Efficacy of Omadacycline and Linezolid Against Characterized Drug Resistant *S. aureus* from Combined Phase 3 ABSSSI Studies

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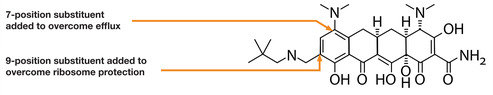
BACKGROUND

- Omadacycline (OMC), a novel aminomethylcycline antibiotic, is in clinical development as once-daily oral and intravenous (iv) monotherapy for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections (ABSSSI)[1,2]
- Alterations in the chemical structure of OMC overcome two tetracycline resistance mechanisms: efflux pumps and ribosomal protection[3] (**Fig. 1**)

Figure 1. Chemical Structure of Omadacycline



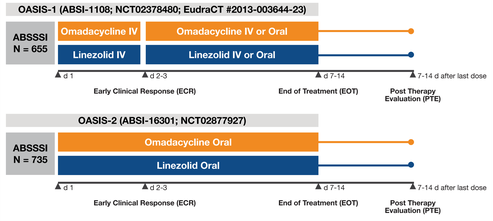
- OMC has potent *in vitro* activity against the common Gram-positive ABSSSI pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), many Gram-negative aerobes, anaerobes, and a number of atypical bacterial pathogens[4,5]
- OMC demonstrated non-inferiority to linezolid (LZD) for treatment of ABSSSI in the **O**madacycline in **A**cute **S**kin and Skin Structure **I**nfections **S**tudy (OASIS)-1 iv-to-oral and OASIS-2 oral-only Phase 3 studies[6,7]
- This analysis combines data from both Phase 3 studies to investigate clinical outcomes of OMC or LZD when MRSA or multidrug-resistant (MDR) *S. aureus* (SA) was the baseline pathogen

METHODS

Population Pooling

- OASIS-1 and OASIS-2 Phase 3 studies had similar designs (**Fig. 2**) and recruitment criteria
  - Eligible subjects were ≥18 years of age who had qualifying ABSSSI with lesions ≥75cm^2 and with evidence of a systemic response to infection within 24 hours before randomization
- Overall, 1380/1390 randomized subjects received at least 1 dose of study drug (**Safety Population**)

Figure 2. Study Design of Phase 3 Clinical Studies



METHODS

Analysis Populations

- **mITT:** modified intent-to-treat (**ITT**), all randomized subjects without a sole Gram-negative causative pathogen at baseline (overall, 1347 subjects)
- **micro-mITT:** microbiological mITT, all mITT subjects with ≥1 Gram-positive causative pathogen at baseline (overall, 1018 subjects)

OASIS-1 and OASIS-2 Study Primary Endpoints

- United States Food and Drug Administration (FDA) primary endpoint: early clinical response (ECR) of ≥20% reduction in primary lesion size at 48–72 hours after the first dose in the mITT population
- European Medicines Agency (EMA) primary endpoint: investigator's assessment of clinical response (IACR) at post therapy evaluation (PTE) 7–14 days after the last dose in the mITT and clinically evaluable populations

Microbiological Assessment

- Isolates were obtained from subjects at the screening visit (prior to initiation of antibiotic therapy)
  - Baseline ABSSSI infection site specimens and blood samples were submitted to the local microbiology laboratory for Gram stain and culture
  - Pathogens were identified to genus and species level (verified by the central laboratory)

Resistance Phenotyping

- Minimum inhibitory concentration (MIC) testing was conducted by the central laboratory
  - MIC was by broth microdilution (CLSI M100-S25) using custom frozen panels (Thermo Fisher Scientific, Cleveland, OH)
- Quality control (QC) and interpretation of results (susceptible, intermediate, or resistant) were performed in accordance with CLSI M100-S25
  - *S. aureus* ATCC 29213 was the QC organism (all results were within the recommended ranges)

PCR Genotyping

- The *mecA* gene (encoding penicillin-binding protein PBP2a) and the *pvl* gene (encoding Panton-Valentine leukocidin, PVL) were detected using multiplex real-time PCR
  - Isolates of SA were selected for PCR testing based on initial oxacillin MIC >2 µg/mL SA isolates

RESULTS

ABSSSI Characteristics

- Infection types were balanced across the treatment arms and wound infection was the most frequent (**Table 1**)

Table 1. ABSSSI Infection Types at Baseline in the OASIS Phase 3 Studies (mITT population)

ABSSSI Characteristic	Omadacycline (N=676)	Linezolid (N=671)	Overall (N=1347)
Infection type, n (%)			
Wound infection	312 (46.2)	318 (47.4)	630 (46.8)
Major abscess	155 (22.9)	151 (22.5)	306 (22.7)
Cellulitis/erysipelas	209 (30.9)	202 (30.1)	411 (30.5)

RESULTS

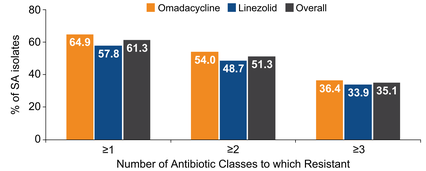
SA Isolates

- Three-quarters (74.7%) of subjects had SA isolates at baseline (**Table 2**)
- Antibiotic resistance was common, occurring in 61.3% of SA isolates (**Fig. 3**)
  - Over one-third were MDR (≥3 antibiotic classes)

Table 2. Distribution of Resistance Phenotypes of *Staphylococcus aureus* (SA) Isolates (micro-mITT)

ABSSSI Characteristic	Omadacycline (N=504) n (% of N)	Linezolid (N=514) n (% of N)	Overall (N=1018) n (% of N)
Staphylococcus aureus	376 (74.6)	384 (74.7)	760 (74.7)
Resistant to ≥1 antibiotic class	244 (48.4)	222 (43.2)	466 (45.8)
Resistant to ≥2 antibiotic class	203 (40.3)	187 (36.4)	390 (38.3)
Resistant to ≥3 antibiotic class	137 (27.2)	130 (25.3)	267 (26.2)

Figure 3. Level of Resistance of *Staphylococcus aureus* (SA) Isolates (micro-mITT)

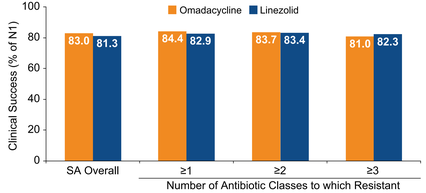


	≥1	≥2	≥3
Omadacycline, n/N1	244/376	203/376	137/376
Linezolid, n/N1	222/384	187/384	130/384
Overall, n/N1	466/760	390/760	267/760

MDR SA

- Clinical success rates at PTE when MDR SA was present with OMC or LZD were comparable to that for overall SA isolates (>80% for all SA resistance phenotypes; **Fig. 4**)
  - Clinical failure rates were low (OMC 2.9% vs LZD 6.2%; **Table 3**)

Figure 4. IACR at PTE (Clinical Success) by *Staphylococcus aureus* (SA) Resistance Phenotype (micro-mITT)



Omadacycline, n/N1	312/376	206/244	170/203	111/137
Linezolid, n/N1	312/384	184/222	156/187	107/130

RESULTS

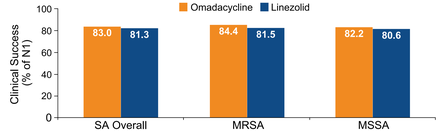
Table 3. IACR at PTE (Clinical Failure/Indeterminate) by *Staphylococcus aureus* (SA) Resistance Phenotype (micro-mITT)

	Omadacycline (N=504)		Linezolid (N=514)	
Baseline Pathogen	Clinical Failure n/N1 (%)	Indeterminate n/N1 (%)	Clinical Failure n/N1 (%)	Indeterminate n/N1 (%)
Staphylococcus aureus	16/376 (4.3)	48/376 (12.8)	26/384 (6.8)	46/384 (12.0)
Resistant to ≥1 antibiotic class	4/244 (1.6)	34/244 (13.9)	12/222 (5.4)	26/222 (11.7)
Resistant to ≥2 antibiotic class	4/203 (2.0)	29/203 (14.3)	11/187 (5.9)	20/187 (10.7)
Resistant to ≥3 antibiotic class	4/137 (2.9)	22/137 (16.1)	8/130 (6.2)	15/130 (11.5)

MRSA

- MRSA was identified in 330/1018 subjects (32.4%)
- Clinical success rates at PTE for subjects with MRSA were high (>80%) in both treatment arms (**Fig. 5**)
  - These rates were comparable to those for subjects with methicillin-sensitive *S. aureus* (MSSA) and overall SA isolates
  - Similarly high rates were seen with MRSA and MSSA across infection types (**Table 4**)

Figure 5. IACR at PTE (Clinical Success) by Methicillin Resistance Status (micro-mITT)



	SA Overall	MRSA	MSSA
Omadacycline, n/N1	312/376	146/173	171/208
Linezolid, n/N1	312/384	128/157	187/232

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; SA, *S. aureus*

Table 4. IACR at PTE by Baseline Pathogen and Infection Type (micro-mITT)

	Omadacycline (N=504)	Linezolid (N=514)
Infection Type Baseline Pathogen	Clinical Success n/N1 (%)	Clinical Success n/N1 (%)
Wound infection		
Staphylococcus aureus	162/199 (81.4)	166/212 (78.3)
MRSA	70/83 (84.3)	69/86 (80.2)
MSSA	94/118 (79.7)	97/127 (76.4)
Major abscess		
Staphylococcus aureus	89/107 (83.2)	83/101 (82.2)
MRSA	47/59 (79.7)	39/48 (81.3)
MSSA	43/49 (87.8)	47/57 (82.5)
Cellulitis/erysipelas		
Staphylococcus aureus	61/70 (87.1)	63/71 (88.7)
MRSA	29/31 (93.5)	20/23 (87.0)
MSSA	34/41 (82.9)	43/48 (89.6)

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

PCR Genotyping

- 96.1% of MRSA isolates were tested for *mecA* and *pvl*
- All MRSA isolates tested were *mecA* positive in OASIS-1 (117/117), and in OASIS-2 all but one isolate (199/200) from an LZD-treated subject were *mecA* positive

RESULTS

- The virulence factor Panton–Valentine leukocidin (PVL) was widespread (present in 89.3% of characterized MRSA isolates)
  - Clinical success rates at PTE for treatment of subjects with PVL + MRSA were high (>80%) in both treatment arms (**Table 5**)

Table 5. IACR at PTE by *Staphylococcus aureus* (SA) Resistance Phenotype (micro-mITT)

	Omadacycline (N=504)	Linezolid (N=514)	
Baseline Pathogen	Clinical Success n/N1 (%)	Clinical Success n/N1 (%)	Response Difference Between Treatments (95% CI)
MRSA/PVL-	19/20 (95.0)	14/14 (100.0)	-5 (-14.6, 4.6)
MRSA/PVL+	125/148 (84.5)	112/135 (83.0)	1.5 (-7.1, 10.1)
Response Difference (95% CI) Between PVL Status	10.5 (-0.7, 21.7)	17.0 (10.7, 23.4) *	

* Significant; CI, confidence interval; MRSA, methicillin-resistant *S. aureus*; PVL, Panton–Valentine leukocidin

CONCLUSIONS

Omadacycline treatment outcomes were successful in the majority of ABSSSI subjects with *S. aureus* isolates

- Notably, subjects with MDR or PVL+ isolates had successful treatment outcomes with omadacycline

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