Effects of Oral Omadacycline versus Oral Linezolid on Lesion Size and Local Signs of ABSSSI in the Phase 3 OASIS-2 Study

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Abstract 2155

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BACKGROUND

- Acute bacterial skin and skin structure infections (ABSSSI) represent a significant clinical and financial burden to healthcare systems[1]
- Omadacycline (OMC) is the first aminomethylcycline in late-stage clinical development. Aminomethylcyclines are semisynthetic antibiotics related to the tetracyclines[2,3]
- OMC is unaffected by two of the main mechanisms of tetracycline resistance, efflux pumps and ribosomal protection[4]
- OMC shows a broad-spectrum of *in vitro* activity against Gram-positive aerobes (including methicillin-resistant *Staphylococcus aureus* [MRSA]), many Gram-negative aerobes, anaerobes, and atypical bacterial pathogens[5,6]
- In the previous OASIS-1 trial, which assessed intravenous (iv) followed by oral (po) administration of OMC compared with iv to po linezolid (LZD), OMC was non-inferior to LZD, and demonstrated rapid and durable reduction in lesion sizes and severity of local signs of ABSSSI[7]
- OASIS-2 was a Phase 3 randomized (1:1), double-blind, United States multicenter study comparing po administration of once-daily OMC to twice-daily LZD over a 7 to 14 day period, for the treatment of adults with ABSSSI known or suspected to be caused by Gram-positive pathogen(s)
- In the OASIS-2 trial, 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)[8]
- Here we provide OASIS-2 efficacy results for lesion size and specific local clinical signs of ABSSSI

METHODS

- Trial eligibility: adults ≥ 18 years of age with qualifying ABSSSI with primary lesions ≥ 75 cm^2, and with evidence of systemic inflammatory response within 24 hours prior to randomization
- Eligible subjects were randomized 1:1 to receive 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 ≤ 30% of subjects]) and receipt of allowed antibiotic therapy within 72 hours prior to dosing (limited to ≤ 25% of subjects)
- The total treatment duration was 7 to 14 days
- Local signs of infection including tenderness, edema, erythema, induration were graded (none, mild, moderate, severe) at screening, during treatment, at end of treatment (EOT; day of last dose), and PTE. Drainage was recorded as serous/serosanguineous, seropurulent, or purulent
- At the same timepoints, lesion surface area was calculated based upon the largest area of contiguous erythema, edema, and/or induration
- Lesion area was calculated as head-to-toe maximum length of the total lesion multiplied by maximum width (perpendicular to maximum length), inclusive of contiguous involvement (erythema, edema and/or induration), as measured with a standardized ruler
- White blood cell (WBC) counts and body temperature were recorded at each study visit as measures of systemic ABSSSI signs
  - WBC data were presented as percentage of subjects with a leukocytosis or leukopenia (WBC count ≥ 10,000 or ≤ 4,000 cells/mm^3)
- Analysis populations used in analyses of lesion size and local ABSSSI signs were:
  - Modified intent-to-treat (mITT): All randomized subjects without a sole Gram-negative 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

RESULTS

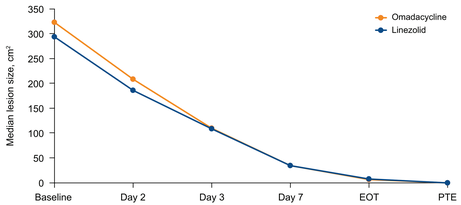
- The median lesion size was 322.3 cm^2 (OMC group) and 293.9 cm^2 (LZD group) at baseline, for the mITT population
  - Median lesion size varied by infection type (**Table 1**)

Table 1. Mean, median and range (min, max) lesion size at baseline by infection type (mITT population)

Infection Type	Omadacycline	Linezolid	p-value
Overall			
n	360	360	0.174
Mean (SD)	421.5 (365.05)	396.3 (341.12)	
Median	322.3	293.9	
Min, max	75, 2601	75, 2243	
Wound infection			
n	210	214	0.027
Mean (SD)	489.8 (386.62)	433.7 (354.06)	
Median	360.5	322.8	
Min, max	78, 2300	100, 2197	
Cellulitis / erysipelas			
n	86	84	0.420
Mean (SD)	311.2 (368.91)	353.9 (386.09)	
Median	205.3	222.8	
Min, max	75, 2601	82, 2243	
Major abscess			
n	64	62	0.617
Mean (SD)	345.7 (204.67)	324.9 (178.08)	
Median	308.5	294.0	
Min, max	86, 1059	75, 801	

- The median decrease in lesion size on Day 3 was 60.7% and 58.8% for the OMC and LZD groups, respectively (**Figure 1**)
- The median decrease in lesion size by EOT was 97.9% (OMC) and 97.5% (LZD), and 100% in both groups by PTE (**Figure 1**)
  - Similar changes were observed in the CE populations at each study visit

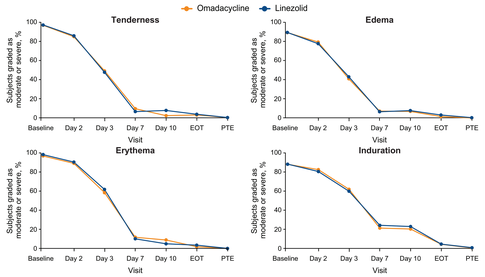
Figure 1. Median lesion size throughout the study for omadacycline and linezolid groups, mITT population



RESULTS

- At baseline, local signs of infection (tenderness, edema, erythema, and induration) were considered moderate to severe for a majority of subjects (> 85%) in the mITT population (**Figure 2**). Results were similar for the CE population
  - By Day 3, < 65% of subjects had signs graded moderate or severe
  - By PTE, < 2% of subjects had signs graded moderate or severe

Figure 2. Effect of omadacycline and linezolid on local signs of ABSSSI, mITT



- Local signs of infection were also similar across infection types (wound infection, cellulitis/erysipelas, major abscess [**Table 2**])

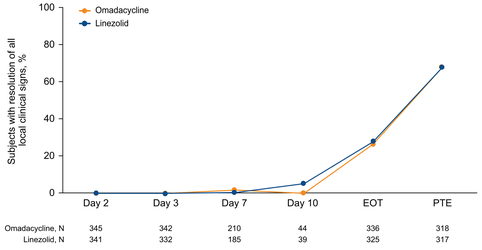
Table 2. Severity of local signs at baseline for overall mITT population and by infection type

Characteristic	Overall mITT		Wound infection		Cellulitis/ Erysipelas		Major abscess	
	OMC	LZD	OMC	LZD	OMC	LZD	OMC	LZD
Subjects, n	356	360	208	214	84	84	64	62
Infection sign and grade, %								
Tenderness								
Moderate	32.6	32.8	26.4	28.5	54.8	51.2	23.4	22.6
Severe	64.3	64.4	70.7	69.2	40.5	44.0	75.0	75.8
Edema								
Moderate	42.4	46.9	38.0	43.5	57.1	60.7	37.5	40.3
Severe	54.2	51.1	58.7	54.2	38.1	36.9	60.9	59.7
Induration								
Moderate	44.9	45.8	46.2	45.8	54.8	54.8	28.1	33.9
Severe	43.3	42.5	44.7	47.2	26.2	23.8	60.9	51.6
Drainage								
None	22.2	19.2	8.2	7.0	69.0	60.7	6.3	4.8
Serous/ Serosanguineous	11.2	16.7	11.1	11.7	15.5	33.3	6.3	11.3
Seropurulent	28.9	30.8	29.8	35.5	6.0	4.8	56.3	50.0
Purulent	37.6	33.3	51.0	45.8	9.5	1.2	31.3	33.9

RESULTS

- All subjects in OMC and LZD groups with seropurulent or purulent drainage at baseline had no drainage or serous/serosanguineous drainage by PTE
- At EOT, 26.2% (OMC) and 27.7% (LZD) of mITT subjects had resolution of all local clinical signs (**Figure 3**)
- At PTE, most subjects had complete resolution (67.6% OMC, 67.8% LZD)
  - Of the subjects who did not have complete resolution, most (92.1% OMC, 81.4% LZD) were determined to be clinical successes by the investigators
  - These subjects had residual/minimal signs and symptoms at PTE that did not require further systemic antimicrobial therapy

Figure 3. Percentage of subjects with complete resolution of all clinical signs, mITT population



- The percentage of subjects with leukocytosis or leukopenia at baseline was 32.1% for OMC and 37.8% for LZD
  - By Day 3, these percentages had decreased to 14.6% for OMC and 14.3% for LZD (**Table 3**)

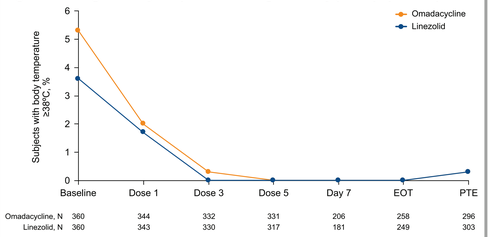
Table 3. Frequency of abnormal (≤ 4000 cells/mm^3 or ≥ 10000 cells/mm^3), white blood cells (WBC), mITT population

Visit	Omadacycline (N = 360)		Linezolid (N = 360)	
	Number of subjects with evaluable WBC	Number (%) with abnormal WBC	Number of subjects with evaluable WBC	Number (%) with abnormal WBC
Screening	352	113 (32.1)	352	133 (37.8)
Day 3	336	49 (14.6)	321	46 (14.3)
Day 7	177	26 (14.7)	155	21 (13.5)
Day 10	36	7 (19.4)	29	3 (10.3)
EOT	306	43 (14.1)	302	36 (11.9)
PTE	291	42 (14.4)	302	46 (15.2)

- The percentage of subjects with fever (temperature ≥ 38°C) at baseline was 5.3% for OMC and 3.6% for LZD (**Figure 4**)
  - By Day 7, these percentages had decreased to 0% for both groups
- WBC and body temperature results were similar for the CE population

RESULTS

Figure 4. Change in body temperature during the study (mITT population)



CONCLUSIONS

- Both po OMC and LZD caused rapid and continual improvement in all evaluated local signs of ABSSSI and lesion size
- The kinetics and magnitude of improvement were similar for both treatments
- Improvements were also seen in the systemic signs of ABSSSI, with comparable improvements in WBC count and rates of fever in the OMC and LZD groups

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