Safety and Efficacy of Omadacycline for Treatment of Acute Bacterial Skin and Skin Structure Infections by Patient Body Mass Index

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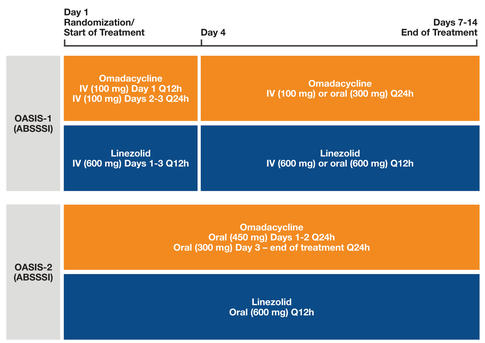
BACKGROUND

- Omadacycline (OMC) is an intravenous (IV) and oral aminomethylcycline antibiotic in the tetracycline class recently approved in the USA to treat acute bacterial skin and skin structure infections (ABSSSI) in adults
- OMC, like linezolid (LZD), is administered on a fixed-dose basis in adults, without regard to body weight or composition
- The pharmacokinetics of many antibacterial agents are altered in obese patients and may negatively impact the clinical outcomes of infections in this population[1,2]
- We compared the safety and efficacy of OMC to LZD by World Health Organization (WHO) body mass index (BMI) categories in patients from two Phase 3 clinical studies (**O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy [OASIS-1 and OASIS-2])[3,4]

METHODS

- OASIS-1 and OASIS-2 were randomized (1:1), double-blind, active comparator-controlled, Phase 3 studies comparing OMC with LZD for the treatment of adults with ABSSSI (**Fig. 1**)[3,4]

Figure 1. Study Treatment Regimens



ABSSSI = acute bacterial skin and skin structure infection; IV = intravenous; OASIS = **O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy; Q12h = every 12 hours; Q24h = every 24 hours

- Patients from the OASIS-1 and OASIS-2 studies were classified on the basis of WHO BMI categories:
  - Underweight: BMI<18.5 kg/m^2
  - Healthy weight: 18.5≤ BMI <25 kg/m^2
    - Overweight: 25 kg/m^2 ≤ BMI <30 kg/m^2
    - Obese: BMI ≥30 kg/m^2
      - Obese Class I: 30 kg/m^2 ≤ BMI <35 kg/m^2
      - Obese Class II: 35 kg/m^2 ≤BMI <40 kg/m^2
      - Obese Class III: BMI ≥40 kg/m^2

METHODS

- Efficacy endpoints:
  - Early clinical response (ECR): survival with ≥20% reduction in lesion size at 48-72 hours after first dose of OMC or LZD
  - Clinical success at post treatment evaluation (PTE) assessed 7-14 days after the last dose of OMC or LZD: survival with resolution of signs and symptoms of the infection such that further antibacterial therapy is not needed
- Safety was assessed based on adverse events (AEs), vital signs, electrocardiograms (ECGs), and standard clinical laboratory tests
- Populations for analysis:
  - Modified intent-to-treat (mITT): all randomized patients without a baseline sole Gram-negative ABSSSI pathogen
  - Clinically evaluable (CE): all randomized patients who received the study drug, had qualifying ABSSSI, an assessment outcome, and met all other criteria for evaluation
  - Safety: all randomized patients who received any dose of OMC or LZD
- A logistic regression was performed, with covariates of BMI at baseline, treatment arm, and the interaction between BMI and treatment

RESULTS

- Approximately two-thirds of patients were overweight (OMC: 32.0%; LZD: 35.3%) or obese (OMC: 30.4%; LZD: 29.0%) (**Table 1**)
  - A small minority of patients (1.6%) were classified as underweight; because this group was so small, it was not shown in the efficacy and safety data by BMI
- Baseline pathogens were similar across the BMI categories, with the most common being *Staphylococcus aureus* (present in ~70% of patients)
- Rates of hypertension, diabetes, and heart disease generally increased with increasing BMI
- Clinical success at ECR and PTE was similar in healthy-weight, overweight and obese patients, with no evidence of lower efficacy with increasing BMI (**Fig. 2, 3**)
- There were no differences in rates of treatment-emergent adverse events (TEAEs) and serious TEAEs across BMI categories in OMC- and LZD-treated patients (**Table 2**)
- No major differences in post-baseline liver transaminase changes, diarrhea or headache were noted across BMI categories or between treatment groups (**Table 3**)
- The rate of nausea and vomiting was approximately two- to four-fold higher in OMC-treated patients compared to LZD-treated patients, but was independent of BMI category
- Changes in liver enzymes were similar across BMI categories (**Table 4**)
- There was no significant effect of BMI, treatment, or the interaction (BMI*Treatment) on ECR or PTE outcomes (all p values >0.05)

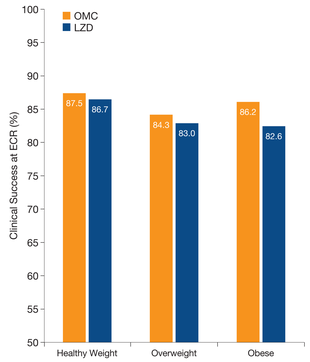
RESULTS

Table 1. BMI Category Distribution (Safety Population)

BMI Category, n (%)	OMC (N=691)	LZD (N=689)
Underweight	8 (1.1)	14 (2.0)
Healthy weight	252 (36.5)	231 (33.5)
Overweight	221 (32.0)	243 (35.3)
Obese	210 (30.4)	200 (29.0)
Obese Class I	127 (18.4)	112 (16.3)
Obese Class II	49 (7.1)	50 (7.3)
Obese Class III	34 (4.9)	38 (5.5)

WHO Classifications - Underweight: BMI <18.5 kg/m^2; Healthy weight: 18.5 ≤BMI<25 kg/m^2; Overweight: 25 kg/m^2 ≤BMI<30 kg/m^2; Obese: BMI ≥30 kg/m^2; Obese Class I: 30 kg/m^2 ≤BMI<35 kg/m^2; Obese Class II: 35 kg/m^2 ≤BMI<40 kg/m^2; Obese Class III: BMI ≥40 kg/m^2
Percentages for obese subgroups are represented as a proportion of the total treatment group.

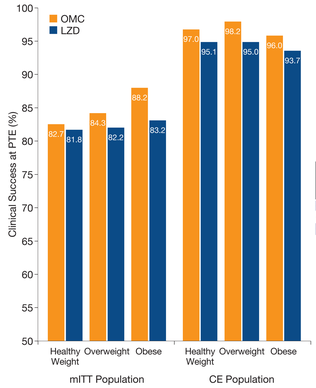
Figure 2. Clinical Success at ECR (mITT Population)[a]



Clinical Success at ECR, mITT Population, %	OMC (N=203)	LZD (N=190)
Obese Class I	87.0	81.0
Obese Class II	83.0	91.5
Obese Class III	87.9	76.3

ECR = early clinical response; LZD = linezolid; mITT = modified intent-to-treat; OMC = omadacycline

Figure 3. Clinical Success at PTE (mITT and CE Populations)[a]



Clinical Success at PTE, %	mITT Population		CE Population	
	OMC (N=203)	LZD (N=190)	OMC (N=176)	LZD (N=158)
Obese Class I	87.8	79.0	97.1	90.4
Obese Class II	91.5	89.4	97.6	97.6
Obese Class III	84.8	86.8	90.0	97.0

CE = clinically evaluable; LZD = linezolid; mITT = modified intent-to-treat; OMC = omadacycline; PTE = post treatment evaluation
[a]Within Figures 2 and 3, data presented in the graphs are for the full study population; data represented in the small tables are for the obesity subpopulation only.

RESULTS

Table 2. TEAEs by Treatment Group and BMI Category (Safety Population)

Number of patients, n (%) with:	Healthy Weight (18.5≤ BMI <25)		Overweight (25≤ BMI <30)		Obese (BMI ≥30)	
	OMC (N=252)	LZD (N=231)	OMC (N=221)	LZD (N=243)	OMC (N=210)	LZD (N=200)
TEAE, Any	136 (54.0)	89 (38.5)	105 (47.5)	110 (45.3)	108 (51.4)	77 (38.5)
Drug-related TEAE	71 (28.2)	32 (13.9)	62 (28.1)	42 (17.3)	62 (29.5)	35 (17.5)
Severe TEAE	6 (2.4)	4 (1.7)	4 (1.8)	7 (2.9)	1 (0.5)	6 (3.0)
Serious TEAE	8 (3.2)	3 (1.3)	4 (1.8)	4 (1.6)	3 (1.4)	6 (3.0)
TEAE leading to premature discontinuation of study drug	6 (2.4)	2 (0.9)	4 (1.8)	4 (1.6)	2 (1.0)	4 (2.0)
Serious TEAEs leading to premature discontinuation of study drug	3 (1.2)	1 (0.4)	2 (0.9)	2 (0.8)	1 (0.5)	2 (1.0)
Death	0	1 (0.4)	0	2 (0.8)	0	0

BMI = body mass index; OMC = omadacycline; LZD = linezolid; TEAE = treatment-emergent adverse event

Table 3. TEAEs Occuring in >2% of Patients in Either Treatment Group by BMI Category (Safety Population)

Number of patients, n (%) with:	Healthy Weight (18.5≤ BMI <25)		Overweight (25≤ BMI <30)		Obese (BMI ≥30)	
	OMC (N=252)	LZD (N=231)	OMC (N=221)	LZD (N=243)	OMC (N=210)	LZD (N=200)
TEAE, Any	136 (54.0)	89 (38.5)	105 (47.5)	110 (45.3)	108 (51.4)	77 (38.5)
Alanine aminotransferase increased	10 (4.0)	5 (2.2)	11 (5.0)	11 (4.5)	7 (3.3)	9 (4.5)
Aspartate aminotransferase increased	9 (3.6)	3 (1.3)	10 (4.5)	10 (4.1)	6 (2.9)	10 (5.0)
Cellulitis	10 (4.0)	5 (2.2)	10 (4.5)	9 (3.7)	7 (3.3)	10 (5.0)
Diarrhea	5 (2.0)	6 (2.6)	4 (1.8)	6 (2.5)	13 (6.2)	8 (4.0)
Headache	5 (2.0)	6 (2.6)	8 (3.6)	7 (2.9)	10 (4.8)	7 (3.5)
Infusion site extravasation	14 (5.6)	5 (2.2)	7 (3.2)	12 (4.9)	6 (2.9)	2 (1.0)
Nausea	50 (19.8)	22 (9.5)	47 (21.3)	23 (9.5)	51 (24.3)	13 (6.5)
Subcutaneous abscess	12 (4.8)	10 (4.3)	5 (2.3)	8 (3.3)	6 (2.9)	7 (3.5)
Vomiting	25 (9.9)	11 (4.8)	22 (10.0)	8 (3.3)	32 (15.2)	7 (3.5)
Wound infection	14 (5.6)	8 (3.5)	9 (4.1)	8 (3.3)	5 (2.4)	5 (2.5)

BMI = body mass index; OMC = omadacycline; LZD = linezolid; TEAE = treatment-emergent adverse event

Table 4. Patients With Post-baseline Liver Chemistry Elevations by Treatment Group and BMI Category (Safety Population)

Lab Parameter (SI unit)	Value	Healthy Weight (18.5≤ BMI <25)		Overweight (25≤ BMI <30)		Obese (BMI ≥30)	
		OMC N=252	LZD N=231	OMC N=221	LZD N=243	OMC N=210	LZD N=200
ALT (U/L)	Normal at baseline, n	184	189	161	196	150	152
	Elevated post-baseline, n	181	185	156	191	146	150
	>3 × ULN, n (%)	3 (1.7)	5 (2.7)	2 (1.3)	8 (4.2)	1 (0.7)	5 (3.3)
AST (U/L)	Normal at baseline, n	193	197	177	208	170	158
	Elevated post-baseline, n	190	192	171	203	166	155
	>3 × ULN, n (%)	4 (2.1)	4 (2.1)	2 (1.2)	5 (2.5)	2 (1.2)	7 (4.5)
Total bilirubin (µmol/L)	Normal at baseline, n	217	194	187	212	182	180
	Elevated post-baseline, n	215	187	179	207	179	176
	>2 × ULN, n (%)	3 (1.4)	0	1 (0.6)	1 (0.5)	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; LZD = linezolid; OMC = omadacycline; ULN = upper limit of normal

CONCLUSIONS

- Omadacycline showed similar efficacy and safety in obese, overweight and healthy-weight ABSSSI patients compared to linezolid
- Observed adverse events were consistent with the known adverse effect profile of the tetracycline class
- These data suggest that a fixed-dosing strategy, regardless of adult body size, did not impact the safety and efficacy of omadacycline used to treat ABSSSI in clinical studies

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