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Omadacycline for Acute Bacterial Skin and Skin Structure Infections: Integrated Analysis of Randomized Clinical Trials

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BACKGROUND

- Omadacycline (OMC) is an aminomethylcycline developed as once-daily oral and intravenous (iv) monotherapy for the treatment of acute bacterial skin and skin structure infections (ABSSSI)
  - Aminomethylcyclines are semisynthetic 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 *in vitro* activity against common Gram-positive aerobes (including methicillin- and penicillin-resistant strains), many Gram-negatives, and atypical bacterial pathogens[4,5]
- This poster reports on the integrated analysis of two Phase 3 studies of OMC in the treatment of adults with ABSSSI
  - In both OASIS-1 and OASIS-2 (**O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy), OMC was non-inferior to linezolid (LZD) for the Primary endpoint of early clinical response (ECR)[6,7]

METHODS

- OASIS-1 (NCT02378480) initiated patients on iv OMC or LZD with a possible transition to oral after at least 3 days of iv therapy (**Table 1**)
  - Patients were eligible to transition to oral therapy if there was evidence of local and systemic improvement (temperature ≤100°F, return of white blood cell count and differential toward normal range, no increase in lesion area compared to baseline, and decrease in extent and intensity of ≥1 inflammatory finding)
- OASIS-2 (NCT02877927) studied oral-only OMC versus LZD
- In both studies, eligible patients were ≥18 years of age who had qualifying ABSSSI (abscess, cellulitis/erysipelas, infected wounds) with lesion size measuring ≥75cm^2, within 24 hours before randomization
- Analysis populations:
  - Modified intent-to treat (mITT): all randomized patients without a sole Gram-negative ABSSSI pathogen, as the comparator LZD does not provide Gram-negative pathogen coverage
  - Micro-mITT: all mITT patients who had ≥1 Gram-positive causative pathogen
  - Clinically evaluable (CE): all randomized patients who received study drug, had qualifying ABSSSI, an assessment outcome, and met all other criteria for evaluation
  - Microbiologically evaluable (ME): all patients included in both micro-mITT and CE populations
  - Safety: all randomized patients who received a study drug
- US Food and Drug Administration (FDA) Primary endpoint: ECR at 48-72 hours – patient was alive with a reduction in lesion area of ≥20% compared to baseline and no receipt of rescue antibacterial therapy, mITT population
- European Medicines Agency (EMA) Primary endpoint: Investigator assessment of clinical response at post treatment evaluation (IACR-PTE) at 7-14 days after last dose of study drug – patient was alive with resolution of infection signs and symptoms such that further antibacterial treatment was not needed, mITT and CE populations

METHODS

- Integrated analysis of OASIS-1 and OASIS-2 data
  - A non-inferiority margin of 10% was used for ECR and for IACR-PTE on the basis of guidance from the FDA and EMA
  - Two-sided 95% confidence intervals (CI) for the differences in the ECR and IACR-PTE clinical success rates were calculated using the Miettinen and Nurminen method, with stratification for study[8]
  - Non-inferiority of OMC to LZD was concluded if the lower limit of 95% CI for treatment difference was greater than -10%
  - No inferential analyses were conducted for other endpoints or populations

Table 1. Study Design Characteristics

Characteristic	OASIS-1	OASIS-2
Treatment duration	7-14 days	7-14 days
Omadacycline dosing	100 mg iv q12h for 2 doses Then 100 mg iv q24h Optional at 3+ days: transition to 300 mg po q24h[a]	450 mg po q24h for 2 doses Then 300 mg po q24h
Linezolid dosing	600 mg iv q12h Optional at 3+ days: transition to 600 mg po q12h	600 mg po q12h
FDA Primary endpoint[b]	ECR at 48-72 h	ECR at 48-72 h
EMA Primary endpoint[c]	Investigator assessment of clinical response at PTE	Investigator assessment of clinical response at PTE
Prior antibiotics prohibited	Within 72 h of randomization, any other systemic or topical antibiotic agent potentially effective for ABSSSI	Within 72 h of randomization, any other systemic or topical antibiotic agent potentially effective for ABSSSI[d]
Concomitant antibiotics prohibited	Any other systemic antibiotic against known/suspected ABSSSI pathogens, except in cases of clinical failure Any topical antibacterial agent active against known/suspected ABSSSI pathogen on study infection	Any other systemic antibiotic agent potentially effective for ABSSSI, except in cases of clinical failure Any topical antibacterial agent active against known/suspected ABSSSI pathogen on study infection

ABSSSI = acute bacterial skin and skin structure infections; ECR = early clinical response; EMA = European Medicines Agency; FDA = US Food and Drug Administration; iv = intravenous; PO = oral; PTE = post treatment evaluation; q12h = every 12 hours; q24h = every 24 hours
[a]Transition from iv to po study drug was an option if there was evidence of local and systemic improvement (e.g., temperature ≤100°F, return of white blood cell count and differential toward normal range, no increase in lesion area compared to baseline, and decrease in extent and intensity of ≥1 inflammatory finding)
[b]ECR defined as: patient was alive, size of lesion reduced by ≥20% without any rescue antibacterial therapy, and no failure/indeterminate criteria were met
[c]PTE occurred at 7-14 days after last dose of study drug, defined as: patient was alive, with resolution of infection signs and symptoms such that further antibacterial treatment was not needed
[d]In OASIS-2 a single dose of short-acting non-oxazolidinone antibacterial administered within 72 h prior to randomization was allowed for up to 25% of patients: 1.7% and 2.2% of patients receiving OMC or LZD, respectively, received a single dose of prior antibiotic

RESULTS

- A total of 691 patients receiving OMC and 689 patients receiving LZD were included
- Patients in integrated OMC and LZD groups had similar baseline characteristics (**Table 2**)
- Median lesion size was 316 cm^2 and 304 cm^2 in OMC and LZD patients, respectively
- OMC showed similar efficacy to LZD for the FDA and EMA Primary endpoints, as well as for mono-microbial and poly-microbial infections (**Fig. 1**)
- Similar efficacy results were seen in both treatment groups for patients who had systemic inflammatory response syndrome or bacteremia at baseline

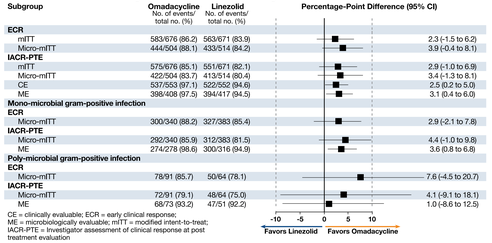
RESULTS

Table 2. Demographic and Baseline Characteristics for Patients in the Combined Phase 3 ABSSSI Studies (Safety Population)

Characteristic	Omadacycline (N=691)	Linezolid (N=689)	All Patients (N=1380)
Age, Years			
Mean (SD)	44.7 (14.2)	45.5 (14.2)	45.1 (14.2)
Median	44	46	45
Categorical Age (Years), n (%)			
18-65	641 (92.8)	637 (92.5)	1278 (92.6)
>65-75	32 (4.6)	26 (3.8)	58 (4.2)
>75	18 (2.6)	26 (3.8)	44 (3.2)
Gender, n (%)			
Male	445 (64.4)	433 (62.8)	878 (63.6)
Race, n (%)			
White	621 (89.9)	641 (93.0)	1262 (91.4)
Region, n (%)			
US	570 (82.5)	570 (82.7)	1140 (82.6)
Non-US	121 (17.5)	121 (17.5)	240 (17.4)
EU[a]	85 (12.3)	88 (12.8)	173 (12.5)
Creatinine Clearance, n (%)			
<60 mL/min	21 (3.1)	21 (3.1)	42 (3.1)
60-89 mL/min	64 (9.3)	51 (7.5)	115 (8.4)
>89 mL/min	603 (87.6)	612 (89.5)	1215 (88.6)
Type of Primary Infection, n (%)	676	671	1347
Wound infection	312 (46.2)	318 (47.4)	630 (46.8)
Cellulitis/erysipelas	209 (30.9)	202 (30.1)	411 (30.5)
Major abscess	155 (22.9)	151 (22.5)	306 (22.7)
Pathogen[b], n (%)	504	1018	514
Gram-positive aerobes	490 (97.2)	497 (96.7)	987 (97.0)
Staphylococcus aureus	376 (74.6)	384 (74.7)	760 (74.7)
MRSA	173 (34.3)	157 (30.5)	330 (32.4)
MSSA	208 (41.3)	232 (45.1)	440 (43.2)
Streptococcus pyogenes	40 (7.9)	34 (6.6)	74 (7.3)
S. anginosus group[c]	104 (20.6)	82 (16.0)	186 (18.3)
Gram-positive anaerobes	33 (6.5)	32 (6.2)	65 (6.4)
Gram-negative aerobes	52 (10.3)	53 (10.3)	105 (10.3)
Gram-negative anaerobes	28 (5.6)	25 (4.9)	53 (5.2)
Relevant Medical History, n (%)	676	671	1347
Infection a result of iv drug abuse	414 (61.2)	406 (60.5)	820 (60.9)
Prior ABSSSI	351 (51.9)	352 (52.5)	703 (52.2)
Diabetes History, n (%)	691	689	1380
Any diabetes mellitus	39 (5.6)	67 (9.7)	106 (7.7)

ABSSSI = acute bacterial skin and skin structure infections; EU = European Union; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; SD = standard deviation; US = United States
The denominator for the percentage was the number of patients who had that parameter assessed
[a]The EU was a subset of non-US and was not a mutually exclusive subgroup
[b]More than 1 pathogen may have been present in each infection; therefore numbers sum to >100%. Pathogens present in >5% of infections are shown
[c]*Streptococcus anginosus* group consists of *S. anginosus*, *S. intermedius*, and *S. constellatus*

Figure 1. Forest Plot for Efficacy Endpoints in Various Analysis Populations Shows that Omadacycline had Statistically Similar Outcomes to Linezolid

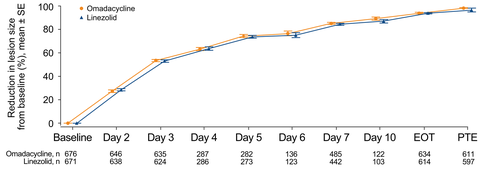


CE = clinically evaluable; ECR = early clinical response; ME = microbiologically evaluable; mITT = modified intent-to-treat; IACR-PTE = Investigator assessment of clinical response at post treatment evaluation

- Lesion area was reduced from baseline in both groups (**Fig. 2**)
  - At day 3, the mean (SD) reduction from baseline in lesion area was 53.4% (25.8) for OMC-treated patients and 53.0% (24.2) for LZD-treated patients
  - At the end of treatment, the mean reduction was 93.9% (14.6) and 93.7% (13.5) for OMC- and LZD-treated patients, respectively

RESULTS

Figure 2. Reduction in Lesion Size from Baseline To Post Treatment Evaluation (mITT Population). Omadacycline Shows a Similar Trend to Linezolid in Lesion Size Over the Study Duration



Error bars represent the standard error. Lines are offset horizontally to better visualize the data points
EOT = end of treatment; mITT = modified intent-to-treat; PTE = post treatment evaluation; SE = standard error

- Omadacycline demonstrated similar efficacy to linezolid in treating infections with causative pathogens including *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, and *S. anginosus* (**Table 3**)

Table 3. Clinical Response by Baseline Pathogen[a] (Micro-mITT Population)

Pathogen, n (%)	Omadacycline (N=504)	Linezolid (N=514)
***Staphylococcus aureus*, n**	376	384
ECR success	332 (88.3)	325 (84.6)
IACR-PTE success	312 (83.0)	312 (81.3)
MRSA, n	173	157
ECR success	159 (91.9)	139 (88.5)
IACR-PTE success	146 (84.4)	128 (81.5)
MSSA, n	208	232
ECR success	178 (85.6)	190 (81.9)
IACR-PTE success	171 (82.2)	187 (80.6)
***Streptococcus pyogenes*, n**	40	34
ECR success	32 (80.0)	30 (88.2)
IACR-PTE success	28 (70.0)	25 (73.5)
***S. anginosus* Group, n[b]**	104	82
ECR success	93 (89.4)	63 (76.8)
IACR-PTE success	84 (80.8)	59 (72.0)

ECR = early clinical response; IACR = investigator-assessed clinical response; mITT = modified intent-to-treat; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; IACR-PTE = Investigator assessment of clinical response at post treatment evaluation
[a]Pathogens present at baseline in ≥5% of infections are shown
[b]*Streptococcus anginosus* group consists of *S. anginosus*, *S. intermedius*, and *S. constellatus*

- Treatment-emergent adverse events (TEAEs) were reported by 51% and 41% of patients receiving OMC or LZD, respectively (**Table 4**); most were mild or moderate

Table 4. Overview of Adverse Events (Safety Population)

	Omadacycline (N=691)	Linezolid (N=689)
Patients with any TEAE, n (%)	353 (51.1)	284 (41.2)
Number of Patients with:		
Death	1 (0.1)	3 (0.4)
TEAE leading to early discontinuation of study drug	12 (1.7)	10 (1.5)
TEAE leading to dose interruption of study drug	2 (0.3)	0
Serious TEAE leading to early discontinuation of study drug	6 (0.9)	5 (0.7)
Drug-related TEAE	197 (28.5)	111 (16.1)
Serious TEAE	16 (2.3)	13 (1.9)
Drug-related serious TEAE	0	1 (0.1)
TEAEs Reported in ≥3% of Patients (by Preferred Term[a]):		
Nausea	151 (21.9)	60 (8.7)
Vomiting	79 (11.4)	27 (3.9)
Wound infection	30 (4.3)	22 (3.2)
ALT increased	28 (4.1)	25 (3.6)
Infusion site extravasation	28 (4.1)	19 (2.8)
Cellulitis	27 (3.9)	24 (3.5)
AST increased	25 (3.6)	24 (3.5)
Headache	23 (3.3)	21 (3.0)
Subcutaneous abscess	23 (3.3)	27 (3.9)
Diarrhea[b]	22 (3.2)	20 (2.9)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event
Percentages were based on the number of patients. If a patient had >1 TEAE with the same preferred term, the patient was counted only once for that preferred term
[a]Coding of preferred terms was based on Medical Dictionary for Regulatory Activities (MedDRA) Version 17.1
[b]There were no cases of *Clostridium difficile* infection in either study

RESULTS

- The most frequently reported TEAEs were nausea (21.9% OMC and 8.7% LZD) and vomiting (11.4% OMC and 3.9% LZD). These events occurred in both ABSSSI studies; however, higher rates for OMC occurred in the loading dose period on Day 1 and Day 2 in the oral-only OASIS-2 study. Two OMC patients discontinued treatment for nausea or vomiting
- Infusion-site extravasation TEAEs occurred in a similar percentage of OMC and LZD patients in OASIS-1. The majority of these patients had a history of iv drug abuse

CONCLUSIONS

- Integrated analysis of the OASIS trials showed that omadacycline was effective in the treatment of ABSSSI
- Omadacycline had clinical efficacy for the most common ABSSSI pathogens, including MRSA
- Omadacycline was safe and well tolerated by patients

REFERENCES

1. Villano S, et al. *Future Microbiol*. 2016;11(11):1421-1434.
2. Honeyman L, et al. *Antimicrob Agents Chemother*. 2015;59(11):7044-7053.
3. Draper MP, et al. *Antimicrob Agents Chemother*. 2014;58(3):1279-1283.
4. Tanaka SK, et al. *Bioorg Med Chem*. 2016;24(24):6409-6419.
5. Macone AB, et al. *Antimicrob Agents Chemother*. 2014;58(2):1127-1135.
6. O'Riordan W, et al. ECCMID 2017 abstract 630.
7. O'Riordan W, et al. ECCMID 2018 abstract 6178.
8. Miettinen O, Nurminen M. *Stat Med*. 1985;4:213–226.

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