Omadacycline versus Moxifloxacin in the Treatment of Adults with Community-acquired Bacterial Pneumonia (CABP): Efficacy Analysis According to EMA Requirements

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Abstract 3894

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BACKGROUND

- Omadacycline (OMC) is the first aminomethylcycline in late-stage clinical development as once-daily per oral (po) and intravenous (iv) monotherapy for the treatment of acute bacterial skin and skin structure infections (ABSSSI), and community-acquired bacterial pneumonia (CABP)
  - Aminomethylcyclines are semisynthetic antibiotics related to the tetracyclines[1,2]
  - Modifications in the chemical structure of OMC allow it to overcome the two main mechanisms of tetracycline resistance: efflux pumps and ribosomal protection (**Figure 1**)[3,4]

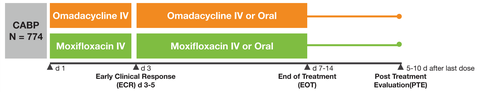
Figure 1. Chemical Structure of Omadacycline

- OMC demonstrates potent, *in vitro* activity against common Gram-positive aerobes (including methicillin- and penicillin-resistant strains), Gram-negative aerobes, anaerobes, and atypical bacterial pathogens[4,5]
- OMC was non-inferior to linezolid in two ABSSSI trials[6,7]
- The Phase 3 **O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity (OPTIC) study compared OMC with moxifloxacin (MOX) in the treatment of adults with CABP (Pneumonia Outcomes Research Team [PORT] Risk Class II–IV)
- OPTIC was designed to address both European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) regulatory requirements
  - OMC was non-inferior to MOX by FDA requirements using an early clinical response endpoint[8]
- **Here we report the OPTIC efficacy analysis according to EMA requirements**

METHODS

- OPTIC was a randomized (1:1), double-blind, global, multicenter, active comparator-controlled Phase 3 study (**Figure 2**)

Figure 2. Study Design for OPTIC



- Treatment
  - OMC administered at 100 mg iv q12h×2 doses, followed by 100 mg iv q24h; optional transition to OMC 300 mg po q24h after ≥ 3 days' iv treatment
  - MOX administered at 400 mg iv q24h; optional transition to 400 mg po q24h after ≥ 3 days' iv treatment
  - Total treatment duration, 7–14 days
- Per EMA guidance, efficacy analyses were conducted in a subset of the population with a PORT Risk Class of III/IV
- Primary endpoint (EMA)
  - Investigator's assessment of clinical response (IACR) at post-therapy evaluation (PTE) visit, 5–10 days after last dose
  - Success: Defined as survival after completion of test regimen without receiving systemic antibacterial therapy other than test article, with resolution of signs and symptoms of infection, no new symptoms or complications attributable to CABP, and no need for further antibiotic therapy
  - Analysis populations: Intent-to-treat (ITT) and clinically evaluable (CE); PORT Risk Class III or IV subjects only
  - Statistical analysis: 2-sided 97.5% confidence interval (CI) for non-inferiority testing based on difference of clinical success rates,[9] adjusted for randomization stratification factors of receipt of an allowed antibacterial therapy in 72 hours prior to study treatment (yes vs. no), and geographic region (Eastern Europe, Western Europe/North America and Rest of World); 10% non-inferiority margin
- Secondary endpoint
  - Clinical success rate: Per-pathogen and per-subject microbiological responses at PTE visit (based on investigator's assessment)
  - Analysis populations, microbiological intent-to-treat (microITT) and microbiologically evaluable (ME)
  - Statistical analysis: 2-sided 97.5% CI, no determination of non-inferiority

METHODS

Key inclusion criteria

- ≥ 3 of the following symptoms:
  - Cough, production of purulent sputum, dyspnea, pleuritic chest pain
- ≥ 2 of the following abnormal vital signs:
  - Fever or hypothermia documented by the investigator (temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
  - Hypotension with systolic blood pressure < 90 mm Hg
  - Heart rate > 90 beats per min
  - Respiratory rate > 20 breaths per min
- ≥ 1 clinical sign or laboratory finding associated with CABP:
  - Hypoxemia (partial pressure of arterial oxygen < 60 mm Hg by arterial blood gas or oxygen saturation < 90% by pulse oximetry)
  - Physical examination findings of pulmonary consolidation (eg, dullness on percussion, bronchial breath sounds, egophony)
  - Elevated total white blood cell (WBC) count (> 12,000 cells/mm^3) or leukopenia (WBC < 4,000 cells/mm^3) or elevated immature neutrophils (> 15% band forms)
- Radiographically confirmed pneumonia (ie, new or progressive pulmonary infiltrate[s] on chest X-ray or chest computed tomography consistent with acute bacterial pneumonia within 24 hours prior to first dose of test agent)
- CABP categorized as PORT Risk Class II, III, or IV at screening

Key exclusion criteria

- ≥ 1 dose(s) of a potentially effective systemic antibacterial treatment within 72 hours prior to first dose of test agent
  - Up to 25% of subjects were allowed a prior single dose of a short-acting antibiotic
- Known or suspected hospital-acquired pneumonia or healthcare-associated pneumonia
- Known or clinically suspected to have ≥ 1 of the following before randomization:
  - Suspected or confirmed empyema (a parapneumonic pleural effusion was not an exclusion criterion) or lung abscess
  - Requires acute pharmacologic intervention to stabilize blood pressure and/or adequate tissue perfusion, OR has evidence of septic shock
  - Evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy)

Analysis populations

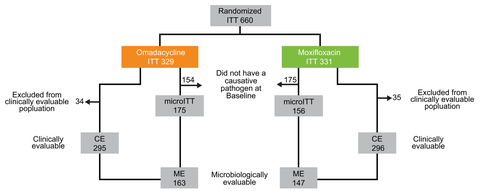
- ITT: All randomized subjects, PORT Risk Class III or IV
- microITT: All ITT subjects with ≥ 1 causative bacterial pathogen identified from culture of respiratory specimen (eg, sputum, bronchoalveolar lavage, pleural fluid), blood culture, or a culture-independent method (ie, positive urine antigen test [UAT] or positive serology)
- CE: All ITT subjects who received test article, had CABP, had an assessment of outcome, and had no other factor that could confound an assessment of the outcome
- Microbiologically Evaluable (ME): All subjects included in both the microITT and CE populations

RESULTS

The OPTIC study was initiated in November 2015 and completed in February 2017

- Number of study sites: 86
- Number of subjects: 774 in full ITT population, including PORT II (OMC 386; MOX 388); 660 included in EMA analysis (PORT III/IV) (**Figure 3**)
- Geographic regions (ITT population):
  - Eastern Europe 64%; Western Europe/North America 24%; Rest of World 12%
- Treatment discontinuation rates were low in both arms (**Figure 3**)
- Subject disposition for the full study population was previously reported[7]

Figure 3. EMA Analysis Study Populations



RESULTS

- Subject demographics were balanced between treatment arms (**Table 1**)

Table 1. Subject Demographics and Baseline Characteristics (ITT Population; PORT Risk Class III/IV)

Characteristics	Omadacycline N = 329	Moxifloxacin N = 331	All Subjects N = 660	p-value*
Gender, n (%)				
Female	144 (43.8)	144 (43.2)	287 (43.5)	
Male	185 (56.2)	188 (56.8)	373 (56.5)	0.9374
Race, n (%)				
White	301 (91.5)	299 (90.3)	600 (90.9)	
Black or African American	10 (3.0)	6 (1.8)	16 (2.4)	
Asian	16 (4.9)	18 (5.4)	34 (5.2)	
American Indian or Alaska Native	0	2 (0.6)	2 (0.3)	
Other	2 (0.6)	6 (1.8)	8 (1.2)	0.3050
Age, years				
Mean (SD)	63.0 (14.64)	63.7 (15.25)	63.4 (14.94)	
> 65	150 (45.6)	163 (49.2)	313 (47.4)	0.5459
> 75 (subset of > 65)	75 (22.8)	82 (24.8)	157 (23.8)	
BMI, kg/m^2				
Mean (SD)	27.2 (5.72)	27.4 (5.57)	27.3 (5.64)	

*p-values for differences between treatment groups were from Fisher's exact test (for categorical variables) or Wilcoxon Rank Sum test (for continuous variables)

- Relevant medical history pertaining to CABP infection is shown in **Table 2**
- The numbers of subjects meeting systemic inflammatory response syndrome (SIRS) criteria at baseline were high and similar in the treatment arms (**Table 2**)
  - SIRS was defined as having 2 or more of the following 4 symptoms: temperature < 36°C or > 38°C (oral or oral equivalent); heart rate > 90 beats per minute; respiratory rate > 20 breaths per minute; WBC count < 4,000 cells/mm^3 or > 12,000 cells/mm^3 or > 10% bands

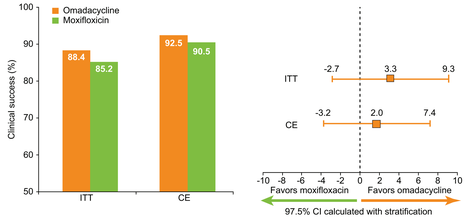
Table 2. Risk Factors for CABP at Baseline (ITT Population; PORT Risk Class III/IV)

Characteristics	Omadacycline N = 329	Moxifloxacin N = 331	All Subjects N = 660	p-value*
PORT risk class, n (%)				
III (71 ≤ Port Score ≤ 90)	227 (69.0)	216 (65.3)	443 (67.1)	
IV (91 ≤ Port Score ≤ 130)	102 (31.0)	115 (34.7)	217 (32.9)	0.3208
Subjects with SIRS, n (%)				
Yes	250 (76.0)	251 (75.8)	501 (75.9)	
No	79 (24.0)	80 (24.2)	159 (24.1)	1.000
Smoking status, n (%)				
Non-smoker	183 (55.6)	198 (59.8)	381 (57.7)	
Current smoker	77 (23.4)	64 (19.3)	141 (21.4)	
Past smoker	69 (21.0)	69 (20.8)	138 (20.9)	0.4095
Prior lung infection				
Yes	41 (12.5)	29 (8.8)	70 (10.6)	
No	288 (87.5)	302 (91.2)	590 (89.4)	0.1307
Mild-to-moderate chronic obstructive pulmonary disease				
Yes	52 (15.8)	42 (12.7)	94 (14.2)	
No	277 (84.2)	289 (87.3)	566 (85.8)	0.2668
Symptomatic asthma with wheezing, n (%)				
Yes	15 (4.6)	16 (4.8)	31 (4.7)	
No	314 (95.4)	315 (95.2)	629 (95.3)	1.000
Received an allowed prior antibiotic (as randomized), n (%)	79 (24.0)	82 (24.8)	161 (24.4)	0.8563

*p-values for differences between treatment groups were from Fisher's exact test (for categorical variables) or Wilcoxon Rank Sum test (for continuous variables)

- OMC demonstrated statistical non-inferiority to MOX (**Figure 4**)
  - Lower limit of the 97.5% CI for PTE was greater than -10%
- IACR of clinical success at PTE visit were high and comparable in ITT and CE populations, for OMC and MOX

Figure 4. Clinical Success at PTE based on IACR (ITT and CE Populations; PORT Risk Class III/IV)



RESULTS

Secondary Efficacy Analysis (PORT Risk Class III/IV)

- Clinical success rates by baseline pathogen were high for both OMC- and MOX-treated subjects at the PTE visit (**Table 3**)
  - Results comparable for ME population (data not shown)
  - Follow-up cultures were uncommon but no isolates had decreased susceptibility to either test article
- Both test articles achieved comparably high microbiologic response rates across the different analysis populations
  - 90.3% of OMC- and 88.5% of MOX-treated subjects had favorable responses at the PTE visit (microITT population)
  - Most had a mono-microbial Gram-positive infection with a clinical success response (84.6% of OMC subjects, 90.0% of MOX subjects)
  - Similar responses were observed in subjects with mixed Gram-positive and Gram-negative infections (83.3% OMC, 88.9% MOX)
  - Comparable results were observed for the ME population
- 1 (0.6%) OMC subject and no MOX subjects had a superinfection (ie, non-baseline pathogen isolated from culture while subject was on test article)
- 2 (1.1%) OMC subjects and 3 (1.9%) MOX subjects had a new infection (ie, non-baseline pathogen isolated from post-treatment culture while subject was assessed as a clinical failure at PTE visit)

Table 3. Overall Clinical Success at the PTE Visit Based on IACR by Baseline Pathogen from Blood Specimens, Respiratory Specimens, UATs, and/or Serology in ≥ 10 Subjects (microITT Population; PORT Risk Class III/IV)

Baseline Pathogen	Omadacycline N = 175		Moxifloxacin N = 156	
	N1	Clinical success N (%)	N1	Clinical sucess N (%)
Gram-positive bacteria (aerobes)	55	48 (87.3)	51	44 (86.3)
Streptococcus pneumoniae[a]	39	35 (89.7)	32	29 (90.6)
PSSP	24	22 (91.7)	20	19 (95.0)
Macrolide-resistant	10	10 (100.0)	5	5 (100.0)
Staphylococcus aureus	10	7 (70.0)	9	7 (77.8)
MSSA	10	7 (70.0)	8	6 (75.0)
Gram-negative bacteria (aerobes)	67	56 (83.6)	60	50 (83.3)
Haemophilus influenzae	26	21 (80.8)	14	14 (100.0)
Haemophilus parainfluenzae	14	11 (78.6)	13	11 (84.6)
Klebsiella pneumoniae	13	10 (76.9)	11	9 (81.8)
Atypical pathogens	104	97 (93.3)	91	84 (92.3)
Mycoplasma pneumoniae	63	60 (95.2)	50	45 (90.0)
Legionella pneumophila[b]	31	30 (96.8)	32	31 (96.9)
Chlamydophila pneumoniae	26	23 (88.5)	24	22 (91.7)

N1 = Number of subjects with the specified baseline pathogen
[a]Overall tabulation of *S.pneumoniae* included identification from a urinary antigen only which did not have susceptibility data
[b]*L.pneumophila* may have been detected from culture, serology, and/or a UAT
Subjects with the same pathogen isolated from multiple specimens were counted only once for that pathogen
Subjects with the same pathogen from a blood specimen, respiratory specimen, UAT, and/or serology were counted only once for that pathogen

- Of the small number of subjects who had bacteremia, subjects on MOX had slightly higher clinical success rates (**Table 4**)

Table 4. Overall Clinical Response at the PTE Visit in subjects with and without bacteremia at baseline (microITT Population; PORT Risk Class III/IV)

Efficacy Outcome	Omadacycline	Moxifloxacin	Difference (97.5% CI)
Subjects with bacteremia at baseline	**N = 13, n (%)**	**N = 16, n (%)**	
Clinical success	10 (76.9)	14 (87.5)	-10.6 (-45.2, 23.1)
Clinical failure or indeterminate	3 (23.1)	2 (12.5)	-
Clinical failure	2 (15.4)	2 (12.5)	-
Indeterminate	1 (7.7)	0	-
Subjects without bacteremia at baseline	**N = 162, n (%)**	**N = 140, n (%)**	
Clinical success	146 (90.1)	124 (88.6)	1.6 (-6.6, 10.1)
Clinical failure or indeterminate	16 (9.9)	16 (11.4)	-
Clinical failure	14 (8.6)	12 (8.6)	-
Indeterminate	2 (1.2)	4 (2.9)	-

RESULTS

- In subjects with SIRS at baseline, slightly higher clinical success rates were observed in subjects treated with OMC (**Table 5**)

Table 5. Overall Clinical Response at the PTE Visit in subjects with and without SIRS at baseline (ITT Population; PORT Risk Class III/IV)

Efficacy Outcome	Omadacycline	Moxifloxacin	Difference (97.5% CI)
Subjects with SIRS at baseline	**N = 250, n (%)**	**N = 251, n (%)**	
Clinical success	220 (88.0)	212 (84.5)	3.5 (-3.4, 10.6)
Clinical failure or indeterminate	30 (12.0)	39 (15.5)	-
Clinical failure	19 (7.6)	31 (12.4)	-
Indeterminate	11 (4.4)	8 (3.2)	-
Subjects without SIRS at baseline	**N = 79, n (%)**	**N = 80, n (%)**	
Clinical success	71 (89.9)	70 (87.5	2.4 (-9.6, 14.5)
Clinical failure or indeterminate	8 (10.1)	10 (12.5)	-
Clinical failure	8 (10.1)	4 (5.0)	-
Indeterminate	0	6 (7.5)	-

CONCLUSIONS

- In the Phase 3 OPTIC study, OMC was effective and non-inferior to MOX for the treatment of adults with CABP (PORT Risk Class III and IV)
- Met primary and secondary EMA objectives
  - Clinical response rates were high
  - Clinical success rates by pathogen were high and similar between treatment groups for common pneumonia pathogens including Gram-positive and Gram-negative pathogens, and atypical pathogens
  - There was no evidence of decreasing susceptibility to OMC during therapy, and superinfections/new infections were uncommon

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