Poster 700

Safety and Efficacy of Omadacycline in Patients With Diabetes in Phase 3 Clinical Studies

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BACKGROUND

- The risks of serious infections and poor treatment outcomes are reported to be higher in people with diabetes compared with the general population[1,2]
- Omadacycline (OMC) is an intravenous (IV) and oral aminomethylcycline and tetracycline-class antibiotic approved in the United States to treat acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in adults[3-5]
- OMC showed non-inferiority to linezolid (LZD) in two ABSSSI studies (**O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy [OASIS]-1 and -2),[3,4] and to moxifloxacin (MOX) in a CABP study (**O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity [OPTIC])[5]

Objective of Secondary Analysis

- To assess the safety and efficacy results from OMC Phase 3 studies (ABSSSI: OASIS-1 and -2; CABP: OPTIC), by diabetes history

METHODS

Phase 3 OASIS-1 Study Design

- IV to oral OMC versus IV to oral LZD in patients with ABSSSI
  - Patients were randomized 1:1 to 7-14 days' therapy, *either*:
    - OMC (100 mg IV every 12 hours [q12h] for two doses, then 100 mg IV every 24 hours [q24h]; option to transition to 300 mg oral OMC q24h after ≥3 days), *or*
    - LZD (600 mg IV q12h, with option to transition to 600 mg oral LZD q12h after ≥3 days)

Phase 3 OASIS-2 Study Design

- Once-daily oral OMC versus twice-daily oral LZD in patients with ABSSSI
  - Patients were randomized 1:1 to 7-14 days' therapy, *either*:
    - Once-daily 450 mg oral OMC (Days 1 and 2), then once-daily 300 mg oral OMC, *or*
    - Twice-daily 600 mg oral LZD

Phase 3 OPTIC Study Design

- IV to oral OMC versus IV to oral MOX in patients with CABP
  - Patients were randomized 1:1 to 7-14 days' therapy, *either*:
    - OMC (100 mg IV q12h for two doses, then 100 mg IV q24h, with option to transition to 300 mg oral OMC q24h after ≥3 days), *or*
    - MOX (400 mg IV q24h, with option to transition to 400 mg oral MOX q24h after ≥3 days)

Study Populations

- ABSSSI: modified intent-to-treat (mITT): all randomized patients without a sole Gram-negative causative pathogen(s) at screening
- CABP: intent-to-treat (ITT): all randomized patients
- Safety: all patients who underwent randomization and received any amount of study drug
- Microbiologic ITT: all patients in ITT (CABP study) or mITT (ABSSSI studies) population who had a causative pathogen(s) identified at baseline

Efficacy Endpoints q24h

- Efficacy was evaluated at:
  - 48-72 hours (ABSSSI) or 72-120 hours (CABP) after first dose of study drug (early clinical response [ECR])
  - 7-14 days (ABSSSI) or 5-10 days (CABP) after last dose of study drug (investigator assessment of clinical response post treatment evaluation [PTE])

Secondary Analysis

- Efficacy and safety outcomes, analyzed by any medical history of diabetes (type 1, type 2, or unspecified)
- Treatment-emergent adverse events (TEAEs)

RESULTS

- 2,150 participants were included; 238/2,150 (11.1%) had any history of diabetes (7.6% [105/1,380] of those in the ABSSSI studies and 17.3% [133/770] of those in the CABP study; safety populations)
  - Median age and median body mass index (BMI) of patients with diabetes were similar between OMC and the respective comparators (**Table 1**):
    - Median BMI was 29.4-33.3; ~50% of the study participants were obese (defined by Centers for Disease Control and Prevention categories, ≥30 kg/m²)

Table 1. Demographics and Baseline Characteristics of Participants With Diabetes Included in Phase 3 Studies of Omadacycline (Safety Populations)

	ABSSSI		CABP	
Parameter	OMC (N=38)	LZD (N=67)	OMC (N=62)	MOX (N=71)
Median age, years (range)	59 (22-86)	60 (22-90)	67 (40-90)	71 (28-92)
Male, n (%)	16 (42.1)	36 (53.7)	32 (51.6)	38 (53.5)
Caucasian race, n (%)	36 (94.7)	62 (92.5)	57 (91.9)	61 (85.9)
Median BMI, kg/m² (range)	33.3 (22.0-53.6)	31.2 (19.4-54.7)	30.2 (20.0-50.6)	29.4 (20.9-54.7)

ABSSSI = acute bacterial skin and skin structure infections; BMI = body mass index; CABP = community-acquired bacterial pneumonia; LZD = linezolid; MOX = moxifloxacin; OMC = omadacycline

- Methicillin-susceptible *S. aureus* was the most frequently reported baseline pathogen in the ABSSSI studies (OASIS-1, -2) in patients for whom a baseline pathogen could be identified (**Table 2**)
- In the CABP study (OPTIC), no particular pathogen predominated, with similar numbers of Gram-positive, Gram-negative, and atypical pathogens identified (**Table 2**)

Table 2. Baseline Pathogens Identified in Participants With Diabetes Included in Phase 3 Studies of Omadacycline (mITT Populations [OASIS-1, -2]; Microbiologic mITT Population [OPTIC])

OASIS-1 and -2 Baseline Pathogen	OMC (N=18), n (%)	LZD (N=38), n (%)
Gram-positive bacteria (aerobes)	18 (100.0)	36 (94.7)
Staphylococcus aureus	13 (72.0)	25 (65.8)
Methicillin resistant	4 (22.2)	8 (21.1)
Methicillin susceptible	10 (55.6)	18 (47.4)
Streptococcus anginosus group	2 (11.1)	2 (5.3)
Enterococcus faecalis	2 (11.1)	6 (15.8)
Vancomycin susceptible	2 (11.1)	6 (15.8)
Gram-negative organisms (aerobes)	2 (11.1)	8 (21.1)
OPTIC Baseline Pathogen	**OMC (N=31), n (%)**	**MOX (N=30), n (%)**
Gram-positive bacteria (aerobes)	12 (38.7)	9 (30.0)
Streptococcus pneumoniae	6 (19.4)	3 (10.0)
S. aureus	3 (9.7)	3 (10.0)
Gram-negative bacteria (aerobes)	12 (38.7)	13 (43.3)
Haemophilus influenzae	5 (16.1)	1 (3.3)
Haemophilus parainfluenzae	3 (9.7)	6 (20.0)
Klebsiella pneumoniae	2 (6.5)	2 (6.7)
Atypical pathogens	16 (51.6)	15 (50.0)
Mycoplasma pneumoniae	10 (32.3)	10 (33.3)
Legionella pneumophila	4 (12.9)	3 (10.0)
Chlamydophila pneumoniae	6 (19.4)	4 (13.3)

LZD = linezolid; mITT = modified intent-to-treat; MOX = moxifloxacin; OASIS = **O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy; OMC = omadacycline; OPTIC = **O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity

- Across the study groups over 70% of patients with diabetes also reported a history of hypertension. Other conditions noted frequently in the OPTIC study included chronic obstructive pulmonary disease, atrial fibrillation, and coronary artery disease (**Table 3**)
- In the ABSSSI studies, there was a similar split by baseline lesion type among participants in both treatment arms. Most patients with diabetes in the CABP study had a Pneumonia Outcomes Research Team (PORT) Risk Class of III or IV (**Table 4**)

RESULTS

Table 3. Select Medical History and Comorbidities of Participants With Diabetes Included in Phase 3 Studies of Omadacycline (Safety Populations)

	ABSSSI		CABP	
Concomitant Condition, n (%)	OMC (N=38)	LZD (N=67)	OMC (N=62)	MOX (N=71)
Hypertension	27 (71.1)	39 (58.2)	56 (90.3)	51 (71.8)
Atrial fibrillation	2 (5.3)	6 (9.0)	10 (16.1)	8 (11.3)
Coronary artery disease	1 (2.6)	0 (0.0)	10 (16.1)	9 (12.7)
Dyslipidemia	1 (2.6)	1 (1.5)	6 (9.7)	7 (9.9)
Obesity	4 (10.5)	10 (14.9)	6 (9.7)	5 (7.0)
Diabetic neuropathy	1 (2.6)	9 (13.4)	5 (8.1)	3 (4.2)
COPD	1 (2.6)	2 (3.0)	15 (24.2)	7 (9.9)
Asthma	2 (5.3)	4 (6.0)	6 (9.7)	5 (7.0)

ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; COPD = chronic obstructive pulmonary disease; LZD = linezolid; MOX = moxifloxacin; OMC = omadacycline

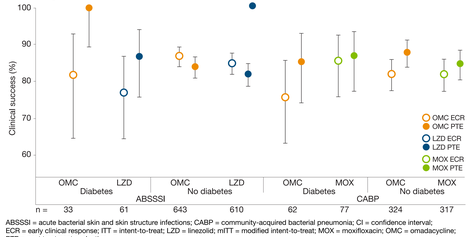
Table 4. Baseline Disease Characteristics of Participants With Diabetes Included in Phase 3 Studies of Omadacycline

	ABSSSI mITT Population	
ABSSSI, Lesion Type, n (%)	OMC (N=18)	LZD (N=38)
Cellulitis/erysipelas	9 (50.0)	12 (31.6)
Wound infection	4 (22.2)	9 (23.7)
Major abscess	5 (27.8)	10 (26.3)
	CABP ITT Population	
PORT Risk Class[a], n%	OMC (N=63)	MOX (N=71)
II	7 (11.1)	9 (12.7)
III	35 (55.6)	31 (43.7)
IV	21 (33.3)	31 (43.7)
V	0	0

[a]PORT Risk Class: II (51 ≤ PORT Score ≤70); III (71 ≤ PORT Score ≤90); IV (91 ≤ PORT Score ≤130); V (PORT Score ≥131).
ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; ITT = intent-to-treat; mITT = modified intent-to-treat; PORT = Pneumonia Outcomes Research Team

- In all three studies, clinical success rates (ECR and PTE) were similar between patients with and without diabetes, and between OMC and the respective comparators, with the exception of 100% clinical success at PTE for those who received OMC in pooled ABSSSI studies versus 87% for those who received LZD, though the 95% confidence intervals (CIs) were overlapping (**Fig. 1**)
- Reasons for clinical failure in the CABP study showed no substantial trends for patients with diabetes who were treated with OMC, compared with those without diabetes

Figure 1. Clinical Success at ECR and PTE Among Patients With Diabetes; ABSSSI Studies, mITT Population; CABP Study, ITT Population in Phase 3 Studies of Omadacycline, With Exact 95% CIs

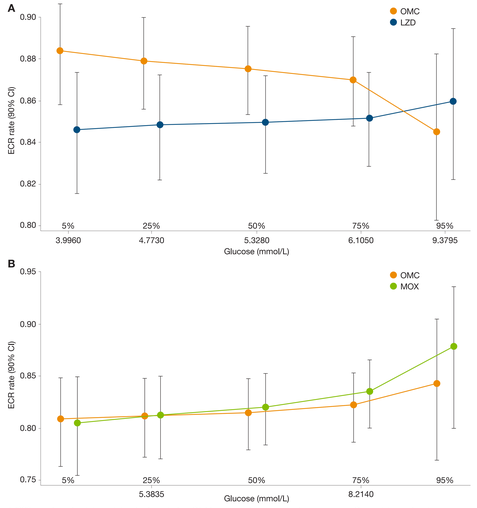


ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; CI = confidence interval; ECR = early clinical response; ITT = intent-to-treat; LZD = linezolid; mITT = modified intent-to-treat; MOX = moxifloxacin; OMC = omadacycline; PTE = post treatment evaluation

RESULTS

- An analysis was conducted for participants with or without diabetes to determine if there was a trend in clinical success by blood glucose measurements. No substantial trends in ECR were observed as a function of patients' blood glucose levels for any study (**Fig. 2**)

Figure 2. ECR by Blood Glucose Measurements at Screening (Absolute Results) From (A) Pooled ABSSSI Studies (mITT Population) and (B) CABP Study (ITT Population), Phase 3 Studies of Omadacycline



ABSSSI = acute bacterial skin and skin structure infection; CABP = community-acquired bacterial pneumonia; CI = confidence interval; ECR = early clinical response; ITT = intent-to-treat; LZD = linezolid; mITT = modified intent-to-treat; MOX = moxifloxacin; OMC = omadacycline

Table 5. TEAEs by History of Diabetes, Pooled Phase 3 Studies (Safety Populations)

	OMC		LZD		MOX	
TEAE, n (%)	Diabetes (N=100)	No Diabetes (N=973)	Diabetes (N=67)	No Diabetes (N=622)	Diabetes (N=71)	No Diabetes (N=317)
Any TEAE	47 (47.0)	463 (47.6)	28 (41.8)	256 (41.2)	35 (49.3)	153 (48.3)
Drug-related TEAE	11 (11.0)	225 (23.1)	11 (16.4)	100 (16.1)	14 (19.7)	55 (17.4)
Serious TEAE	7 (7.0)	32 (3.3)	3 (4.5)	10 (1.6)	4 (5.6)	22 (6.9)
Drug-related serious TEAE	1 (1.0)	1 (0.1)	0	1 (0.2)	1 (1.4)	1 (0.3)
TEAE leading to death	4 (4.0)	4 (0.4)	0	3 (0.5)	1 (1.4)	3 (0.9)
TEAE leading to study drug discontinuation	6 (6.0)	27 (2.8)	1 (1.5)	9 (1.4)	4 (5.6)	23 (7.3)
Serious TEAE leading to study drug discontinuation	3 (3.0)	13 (1.3)	1 (1.5)	4 (0.6)	2 (2.8)	9 (2.8)

LZD = linezolid; MOX = moxifloxacin; OMC = omadacycline; TEAE = treatment-emergent adverse event

RESULTS

- TEAEs were reported in similar proportions of OMC-, LZD-, and MOX-treated patients with and without diabetes (**Table 5**)
  - Serious TEAEs (SAEs) were reported in higher proportions of patients with diabetes (vs no diabetes) for both OMC and LZD, but SAEs were rarely considered drug related for any of the study drugs
  - Four of the eight patients (50%) with TEAEs leading to death in the OMC arm had diabetes
- Nausea and vomiting rates in patients with diabetes were similar across treatment arms (**Table 6**)
  - Compared to those without diabetes, neither nausea nor vomiting rates were substantially higher in patients with diabetes for any of the study drugs
  - For OMC, nausea in particular was notably less frequent in patients with, versus those without, diabetes

Table 6. Most Frequently Observed (≥2% in Omadacycline Group With Diabetes) TEAEs, Pooled Phase 3 Studies (Safety Populations)

	OMC		LZD		MOX	
TEAE, n (%)	Diabetes (N=100)	No Diabetes (N=973)	Diabetes (N=67)	No Diabetes (N=622)	Diabetes (N=71)	No Diabetes (N=317)
Anemia	5 (5.0)	7 (0.7)	1 (1.5)	3 (0.5)	0	3 (0.9)
Nausea	5 (5.0)	155 (15.9)	5 (7.5)	55 (8.8)	5 (7.0)	16 (5.0)
Vomiting	5 (5.0)	84 (8.6)	4 (6.0)	23 (3.7)	2 (2.8)	4 (1.3)
Diarrhea	4 (4.0)	22 (2.3)	3 (4.5)	17 (2.7)	4 (5.6)	27 (8.5)
Headache	3 (3.0)	28 (2.9)	2 (3.0)	19 (3.1)	2 (2.8)	3 (0.9)
ALT increased	2 (2.0)	40 (4.1)	1 (1.5)	24 (3.9)	3 (4.2)	15 (4.7)
Hepatic steatosis	2 (2.0)	1 (0.1)	0	0	2 (2.8)	2 (0.6)
Pleural effusion	2 (2.0)	2 (0.2)	0	0	3 (4.2)	2 (0.6)
AST increased	2 (2.0)	31 (3.2)	1 (1.5)	23 (3.7)	1 (1.5)	14 (4.4)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LZD = linezolid; MOX = moxifloxacin; OMC = omadacycline; TEAE = treatment-emergent adverse event

CONCLUSIONS

- Omadacycline efficacy and safety findings were generally consistent in participants with or without diabetes
- Gathering more data on omadacycline from patients with diabetes would help to expand the efficacy and safety trends in this subgroup

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