Safety and Efficacy of Omadacycline for Treatment of Community-Acquired Bacterial Pneumonia and Acute Bacterial Skin and Skin Structure Infections in Patients With Mild to Moderate Renal Insufficiency

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Poster O0304
Abstract 1309

BACKGROUND

- Omadacycline (OMC), an aminomethylcycline antibiotic, is approved in the USA for the treatment of adults with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI)[1]
- In the Phase 3 studies **O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity (OPTIC) and **O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy (OASIS)-1 and OASIS-2, OMC showed non-inferiority to moxifloxacin (MOX) and linezolid (LZD) comparators for the treatment of CABP and ABSSSI, respectively[2-4]
- Although predominantly eliminated in feces, ~30% of OMC is cleared renally[5]
- Renal insufficiency may impact the pharmacokinetics (PK) of antibiotics, requiring dosage adjustments[6]
- No OMC dosage adjustments are required in patients with renal insufficiency based on a Phase 1 PK study in patients with end-stage renal disease[7,8]
- In this analysis, we further assess the safety and efficacy results from the OPTIC, OASIS-1, and OASIS-2 studies by renal function

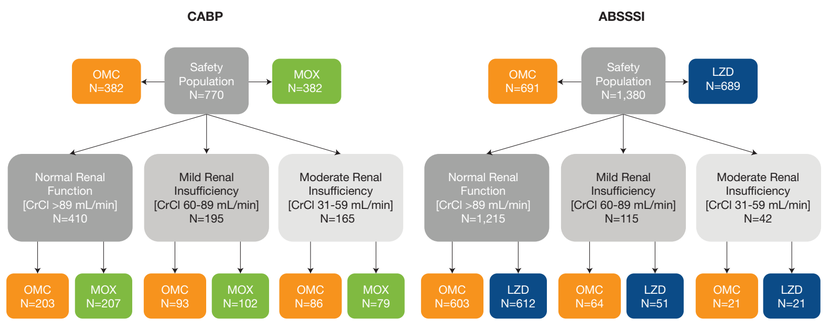
METHODS

- In OPTIC, OMC patients received 100 mg intravenously (IV) every 12 hours (q12h) for two doses, then every 24 hours (q24h) for a minimum of 3 days. They could then transition to 300 mg administered orally q24h. Comparator patients received MOX 400 mg IV q24h for at least 3 days, with the option to transition to oral
- In OASIS-1, OMC patients received the same regimen as described for OPTIC. Comparator patients received LZD 600 mg IV q12h for at least 3 days, with the option to transition to oral
- In OASIS-2, patients received either OMC 450 mg orally q24h for two doses followed by 300 mg orally q24h; or LZD 600 mg orally q12h
- For this analysis, patients in each of the three studies were stratified by renal function:
  - Normal renal function: creatinine clearance (CrCl) >89 mL/min
  - Mild renal insufficiency: CrCl 60-89 mL/min
  - Moderate renal insufficiency: CrCl 31-59 mL/min
- All three studies excluded patients with history or evidence of severe renal disease or a calculated CrCl ≤30 mL/min
- Efficacy endpoints:
  - Early clinical response (ECR): Survival with improvement in ≥2 symptoms of CABP (cough, sputum production, pleuritic chest pain, dyspnea), no worsening in other symptoms, and no rescue antibacterial therapy (CABP study; 72-120 hours after first dose) OR survival with a ≥20% reduction in lesion size (ABSSSI studies; 42-72 hours after first dose)
  - Investigator's assessment of clinical response at post treatment evaluation (PTE): Survival with resolution of signs and symptoms of infection with no further antibacterial therapy (all studies). PTE was 5-10 days after last dose for CABP, and 7-14 days after last dose for ABSSSI
- Safety assessments:
  - Treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms, and clinical laboratory tests

RESULTS

- 774 CABP patients and 1,390 ABSSSI patients were included in the intent-to-treat (ITT) population (all randomized patients)
  - Of these, 770 and 1,380 were included in the safety populations (received a study drug), respectively
- In the CABP study, 46.8% (360/770) of patients had mild or moderate renal insufficiency, compared with 11.4% (157/1,380) across the two ABSSSI studies (**Fig. 1**)

Figure 1. Patient Stratification in the CABP and ABSSSI Studies (Safety Population)

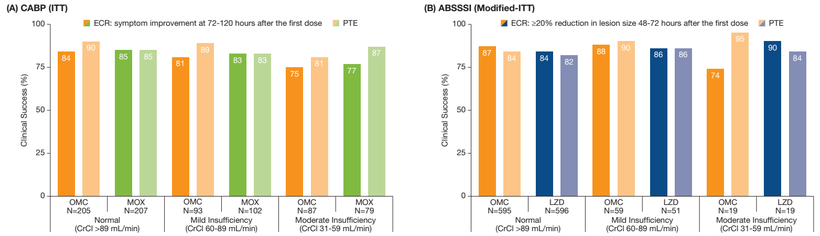


ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; CrCl = creatinine clearance; LZD = linezolid; MOX = moxifloxacin; OMC = omadacycline
Safety population included all randomized patients who received a dose of LZD, MOX, or OMC.

RESULTS

- Patients with mild to moderate renal insufficiency were older (CABP: 71 years vs 53 years; ABSSSI: 62 years vs 43 years), had lower mean body weight (both studies: 72 kg vs 83 kg), and more comorbidities (diabetes, CABP: 20.0% vs 14.9%; ABSSSI: 18.5% vs 6.2%; hypertension, CABP: 64.2% vs 37.3%; ABSSSI: 38.9% vs 16.2%) than patients with normal renal function
- Rates of clinical success with OMC were comparable with LZD and MOX (**Fig. 2**) at both assessment points

Figure 2. Clinical Success Rates at ECR and PTE Were Similar in Patients Irrespective of Renal Function in the (A) CABP and (B) ABSSSI Studies



ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; CrCl, creatinine clearance; ECR, early clinical response; ITT, intent-to-treat; LZD, linezolid; MOX, moxifloxacin; OMC, omadacycline; PTE, post treatment evaluation
Modified-ITT population included all randomized patients without a baseline sole Gram-negative ABSSSI pathogen.

- CABP:
  - TEAEs were reported more frequently in patients with moderate renal insufficiency. Nausea rates were higher in MOX patients and vomiting rates were higher in OMC patients with moderate renal insufficiency
  - Serious TEAEs were more frequent in CABP patients with moderate renal insufficiency (**Table 1**)

Table 1. TEAEs Were More Frequent in CABP Patients With Renal Insufficiency Than Those With Normal Renal Function (Safety Population)

	Normal Renal Function		Mild Renal Insufficiency		Moderate Renal Insufficiency	
Patients, n (%) with:	**OMC (N=203)**	**MOX (N=207)**	**OMC (N=93)**	**MOX (N=102)**	**OMC (N=86)**	**MOX (N=79)**
TEAE, Any	70 (34.5)	94 (45.4)	35 (37.6)	50 (49.0)	52 (60.5)	44 (55.7)
Serious TEAE	7 (3.4)	10 (4.8)	3 (3.2)	8 (7.8)	13 (15.1)	8 (10.1)
Most Frequent TEAEs[a]						
Alanine aminotransferase increased	8 (3.9)	10 (4.8)	6 (6.5)	4 (3.9)	0 (0.0)	4 (5.1)
Aspartate aminotransferase increased	3 (1.5)	8 (3.9)	5 (5.4)	3 (2.9)	0 (0.0)	3 (3.8)
Constipation	3 (1.5)	1 (0.5)	2 (2.2)	1 (1.0)	4 (4.7)	4 (5.1)
Gamma-glutamyltransferase increased	6 (3.0)	4 (1.9)	4 (4.3)	2 (2.0)	0 (0.0)	2 (2.5)
Headache	3 (1.5)	4 (1.9)	3 (3.2)	0 (0.0)	2 (2.3)	1 (1.3)
Hypertension	9 (4.4)	5 (2.4)	2 (2.2)	3 (2.9)	2 (2.3)	3 (3.8)
Insomnia	6 (3.0)	3 (1.4)	0	2 (2.0)	4 (4.7)	3 (3.8)
Nausea	4 (2.0)	7 (3.4)	1 (1.1)	3 (2.9)	4 (4.7)	11 (13.9)
Vomiting	2 (1.0)	2 (1.0)	1 (1.1)	2 (2.0)	7 (8.1)	2 (2.5)

CABP = community-acquired bacterial pneumonia; MOX = moxifloxacin; OMC = omadacycline; TEAE = treatment-emergent adverse event
[a]Reported by at least 2% of patients in either treatment group.

- ABSSSI:
  - There was no difference in the number of patients reporting TEAEs by renal function. More patients reported nausea and vomiting with OMC (19%-23% and 10%-12%, respectively) compared with LZD (5%-10% and 0%-8%, respectively) across renal insufficiency groups
  - Rates of serious TEAEs were similar across renal function groups (**Table 2**)

Table 2. No Difference in the Proportion of Patients Reporting TEAEs by Renal Function Was Observed in the ABSSSI Studies (Safety Population)

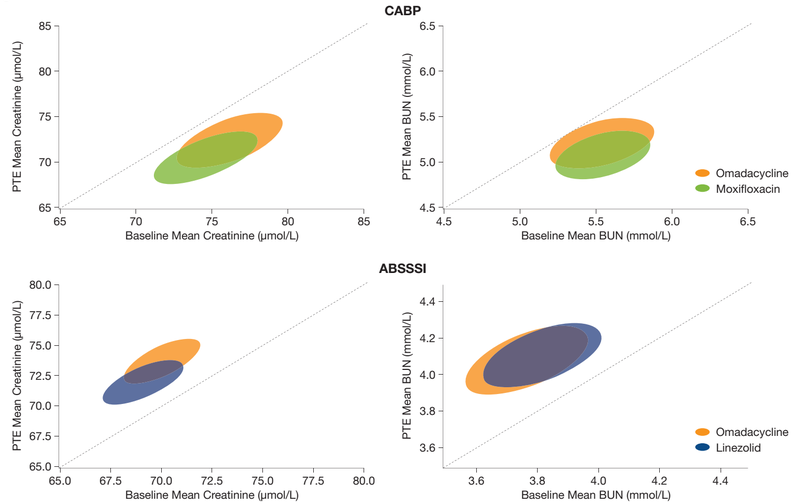
	Normal Renal Function		Mild Renal Insufficiency		Moderate Renal Insufficiency	
Patients, n (%) with:	**OMC (N=603)**	**LZD (N=612)**	**OMC (N=64)**	**LZD (N=51)**	**OMC (N=21)**	**LZD (N=21)**
TEAE, Any	313 (51.9)	256 (41.8)	27 (42.2)	20 (39.2)	11 (52.4)	7 (33.3)
Serious TEAE	15 (2.5)	11 (1.8)	0 (0.0)	1 (2.0)	1 (4.8)	1 (4.8)
Most Frequent TEAEs[a]						
Alanine aminotransferase increased	27 (4.5)	24 (3.9)	0 (0.0)	1 (2.0)	1 (4.8)	0 (0.0)
Aspartate aminotransferase increased	25 (4.1)	22 (3.6)	0 (0.0)	2 (3.9)	0 (0.0)	0 (0.0)
Cellulitis	27 (4.5)	23 (3.8)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Diarrhea	19 (3.2)	18 (2.9)	3 (4.7)	2 (3.9)	0 (0.0)	0 (0.0)
Headache	21 (3.5)	19 (3.1)	2 (3.1)	0 (0.0)	0 (0.0)	2 (9.5)
Infusion site extravasation	26 (4.3)	17 (2.8)	2 (3.1)	2 (3.9)	0 (0.0)	0 (0.0)
Nausea	131 (21.7)	54 (8.8)	15 (23.4)	5 (9.8)	4 (19.0)	1 (4.8)
Subcutaneous abscess	22 (3.6)	25 (4.1)	1 (1.6)	1 (2.0)	0 (0.0)	0 (0.0)
Vomiting	70 (11.6)	23 (3.8)	7 (10.9)	4 (7.8)	2 (9.5)	0 (0.0)
Wound infection	27 (4.5)	20 (3.3)	1 (1.6)	2 (3.9)	2 (9.5)	0 (0.0)

ABSSSI, acute bacterial skin and skin structure infection; LZD, linezolid; OMC, omadacycline; TEAE, treatment-emergent adverse event
[a]Reported by at least 2% of patients in either treatment group.

RESULTS

- Elevations in creatinine and blood urea nitrogen (BUN) at PTE were mostly observed in patients with high baseline values (**Fig. 3**)
- For CABP, the mean BUN and creatinine at PTE is lower than at baseline (confidence ellipses below the diagonal). For ABSSSI, the mean BUN and creatinine at PTE is higher than at baseline (confidence ellipses above the diagonal). For both omadacycline and moxifloxacin, the confidence regions are similar for BUN and creatinine

Figure 3. Creatinine Shifts and BUN Shifts at PTE



ABSSSI = acute bacterial skin and skin structure infections; BUN = blood urea nitrogen; CABP = community-acquired bacterial pneumonia; PTE, post treatment evaluation
Ellipses represent the 95% joint confidence region for baseline and PTE.

CONCLUSIONS

- Clinical success at early clinical response and post treatment evaluation was similar across patients irrespective of renal sufficiency
- Observed clinical success rates from omadacycline treatment were comparable to moxifloxacin and linezolid
- More TEAEs were observed in omadacycline- or moxifloxacin-treated patients with CABP who had renal insufficiency compared with those with normal renal function
- No differences were seen in overall rates of TEAEs in omadacycline- or linezolid-treated patients with ABSSSI across the renal function groups
- This integrated analysis of three CABP and ABSSSI Phase 3 studies demonstrated that omadacycline was effective and had a similar safety profile to comparators in patients with mild to moderate renal insufficiency

REFERENCES

1. US Department of Health and Human Sciences, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/209816Orig1s000,209817Orig1s000Ltr.pdf accessed Mar 2019.
2. Stets R, et al. N Engl J Med. 2019;380(6):517-527.
3. O'Riordan W, et al. N Engl J Med. 2019;380(6):528-538.
4. O'Riordan W, et al. ECCMID 2018 presentation O0425.
5. Flarakos J, et al. Xenobiotica. 2017;47(8):682-696.
6. Eyler RF, Mueller BA. Adv Chronic Kidney Dis. 2010;17:392-403.
7. Berg JK, et al. Antimicrob Agents Chemother. 2018;62(2): e02057-17.
8. Nuzyra™ (omadacycline), Prescribing Information. 2018.

FUNDING AND DISCLOSURES

Oliver A. Cornely is a consultant to Paratek Pharmaceuticals, Inc. Lynne Garrity-Ryan, Marla Curran and Paul C. McGovern are employees of Paratek Pharmaceuticals, Inc. Surya Chitra is a consultant to Paratek Pharmaceuticals, Inc. This study was sponsored by Paratek Pharmaceuticals, Inc. Medical editorial assistance, funded by Paratek Pharmaceuticals, Inc., was provided by Innovative Strategic Communications.

ACKNOWLEDGMENTS

The authors wish to thank the patients and investigators involved in the OPTIC, OASIS-1, and OASIS-2 studies.

Presented at: ECCMID 2019; 13-16 April, 2019; Amsterdam, The Netherlands