

Early Clinical Response and Clinical Stability as Predictors of Overall Clinical Response in Community-Acquired Bacterial Pneumonia

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Abstract 1323



BACKGROUND

- Community-acquired pneumonia is one of the leading causes of mortality worldwide¹⁻⁴
- Omadacycline (OMC) is an aminomethylcycline antibiotic in the tetracycline class approved for the treatment of community-acquired bacterial pneumonia (CABP) in adults in the USA⁵
- In the Phase 3 Omadacycline for Pneumonia Treatment In the Community (OPTIC) study, the FDA-required primary endpoint was early clinical response (ECR)⁶
- The achievement of clinical stability is an opportunity to consider a switch to oral therapy and hospital discharge in patients initially hospitalized and treated with intravenous (IV) antibiotics
- OPTIC demonstrated non-inferiority of OMC to moxifloxacin (MOX) for treatment of CABP⁷
- Here we describe the performance of ECR and clinical stability during OPTIC relative to investigator assessment of clinical response (IACR) at the post treatment evaluation (PTE)

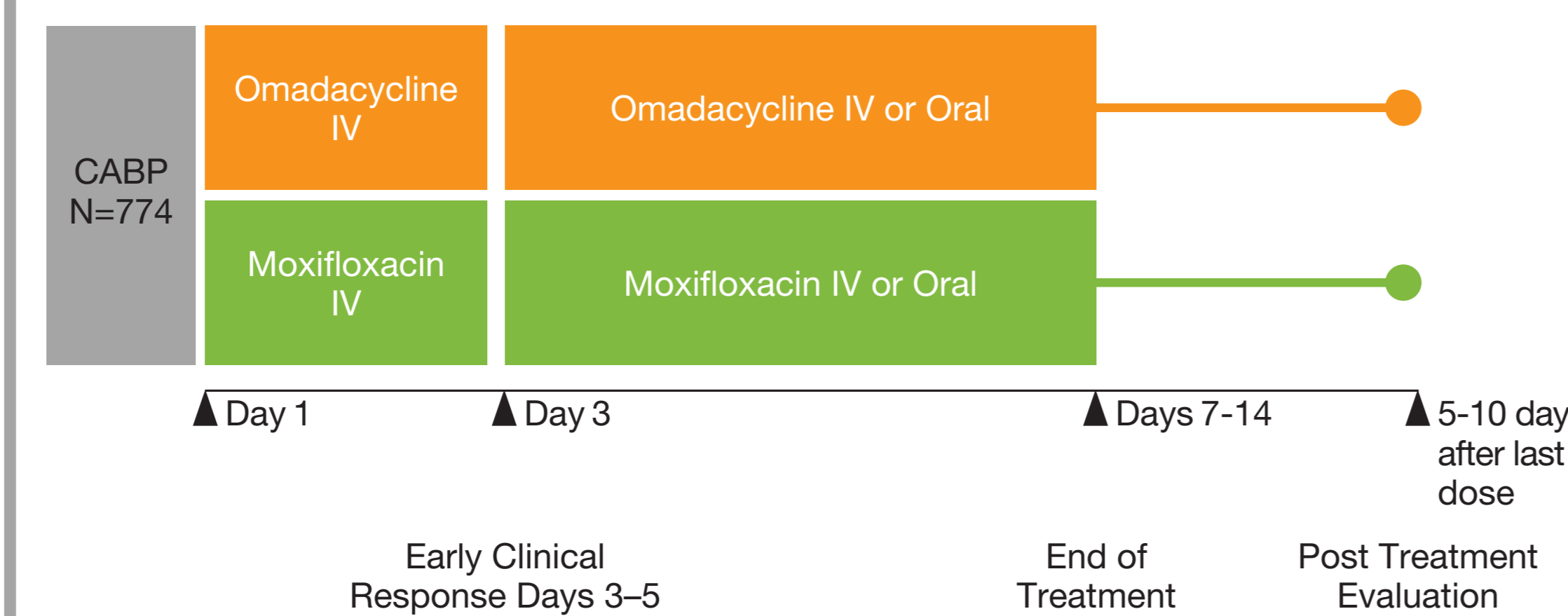
METHODS

- The OPTIC study was a multicenter, randomized, double-blind study that compared OMC to MOX for treatment of adults with CABP (Fig. 1)
- Patients received OMC (100 mg IV every 12 hours on Day 1 followed by 100 mg IV every 24 hours [q24h]) or MOX (400 mg IV q24h) IV treatment ≥3 days, then could transition to oral treatment (OMC: 300 mg orally, MOX: 400 mg orally)
- Total treatment duration was 7-14 days
- Enrolled patients were ≥18 years of age with ≥3 protocol-specified CABP symptoms (cough, production of purulent sputum, dyspnea, pleuritic chest pain), abnormal vital signs, laboratory abnormalities associated with CABP, disease categorized as being Pneumonia Outcomes Research Team (PORT) Risk Class II, III, or IV at screening, and radiographically confirmed pneumonia⁷
- ECR was defined as symptom improvement 72-120 hours after first dose of study drug (ECR window), no use of rescue antibiotics, and survival
 - CABP symptoms were characterized using a 4-point scale (absent, mild, moderate, or severe) by the investigator
 - Symptom improvement was defined as ≥1 level improvement (e.g., severe to moderate) in ≥2 CABP symptoms with no worsening by ≥1 level in other CABP symptoms
- Investigator assessment of clinical response was determined at PTE (5-10 days after last dose)
 - Clinical success at PTE was defined as survival with resolution of signs and symptoms of the infection such that further antibacterial therapy was not necessary

METHODS

- Patients achieved clinical stability^{8,9} if they met all of the following criteria: 1) temperature ≤37.8°C (100°F); 2) heart rate ≤100 beats/minute; 3) respiratory rate ≤24 breaths/minute; 4) systolic blood pressure ≥90 mmHg; and 5) arterial oxygen saturation ≥90% or partial pressure of oxygen ≥60 mmHg on room air
- If multiple ECR or clinical stability measurements were made during the 72-120-hour window, the last measurement within the window was used for analysis
- For each clinical stability criteria, last observation carried forward (LOCF) was utilized to impute missing values
- Dichotomized ECR response and clinical stability during the ECR measurement window were combined to demonstrate the clinical trajectory of patients who did or did not meet symptom improvement and clinical stability criteria at 72-120 hours
- Concordance of ECR or clinical stability with clinical success at PTE, and the test characteristics (sensitivity, specificity, positive predictive value, negative predictive value) of ECR or clinical stability with clinical success at PTE, were determined

Figure 1. OPTIC Study Design



CABP = community-acquired bacterial pneumonia; IV = intravenous; OPTIC = Omadacycline for Pneumonia Treatment In the Community

RESULTS

- Patients had similar baseline characteristics and demographics between treatment groups
- Among all of the intent-to-treat (ITT) patients, 41.9% were >65 years of age and 85.4% had a PORT (Pneumonia Severity Index) Risk Class of III or IV⁷
- Most patients achieved ECR (OMC: 81.1%, MOX: 82.7%) and clinical stability (OMC: 74.6%, MOX: 77.6%) during the 72-120 hour window, when stability was evaluated in patients with a measurement for all five vital signs
- The results demonstrate that ECR, clinical success at PTE, and clinical stability rates by PORT Risk Class were similar between OMC and MOX patients (Table 1)
- Clinical success rates at PTE were higher than ECR rates in the ITT population for both treatment groups and by PORT Risk Class

RESULTS

Table 1. ECR, Clinical Success at PTE, and Clinical Stability (Using LOCF) by PORT Risk Class (ITT Population)

PORT Risk Class	Endpoint	Omadacycline n/N (%)	Moxifloxacin n/N (%)	Difference (95% CI)
II	ECR	43/57 (75.4)	41/56 (73.2)	2.2 (-14.0 to 18.4)
	PTE	47/57 (82.5)	47/56 (83.9)	-1.5 (-15.7 to 12.8)
	Clinical stability	41/57 (71.9)	43/56 (76.8)	-4.9 (-22.7 to 12.9)
III	ECR	191/227 (84.1)	187/216 (86.6)	-2.4 (-9.1 to 4.2)
	PTE	206/227 (90.7)	190/216 (88.0)	2.8 (-3.0 to 8.7)
	Clinical stability	182/227 (80.2)	175/216 (81.0)	-0.8 (-8.6 to 7.0)
IV	ECR	79/102 (77.5)	93/116 (80.2)	-2.7 (-13.8 to 8.1)
	PTE	85/102 (83.3)	93/116 (80.2)	3.2 (-7.4 to 13.4)
	Clinical stability	78/102 (76.5)	92/116 (79.3)	-2.8 (-14.8 to 9.2)

CI = confidence interval; ECR = early clinical response; ITT = intent-to-treat; LOCF = last observation carried forward; PORT = Pneumonia Outcomes Research Team; PTE = post treatment evaluation

- The clinical stability rate was higher in PORT Risk Classes III and IV patients compared to PORT Risk Class II patients
- The clinical stability rate was similar to ECR rate in all PORT Risk Classes in both treatment groups
- Both ECR and clinical stability exhibited high concordance (>75%) with clinical success at PTE (Table 2)

Table 2. Concordance of ECR and Clinical Stability with Clinical Success at PTE (ITT Population)

Treatment Group	ECR (72-120 hours)	Clinical Success at PTE, n (%)		
		Clinical Success	Clinical Failure	Indeterminate ^a
Omadacycline (N=386)	Clinical success	298 (77.2)	9 (2.3)	6 (1.6)
	Clinical failure	35 (9.1)	13 (3.4)	1 (0.3)
	Indeterminate ^a	5 (1.3)	10 (2.6)	9 (2.3)
Moxifloxacin (N=388)	Clinical success	295 (76.0)	17 (4.4)	9 (2.3)
	Clinical failure	30 (7.7)	15 (3.9)	2 (0.5)
	Indeterminate ^a	5 (1.3)	10 (2.6)	5 (1.3)

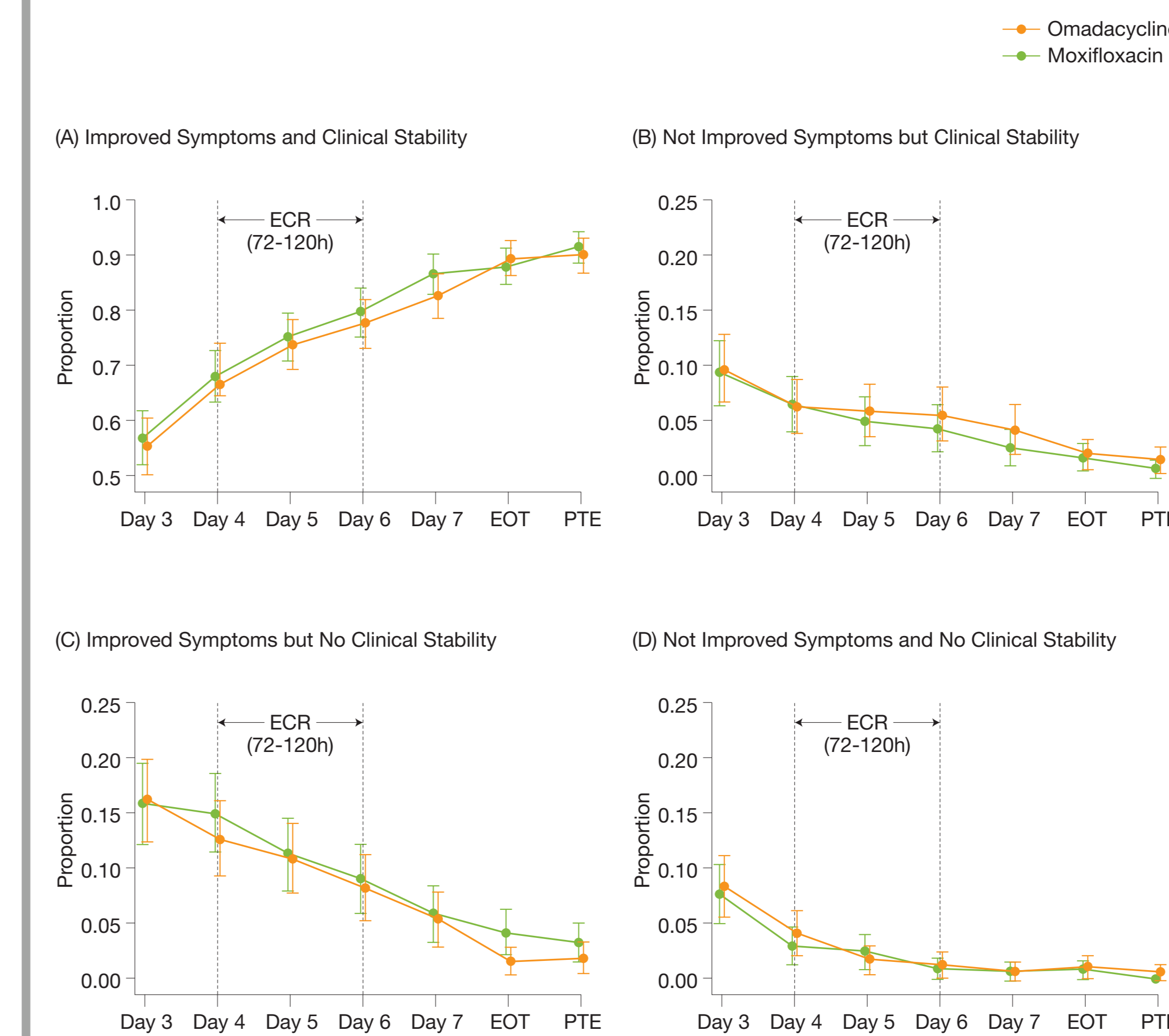
Treatment Group	Clinical Stability (72-120 hours)	Clinical Success at PTE, n (%)		
		Clinical Success	Clinical Failure	Indeterminate ^a
Omadacycline (N=386)	Stable	271 (70.2)	13 (3.4)	4 (1.0)
	Not stable	62 (16.1)	10 (2.6)	3 (0.8)
	Indeterminate ^a	5 (1.3)	9 (2.3)	9 (2.3)
Moxifloxacin (N=388)	Stable	275 (70.9)	17 (4.4)	9 (2.3)
	Not stable	49 (12.6)	13 (3.4)	2 (0.5)
	Indeterminate ^a	6 (1.6)	12 (3.1)	5 (1.3)

ECR = early clinical response; ITT = intent-to-treat; PTE = post treatment evaluation
^a Due to missing data.

RESULTS

- Fewer OMC patients than MOX patients with ECR subsequently had clinical failure at PTE (2.3% vs 4.4%)
- More OMC patients than MOX patients who did not have an ECR were subsequently considered as having achieved clinical success at PTE (9.1% vs 7.7%)
- ECR and clinical stability demonstrated high sensitivity (>80%) and positive predictive value (>90%) for clinical success at PTE, whereas negative predictive value was poor for both assessments (<50%)

Figure 2. Symptom Improvement and Clinical Stability (using LOCF) During the OPTIC Study



Treatment Group	Day 3	Day 4	Day 5	Day 6	Day 7	EOT	PTE
Omadacycline (N=386)	369	367	356	326	314	373	362
Moxifloxacin (N=388)	376	372	363	330	321	376	366

ECR = early clinical response window; EOT = end of treatment; LOCF = last observation carried forward; OPTIC = Omadacycline for Pneumonia Treatment In the Community; PTE = post treatment evaluation

- Fig. 2 shows the four possible trajectories of CABP symptoms and clinical stability for each visit during the OPTIC study (Day 3 through PTE; panels A-D)
- The proportion of patients with improved symptoms and considered clinically stable (Fig. 2A) increased from the beginning (Day 4) to the end (Day 6) of the ECR window: 69.2%-77.6% for OMC; 68.0%-79.7% for MOX
- By the end of treatment (EOT), 89.5% of OMC patients and 88.0% of MOX patients had symptom improvement and were considered clinically stable

CONCLUSIONS

- Patients with CABP achieve both ECR and clinical stability at high rates 72-120 hours after omadacycline treatment initiation
- ECR and clinical stability are good predictors of clinical success at PTE but poor predictors of clinical failure at PTE
- Further studies are needed to validate the clinical utility of the ECR assessment
- Additionally, future research measuring both ECR and clinical stability daily and determining a time to improvement for both, could improve our understanding of the most appropriate window for ECR and clinical stability measurement, and its optimal concordance with clinical success at PTE

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