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Omadacycline for Community-Acquired Bacterial Pneumonia

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ABSTRACT

BACKGROUND

Omadacycline, a new once-daily aminomethylcycline antibiotic agent that can be administered intravenously or orally, reaches high concentrations in pulmonary tissues and is active against common pathogens that cause community-acquired bacterial pneumonia.

METHODS

In a double-blind trial, we randomly assigned (in a 1:1 ratio) adults with community-acquired bacterial pneumonia (Pneumonia Severity Index risk class II, III, or IV) to receive omadacycline (100 mg intravenously every 12 hours for two doses, then 100 mg intravenously every 24 hours), or moxifloxacin (400 mg intravenously every 24 hours). A transition to oral omadacycline (300 mg every 24 hours) or moxifloxacin (400 mg every 24 hours), respectively, was allowed after 3 days; the total treatment duration was 7 to 14 days. The primary end point was early clinical response, defined as survival with improvement in at least two of four symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) and no worsening of symptoms at 72 to 120 hours, without receipt of rescue antibacterial therapy. A secondary end point was investigator-assessed clinical response at a post-treatment evaluation 5 to 10 days after the last dose, with clinical response defined as resolution or improvement in signs or symptoms to the extent that further antibacterial therapy was unnecessary. A noninferiority margin of 10 percentage points was used.

RESULTS

The intention-to-treat population included 386 patients in the omadacycline group and 388 patients in the moxifloxacin group. Omadacycline was noninferior to moxifloxacin for early clinical response (81.1% and 82.7%, respectively; difference, –1.6 percentage points; 95% confidence interval [CI], –7.1 to 3.8), and the rates of investigator-assessed clinical response at the post-treatment evaluation were 87.6% and 85.1%, respectively (difference, 2.5 percentage points; 95% CI, –2.4 to 7.4). Adverse events that emerged after treatment initiation were reported in 41.1% of the patients in the omadacycline group and 48.5% of the patients in the moxifloxacin group; the most frequent events were gastrointestinal (10.2% and 18.0%, respectively), and the largest difference was for diarrhea (1.0% and 8.0%). Twelve deaths (8 in the omadacycline group and 4 in the moxifloxacin group) occurred during the trial.

CONCLUSIONS

Omadacycline was noninferior to moxifloxacin for the treatment of community-acquired bacterial pneumonia in adults. (Funded by Paratek Pharmaceuticals; OPTIC ClinicalTrials.gov number, NCT02531438.)

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The investigators in the OPTIC Study are listed in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Community-acquired pneumonia is the most common infection leading to hospitalization and death in all age groups, especially the elderly.[1-3] The economic effect is substantial, with annual costs in excess of $17 billion in the United States and €10 billion in Europe.[2,3] For pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, increased rates of resistance to beta-lactams, macrolides, and earlier-generation tetracyclines highlight the need for new antibiotic agents.[4-6]

Omadacycline is a new aminomethylcycline antibiotic, derived from the tetracycline class,[7] that overcomes the efflux and ribosomal protection mechanisms of tetracycline resistance.[7] Omadacycline has in vitro activity against pathogens that cause community-acquired bacterial pneumonia, including *S. pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, and atypical pathogens (*Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*).[8-10] Omadacycline showed activity against *S. pneumoniae* in a murine model of pneumonia[11] and attained high and sustained concentrations in human pulmonary tissues.[12] In the Omadacycline for Pneumonia Treatment in the Community (OPTIC) trial, we compared the efficacy and safety of once-daily omadacycline and moxifloxacin for the treatment of adults with community-acquired bacterial pneumonia.

Methods

Trial Design and Oversight

Our trial was a phase 3, double-blind, double-dummy, randomized, noninferiority trial conducted at 86 sites in Europe, North America, South America, the Middle East, Africa, and Asia between November 2015 and February 2017 (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by the institutional review board or ethics committee at each participating site. Each patient provided written informed consent. A data and safety monitoring committee that was independent of the trial sponsor provided ongoing monitoring of safety data.

Paratek Pharmaceuticals designed and conducted the trial and prepared the statistical analysis plan. Analyses were performed and data interpreted by Paratek Pharmaceuticals in conjunction with the authors. All the authors vouch for the integrity, completeness, and accuracy of the data and analyses and assume responsibility for the fidelity of the trial to the protocol and statistical analysis plan, which are available at NEJM.org. A medical writer supported by the sponsor assisted with preparation of a first draft of the manuscript.

Patient Population and Treatment

Adults who were 18 years of age or older were eligible if they had three or more of the following four symptoms: cough, purulent sputum production, dyspnea, or pleuritic chest pain; and if they had at least two abnormal vital signs, had at least one clinical sign or laboratory finding associated with community-acquired bacterial pneumonia, had radiologically confirmed pneumonia, and were characterized as being in Pneumonia Severity Index (PSI) risk class II (limited to ≤15% of the patients who underwent randomization), III, or IV (PSI risk classes range from I to V, with higher class numbers indicating a greater risk of death[13]; details are provided in the protocol). Patients were excluded if they had received one or more doses of potentially effective systemic antibacterial treatment within 72 hours before the first dose of trial drug (a single dose of a short-acting antibacterial was allowed in ≤25% of the patients), had hospital-acquired pneumonia or empyema, had clinically significant liver or renal insufficiency, or were immunocompromised. A complete list of the entry criteria is provided in the Supplementary Appendix.

Patients were randomly assigned in a 1:1 ratio to receive 7 to 14 days of omadacycline (100 mg administered intravenously every 12 hours for two doses, then 100 mg administered intravenously every 24 hours, with the option to transition to 300 mg taken orally every 24 hours after ≥3 days) or moxifloxacin (400 mg administered intravenously every 24 hours, with the option to transition to 400 mg taken orally every 24 hours after ≥3 days) (Fig. S1 in the Supplementary Appendix). Randomization was performed with the use of an interactive response system involving a computer-generated schedule and a block sequence with a size of 6, stratified according to PSI risk class (II vs. III or IV), whether allowed antibacterial therapy was received within 72 hours before trial treatment, and geographic region.

The investigator and sponsor were unaware of the treatment assignments. Trial personnel who were unaware of the treatment assignments administered intravenous infusions and collected, reviewed, and entered data. Adherence to oral medication regimens was monitored by trial site personnel on the basis of medication return and patient-completed diaries.

ANALYSIS POPULATIONS, END POINTS, AND ASSESSMENTS

The intention-to-treat population included all patients who underwent randomization. Patients who underwent randomization and received any amount of trial drug were included in the safety population. The microbiologic intention-to-treat population included all patients in the intention-to-treat population who had a causative pathogen or pathogens identified at baseline from culture of a respiratory specimen or blood or with the use of a culture-independent method. The clinical per-protocol population included patients in the intention-to-treat population who had a qualifying infection as defined by the trial-entry criteria, had received a trial drug, had not received any antibacterial agent that was not assigned within the trial that could confound interpretation of the results, and had undergone an assessment of outcome during the protocol-defined window. The microbiologic per-protocol population included the patients in both the microbiologic intention-to-treat population and the clinical per-protocol population.

The primary efficacy end point was early clinical response, assessed at 72 to 120 hours after the first dose of trial drug in the intention-to-treat population, determined programmatically on the basis of the investigator's assessment of symptoms of community-acquired bacterial pneumonia (cough, sputum production, pleuritic chest pain, and dyspnea) on a 4-point scale (absent, mild, moderate, or severe) (Table S1 in the Supplementary Appendix). Early clinical response was defined as survival with improvement of one or more levels (e.g., from moderate to mild) relative to baseline in two or more symptoms of community-acquired bacterial pneumonia and no worsening of one or more levels in other symptoms of community-acquired bacterial pneumonia, without receipt of rescue antibacterial therapy.

Key secondary efficacy end points were investigator-assessed clinical response at the post-treatment evaluation (5 to 10 days after the last dose of trial drug) in the intention-to-treat population and in the clinical per-protocol population. The investigator also assessed clinical response at the end-of-treatment visit. Investigator-assessed clinical response was defined as survival with resolution or improvement in signs and symptoms of infection to the extent that further antibacterial therapy was unnecessary. Microbiologic response (defined in the Supplementary Appendix) was determined at the end-of-treatment and post-treatment evaluation visits in the microbiologic intention-to-treat population and the microbiologic per-protocol population. Missing data were classified as indeterminate responses and counted as failures in analyses of the intention-to-treat population and the microbiologic intention-to-treat population.

At the screening visit, expectorated or induced sputum or another specimen from the lower respiratory tract was collected for Gram's staining and culture, blood cultures were collected, and urine was tested for *L. pneumophila* and *S. pneumoniae* antigens. Blood also was collected at the screening and post-treatment evaluation visits for acute- and convalescent-phase serologic testing for *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*. Safety variables included adverse events, clinical laboratory evaluations, vital signs, and electrocardiographic (ECG) findings. Adverse events that emerged after treatment initiation were those with an onset or worsening of severity that occurred at or any time after administration of the first dose of trial drug through the final follow-up visit (30 to 37 days after the first dose of a trial drug).

STATISTICAL ANALYSIS

The trial was designed to have sufficient power for the primary and secondary efficacy analyses. For the end point of investigator-assessed clinical response at the post-treatment evaluation, assuming a clinical response rate of 79% in both treatment groups, a noninferiority margin of 10 percentage points, 80% power, and a one-sided alpha level of 0.0125 (required by regulatory agencies outside the United States) and using the sample-size determination method of Farrington and Manning,[14] we calculated that a total of 638 patients (PSI risk class III and IV) were required. Under the assumption that the clinical response

rate would be 85% in both treatment groups and that 80% of the participants would be able to be evaluated, the use of a noninferiority margin of 10 percentage points and a one-sided alpha level of 0.0125 would result in 81% power to show noninferiority for investigator-assessed clinical response at the post-treatment evaluation in the clinical per-protocol population. For the end point of early clinical response, if 15% of the patients were in PSI risk class II, there would be a total of 750 patients in the intention-to-treat population. With an early clinical response rate of 79% in both treatment groups, a noninferiority margin of 10 percentage points, and a one-sided alpha level of 0.025, a total sample of 750 patients would provide 92% power to show noninferiority.

A noninferiority margin of 10 percentage points was used for early clinical response on the basis of an analysis of observational studies comparing no treatment and antibacterial therapy.[15] From these studies, the treatment effect was conservatively estimated as 20 percentage points, and a 10-percentage-point noninferiority margin preserved 50% of the treatment effect. A two-sided 95% confidence interval calculated by means of the Miettinen and Nurminen method[16] without stratification for the difference in the early clinical response rate in the intention-to-treat population was used to test for noninferiority of omadacycline as compared with moxifloxacin. Noninferiority of omadacycline to moxifloxacin was concluded if the lower limit of the 95% confidence interval for the between-group difference exceeded –10 percentage points. A post hoc analysis of early clinical response in the clinical per-protocol population was also conducted. The 95% confidence intervals for the between-group differences for secondary and additional end points were calculated with the same methods used for early clinical response. No inferential analyses were conducted for secondary and additional end points, and therefore no adjustment for multiplicity was used. The analyses of the secondary and additional end points were descriptive. Differences between the treatment groups in baseline variables were analyzed with the use of Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

RESULTS

TRIAL POPULATION

The numbers of patients included in the different analysis populations are shown in Figure 1. Of the 774 patients who underwent randomization (intention-to-treat population), 770 received one or more doses of trial drug (safety population) (Fig. 1). In the safety population, 98.8% of patients were inpatients when the trial regimen was initiated. The treatment groups were well matched with regard to baseline demographic and clinical characteristics (Table 1). Overall, 41.9% and 20.4% of patients in the intention-to-treat population were older than 65 years and older than 75 years of age, respectively, and 85.4% had PSI risk class III or IV.

A pathogen that causes community-acquired bacterial pneumonia was identified at baseline in 49.9% of the patients in the intention-to-treat population; within this population, the most frequently identified pathogens were *M. pneumoniae* (33%), *S. pneumoniae* (20%), *L. pneumophila* (19%), *C. pneumoniae* (15%), and *H. influenzae* (12%) (Table S2 in the Supplementary Appendix). The minimum inhibitory concentration (MIC) required to inhibit the growth of 90% of organisms for omadacycline was 0.06 mg per liter for *S. pneumoniae* isolates and was 2 mg per liter for *H. influenzae* isolates. Baseline demographic characteristics were well balanced between the treatment groups in the microbiologic intention-to-treat population, the intention-to-treat population in which a causal pathogen was not identified, and the microbiologic per-protocol population (Tables S3 through S6 in the Supplementary Appendix). The mean duration of intravenous therapy was 5.7 days and the mean total duration of therapy was 9.6 days in each group. A transition from intravenous to oral therapy occurred in 77.2% of the patients in the omadacycline group and 75.8% of the patients in the moxifloxacin group. The percentage of patients with 80% or greater treatment adherence was 99.2% in the omadacycline group and 99.5% in the moxifloxacin group.

EFFICACY

Omadacycline was noninferior to moxifloxacin with regard to early clinical response (response rate, 81.1% and 82.7%, respectively; difference,

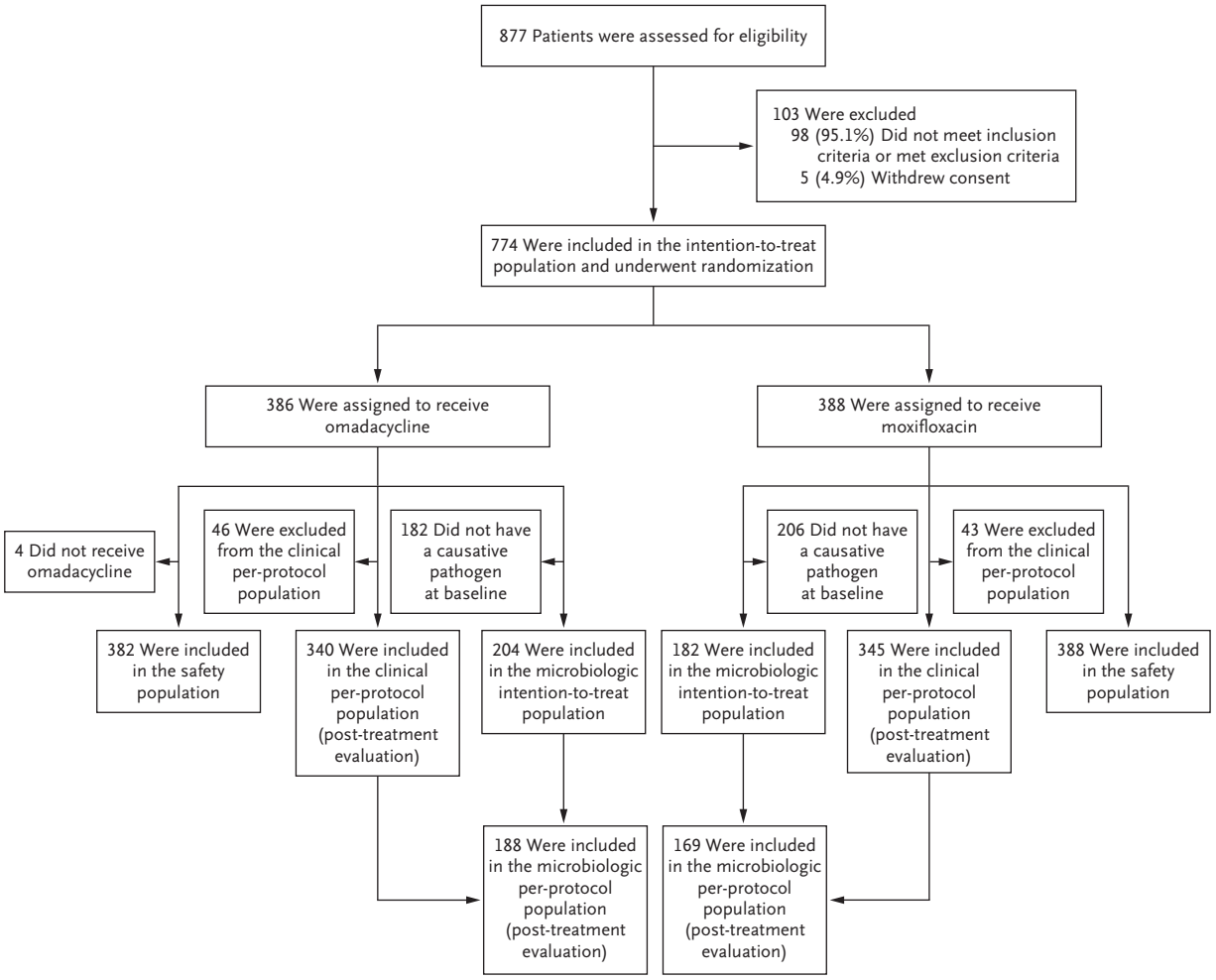

Figure 1. Randomization and Populations Included in Analysis.

The intention-to-treat population included all patients who underwent randomization. The safety population included patients who underwent randomization and received any amount of trial drug. The microbiologic intention-to-treat population included patients in the intention-to-treat population who had a causative pathogen or pathogens identified at baseline from culture of a respiratory specimen (adequate sputum samples were defined as those with a Gram's stain showing >25 polymorphonuclear neutrophils per low-power field and <10 squamous epithelial cells per low-power field) or blood or with the use of a culture-independent method (e.g., positive urinary antigen test or serologic test). The clinical per-protocol population included patients in the intention-to-treat population who had a qualifying infection as defined by the trial-entry criteria, had received a trial drug, had not received any antibacterial agent that was not assigned within the trial that could confound interpretation of the results, and had undergone an assessment of outcome during the protocol-defined window. The microbiologic per-protocol population included the patients in both the microbiologic intention-to-treat population and the clinical per-protocol population.

–1.6 percentage points; 95% confidence interval [CI], –7.1 to 3.8) (Fig. 2, and Table S7 in the Supplementary Appendix). The early clinical failures included instances of missing data (i.e., indeterminate outcomes) in 24 patients (6.2%) in the omadacycline group and 20 patients (5.2%) in the moxifloxacin group; the reasons for early clinical failures and indeterminate outcomes are shown in Table S8 in the Supplementary Appendix. In sensitivity analyses assessing the effect of missing data, omadacycline remained noninferior to moxifloxacin. In a post hoc analysis of the

Table 1. Baseline Demographic and Clinical Characteristics in the Intention-to-Treat Population.*

Characteristic	Omadacycline (N=386)	Moxifloxacin (N=388)
Median age (range) — yr	61 (19–97)	63 (19–94)
Age >65 yr — no. (%)	152 (39.4)	172 (44.3)
Male sex — no. (%)	208 (53.9)	219 (56.4)
Race — no. (%)†		
White	356 (92.2)	355 (91.5)
Black	11 (2.8)	7 (1.8)
Asian	17 (4.4)	18 (4.6)
Other	2 (0.5)	8 (2.1)
Geographic region — no. (%)		
Western Europe or North America	91 (23.6)	92 (23.7)
Eastern Europe	249 (64.5)	248 (63.9)
Rest of world	46 (11.9)	48 (12.4)
Body-mass index‡	27.2±5.8	27.4±5.8
Creatinine clearance — no. (%)		
>80 ml/min	187 (48.4)	207 (53.4)
>50–80 ml/min	128 (33.2)	119 (30.7)
30–50 ml/min	70 (18.1)	62 (16.0)
<30 ml/min	1 (0.3)	0
Current smoker — no. (%)	105 (27.2)	82 (21.1)
Past smoker — no. (%)	76 (19.7)	79 (20.4)
Previous lung infection — no. (%)	48 (12.4)	37 (9.5)
Mild-to-moderate COPD — no. (%)§	57 (14.8)	51 (13.1)
Symptomatic asthma with wheezing — no. (%)	18 (4.7)	20 (5.2)
PSI score¶	83.2±16.5	84.0±16.0
PSI risk class — no. (%)¶		
II	55 (14.2)	54 (13.9)
III	227 (58.8)	216 (55.7)
IV	102 (26.4)	115 (29.6)
Modified ATS criteria for severe CABP — no./total no. (%)‖	44/368 (12.0)	53/370 (14.3)
Antibiotics before randomization — no. (%)**	89 (23.1)	90 (23.2)
Bacteremia — no. (%)	15 (3.9)	18 (4.6)

* The intention-to-treat population included all patients who underwent randomization. Plus–minus values are means ±SD. There were no significant between-group differences (P<0.05) calculated with the use of Fisher's exact test (for categorical variables) or the Wilcoxon rank-sum test (for continuous variables). Percentages may not total 100 because of rounding. ATS denotes American Thoracic Society, CABP community-acquired bacterial pneumonia, and COPD chronic obstructive pulmonary disease.

† Race was reported by the patient.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Patients with severe COPD were excluded.

¶ Scores on the Pneumonia Severity Index (PSI) are used to place patients with pneumonia into risk classes that range from I to V, with higher risk classes indicating a greater risk of death (additional details are provided in the protocol); in this trial, only patients in risk class II (PSI score, 51 to 70), III (71 to 90), or IV (91 to 130) were eligible for participation. Five patients (two in the omadacycline group and three in the moxifloxacin group) underwent randomization but were found to have a nonqualifying PSI risk class (I or V).

‖ Severe CABP according to modified ATS criteria was defined as the presence of three or more of the following nine criteria at baseline: respiratory rate of at least 30 breaths per minute or higher, oxygen saturation less than 90% or partial pressure of arterial oxygen less than 60 mm Hg, urea level at least 20 mg per deciliter, white-cell count less than 4000 per cubic millimeter, confusion, multilobar infiltrates, platelet count less than 100,000 per cubic millimeter, body temperature less than 36°C, and systolic blood pressure less than 90 mm Hg.

** This refers to a dose of short-acting antibiotic as allowed per the protocol in up to 25% of patients.

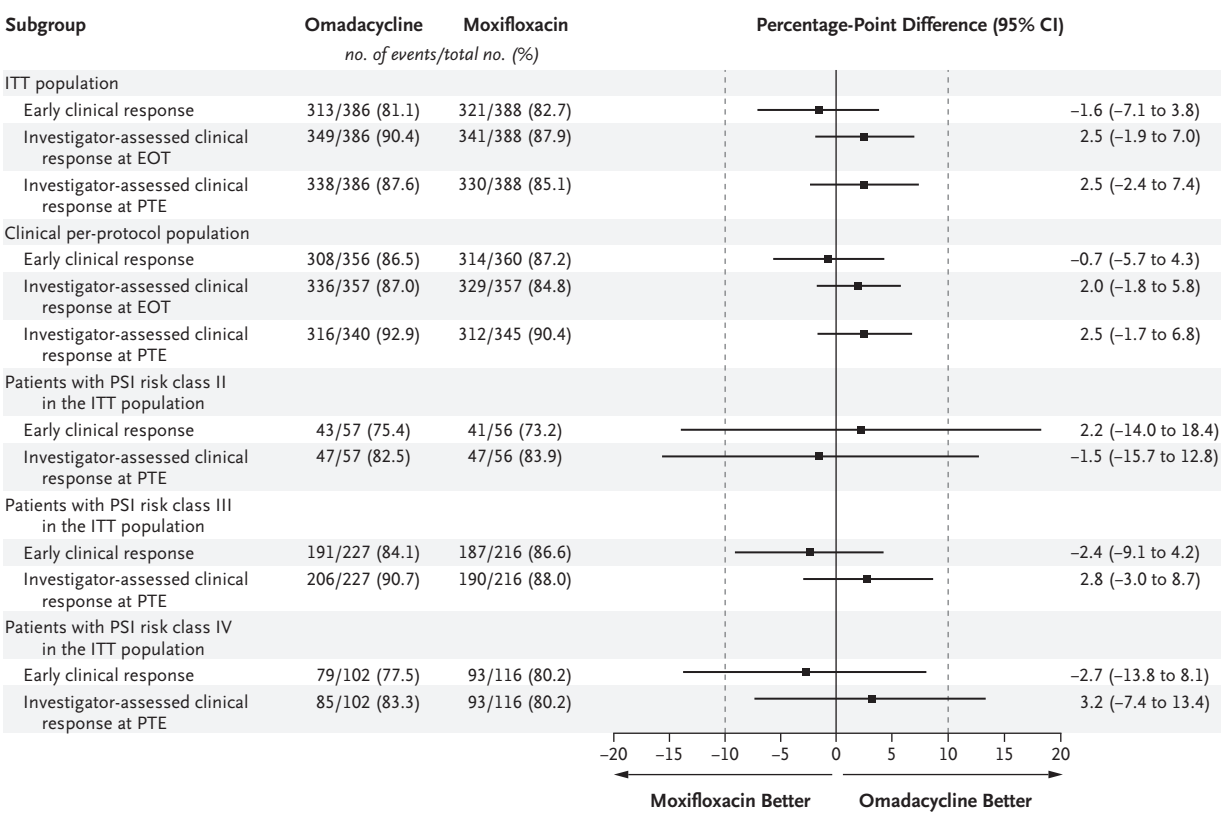

Figure 2. Forest Plot of Primary and Secondary End Points.

The 95% confidence intervals are based on the Miettinen and Nurminen method without stratification.[16] Scores on the Pneumonia Severity Index (PSI) are used to place patients with pneumonia into risk classes that range from I to V, with higher risk classes indicating a greater risk of death (additional details are provided in the protocol); in this trial, only patients in risk class II (PSI score, 51 to 70), III (71 to 90), or IV (91 to 130) were eligible for participation. EOT denotes end of treatment, ITT intention to treat, and PTE post-treatment evaluation.

clinical per-protocol population, omadacycline was noninferior to moxifloxacin for early clinical response (86.5% and 87.2%, respectively; difference, –0.7 percentage points; 95% CI, –5.7 to 4.3). Temperature, blood pressure, and the partial pressure of arterial oxygen normalized within 60 to 120 hours after the first dose in more than 90% of patients (Table S10 in the Supplementary Appendix).

The clinical response rates associated with omadacycline and moxifloxacin were similar for investigator-assessed clinical response at the post-treatment evaluation in the intention-to-treat population (87.6% and 85.1%, respectively; difference, 2.5 percentage points; 95% CI, –2.4 to 7.4) and in the clinical per-protocol population (92.9% and 90.4%; difference, 2.5 percentage points; 95% CI, –1.7 to 6.8). The reasons for clinical failure and indeterminate assessments at the post-treatment evaluation are shown in Table S9 in the Supplementary Appendix. In the microbiologic intention-to-treat population, the clinical response rates at the post-treatment evaluation in the omadacycline and moxifloxacin groups were 89.2% and 87.4%, respectively (difference, 1.9 percentage points; 95% CI, –4.6 to 8.5). Similar efficacy in the two treatment groups was also observed within subgroups based on PSI risk class (Fig. 2). Data on clinical response according to geographic region and previous receipt of antibiotics and on microbiologic response are provided in Table S11 in the Supplementary Appendix.

Omadacycline had clinical efficacy similar to that of moxifloxacin against pathogens causing community-acquired bacterial pneumonia that

Table 2. Investigator-Assessed Clinical Response at the Post-Treatment Evaluation According to Pathogen Detected at Baseline (Microbiologic Intention-to-Treat Population).*

Pathogen Detected at Baseline	Omadacycline (N=204)		Moxifloxacin (N=182)	
	Patients with Pathogen	Patients with Clinical Response	Patients with Pathogen	Patients with Clinical Response
	no.	*no. (%)*	*no.*	*no. (%)*
Gram-positive aerobic bacteria	61	52 (85)	56	49 (88)
Streptococcus pneumoniae†	43	37 (86)	34	31 (91)
Penicillin-susceptible	26	23 (88)	22	21 (95)
Macrolide-resistant	10	10 (100)	5	5 (100)
Tetracycline-resistant	16	14 (88)	17	13 (76)
Staphylococcus aureus‡	11	8 (73)	11	9 (82)
Gram-negative aerobic bacteria	79	67 (85)	69	56 (81)
Haemophilus influenzae	32	26 (81)	16	16 (100)
H. parainfluenzae	18	15 (83)	17	13 (76)
Klebsiella pneumoniae	13	10 (77)	13	11 (85)
Atypical bacteria, SAP definition of positivity§	118	109 (92)	106	97 (92)
Mycoplasma pneumoniae¶	70	66 (94)	57	50 (88)
Legionella pneumophila‖	37	35 (95)	37	36 (97)
Chlamydia pneumoniae¶	28	25 (89)	28	25 (89)
Atypical bacteria, conservative definition of positivity**	73	66 (90)	64	58 (91)
M. pneumoniae¶	35	31 (89)	29	25 (86)
L. pneumophila‖	29	27 (93)	28	27 (96)
C. pneumoniae¶	15	14 (93)	14	13 (93)

* The microbiologic intention-to-treat population included patients in the intention-to-treat population who had a causative pathogen or pathogens identified at baseline from culture of a respiratory specimen or blood or with the use of a culture-independent method. Patients with the same pathogen isolated from multiple specimens were counted only once for that pathogen. Patients with the same pathogen from a blood specimen, respiratory specimen, urinary antigen testing, or serologic testing (or from more than one of these tests) were counted only once for that pathogen. Patients were counted only once in the overall tabulations for gram-positive aerobic bacteria, gram-negative aerobic bacteria, and atypical bacteria if they had more than one respective pathogen identified at baseline. The pathogens listed are those detected in at least 10 patients in either treatment group.

† The overall tabulation of *S. pneumoniae* included identification from urinary antigen testing only, which would not have associated susceptibility data. Resistance was defined in accordance with Clinical Laboratory Standards Institute document M100-S25.

‡ Methicillin resistance was observed in only one *S. aureus* isolate, in the moxifloxacin group.

§ In the statistical analysis plan (SAP), an indeterminate convalescent-phase serologic test result is considered to be positive. In accordance with the SAP, a positive serologic test result was defined as one of the following: a positive baseline or post-treatment evaluation IgM serologic test result, a negative baseline and indeterminate post-treatment evaluation IgG serologic test result, or a negative baseline and positive post-treatment evaluation IgG serologic test result.

¶ *M. pneumoniae* and *C. pneumoniae* were identified by serologic testing only.

‖ *L. pneumophila* was identified by serologic or urinary antigen testing.

** For identification by serologic testing, only a positive convalescent result was considered to be positive, which is the more stringent criterion described in the package inserts for the serologic test kits.

were identified at baseline, with regard to both early clinical response (Table S12 in the Supplementary Appendix) and investigator-assessed clinical response at the post-treatment evaluation (Table 2). No correlation was found between omadacycline MIC values for community-acquired bacterial pneumonia pathogens and clinical outcome (Table S13 in the Supplementary Appendix). In the small group of patients with bacteremia, the rate of clinical response at the post-treatment evaluation was 73% (11 of 15) with omadacycline and 83% (15 of 18) with moxifloxacin. The differences between the treatment groups in the rates of investigator-assessed

clinical response at the post-treatment evaluation according to pathogen or in patients with bacteremia were attributable to small sample sizes and indeterminate (i.e., missing) responses.

SAFETY

Adverse events that emerged after treatment initiation occurred in 41.1% of the patients in the omadacycline group and 48.5% of the patients in the moxifloxacin group (Table 3, and Tables S14 through S18 in the Supplementary Appendix). Gastrointestinal events were the most frequent (10.2% of patients in the omadacycline group and 18.0% of those in the moxifloxacin group). The largest difference between the groups was in the incidence of diarrhea (1.0% in the omadacycline group and 8.0% in the moxifloxacin group). *Clostridium difficile* infection was reported in no patients in the omadacycline group and in 2.1% of the patients in the moxifloxacin group. Discontinuation of the trial regimen for gastrointestinal events occurred in two patients in each group. Serious adverse events that emerged after treatment initiation occurred with similar incidence in the two groups (6.0% in the omadacycline group and 6.7% in the moxifloxacin group); infection-related events were the most frequent of these events (2.1% in the omadacycline group and 4.1% in the moxifloxacin group), most of which were a result of progression or complications of community-acquired bacterial pneumonia (Table S16 in the Supplementary Appendix).

A total of 12 deaths (8 in the omadacycline group and 4 in the moxifloxacin group) occurred during the conduct of the trial. All the patients who died were older than 65 years of age. The causes of death were progression of the underlying pneumonia or respiratory compromise, hospital-acquired pneumonia, cardiac or vascular events, and cancer (Table S18 in the Supplementary Appendix). Neither group had clinically relevant changes from baseline in vital signs, laboratory tests, or ECG findings. Maximum shifts in levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to more than 3 times the upper limit of the normal range occurred in 3.5% and 1.6%, respectively, of the patients in the omadacycline group and in 4.5% and 3.2% of the patients in the moxifloxacin group.

Table 3. Adverse Events That Emerged after Treatment Initiation (Safety Population).*

Type of Event	Omadacycline (N=382)	Moxifloxacin (N=388)
	no. of patients (%)	
Any adverse event	157 (41.1)	188 (48.5)
Treatment-related adverse event†	39 (10.2)	69 (17.8)
Severe adverse event	25 (6.5)	26 (6.7)
Serious adverse event	23 (6.0)	26 (6.7)
Treatment discontinuation for adverse event	21 (5.5)	27 (7.0)
Death	8 (2.1)	4 (1.0)
Adverse events that occurred in >2% of patients in either group		
ALT increased	14 (3.7)	18 (4.6)
Hypertension	13 (3.4)	11 (2.8)
γ-Glutamyltransferase increased	10 (2.6)	8 (2.1)
Insomnia	10 (2.6)	8 (2.1)
Vomiting	10 (2.6)	6 (1.5)
Constipation	9 (2.4)	6 (1.5)
Nausea	9 (2.4)	21 (5.4)
AST increased	8 (2.1)	14 (3.6)
Headache	8 (2.1)	5 (1.3)
Diarrhea‡	4 (1.0)	31 (8.0)

* The safety population included patients who underwent randomization and received any amount of trial drug. Adverse events that emerged after treatment initiation were those with an onset or worsening of severity that occurred at or any time after administration of the first dose of trial drug through the final follow-up visit. Full lists of adverse events are provided in Tables S14 through S18 in the Supplementary Appendix. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† The investigator, who was unaware of the treatment-group assignments, assessed whether an adverse event was related to treatment.

‡ *Clostridium difficile* infection (reported as *C. difficile* infection, *C. difficile* colitis, or pseudomembranous colitis) was reported in no patients in the omadacycline group and in 8 patients (2.1%) in the moxifloxacin group.

DISCUSSION

The efficacy of once-daily omadacycline, administered intravenously with the option to transition to oral administration, was noninferior to that of moxifloxacin for the treatment of hospitalized adults (not in an intensive care unit [ICU]) who had community-acquired bacterial pneumonia in the analysis of the primary end point of early clinical response. These results are consistent with the observed stabilization of vital signs and the expected time course for the initial response to therapy.[17-19] Durable efficacy was also shown for investigator-assessed clinical response at the

post-treatment evaluation 5 to 10 days after the end of therapy. The efficacy results were consistent across analysis populations, PSI risk classes, and causative pathogens.

The observed safety profile of omadacycline was consistent with the known safety profile of the tetracycline class. Nausea and vomiting occurred in 2% of the patients in the omadacycline group and were treatment-limiting in two of those patients. No cases of *C. difficile* infection occurred in the omadacycline group, a finding consistent with the known effects of drugs in the tetracycline class.[20-22] Transient and reversible increases in ALT or AST levels, reported either as adverse events that emerged after treatment initiation or as postbaseline maximum shifts, were mostly of low magnitude and were similar to those reported in association with moxifloxacin. No cases of drug-induced liver injury (i.e., Hy's law cases) were observed.

Serious adverse events that emerged after treatment initiation were reported in 6 to 7% of the patients in each group, which is similar to the rates found in other modern phase 3 trials involving community-acquired bacterial pneumonia.[23-25] The mortality rate was 2.1% in the omadacycline group, as compared with 1.0% in the moxifloxacin group. The cause of the mortality imbalance was not established. The causes of the deaths were consistent with the population, and the mortality rates are consistent with the expected range of 1 to 3% in other phase 3 community-acquired bacterial pneumonia trials.[23-27] The mortality rate of 0.9% among patients in both treatment groups who had a PSI risk class of III, as well as the mortality rates of 5.9% in the omadacycline group and 1.7% in the moxifloxacin group among patients who had a PSI risk class of IV, were consistent with or lower than the expected mortality rates of 0.9 to 2.8% and 8.2 to 9.3%, respectively, in these risk classes.[13]

Antibiotic resistance among common community respiratory pathogens has resulted in a need for new antibiotics for community-acquired bacterial pneumonia; the World Health Organization priority pathogen list for the development of new antibiotics includes penicillin-nonsusceptible *S. pneumoniae* and ampicillin-resistant *H. influenzae*.[6,28] U.S. surveillance of pathogens that cause community-acquired bacterial pneumonia has shown higher than 30% ampicillin resistance in *H. influenzae* isolates, as well as *S. pneumoniae* resistance to multiple classes of antibiotics (penicillin, 12.7%; tetracycline, 21.5%; and macrolide, 45.6%).[29,30]

In our trial, extensive microbiologic testing identified a bacterial pathogen in 50% of patients; however, in the real world, probable causative pathogens in community-acquired bacterial pneumonia are identified in less than 10% of cases.[31] Therefore, empirical therapy for community-acquired bacterial pneumonia must be chosen with common respiratory pathogens and contemporary local susceptibility taken into consideration. The spectrum of activity of omadacycline against typical and atypical respiratory pathogens, the absence of cross-resistance with other antibiotic classes, and the efficacy of the drug shown in our trial suggest a potential role in the treatment of community-acquired bacterial pneumonia in an era of increasing antimicrobial resistance.

Strengths of this trial include its extensive microbiologic testing and consistent results observed across populations and subgroups of patients. Because patients with PSI risk class I or II have a lower risk of death and are less commonly admitted to the hospital for initial treatment than are those with higher risk classes, enrollment of these patients was excluded or limited. The patients with the most severe community-acquired bacterial pneumonia (i.e., PSI risk class V) and immunocompromised patients were also excluded, which limits the generalizability of the results to these important subpopulations of patients. Although the majority of patients in this trial were enrolled outside of the United States, the age, demographic characteristics, PSI risk class, and microbiologic test results are similar to those described among U.S. hospitalized non-ICU patients with community-acquired bacterial pneumonia.[32]

In summary, once-daily omadacycline, administered intravenously with the option to transition to oral administration, was noninferior to moxifloxacin as empirical monotherapy for non-ICU hospitalized adults with community-acquired bacterial pneumonia.

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