; BL, baseline, EOT, end of treatment; LZD, linezolid; mITT, modified intent-to-treat; OMC, omadacycline; PTE, post therapy evaluation

- The rate and extent of lesion size reduction were similar in OMC and LZD groups, with median area reduced by ~50% on Day 3 and ~99% at EOT
- Clinical success as defined by Early Clinical Response (≥20% reduction in lesion size 48 to 72 hours after the first dose of study drug) was observed in 84.8% of OMC subjects and 85.5% of LZD subjects (mITT population; data not shown)
- The rate of clinical success as defined by investigator-assessed Clinical Response at post therapy evaluation was 86.1% (OMC) and 83.6% (LZD) (mITT population; data not shown)

RESULTS

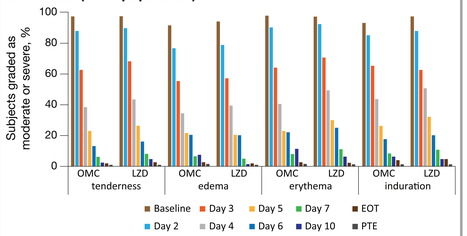
Table 2. Severity of Local Signs of ABSSSI at Baseline: mITT Population Overall and by Type of Infection[a]

	Overall mITT		Wound infection		Cellulitis/ erysipelas		Major absecss	
	OMC	LZD	OMC	LZD	OMC	LZD	OMC	LZD
Subjects, n	316	311	102	104	123	118	91	89
Infection sign and grade, %[b]								
Tenderness								
Moderate	27.8	28.3	17.6	19.2	39	39.8	24.2	23.6
Severe	69.3	69.1	81.4	80.8	54.5	54.2	75.8	75.3
Edema								
Moderate	41.8	46.3	38.2	40.4	43.1	43.2	44	57.3
Severe	49.7	47.6	53.9	57.7	48	45.8	47.3	38.2
Erythema								
Moderate	38.6	34.7	25.5	26.9	48.8	41.5	39.6	34.8
Severe	59.2	62.4	71.6	72.1	48.8	53.4	59.3	62.9
Induration								
Moderate	40.2	38.3	30.4	31.7	45.5	43.2	44.0	39.3
Severe	52.8	55.3	67.6	66.3	41.5	42.4	51.6	59.6
Drainage								
None	44.3	42.1	13.7	6.7	81.3	81.4	28.6	31.5
Serous/Serosanguineous	5.7	6.4	5.9	5.8	8.1	8.5	2.2	4.5
Seropurulent	18.0	23.8	33.3	40.4	3.3	4.2	20.9	30.3
Purulent	32.0	27.7	47.1	47.1	7.3	5.9	48.4	33.7

[a] Differences between treatment groups were all statistically non-significant, $P \geq 0.13$ by Wilcoxon Rank Sum test.
[b] Subjects graded as "none" or "mild" for tenderness, edema, erythema, and induration are not shown.
ABSSSI, acute bacterial skin and skin structure infection; LZD, linezolid; mITT, modified intent-to-treat; OMC, omadacycline.

- OMC and LZD groups showed similar presence and severity of local signs of infection at baseline, with >90% of subjects in overall mITT populations having moderate or severe tenderness, edema, erythema, and induration, and ~50% having seropurulent or purulent drainage
- Local signs of infection were also comparable between OMC and LZD subjects in subgroups with different types of infection (wound infection, cellulitis/ erysipelas, major abscess)

Figure 2. Effect of OMC and LZD treatment on local clinical signs of ABSSSI (mITT population).

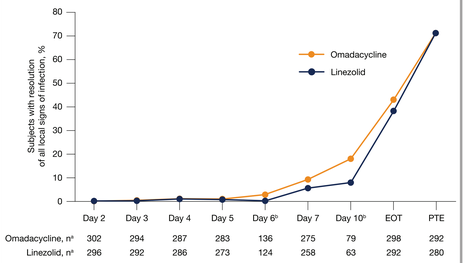


ABSSSI, acute bacterial skin and skin structure infection; EOT, end of treatment; LZD, linezolid; mITT, modified intent-to-treat; OMC, omadacycline; PTE, post therapy evaluation.

- Both OMC and LZD caused rapid and continual improvement in all evaluated local signs of infection and achieved similar levels of improvement; in both groups <2% of subjects had tenderness, edema, erythema, or induration graded moderate or severe at PTE. Subjects with seropurulent or purulent drainage at baseline had no drainage or serous/serosanguineous drainage at EOT and PTE (data not shown)

RESULTS

Figure 3. Efficacy of OMC and LZD as indicated by complete resolution of all local signs of infection present at baseline (tenderness, edema, erythema, induration and drainage) in the mITT population.



[a] n, number of subjects evaluated at the indicated visit.
[b] Visits on Day 6 and Day 10 were not required for all subjects (see Methods).
EOT, end of treatment; LZD, linezolid; mITT, modified intent-to-treat; OMC, omadacycline; PTE, post therapy evaluation.

- Absence of all local clinical signs of infection that were present at baseline was observed in 43% (OMC) and 38% (LZD) of subjects at EOT and 71% (OMC) and 71% (LZD) at PTE. Most subjects that did not meet the criteria for complete resolution at EOT had residual or minimal signs of infection that did not require further systemic antibacterial treatment and were later determined to be clinical successes at PTE (OMC, 82%; LDZ, 84%; data not shown)

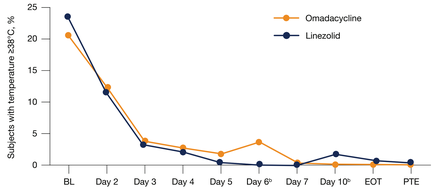
Table 3. Effect of OMC and LZD Treatment on White Blood Cell Counts in ABSSSI Subjects (mITT Population)

	OMC (N = 316)		LZD (N = 311)	
Visit	No. of subjects evaluated for WBC at visit	No. (%) of subjects with abnormal WBC count[a]	No. of subjects evaluated for WBC at visit	No. (%) of subjects with abnormal WBC counta
Screening	306	130 (42.5)	300	130 (43.3)
Day 4	269	44 (16.4)	270	42 (15.6)
Day 7	265	44 (16.6)	247	46 (18.6)
Day 10[b]	69	13 (18.8)	62	11 (17.7)
EOT	283	39 (13.8)	280	37 (13.2)
PTE	284	36 (12.7)	275	54 (19.6)

[a] Abnormal WBC defined as ≤ 4,000 cells/mm^3 or ≥ 10,000 cells/mm^3.
[b] Subjects who ended treatment on Day 9 or earlier did not have a Day 10 visit.
EOT, end of treatment; LZD, linezolid; mITT, modified intent-to-treat; OMC, omadacycline; PTE, post therapy evaluation; WBC, white blood cell.

RESULTS

Figure 4. Change in body temperature during the course of OMC and LZD treatment (mITT population)



[a] Number of subjects with temperature measured at the indicated timepoint.
[b] Visits on Day 6 and Day 10 were not required for all subjects (see Methods).
BL, baseline, EOT, end of treatment; LZD, linezolid; mITT, modified intent-to-treat; OMC, omadacycline; PTE, post therapy evaluation.

CONCLUSIONS

- In the phase 3 OASIS trial, treatment of ABSSSI with omadacycline (OMC) or the comparator drug linezolid (LZD) led to rapid and durable reductions in skin lesion size and in the severity of local signs of ABSSSI (tenderness, edema, erythema, induration and drainage). The kinetics and extent of resolution of these signs of infection were comparable between the OMC and LZD groups
- Analysis of abnormal white blood cell count and fever as systemic signs of ABSSSI showed that OMC and LZD groups had similar baseline values and comparable improvement during the course of treatment

REFERENCES

1. Villano S, et al. Omadacycline: development of a novel aminomethylcycline antibiotic for treating drug-resistant bacterial infections. *Future Microbiol*. 2016;11(11):1421-1434.
2. Honeyman L, et al. Structure-activity relationship of the aminomethylcyclines and the discovery of omadacycline. *Antimicrob Agents Chemother*. 2015;59(11):7044-7053.
3. Draper MP, et al. Mechanism of action of the novel aminomethylcycline antibiotic omadacycline. *Antimicrob Agents Chemother*. 2014;58(3):1279-1283.
4. Tanaka SK, et al. Discovery, pharmacology, and clinical profile of omadacycline, a novel aminomethylcycline antibiotic. *Bioorg Med Chem*. 2016;24(24):6409-6419.
5. Macone AB, et al. In vitro and in vivo antibacterial activities of omadacycline, a novel aminomethylcycline. *Antimicrob Agents Chemother*. 2014;58(2):1127-1135.
6. Sun H, et al. Randomized, open-label study of the pharmacokinetics and safety of oral and intravenous administration of omadacycline to healthy subjects. *Antimicrob Agents Chemother*. 2016;60(12):7431-7435.
7. Noel GJ, et al. A randomized, evaluator-blind, phase 2 study comparing the safety and efficacy of omadacycline to those of linezolid for treatment of complicated skin and skin structure infections. *Antimicrob Agents Chemother*. 2012;56(11):5650-5654.
8. US National Institutes of Health. Clinicaltrials.gov: NCT02378480. Last updated, July 6, 2016. Accessed February 24, 2017.

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