Omadacycline versus moxifloxacin for community-acquired bacterial pneumonia (OPTIC-2): a phase 3b, randomised, double-blind, multicentre, controlled, noninferiority trial

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Summary

Background Omadacycline is a first-in-class aminomethylcycline antibiotic approved to treat adults with community-acquired bacterial pneumonia (CABP). This trial was conducted as a postmarketing regulatory commitment to confirm the efficacy and safety of omadacycline.

Methods This phase 3b, randomised, double-blind, multicentre, noninferiority trial enrolled adults in Eastern Europe between February 2021 (first patient enrolled) and March 2024 (last patient follow-up visit) who had CABP (NCT04779242). Participants with Pneumonia Severity Index (PSI) class III or IV CABP were randomised 1:1 to omadacycline (100 mg IV every 12 h for two doses, then 100 mg IV QD) or moxifloxacin (400 mg IV QD), with an oral option after ≥2 days of treatment (omadacycline, 300 mg QD; or moxifloxacin, 400 mg QD), for a total of 7–10 days. Primary efficacy endpoint was early clinical response (ECR), assessed 72–120 h after first dose, with a noninferiority margin of 10%. Key secondary endpoint was investigator's assessment of clinical response at post-therapy evaluation (PTE), 5–10 days after last dose. Microbiological response was determined by subject and pathogen. Treatment-emergent adverse events (TEAEs) were reported through 30–37 days after first dose.

Findings Of 670 participants randomised (omadacycline, n = 336; moxifloxacin, n = 334), approximately half were aged >65 years, and 76% had PSI class III disease. Omadacycline was noninferior to moxifloxacin at ECR and PTE (ECR, 89.6% versus 87.7%, treatment difference [95% CI]: 1.9 [–3.0, 6.8]; PTE, 86.0% versus 87.7%, treatment difference [95% CI]: –1.7 [–6.9, 3.4]). Clinical success rates were consistently high across select pathogens: 74.4–100% for omadacycline, 75.0–97.4% for moxifloxacin. Omadacycline was generally safe and well tolerated. Most commonly reported TEAEs (≥2%) in the omadacycline and moxifloxacin groups, respectively, were headache (3.6%, 4.5%), AST increase (2.1%, 0%), insomnia (0.6%, 2.1%), and diarrhoea (0%, 3.0%).

Interpretation This trial demonstrates the safety and efficacy of omadacycline in CABP. Omadacycline offers a once-daily monotherapy oral and IV option to treat CABP, including in patients with comorbidities.

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Research in context

Evidence before this study

Treatment of community-acquired bacterial pneumonia (CABP) involves empirical antimicrobial therapy, considering local epidemiology and pathogen resistance patterns, as well as patient risk factors. Numerous challenges exist to selecting a safe, effective, and appropriate antimicrobial that meets the needs of the patient. Omadacycline is an aminomethylcycline antibiotic that was approved in 2018 to treat adults with CABP and is available in once-daily oral and intravenous formulations.

Added value of this study

This phase 3b clinical trial of omadacycline versus moxifloxacin, a guideline-directed first-line treatment option for some patients, in adults with CABP was conducted as part of postmarketing regulatory commitments and confirmed the efficacy and safety of omadacycline.

Implications of all the available evidence

This trial, combined with the pivotal, registrational OPTIC trial, represent the largest contemporary phase 3 dataset for the treatment of CABP, and confirm omadacycline as an effective, once-daily oral and IV monotherapy option to treat CABP.

Introduction

Omadacycline is a first-in-class aminomethylcycline antibiotic that was approved by the US Food and Drug Administration (FDA) in 2018 to treat adults with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infection.[1] Omadacycline contains modifications at the C-7 and C-9 positions on the tetracycline D-ring that confer protection against common tetracycline resistance mechanisms, including tetracycline-specific efflux pumps and ribosomal protection.[2]

The pivotal phase 3 OPTIC clinical trial found that omadacycline was noninferior to moxifloxacin in adults with CABP.[3] This phase 3b clinical trial of omadacycline versus moxifloxacin in patients with CABP was conducted as part of postmarketing regulatory commitments to the US FDA to confirm the efficacy and safety of omadacycline. Omadacycline is available in the US and China as oral and intravenous once-daily formulations and is active against the most common CABP pathogens, including *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*, and the atypical pathogens *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*.[1]

Community-acquired pneumonia is one of the leading causes of hospitalisation and death in Europe and the United States.[4–8] Community-acquired pneumonia is the third leading cause of hospital admission from the emergency department, accounting for over half a million admissions in the US annually.[9] Together with influenza, pneumonia was the ninth leading cause of death in the US in 2022, accounting for 12.3 deaths per 100,000 individuals.[10]

Treatment of CABP revolves around empirical antimicrobial therapy that should take into account local epidemiology and pathogen resistance patterns, as well as patient risk factors.[11,12] In recent years, antimicrobial resistance to empirical therapy has grown, with almost half (46.6%) of respiratory isolates of *S. pneumoniae* being resistant to one or more antibiotics, including 38% of isolates that were resistant to macrolides.[13] In part due to antimicrobial resistance and use of guideline-discordant therapy, 22.1% of patients with CABP experience outpatient treatment failure.[14] Among all adults who failed treatment for pneumonia, 18.1% died within the next 30 days, compared with 4.6% of patients who died without experiencing prior treatment failure.[13]

Considering the growing problem of antibiotic resistance, clinicians and patients would benefit from having another safe and effective monotherapy option to treat CABP, as macrolide use is limited due to resistance and fluoroquinolone use is limited due to safety concerns.[5]

Here, we describe the efficacy and safety of omadacycline versus moxifloxacin in patients with CABP.

Methods

Study design and participants

The study was a phase 3b, randomised, double-blind, multicentre, noninferiority trial (registered at ClinicalTrials.gov, NCT04779242) enrolling participants at 40 study sites in Eastern Europe between February 2021 (first patient enrolled) and March 2024 (last patient follow-up visit). The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and the study protocol was approved by the local institutional review boards. Each patient provided written informed consent to participate. A data monitoring committee, independent of the study sponsor, provided ongoing monitoring of safety data.

Adults aged ≥18 years were eligible for the trial if they had at least three of the following symptoms:

cough, purulent sputum, dyspnoea, or pleuritic chest pain; at least two abnormal vital signs (see Appendix p 3 for details); at least one clinical sign or laboratory finding of CABP; radiologically confirmed pneumonia; and Pneumonia Severity Index (PSI) risk class III or IV at screening.

Patients were excluded from the study if they had received one or more doses of potentially effective systemic antibacterial treatment within 72 h before the first dose of trial drug (a single dose of a short-acting antibacterial was allowed in ≤25% of the patients). Further, patients were excluded for confirmed empyema or lung abscess; current residence in a long-term care or subacute healthcare facility or overnight hospital admission within 90 days before current admission; active COVID at screening (confirmed or suspected based on local testing guidelines); required or expected intensive care unit (ICU) admission or mechanical ventilation at the time of screening; clinically significant renal or liver insufficiency; or if they were immunocompromised.

Randomisation

Participants were randomised 1:1 to receive omadacycline or moxifloxacin. Randomisation was performed with a computer-generated schedule and block sequence (size 4), stratified by PSI risk class III or IV, and prior antibiotic use (Yes/No).

Participants, investigators, study personnel administering the study drugs, and the study sponsor were blinded to the assigned treatment.

Interventions

Treatment followed FDA-approved dosing for CABP: omadacycline, 100 mg intravenously (IV) every 12h for 2 doses (or 200 mg IV once) on day 1, followed by 100 mg IV once daily; or moxifloxacin, 400 mg IV once daily. After at least 2 days of IV treatment, investigators could transition the participant to oral therapy (omadacycline 300 mg once daily, or moxifloxacin 400 mg once daily). Total treatment duration was 7–10 days (up to 14 days if the participant had bacteraemia at baseline).

Outcomes

The primary efficacy endpoint was early clinical response (ECR), assessed at 72–120 h after the first dose, in the intent-to-treat (ITT) population. Clinical success at ECR was defined as participant survival, with no receipt of rescue antibacterial therapy, and improvement in at least two of four symptoms present at baseline (cough, sputum production, pleuritic chest pain, dyspnoea; assessed on 4-point scale [absent, mild, moderate, severe]) without deterioration of any symptoms. Clinical failure was determined if the participant met any of the following: no improvement from baseline in at least two symptoms; any baseline symptom worsened; need for alternative antimicrobial therapy for CABP; or death.

The key secondary efficacy endpoint was investigator's assessment of clinical response at post-therapy evaluation (PTE), 5–10 days after the last dose, in the ITT population. Clinical success at PTE was defined as participant survival, with resolution of CABP signs and symptoms that were present at baseline, no new symptoms attributed to CABP, and no need for further antibacterial therapy.

An additional efficacy endpoint was investigator's assessment of clinical response at end of treatment (EOT; ie, on the day of or within 2 days of last dose), in the ITT population. Clinical success was defined as participant survival, with resolution of CABP signs and symptoms such that no further antibacterial therapy was needed.

Microbiological response was determined at EOT and PTE (see Appendix p 3 for details on response criteria). At baseline for every participant, a respiratory specimen (eg, expectorated or induced sputum, or bronchoalveolar lavage) was collected for Gram staining and culture, blood cultures were collected, and urine was tested for antigens for *L. pneumophila* and *S. pneumoniae*. At baseline and PTE visits, blood was also collected for acute- and convalescent-phase serological testing for *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*.

All-cause mortality at 15 and 30 days was assessed in the ITT population.

Safety was assessed by reports of treatment-emergent adverse events (TEAEs) as classified by the Medical Dictionary for Regulatory Activities; vital signs; electrocardiogram data; and laboratory tests. TEAEs were collected at any time after the first dose was administered through the last follow-up visit (30–37 days after the first dose). Testing for *Clostridioides difficile* in participants reporting diarrhoea was not specified in the protocol.

Statistical analysis

The trial was designed to have sufficient power to show noninferiority for the primary efficacy outcome of ECR (at 72–120 h after first dose of study drug) in the ITT population with a noninferiority margin of 10%. Based on data from the phase 3 OPTIC trial,[3] assuming a response rate of 80% clinical success for both treatment groups, 90% power and a 1-sided alpha level = 0.025, the trial needed to enrol at least 670 participants to be powered show noninferiority.

The ITT population was all participants as randomised. The safety population was all randomised participants who received at least one dose of study drug. The microbiological ITT (micro-ITT) population was all participants in the ITT population who had at least one causative pathogen identified at screening. The clinically evaluable (CE) population was all participants who

met all study criteria (see Appendix p 3–4), most notably: had a qualifying infection based on inclusion criteria, received the study drug, did not receive concomitant antimicrobial therapy that could be effective against CABP pathogen(s), did not have a potentially confounding respiratory condition (such as lung cancer or COVID-19), and had a clinical response assessment (success or failure) at the evaluable time point. The microbiologically evaluable (ME) population was all participants in the CE population who had at least one causative pathogen identified at screening.

Missing data (such as in cases with insufficient data to determine a response, an assessment made outside the defined window, or lack of required symptoms at baseline) were classified as indeterminate responses and were counted as failures in the efficacy analyses of ITT and micro-ITT populations.

Demographic and baseline characteristics were descriptively summarised. Noninferiority of omadacycline to moxifloxacin was concluded if the lower limit of the 95% CI for the between-group difference exceeded –10 percentage points. TEAEs were summarised by organ class and preferred term, and by relatedness to the study drug.

A post-hoc analysis examined clinical stability and symptom improvement over the duration of the study. Participants were considered clinically stable if they met all the following criteria: temperature ≤37.8 °C, HR ≤ 100 bpm, RR ≤ 24 breaths/min, SBP ≥90 mm Hg, and arterial oxygen saturation ≥90% or PaO_2 ≥60 mm Hg on room air. The severity of the participant's CABP symptoms (cough, pleuritic chest pain, dyspnoea, and phlegm/sputum production) were evaluated on a 4-point scale (absent, mild, moderate, or severe) based on guidance provided to investigators (Appendix p 5). Any participant for whom all symptoms improved from baseline (symptom score dropped by at least 1 point from baseline) was considered a responder for symptom improvement.

Role of the funding source

The funder provided support for study implementation and the statistical analysis plan. Data analyses and interpretation were completed by the funder in conjunction with the authors. All authors contributed to writing the report and made the decision to submit the report for publication. A medical writer, paid by the study sponsor, assisted with preparation of the report. All authors vouch for the integrity, completeness, and accuracy of the data and analyses, and confirm that they had full access to all the data in the study.

Results

A total of 670 participants were randomised (omadacycline, n = 336; moxifloxacin, n = 334) (Fig. 1); of these, 20 (6.0%) and 24 (7.2%) participants, respectively, discontinued treatment early. Approximately half of the participants were >65 years of age, about half were male, and 76% of participants had PSI class III disease (Table 1). Most participants (635 [95.0% of the Safety analysis set]) were treated as inpatient.

Demographics and baseline characteristics of micro-ITT (total n = 376) and CE-PTE (total n = 544) populations were largely similar to the overall ITT population (Appendix p 6–7). Approximately 5% of participants were excluded from the CE population due to diagnosis of COVID-19 infection within 5 days of the first dose of study drug.

Overall, at least one causative pathogen was identified in 56.1% (376/670) of participants (60.1% of omadacycline-treated and 52.1% of moxifloxacin-treated participants) by culture and non-culture methods. The most commonly identified pathogens in the omadacycline and moxifloxacin groups, respectively, were *Haemophilus parainfluenzae* (20.3% and 22.4%), *S. aureus* (19.3% and 18.4%), *L. pneumophila* (19.3% and 18.4%), *M. pneumoniae* (17.8% and 16.7%), *H. influenzae* (13.9% and 11.5%), and *S. pneumoniae* (12.9% and 11.5%; Appendix p 8). Approximately 4% of participants in each treatment group had bacteraemia at baseline. Pathogens identified in blood cultures included *Escherichia coli* (6 participants), *S. pneumoniae* (4), *S. aureus* (4), and *Klebsiella pneumoniae* (4).

The baseline minimum inhibitory concentration (MIC) values for all Gram-positive aerobic pathogens ranged from 0.015 to 0.25 µg/mL for omadacycline and 0.03 to 2 µg/mL for moxifloxacin (Appendix p 8). For the Gram-negative aerobic pathogens, omadacycline MIC values ranged from ≤0.008 to >16 µg/mL, and moxifloxacin MIC values ranged from ≤0.004 to >8 µg/mL. For bacteraemia pathogens, MIC values for randomised therapy ranged from 0.03 to 2 µg/mL for both omadacycline and moxifloxacin, excluding one *K. pneumoniae* isolate that was resistant to randomised therapy, moxifloxacin MIC >8 µg/mL.

The mean (SD) total duration of exposure was 9.0 (2.0) days for omadacycline and 8.9 (2.2) days for moxifloxacin. Transition from IV to oral therapy occurred in 54.2% (182/336) participants receiving omadacycline and 63.6% (211/332) participants receiving moxifloxacin. For these participants, the mean (SD) duration of IV therapy before the transition was 4.8 (1.8) days for omadacycline and 4.7 (1.9) days for moxifloxacin; and they received oral therapy for 4.5 (1.5) days and 4.7 (1.6) days, respectively.

Omadacycline was noninferior to moxifloxacin for ECR and PTE (ECR, 89.6% versus 87.7%, treatment difference [95% CI]: 1.9 [–3.0, 6.8]; PTE, 86.0% versus 87.7%, treatment difference [95% CI]: –1.7 [–6.9, 3.4]; Fig. 2; Appendix p 9). Reasons for treatment failure at ECR in the omadacycline and moxifloxacin groups, respectively, were as follows (participants could have had more than one reason for failure): no improvement

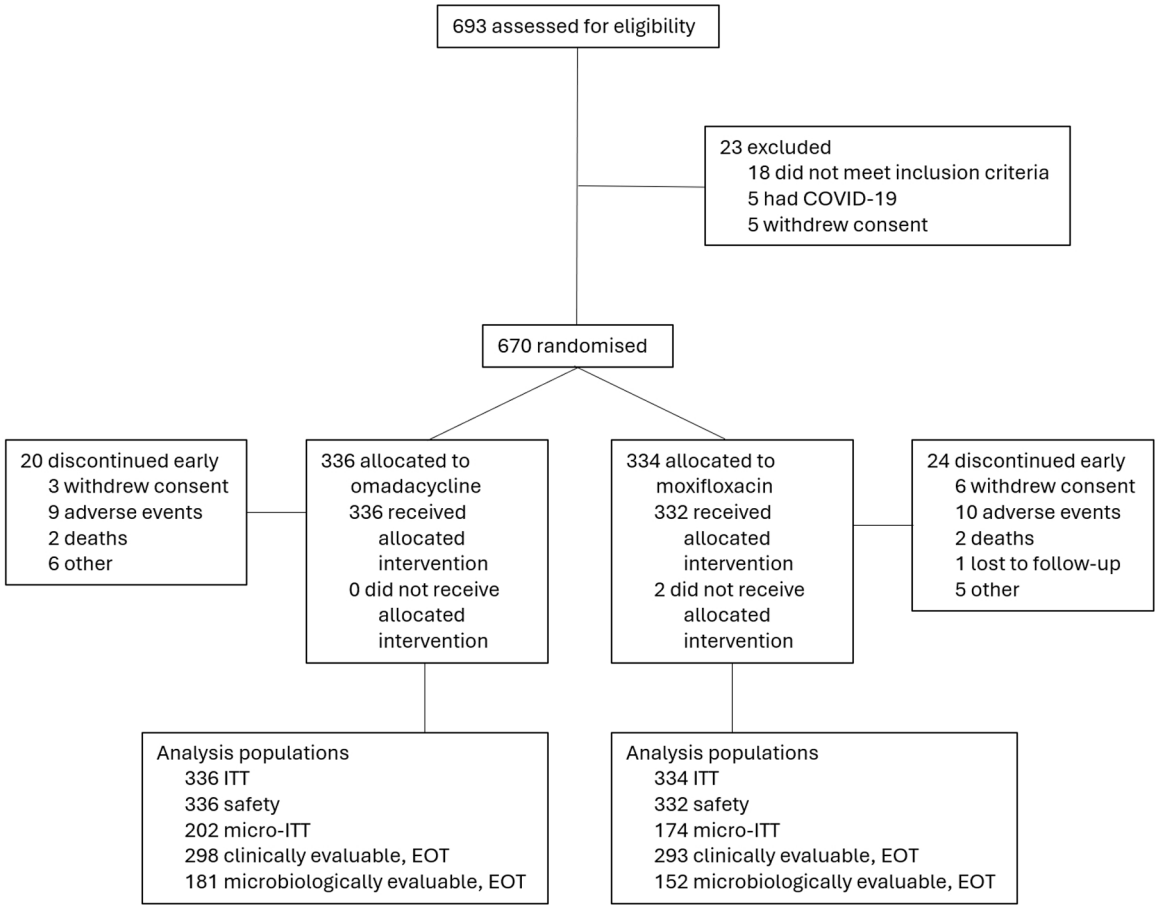


Fig. 1: Trial profile. EOT = end of treatment. ITT = intent-to-treat. Micro-ITT = microbiological ITT.

in two or more CABP symptoms (n = 20, n = 15); at least one CABP symptom worsened (n = 8, n = 5); the participant required rescue antimicrobial treatment (n = 6, n = 3); the participant received antibacterial therapy (for another reason) that could be effective for CABP (n = 0, n = 6); the participant developed an adverse event that required discontinuing the study drug (n = 3, n = 5); and the participant died before the evaluation time point (n = 0, n = 3). Indeterminate outcomes (see Appendix p 3 for definition) occurred for 6 participants in the omadacycline group and 10 in the moxifloxacin group. Similar outcomes were seen at EOT and PTE in the ITT population. Clinical response data at ECR were missing for 4 (1.2%) omadacycline participants and 7 (2.1%) moxifloxacin participants, and at PTE for 20 (6.0%) and 19 (5.7%) participants, respectively.

In the CE population, 94.3% (281/298) and 95.9% (281/293) of participants in the omadacycline and moxifloxacin groups, respectively, had clinical success at EOT (treatment difference [95% CI]: −1.6 [−5.3, 2.0]). Similarly, 94.1% (257/273) and 95.9% (260/271) of the CE populations had clinical success at PTE (treatment difference [95% CI]: −1.8 [−5.7, 2.0]).

The proportion of participants with improved symptoms who were clinically stable increased from the first observation (at 48 h) and continued through the ECR period to PTE (Fig. 3). By EOT, 97.1% and 96.6% of participants in the omadacycline and moxifloxacin groups, respectively, had improved symptoms and were clinically stable.

Clinical success by comorbidities was similar across the omadacycline and moxifloxacin treatment groups, and was similar to the overall ECR and PTE outcomes (Appendix p 9). When analysed by CABP severity, clinical success in participants with PSI class III for omadacycline was 90.3% at ECR and 87.9% at PTE; the corresponding results for moxifloxacin were 90.2% and 89.8%, respectively. For participants with PSI class IV, clinical success at ECR and PTE, respectively, was 87.3% and 79.7% for omadacycline, and 79.5% and 80.8% for moxifloxacin. Similar efficacy results were observed across participants stratified by baseline CURB-65 score (Appendix p 10) as well as between

	Omadacycline (n = 336)	Moxifloxacin (n = 334)	All participants (N = 670)
Male; n (%)	178 (53.0)	168 (50.3)	346 (51.6)
Race; n (%)			
White	335 (99.7)	333 (99.7)	668 (99.7)
Asian	1 (0.3)	1 (0.3)	2 (0.3)
Geographic region, Eastern Europe; n (%)	336 (100)	334 (100)	670 (100)
Age, years; mean (SD)	63.3 (14.4)	62.2 (15.4)	62.8 (14.9)
>65 years; n (%)	160 (47.6)	163 (48.8)	323 (48.2)
Body mass index, kg/m^2; mean (SD)	27.0 (5.2)	27.0 (4.7)	27.0 (4.9)
Past medical history; n (%)[a]			
Heart disease	58 (17.3)	43 (12.9)	101 (15.1)
Diabetes mellitus	66 (19.6)	63 (18.9)	129 (19.3)
Mild/moderate asthma or COPD	40 (11.9)	40 (12.0)	80 (11.9)
Renal impairment[b]	166 (49.4)	146 (43.7)	312 (46.6)
Mild	123 (36.6)	103 (30.8)	226 (33.7)
Moderate	43 (12.8)	43 (12.9)	86 (12.8)
Known pneumococcal vaccination; n (%)	1 (0.3)	1 (0.3)	2 (0.3)
PSI risk class (actual); n (%)[c]			
Class III	254 (75.6)	256 (76.6)	510 (76.1)
Class IV	82 (24.4)	78 (23.4)	160 (23.9)
CURB-65 score; n (%)[d]			
0	50 (14.9)	51 (15.3)	101 (15.1)
1	153 (45.5)	149 (44.6)	302 (45.1)
2	112 (33.3)	124 (37.1)	236 (35.2)
3	20 (6.0)	9 (2.7)	29 (4.3)
4	1 (0.3)	1 (0.3)	2 (0.3)
5	0	0	0
Bacteraemia; n (%)	12 (3.6)	14 (4.2)	26 (3.9)
Baseline pathogen identified (micro-ITT)[e]; n (%)	202 (60.1)	174 (52.1)	376 (56.1)

Intent-to-treat (ITT) population: all randomised participants. COPD = chronic obstructive pulmonary disease. PSI=Pneumonia Severity Index. [a]Heart disease, diabetes mellitus, asthma, and COPD were identified by patient reports of medical history at screening. [b]Renal impairment was identified by calculated creatinine clearance (CrCl), which was estimated using the Cockcroft–Gault equation. Mild renal impairment was defined as 50 < CrCl ≤80 mL/min; moderate renal impairment was defined as 30 < CrCl ≤50 mL/min. Patients with severe renal impairment (CrCl <30 mL/min) were excluded from the trial. [c]Pneumonia Outcomes Research Team PSI risk class (actual) are based on PSI score calculated by the site during the screening evaluation. [d]CURB-65 (confusion, uraemia, respiratory rate, blood pressure, and age ≥65 years) Score was derived from the electronic data captured at baseline and ranges from 0 to 5, where 1 point is given for each of the following: confusion (altered mental status); blood urea nitrogen >19 mg/dL (urea >6.8 mmol/L); respiratory rate ≥30 breaths/min; systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg; and age ≥65 years. [e]Microbiological ITT (micro-ITT) population: all participants in ITT population who had at least one causative pathogen identified at screening.

Table 1: **Demographic and baseline characteristics, ITT population.**

those who did and did not receive a prior antibiotic (ie, a single dose short-acting antibiotic ≤72 h before the first dose of study drug) at both the ECR and PTE assessments (Appendix p 11).

For participants who had a pathogen identified at baseline (micro-ITT population), clinical success at ECR was 89.6% (181/202) for omadacycline and 85.6% (149/174) for moxifloxacin; likewise, at PTE, clinical success rates were 84.7% (171/202) and 87.4% (152/174), respectively. At ECR and PTE, clinical success rates were high and consistent across select pathogens, ranging from 74.4% to 100% for omadacycline and 75.0% to 97.4% for moxifloxacin (Table 2). There were no isolates identified with decreased susceptibility in the omadacycline treatment group, but pathogens isolated from two participants (one with *K. pneumoniae* and one with *H. parainfluenzae*) had decreased susceptibility in the moxifloxacin group, which was defined as a >4-fold increase in MIC.

For participants who had bacteraemia at baseline, 91.7% (11/12) of those receiving omadacycline and 71.4% (10/14) of those receiving moxifloxacin had clinical success at ECR. Pathogens associated with failures at ECR were: *E. coli* (1) in the omadacycline group, and *K. pneumoniae* (2), *E. coli* (1), and *S. pneumoniae* (1) in the moxifloxacin group. One of the four moxifloxacin failures was a participant whose blood isolate was resistant to moxifloxacin, and failure was due to lack of improvement of two symptoms and receipt of alternative therapy. Likewise, at PTE, clinical success was seen in 75.0% (9/12) and 64.3% (9/14) of omadacycline- and moxifloxacin-treated participants with baseline bacteraemia, respectively. Failures at ECR continued to be failures at PTE. Additional failures at PTE were 2 omadacycline patients and 1 moxifloxacin. Reasons for failure included indeterminant response due to loss to follow-up and failure due to receipt of

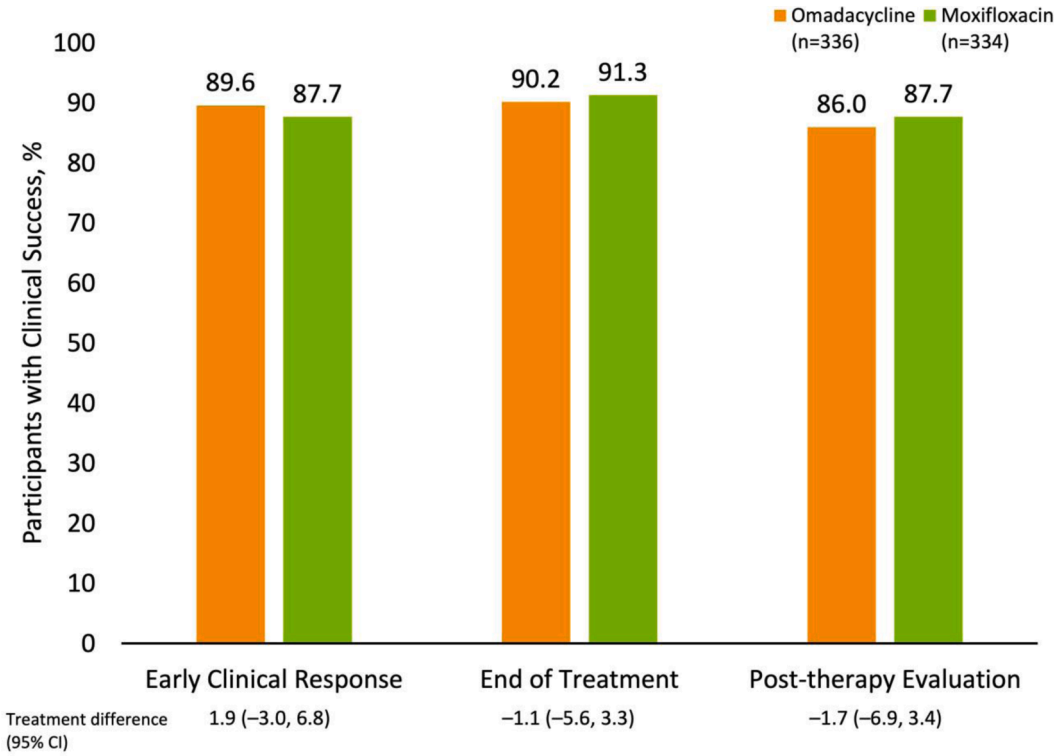
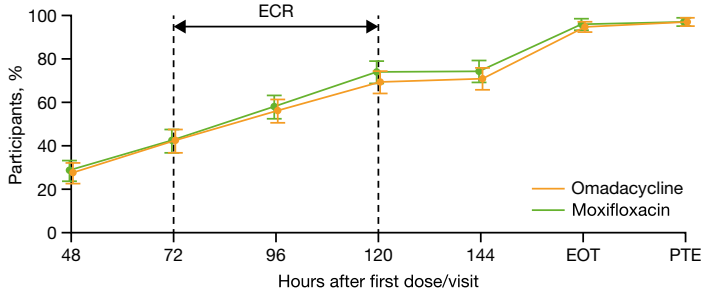


Fig. 2: Clinical success at ECR, EOT, and PTE, intent-to-treat population. Early clinical response (ECR; 72–120 h after first dose) was defined as survival, no receipt of rescue antibacterial therapy, and improvement in at least two of four symptoms (cough, sputum production, pleuritic chest pain, dyspnoea) without deterioration in any of these symptoms. Secondary endpoints included investigator's assessment of clinical response at end of treatment (EOT; 0–2 days after last dose) and post-therapy evaluation (PTE; 5–10 days after last dose), defined as survival with resolution of signs and symptoms of infection such that further antibacterial therapy was unnecessary.

potentially effective antibiotic for omadacycline, and clinical deterioration requiring additional antibiotics for infection related complication and death for moxifloxacin.

Omadacycline was generally safe and well tolerated, showing a safety profile consistent with previous studies (Table 3). At least one TEAE was reported in 27.7% of participants in the omadacycline group and 23.5% in the moxifloxacin group, the most common being headache (3.6% and 4.5%, respectively), and COVID-19 (3.3% and 1.2%, respectively). TEAEs considered related to study drug were reported in 2.7%



Sample Size, n	48 hrs	72 hrs	96 hrs	120 hrs	144 hrs	EOT	PTE
Omadacycline (n=336)	331	326	322	310	312	327	310
Moxifloxacin (n=334)	325	318	313	291	292	319	310

Fig. 3: Clinical stability and symptom improvement during the study, ITT population. Data are presented as mean (95% CI). ECR = early clinical response. EOT = end of treatment. ITT = intent-to-treat. PTE = post-therapy evaluation.

	Early clinical response		Post-therapy evaluation	
	Omadacycline	Moxifloxacin	Omadacycline	Moxifloxacin
Gram-positive bacteria (aerobes)	60/66 (90.9)	50/59 (84.7)	52/66 (78.8)	51/59 (86.4)
Streptococcus pneumoniae	26/26 (100)	15/20 (75.0)	21/26 (80.8)	16/20 (80.0)
Penicillin susceptible	11/11 (100)	1/3 (33.3)	9/11 (81.8)	3/3 (100)
Penicillin non-susceptible	5/5 (100)	4/4 (100)	5/5 (100)	4/4 (100)
Macrolide resistant	8/8 (100)	3/4 (75.0)	7/8 (87.5)	4/4 (100)
Multidrug resistant[a]	7/7 (100)	1/2 (50.0)	6/7 (85.7)	2/2 (100)
Staphylococcus aureus[b]	33/39 (84.6)	30/32 (93.8)	29/39 (74.4)	31/32 (96.9)
Gram-negative bacteria (aerobes)	104/116 (89.7)	90/104 (86.5)	99/116 (85.3)	96/104 (92.3)
Haemophilus parainfluenzae	36/41 (87.8)	33/39 (84.6)	37/41 (90.2)	38/39 (97.4)
Haemophilus influenzae	26/28 (92.9)	18/20 (90.0)	26/28 (92.9)	18/20 (90.0)
Klebsiella pneumoniae	15/16 (93.8)	15/19 (78.9)	16/16 (100)	16/19 (84.2)
Atypical pathogens	73/83 (88.0)	54/62 (87.1)	73/83 (88.0)	56/62 (90.3)
Legionella pneumophila	33/39 (84.6)	28/32 (87.5)	33/39 (84.6)	30/32 (93.8)
Mycoplasma pneumoniae	33/36 (91.7)	25/29 (86.2)	35/36 (97.2)	26/29 (89.7)
Chlamydophila pneumoniae	22/23 (95.7)	12/14 (85.7)	20/23 (87.0)	13/14 (92.9)

All values are shown as n (%). Microbiological ITT (micro-ITT) population: all participants in ITT population who have at least one causative pathogen identified at screening. At baseline, a respiratory specimen (eg, expectorated or induced sputum, bronchoalveolar lavage) was collected for Gram staining and culture, blood cultures were collected, and urine was tested for antigens for *L. pneumophila* and *S. pneumoniae*. At baseline and PTE visits, blood was also collected for acute- and convalescent-phase serological testing for *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*. [a]A pathogen was considered multidrug resistant if susceptibility testing showed resistance to at least one antibiotic within three or more different classes of antibiotics. For *Streptococcus* spp., isolates resistant to macrolides but susceptible to lincosamides and D-test positive (>4/0.5 μg/mL) were considered resistant to both macrolides and lincosamides. [b]All *S. aureus* isolates were methicillin susceptible.

Table 2: **Clinical success by select baseline pathogen(s), micro-ITT population.**

of participants in the omadacycline group and 6.9% in the moxifloxacin group. No individual drug-related TEAE occurred in ≥1% of those in the omadacycline group; in the moxifloxacin group there was one such TEAE (diarrhoea in 2.7% of participants).

	Omadacycline (n = 336)	Moxifloxacin (n = 332)
Participants with at least one TEAE	93 (27.7)	78 (23.5)
TEAEs >1% in either group		
Headache	12 (3.6)	15 (4.5)
COVID-19[a]	11 (3.3)	4 (1.2)
Aspartate aminotransferase increase	7 (2.1)	0 (0)
Alanine aminotransferase increase	6 (1.8)	1 (0.3)
COPD	5 (1.5)	1 (0.3)
Insomnia	2 (0.6)	7 (2.1)
Nausea	2 (0.6)	5 (1.5)
Abdominal discomfort	0 (0)	4 (1.2)
Diarrhoea[b]	0 (0)	10 (3.0)
Drug-related TEAE	9 (2.7)	23 (6.9)
Serious TEAE	17 (5.1)	15 (4.5)
TEAE leading to premature discontinuation of study drug[c]	9 (2.7)	9 (2.7)
Death[d]	6 (1.8)	6 (1.8)

All values are shown as n (%). COPD = chronic obstructive pulmonary disease. TEAE = treatment-emergent adverse event. [a]COVID-19 identified after baseline. [b]There were no cases of *Clostridioides difficile*-associated diarrhoea reported in either treatment group. [c]TEAEs that led to treatment discontinuation for the omadacycline group were: cardiac failure, gastrointestinal haemorrhage, administration site reaction, COVID-19, ALT/AST increase, liver metastases, delirium tremens, acute kidney injury, and organising pneumonia. TEAEs that led to treatment discontinuation in the moxifloxacin group were: administration site reaction, infusion site reaction, empyema, pyelonephritis, pyoderma streptococcal, psychotic disorder, acute respiratory failure (2 participants), and allergic dermatitis. [d]All-cause mortality at 15 days was 1.2% (4 participants) in each treatment group; at 30-days, all-cause mortality was 1.5% (5 participants) in the omadacycline group and 1.8% (6 participants) in the moxifloxacin group. After day 30, one additional participant in the omadacycline group died on study day 34.

Table 3: **Treatment-emergent adverse events, safety population.**

Serious adverse events were reported in 5.1% of participants in the omadacycline group and 4.5% in the moxifloxacin group. No individual serious adverse event occurred in ≥1% of participants in either treatment group. Overall, the most frequent category of serious adverse event was infection and infestation, such as worsening or complications of the study CABP, or COVID-19. The single serious adverse event in the study that was considered related to the study drug was an event of cardiac failure in a participant in the omadacycline group who had a history of heart valve disease and heart failure, and who received two doses of study drug before treatment was discontinued; the adverse event resolved within 2 weeks. Six participants in each treatment group (1.8% each) died during the study. Causes of deaths in omadacycline group were cerebral infarction, cardiogenic shock, death of unknown reason, liver metastases, pneumonia, and pulmonary embolism. Causes of death in moxifloxacin group were cardiac arrest (2 participants), cardiac failure, cardiopulmonary failure, multiorgan dysfunction syndrome, and pneumonia. None of the deaths in either group were considered related to the study drug by the investigators or a blinded independent committee.

In analyses of laboratory data, few participants in either group showed maximum elevations above 3× upper limit of normal for alanine aminotransferase (omadacycline: 8 [2.8%]; moxifloxacin: 4 [1.4%]) and aspartate transaminase (omadacycline: 5 [1.7%];

moxifloxacin: 1 [0.4%]). No participants met the criteria for Hy's law.

Discussion

OPTIC-2 is an important randomised clinical trial that provides meaningful data supporting the noninferiority of omadacycline for the treatment of moderate to severe CABP. In this study, omadacycline monotherapy showed good efficacy in patients with PSI III and IV CABP, and was also efficacious across common CABP pathogens.

This trial, combined with the pivotal, registrational OPTIC trial, represent the largest contemporary phase 3 dataset for the treatment of CABP. In both phase 3 trials, omadacycline was as effective as a guideline-directed, first-line antimicrobial for CABP treated outside of the ICU.[3] OPTIC and OPTIC-2 study designs were very similar, with noteworthy exceptions as follows: OPTIC was a global trial that included participants with PSI class II, III, or IV, while this study was a European trial that included only participants with PSI class III or IV; OPTIC allowed a transition to oral therapy after ≥3 days of treatment versus ≥2 days of treatment in OPTIC-2; and total treatment duration was 7–14 days in OPTIC and 7–10 days in OPTIC-2 (up to 14 days if the participant had baseline bacteraemia).

No new safety signals were seen in this trial. The overall rates of TEAEs were lower than other trials in CABP, and there were fewer gastrointestinal adverse events for the omadacycline group in this study compared to OPTIC. Additionally, there were no reports of *C. difficile* infection in either treatment group. Mortality was evenly balanced in the omadacycline and moxifloxacin groups, and all deaths were adjudicated by a blinded committee as unrelated to study drug.

In this trial, extensive microbiologic testing identified a bacterial pathogen in 56% of patients, similar to the rate reported in the first OPTIC study.[3] In clinical practice, a causative pathogen is identified in less than 10–15% of cases of community-acquired pneumonia, highlighting the importance of empirical antibiotic treatment with reliable activity against the most common bacterial pathogens associated with this disease.[15] Omadacycline offers a once-daily oral and IV monotherapy option to treat CABP, including in patients who have comorbidities.[16] The majority of the most common respiratory pathogens, including drug-resistant *S. pneumoniae*, are susceptible to omadacycline.[17] In a recent US surveillance study, approximately 20% of *S. pneumoniae* isolates were non-susceptible to doxycycline, the majority of which carried the tet(M) resistance gene. The presence of tet(M) did not affect omadacycline activity; 99.8% of *S. pneumoniae* isolates were susceptible.[18] Existing guideline-recommended empirical treatments for CABP have limitations related to pathogen resistance and treatment side effects. Omadacycline represents an attractive treatment option for CABP and can be used as monotherapy in ambulatory and hospitalised patients with CABP. Compared to treatment with a fluoroquinolone, use of omadacycline to treat patients hospitalised with CABP may provide attributable cost savings related to the reduced rate of developing *C. difficile* infection.[19] For atypical pathogens, clinical success was high and consistent with a fluoroquinolone, a preferred antibiotic, which is particularly important given the few therapeutic options for these pathogens.

Strengths of this study are the randomised, double-blind, controlled design, the inclusion of both intravenous and oral formulations, the severity of pneumonia in the enrolled participants, the large sample size, and the wide age range enrolled with many older adults. Limitations of the study include the exclusion of immunocompromised patients and those with the most severe community-acquired bacterial pneumonia (i.e., PSI risk class V), which limits the generalisability of the results to these important subpopulations of patients. Additional limitations include the confounding factor of the COVID-19 pandemic that began after this trial was underway, which suspended enrolment at various study sites and extended the expected duration of the study. During the conduct of this trial, testing methods to identify COVID-19 were evolving rapidly and varied across study sites. The study protocol incorporated polymerase chain reaction testing of a nasopharyngeal swab at screening for severe acute respiratory syndrome coronavirus 2, but those results were commonly not available until after participants were randomised and had begun study treatment. Further, individual institutions followed their own COVID-19 testing protocols, which could have included other COVID-19 test methods at various time points during a hospitalisation. For these reasons, approximately 5% of the participants were diagnosed with COVID-19 within 5 days of the first dose of study drug. Because of the challenge in distinguishing the cause of the respiratory illness in these cases (CABP or COVID-19 or both), these participants were excluded from the CE analysis population. It was reassuring that analyses demonstrated efficacy of omadacycline in both the ITT and CE populations.

Omadacycline is an important monotherapy treatment option for patients with CABP, including patients with comorbidities and PSI class III or IV disease.

Contributors

TF, KSK, SI, IH: Formal analysis; Investigation; Writing (original draft and revisions).

CK, AM: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing (original draft and revisions).

KS, KG: conceptualisation, data curation, formal analysis, investigation, methodology, resources, supervision, validation, visualisation, writing (original draft and revisions).

DD: formal analysis, writing (original draft and revisions).

DA: conceptualisation, data curation, formal analysis, investigation, methodology, validation, writing (original draft and revisions).

SC: conceptualisation, data curation, formal analysis, investigation, methodology, resources, supervision, validation, visualisation, writing (original draft and revisions).

SV: conceptualisation, data curation, formal analysis, investigation, methodology, supervision, writing (original draft and revisions).

All authors had full access to the data in the study and accept responsibility to submit for publication.

Data sharing statement

Paratek Pharmaceuticals has a commitment to ensure that access to clinical trial data is available to regulators, researchers, and trial participants, when permitted, feasible, and appropriate. Requests for de-identified patient-level data can be submitted to medinfo@paratekpharma.com for review. Datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of interests

TF reports support for meeting attendance/travel from HealthTrackRx; consultancy/advisor fees from Merck, MicroGenDx, Paratek Pharmaceuticals, Inc., and Shionogi; and honoraria from Paratek Pharmaceuticals, Inc. and ThermoFisher. KSK reports honoraria from GSK and consultancy/advisor fees from Paratek Pharmaceuticals, Inc. SI, IH, and VK have received research funding from Paratek Pharmaceuticals, Inc. KS and KG are employees of MMS Holdings, consultants to Paratek Pharmaceuticals, Inc. CK, AM, DD, and DA are employees and shareholders of Paratek Pharmaceuticals, Inc. SC reports consultancy fees from Paratek Pharmaceuticals, Inc. SV is a consultant and shareholder of Paratek Pharmaceuticals, Inc.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103656.

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