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MAJOR ARTICLE

Omadacycline Monotherapy in Nontuberculous Mycobacterial Pulmonary Disease Caused by *Mycobacterium abscessus*: Results From a Phase 2, Double-blind, Randomized, Placebo-controlled Study

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Background. Omadacycline is an FDA-approved oral and intravenous treatment for adults with community-acquired bacterial pneumonia and acute bacterial skin and skin structure infection that demonstrates potent in vitro activity and in vivo efficacy versus *Mycobacterium abscessus*.

Methods. A randomized, double-blind, placebo-controlled, multicenter phase 2 study of omadacycline monotherapy was conducted in adults with nontuberculous mycobacterial pulmonary disease (NTM-PD) caused by *M. abscessus*. Eligible patients meeting the diagnostic criteria for NTM-PD were randomized 1.5:1 to receive omadacycline 300 mg orally once daily or placebo for 84 days. Randomization was stratified by prior antibiotic treatment for *M. abscessus* (yes/no).

Results. Sixty-six patients were randomized (41 omadacycline, 25 placebo). At baseline, cough, fatigue, mucus production, shortness of breath, and throat clearing were the most bothersome and common symptoms (68.2%–95.4% of patients). For the primary endpoint, 34.1% and 20.0% of omadacycline and placebo patients, respectively, were responders by definition 1 (improvement in symptom severity at day 84 for at least half of baseline symptoms) and 34.1% and 12.0%, respectively, were responders by definition 2 (definition 1 plus no deterioration in severity of any baseline symptom). Key secondary and exploratory clinical and microbiological endpoints also favored omadacycline compared with placebo. Four (9.8%) patients discontinued omadacycline therapy due to a treatment-emergent adverse event (TEAE). The most frequent omadacycline-related TEAEs were gastrointestinal, particularly nausea.

Conclusions. Results consistently favored omadacycline monotherapy over placebo across several endpoints in NTM-PD caused by *M. abscessus*. Omadacycline was well tolerated; nausea was the most frequent TEAE. Further investigations are warranted.

Keywords. *mycobacterium abscessus*; omadacycline; nontuberculous mycobacterial pulmonary disease.

Mycobacterium abscessus is a rapidly growing nontuberculous mycobacterial (NTM) species composed of 3 subspecies—*abscessus, bolletii, and massiliense*—that causes pulmonary disease (PD) often associated with bronchiectasis [1–4]. Subspecies *abscessus* predominates in the United States, while subspecies *massiliense* is at least as common in parts of Asia [5, 6].

Mycobacterium abscessus is resistant to most antibiotics, and there are currently no approved therapies for NTM-PD caused by *M. abscessus* [7, 8]. Guideline-recommended treatment regimens consist of a nonstandardized combination of 2–5 antibiotics, typically administered for multiple months, with few oral options. Parenteral antibiotics are often used in the initial treatment regimen, but use beyond 4–8 weeks poses multiple challenges including drug toxicities [1, 5, 9–11]. Subsequently, the treatment regimen typically consists of at least 2–3 oral or inhaled antibiotics. The optimal treatment duration is currently unknown. Treatment guidelines suggest either a shorter or longer treatment regimen can be used in consultation with experts [1]. Macrolide-based treatment regimens are recommended for

Received 15 August 2025; accepted 18 December 2025; published online 3 March 2026

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https://doi.org/10.1093/cid/ciag062

susceptible isolates; however, subspecies *bolletii* and most subspecies *abscessus* are intrinsically resistant, further limiting oral treatment options [1, 5]. Given these challenges, there is an urgent need for new treatment alternatives, especially those administered orally.

Omadacycline is an aminomethylcycline antibiotic in the tetracycline class approved by the US Food and Drug Administration in 2018 to treat adults with community-acquired bacterial pneumonia and acute bacterial skin and skin structure infection [12]. Omadacycline is available as oral and intravenous once-daily formulations and obtains good penetration into pulmonary tissue [12, 13].

Omadacycline demonstrated potent in vitro activity against rapidly growing NTM species including *M. abscessus,* as well as intracellular activity against *M. abscessus* within macrophages [14, 15]. In mouse models of pulmonary disease caused by *M. abscessus*, omadacycline demonstrated bactericidal activity at a human dose equivalent when administered alone [16] or in combination with other antibiotics, including against isolates resistant to clarithromycin and amikacin [17–19].

Previous retrospective studies and case series reporting the off-label use of omadacycline show favorable results in NTM-PD caused by *M. abscessus* [20–24]. Here, results are presented from a phase 2 study of oral omadacycline monotherapy in adults with NTM-PD caused by *M. abscessus*.

METHODS

Study Design

This randomized, double-blind, placebo-controlled, phase 2 study evaluated the efficacy, safety, and tolerability of oral omadacycline in adults with NTM-PD caused by *M. abscessus* (NCT04922554). The study enrolled patients at 17 US sites between October 2021 (first patient enrolled) and July 2024 (last follow-up).

The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by local institutional review boards, and patients provided written informed consent. Following a screening period of up to 8 weeks, eligible patients were randomized to receive study treatment for 3 months, with visits at days 1, 28, 56, 84 (or end of treatment [EOT] for early discontinuations) and a follow-up safety assessment 30 days after the last dose of study treatment.

Eligibility Criteria

Adults aged ≥18 years were eligible if they were diagnosed with NTM-PD caused by *M. abscessus* per clinical guidelines (≥2 symptoms at screening and day 1 of treatment; at least 1 positive pulmonary culture for *M. abscessus* before screening; and radiographic evidence consistent with *M. abscessus* infection) [1]. At least 1 of the positive pulmonary cultures must have been within 6 months before screening, and a pulmonary culture obtained at screening must also have been positive. Additionally, patients were eligible if they were deemed by the investigator not to require initiation of guideline-directed antimicrobial therapy within the following 3 months, consistent with expert opinion that deferring antibiotic treatment in favor of "watchful waiting" is appropriate for some patients with NTM-PD [1]. Patients were excluded if they had received antibiotic treatment for *M. abscessus* or *M. avium* complex (MAC) within 6 months before screening; received systemic or inhaled antimicrobial therapy within 4 weeks before screening; had active pulmonary malignancy, cystic fibrosis, cavitary disease, active pulmonary tuberculosis, lung transplant, known HIV infection, extrapulmonary NTM disease, any condition requiring chronic treatment with systemic corticosteroids within 90 days before screening, or had been previously treated with omadacycline.

Randomization

Patients were randomized via a central electronic interactive response system in a 1.5:1 ratio to oral omadacycline or placebo (Supplementary Table 1). A computer-generated blocked (block size 5) randomization sequence was used to assign patients to treatment groups. Randomization was stratified by any prior use of antibiotics directed against *M. abscessus* (yes/no). All investigators, patients, and sponsor staff were blinded to the randomized treatment.

Interventions

Patients received omadacycline 300 mg (2 × 150 mg tablets) or matching placebo once daily. Total treatment duration was 84 days.

Assessments

As there were no validated instruments to assess symptoms in patients with NTM-PD at the time of study design, the sponsor developed the NTM Symptom Assessment Questionnaire in which patients rated 12 common NTM-PD symptoms (chest pain, chronic cough, coughing up blood, fatigue, fever, mucus production, night sweats, poor appetite, shortness of breath, throat clearing, wheezing, and weight loss), each on a 4-point scale (absent, mild, moderate, severe). Patients rated their symptoms at screening, day 1, and at all subsequent visits through day 84 (or EOT). At day 1, patients also ranked up to 3 symptoms as most bothersome.

At day 1 and at subsequent visits, the following were performed: Quality of Life–Bronchiectasis (QOL-B) (a 37-item questionnaire with 7 domains measuring symptoms, functioning, and health-related quality of life [HRQoL] in patients with bronchiectasis) [25], St. George's Respiratory Questionnaire (assessing HRQoL across 3 domains in individuals with chronic pulmonary disease) [26], and Patient-Reported Outcomes Measurement Information System (PROMIS) Short-Form Fatigue questionnaire (assessing fatigue and its impact on physical, mental, and social activities over the past 7 days) [27].

Patients completed the Patient Global Impressions of Severity (PGI-S) to assess on a 7-point scale their perception of

NTM-PD severity [28], and the Patient Global Impression of Change (PGI-C) to assess their perceived change in clinical status and overall improvement [29]. PGI-S was assessed at day 1, and PGI-S and PGI-C at all subsequent visits. Similarly, investigators completed the Clinical Global Impression–Severity of Illness (CGI-S), a 1-item assessment to rate illness severity based on observed and reported symptoms, behavior, and function during the past 7 days; and the Clinician Global Impression–Improvement (CGI-I) to rate any patient improvement compared to day 1 per clinical judgment. CGI-S was assessed at day 1, and both CGI-S and CGI-I at all subsequent visits [30].

Microbiological assessments were performed on sputum specimens at screening and days 1, 28, 56, and 84/EOT. To meet the definition of a negative sputum culture at any visit, all sputum samples from that visit must have shown no growth (negative) for *M. abscessus* both in liquid and on solid media.

Susceptibility testing for omadacycline and other common antimicrobials used to treat NTM-PD was performed on *M. abscessus* isolates on custom produced (Thermo Fisher) frozen panels (Supplementary Materials).

Safety was monitored through recording of adverse events throughout the study, and vital signs, physical examinations, electrocardiograms (ECGs), clinical laboratory analyses, and CT scans at selected time points.

Endpoints

The primary efficacy endpoint was clinical response based on the NTM Symptom Assessment Questionnaire at day 84. Clinical response was defined in 2 ways: 1 = improvement in severity of at least half of symptoms present at day 1; and 2 = improvement in severity of at least half of symptoms present at day 1 plus no deterioration in severity of any symptom present at day 1.

Key secondary efficacy endpoints included change from day 1 to day 84/EOT for each domain score of the QOL-B (a numerical increase in score indicates improvement). Additionally, the proportion of patients who reported a new moderate or severe symptom by day 84 was calculated.

Key secondary and exploratory microbiological endpoints were proportion of patients with consecutive negative *M. abscessus* sputum cultures, either 3 (days 28, 56, and 84) or 2 (days 56 and 84); a negative culture at day 84/EOT; and a reduction in the *M. abscessus* semiquantitative sputum culture (SSC) score from baseline to day 84, for which a lower score reflects a decrease in the mycobacterial load (Supplementary Materials) [31]. A decrease in susceptibility was defined as a >4-fold increase in minimum inhibitory concentration (MIC) to a given antimicrobial agent from baseline to post-baseline samples.

Safety endpoints included incidence of adverse events and post-baseline changes in vital signs, ECGs, and laboratory parameters.

Statistical Analyses

A sample size of 75 patients (45 omadacycline, 30 placebo) was identified to provide an initial assessment of omadacycline efficacy in NTM-PD caused by *M. abscessus*, with 80% power to detect an absolute treatment difference of 30% in clinical response rate at day 84 (eg, clinical response rates of 15% and 45% in the placebo and omadacycline treatment groups, respectively), using a Mantel–Haenszel test with 2-sided alpha level of 0.05 (see Supplementary Materials for more details). The estimated effect size of 30% was based on the difference in response rates observed with macrolide-based treatment of macrolide-susceptible and -resistant *M. abscessus*.

There was no formal inferential testing or control for multiplicity, therefore *P*-values are provided for the primary and certain prespecified secondary efficacy outcomes for descriptive purposes only, which may inform subsequent trials. The intent-to-treat analysis set was all randomized patients. The safety analysis set was all patients who received ≥1 dose of study drug.

For the primary efficacy endpoint of clinical response, any patient who withdrew consent, died before reaching day 84, or received an alternative antimicrobial therapy for NTM was considered not to have achieved clinical response. Patients could have had >1 reason for being a non-responder. For each definition of the primary endpoint, treatment difference, odds ratio (OR; omadacycline vs placebo), and corresponding 95% confidence interval (CI) were calculated. The *P*-value was determined using a chi-squared test.

For secondary and exploratory endpoints, results are based on observed data only; no imputations were made for missing data. If the patient discontinued treatment before day 84, available data from the most recent prior visit was used for EOT analyses. Least-square means were calculated for QOL-B scores using ANCOVA with a dependent variable of change from baseline at the given time point, fixed factors of randomized treatment and stratification status of prior antibiotic treatment for NTM-PD caused by *M. abscessus*, and baseline score as a covariate. Baseline was defined as the most recent measurement before the first dose of study drug. The treatment difference for the percentage of patients with a decrease from baseline (definition provided in Supplementary Materials) in semiquantitative *M. abscessus* sputum culture score was determined (Supplementary Table 2), and the *P*-value calculated using a chi-squared test. A post hoc *P*-value for difference between treatment groups in the percentage of patients with 1, 2, or 3 negative sputum cultures was calculated using Fisher's exact test.

RESULTS

Demographics and Baseline Characteristics

Of 66 patients randomized (n = 41 omadacycline, n = 25 placebo; Figure 1), 5—all in the omadacycline group—discontinued treatment early (1 withdrawal of consent; 4 adverse events). Baseline characteristics were well matched in the treatment groups. Patients' overall mean age was 70.6 years, 68% were female, and 88% had a history of bronchiectasis (Table 1). Patients

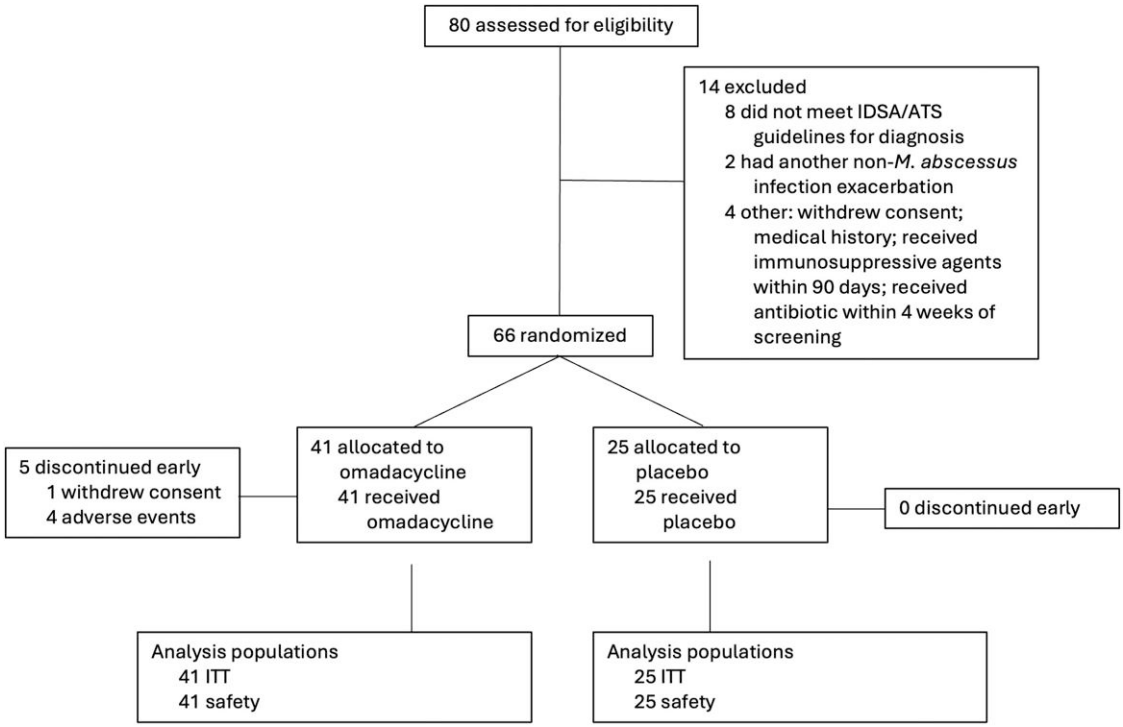

Figure 1. Study disposition. Abbreviations: ATS, American Thoracic Society; IDSA, Infectious Disease Society of America; ITT, intent-to-treat.

had a mean duration of *M. abscessus* infection of 2.4 years before enrolling in the study, and few (14%) had received prior treatment for *M. abscessus*.

At baseline, 83% of patients had subspecies *abscessus* identified from the sputum sample; the remaining patients had subspecies *massiliense*. Although there was a history of NTM-PD caused by MAC in fewer patients in the omadacycline group (39%) than the placebo group (60%), MAC was isolated in sputum at baseline with similar frequency in both groups (32% and 40%, respectively; Table 1). All baseline *M. abscessus* isolates were multidrug resistant (nonsusceptible [MIC value interpreted as intermediate or resistant] to ≥1 agent in ≥3 antimicrobial categories), as expected (Supplementary Table 3). The omadacycline MIC range for *M. abscessus* baseline isolates across both groups was ≤0.008 to 1 µg/mL, with MIC_{50} values of 0.5 and 0.25 µg/mL in the omadacycline and placebo treatment groups, respectively, and MIC_{90} values of 1 µg/mL in both groups.

The most frequently reported symptoms in both treatment groups at baseline were mucus production, cough, throat clearing, fatigue, and shortness of breath (Figure 2), rated by most patients as mild/moderate; these also ranked as the top 5 most bothersome symptoms at baseline.

Efficacy

For the primary efficacy endpoint, clinical response at day 84 (Table 2), 34.1% of omadacycline patients and 20.0% of placebo patients were clinical responders per definition 1 (treatment difference 14.2, OR 2.07 [95% CI 0.64, 6.71]; $P = .218$). Per definition 2, 34.1% and 12.0% of patients, respectively, were clinical responders (treatment difference 22.2, OR 3.80 [95% CI 0.97, 14.94]; $P = .046$).

For the top 5 most frequently reported symptoms, favorable shifts in severity from baseline to day 84/EOT were observed in omadacycline-treated patients relative to placebo (Figure 3). Further analysis of these symptoms showed that the proportion of patients with moderate/severe symptoms at each visit trended downward during the study in the omadacycline group, whereas in the placebo group it remained relatively stable or increased (Supplementary Figure 1). At day 84, new moderate/severe symptom(s) were reported by 5.6% (2/36) of patients receiving omadacycline and 24.0% (6/25) of patients receiving placebo. Consistent numerical improvement with omadacycline treatment was seen from day 1 to day 84/EOT in all 8 domain scores of the QOL-B, with score increases ranging from 2.8 to 9.6. For the corresponding scores in the placebo group, for each QOL-B domain there was either a smaller magnitude of increase compared with the omadacycline group or a decrease in score (indicating worsening in that domain; Figure 4).

A numerically higher proportion of patients in the omadacycline group had negative *M. abscessus* sputum cultures (negative both in liquid and on solid media) compared with the placebo group (Figure 5). Three consecutive negative

Table 1. Demographic and Baseline Characteristics, ITT Population

	Omadacycline (n = 41)	Placebo (n = 25)	Total (n = 66)
Female; n (%)	30 (73.2)	15 (60.0)	45 (68.2)
Age, y; mean (SD)	69.3 (9.6)	72.8 (7.6)	70.6 (9.0)
>65 y; n (%)	30 (73.2)	21 (84.0)	51 (77.3)
BMI, kg/m^2; mean (SD)	22.5 (3.5)	24.5 (4.7)	23.2 (4.1)
Duration of *M. abscessus* NTM pulmonary disease, y			
Mean (SD)	2.7 (3.6)	2.0 (3.1)	2.4 (3.4)
Min, max	0, 14	0, 10	0, 14
Received prior treatment for *M. abscessus*; n (%)	6 (14.6)	3 (12.0)	9 (13.6)
Patients with known COPD	8 (19.5)	5 (20.0)	13 (19.7)
Patients with known bronchiectasis	36 (87.8)	22 (88.0)	58 (87.9)
Patients who have never smoked	24 (58.5)	15 (60.0)	39 (59.1)
Current smoking	0	0	0
Medical history of MAC pulmonary disease; n (%)	16 (39.0)	15 (60.0)	31 (47.0)
Positive sputum AFB smear; n (%)	7 (17.0)	7 (28.0)	14 (21.2)
Positive sputum cultures; n (%)			
M. abscessus	41 (100)	25 (100)	66 (100)
Subspecies *abscessus*	35 (85.4)	20 (80.0)	55 (83.3)
Subspecies *massiliense*	6 (14.6)	5 (20.0)	11 (16.7)
MAC	13 (31.7)	10 (40.0)	23 (34.8)

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ITT, intent-to-treat; *M. abscessus*, *Mycobacterium abscessus*; MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria; SD, standard deviation.

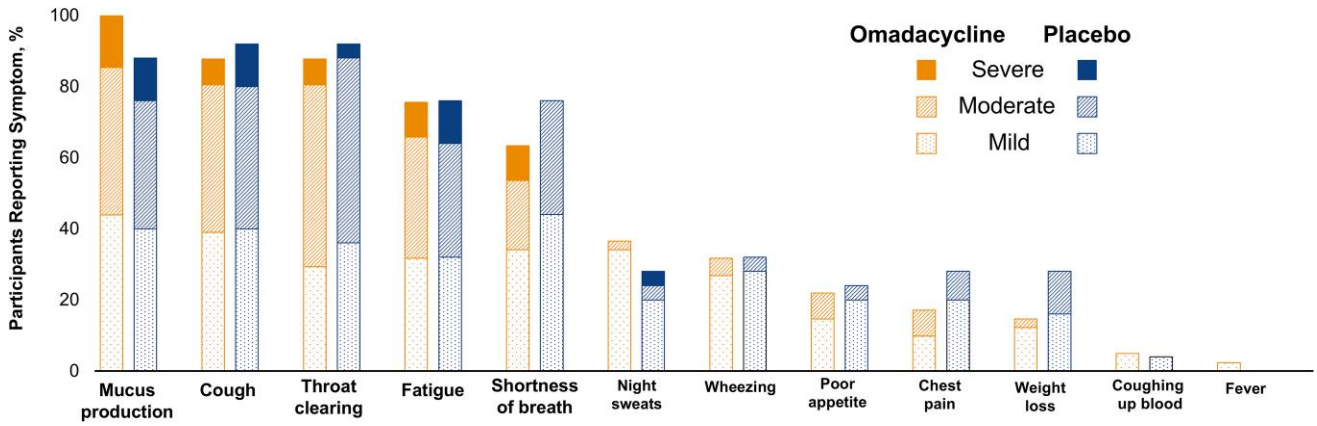

Figure 2. Baseline symptoms of nontuberculous mycobacteria pulmonary disease. Patients rated the severity of 12 symptoms on a 4-point scale (absent, mild, moderate, severe). The 5 most frequently reported symptoms were also ranked as the top 5 most bothersome symptoms (labels shown in larger font).

cultures starting on day 28 were reported for 31.3% of omadacycline patients and 8.7% of placebo patients ($P = .055$). Two consecutive negative cultures starting on day 56 were reported for 41.7% and 13.0% of omadacycline and placebo patients, respectively ($P = .023$). At day 84/EOT, a negative culture was reported in 53.8% and 25.0% of omadacycline and placebo patients, respectively ($P = .036$). Among both treatment groups, no *M. abscessus* isolates recovered at day 84/EOT demonstrated decreased susceptibility to omadacycline (>4-fold shift in MIC value vs baseline). Using a more conservative definition of decreased susceptibility, a 4-fold increase in the omadacycline MIC value from baseline to day 84/EOT was observed for only 1 patient's isolate in each treatment group (Supplementary Table 4). A decrease in SSC score from baseline to day 84 was seen in 76.5% (26/34) of omadacycline-treated patients and 45.8% (11/24) of placebo-treated patients (treatment difference 30.6; $P = .017$).

Safety

The most frequent treatment-related adverse events (TEAEs) were gastrointestinal symptoms, particularly nausea, which was more common in the omadacycline group, usually mild in severity, and did not result in treatment discontinuation (Table 3). There

Table 2. Clinical Response at Day 84, ITT Population

	Omadacycline (n = 41)		Placebo (n = 25)
Clinical Responder, Definition 1[a]; n (%)	14 (34.1)		5 (20.0)
Treatment difference		14.2	
P-value[b]		0.218	
Odds ratio (95% CI)		2.07 (0.64, 6.71)	
Reasons for nonresponse[c]; n (%)			
Improvement in fewer than half of symptoms present at baseline	23 (85.2)		20 (100)
Received alternative antibiotic therapy for NTM (not including macrolide)	1 (3.7)		1 (5.0)
Withdrew from treatment before day 84	5 (18.5)		0
Died on or before day 28	0		0
Clinical Responder, Definition 2[a]; n (%)	14 (34.1)		3 (12.0)
Treatment difference		22.2	
P-value[b]		0.046	
Odds ratio (95% CI)		3.80 (0.97, 14.94)	
Reasons for nonresponse[c]; n (%)			
Improvement in fewer than half of symptoms present at baseline	23 (85.2)		20 (90.9)
Received alternative antibiotic therapy for NTM (not including macrolide)	1 (3.7)		1 (4.5)
Withdrew from treatment before day 84	5 (18.5)		0
Died on or before day 28	0		0
Worsening in severity of ≥1 symptom present at baseline	9 (33.3)		12 (54.5)

Abbreviations: CI, confidence interval; ITT, intent-to-treat; NTM, nontuberculous mycobacteria.

[a]Clinical response was defined in 2 ways: definition 1 = improvement in severity of at least half of symptoms present at baseline; definition 2 = improvement in severity of at least half of symptoms present at baseline plus no deterioration in severity of any symptom present at baseline.

[b]Statistics were calculated using a chi-squared test. An analysis stratified by receipt of prior antibiotic treatment for NTM was not performed due to the small sample size in one of the randomization stratification subgroups.

[c]Patients could have had >1 reason for nonresponse. Percentage is calculated as a proportion of the non-responder population.

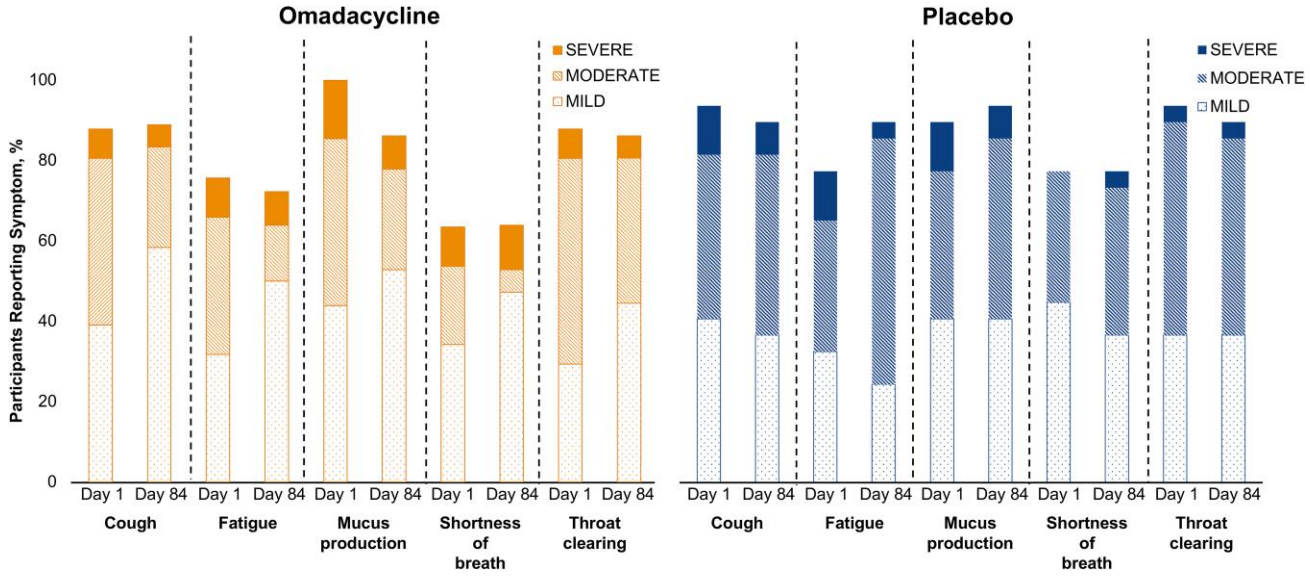

Figure 3. Severity of the most frequently reported NTM symptoms at day 1 and day 84/EOT: (left) omadacycline, (right) placebo. Abbreviations: EOT, end of treatment; NTM, nontuberculous mycobacteria.

were no deaths in the study, and only 2 patients (both in the placebo group) had serious adverse events, deemed unrelated to study drug. TEAEs led to treatment discontinuation in 4 (9.8%) omadacycline patients, all for different reasons. There were no adverse trends in vital signs or ECGs. Laboratory findings were notable only for mild/moderate serum transaminase elevations. TEAEs of alanine aminotransferase (ALT) increase occurred in 4 (9.8%) patients in the omadacycline group (peak values, 2.2–4.2 × upper

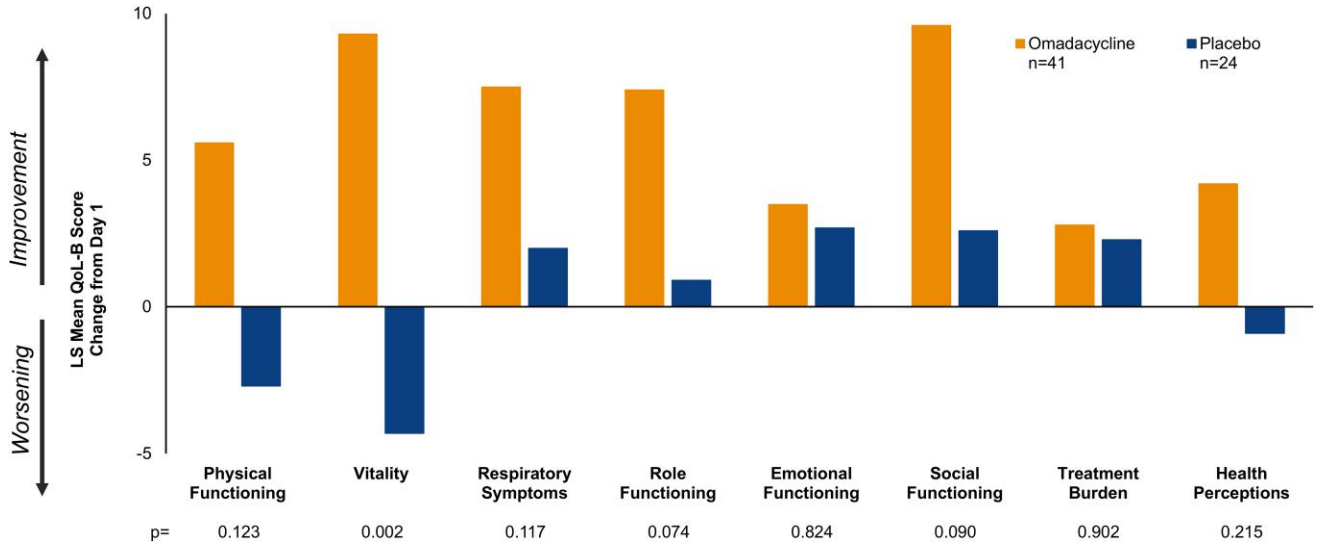

Figure 4. LS mean QOL-B domain changes from day 1 to day 84/EOT. Data shown are LS means from an analysis of covariance. Abbreviations: EOT, end of treatment; LS, least-square; QOL-B, Quality of Life—Bronchiectasis.

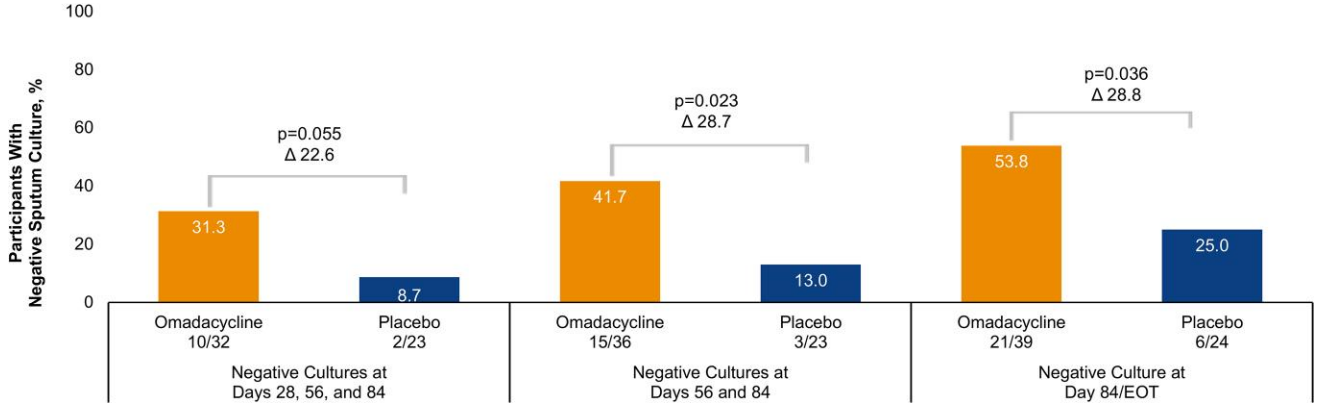

Figure 5. Negative *M. abscessus* sputum cultures: proportion of patients who had negative culture results for both liquid and solid media. Subgroups are not mutually exclusive; eg, patients who had ≥2 negative cultures from day 56 (middle graph) were also counted in the group of patients who had ≥1 negative culture at day 84/EOT (end of treatment). *P*-values were calculated post hoc using Fisher's exact test. Abbreviations: EOT, end of treatment; *M. abscessus*, *Mycobacterium abscessus*.

limit of normal) and none in the placebo group. These events were not associated with any elevation in serum bilirubin or attributable symptoms. One patient discontinued treatment (day 50) due to liver enzyme elevations. There was no interruption or discontinuation for the other 3 patients, and the findings resolved either spontaneously during treatment (2 patients) or after EOT (2 patients).

DISCUSSION

This phase 2 trial evaluated the efficacy and safety of 3 months of omadacycline monotherapy versus placebo in NTM-PD caused by *M. abscessus*, and was the first prospective, randomized controlled study of any therapeutic for this disease. The study was designed in consultation with NTM experts and the US FDA. Ultimately, it was agreed that a 3-month monotherapy, placebo-controlled study allowed for the assessment of omadacycline without any confounding influence of other antibiotic treatments and would provide valuable, controlled data in this population within an adequate timeframe to observe a treatment effect. Additionally, the treatment period was selected to limit the time in which the placebo group was without antimicrobial therapy and minimize the risk of selecting for isolates with decreased susceptibility to omadacycline.

Table 3. Summary of Treatment-Emergent Adverse Events, Safety Population

Patients With; N (%)	Omadacycline (n = 41)	Placebo (n = 25)
Any TEAE	35 (85.4)	21 (84.0)
Nausea	22 (53.7)	2 (8.0)
Headache	7 (17.1)	4 (16.0)
Fatigue	7 (17.1)	1 (4.0)
Abdominal pain	6 (14.6)	1 (4.0)
Vomiting	6 (14.6)	0
Diarrhea	5 (12.2)	1 (4.0)
Alanine aminotransferase increase	4 (9.8)	0
Night sweats	4 (9.8)	0
Aspartate aminotransferase increased	3 (7.3)	0
Hemoptysis	3 (7.3)	3 (12.0)
TEAE of maximum severity:		
Mild	11 (26.8)	9 (36.0)
Moderate	20 (48.8)	11 (44.0)
Severe[a]	4 (9.8)	1 (4.0)
Serious TEAE[b]	0	2 (8.0)
TEAE leading to death	0	0
Early treatment discontinuation for AE[c]	4 (9.8)	0

Data are shown for individual TEAEs with ≥5% incidence in the omadacycline group.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

[a]Severe TEAEs: Omadacycline (abdominal pain in 2 patients, nausea in 1 patient, headache in 1 patient), placebo (gastrointestinal hemorrhage in 1 patient).

[b]Serious TEAEs: Placebo (gastrointestinal hemorrhage in 1 patient, COVID-19 in 1 patient).

[c]Reasons for treatment discontinuation: Omadacycline (heart failure, elevated liver enzymes, abdominal pain, parasomnia; each reported in 1 patient).

These results suggest that further development of omadacycline as a treatment of NTM-PD caused by *M. abscessus* is warranted.

Patient-reported outcomes (PROs) have been proposed by the US FDA, NTM clinicians, and patient advocacy groups as favored primary clinical trial endpoints to assess the effectiveness of treatment in NTM-PD [32, 33]. At the time of study design, only preliminary validation of the QOL-B and NTM Module instruments in MAC-PD was available. Therefore, the NTM Symptom Assessment Questionnaire was developed to assess 12 of the most common respiratory and systemic symptoms associated with NTM-PD and was based on the monitoring methodology used in the NTM Module [34]. Here, patients receiving omadacycline reported an improvement in symptoms and quality of life greater than those receiving placebo in both the NTM Symptom Assessment and QOL-B questionnaires. The former demonstrated a reduction in the severity of the most common and bothersome NTM-PD symptoms (cough, fatigue, mucus production, shortness of breath, throat clearing), though this tool is not validated in this population [32, 35]. The QOL-B demonstrated notable improvements in the physical functioning, respiratory, and vitality domains. Previous studies have shown good reliability and validity of these 3 QOL-B domains for assessing disease symptoms and quality of life in NTM-PD [36–38]. The QOL-B respiratory domain was shown to be an effective PRO tool in patients with MAC-PD and now serves as the primary efficacy endpoint in a phase 3 trial in this disease (NCT04677543, NCT04677569).

Omadacycline-treated patients had improved microbiologic outcomes compared with placebo, as assessed by negative sputum cultures and reduction in SSC scores. Given the length of this study, to achieve the most rigorous definition of sputum culture conversion as defined by NTM experts (≥3 negative cultures collected ≥4 weeks apart) [39] required an initial negative culture at day 28; despite this, almost one-third (31.3%) of omadacycline-treated patients achieved conversion. When analyzed as 2 consecutive negative cultures starting at day 56, this percentage increased to 41.7%. Although there was no microbiologic follow-up beyond the treatment period in this study, these results with 3 months of omadacycline monotherapy compare favorably with the reported conversion rates for subspecies *abscessus* with prolonged (>6 months) multidrug treatment (25%–42%) [5]. The patient population in these prior observational studies included those with cavitary disease and/or high rates of acid-fast bacilli (AFB) smear positivity, 2 findings that would favor prompt initiation of guideline-directed therapy, [1] and the studies generally used a phased therapy approach consisting of 1 month of multiple IV antibiotics followed by a longer continuation phase using a combination of oral or inhaled antibiotics, including 1 study where the regimen was consistent with current treatment guidelines [40]. More recently, an open-label study evaluating inhaled liposomal amikacin-based combination regimens in NTM-PD caused by *M. abscessus* reported 50% of patients achieved sputum culture conversion; however, 18% developed amikacin resistance during treatment [41].

Patients receiving omadacycline also had a greater reduction in the SSC score versus those receiving placebo, suggesting a reduction in overall mycobacterial burden. Although it is not certain that this would result in negative sputum cultures if treatment were continued, a reduction in the SSC score from baseline to month 3 was highly predictive of subsequent long-term sputum conversion in a retrospective analysis of MAC-PD [31].

Among patients who did not have negative sputum cultures at day 84/EOT, no decrease in in vitro susceptibility of *M. abscessus* to omadacycline, measured by MIC shift, was observed. Published in vitro and in vivo data also suggest low potential for *M. abscessus* to develop decreased susceptibility to omadacycline, and no mechanism of resistance to omadacycline in this species has yet been identified [16, 18, 19]. However, it is unknown whether a decrease in susceptibility would be observed after longer durations of therapy. It is also important to note that clinical breakpoints for omadacycline versus *M. abscessus* are not yet established.

Oral omadacycline treatment for 3 months was generally safe and well tolerated using a daily dose approved by the US FDA for existing indications [12]. Consistent with the established

safety profile for oral omadacycline, the most frequent TEAEs were gastrointestinal symptoms, particularly nausea of mild/moderate intensity. There were no serious TEAEs in patients treated with omadacycline. Treatment discontinuation due to TEAEs in the omadacycline group was uncommon (9.8%).

Several retrospective observational studies and case series have been published describing the use of omadacycline in the treatment of NTM-PD caused by *M. abscessus*, generally as combination therapy, with promising initial results [20–24, 42]. Considering the reported in vitro activity and early favorable clinical experience, published expert reviews have included omadacycline among the recommended antibiotics for constructing a multidrug regimen for the initial treatment of NTM-PD caused by *M. abscessus*, for both macrolide-susceptible and -resistant isolates [2, 5, 43].

Limitations of this study include exclusion of patients with cystic fibrosis, cavitary disease, and those receiving immunosuppressive medications—all important subsets of patients with NTM-PD. Therefore, the results of this study may not be generalizable to these groups of patients, nor to those with more advanced disease. Another limitation was the treatment duration of 3 months—a relatively short monitoring period for antimycobacterial treatment. However, as noted previously, these design elements were selected because they allowed for inclusion of the placebo comparator group. This study also did not include post-treatment microbiologic assessments to evaluate rates of sustained culture conversion. Although slower than expected enrollment led to the study being stopped at 66 patients (vs the intended 75 patients), the statistical power for the primary endpoint remained sufficiently high (76%) for an exploratory study.

In conclusion, this study suggests that omadacycline has potential efficacy in the treatment of NTM-PD caused by *M. abscessus*. Furthermore, the optimal duration of omadacycline therapy and the potential contribution of companion drugs require further investigation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. Kevin L. Winthrop, MD, MPH: conceptualization, methodology, investigation, writing—review & editing. Patrick A. Flume, MD: investigation, writing—review & editing. Reeti Khare, PhD: investigation, resources, writing—review & editing. Chakrapol Sriaroon, MD: investigation, writing—review & editing. Alissa Sirbu, BSN: conceptualization, methodology, project administration, writing-original draft, writing- review and editing. Amy Manley, BS: conceptualization, methodology, supervision, writing-original draft, writing—review & editing. Anita F. Das, PhD: methodology, formal analysis, validation, writing—review & editing. Surya Chitra, PhD: methodology, software, formal analysis, data curation, writing—review & editing. Daniel H. Deck, PharmD: conceptualization, methodology, writing- original draft, writing—review and editing. Alisa W. Serio, PhD: conceptualization, methodology, writing—original draft, writing—review & editing. Diane M. Anastasiou, BS: methodology, project administration, writing—original draft, writing—review & editing. Stephen Villano, MD: Supervision, formal analysis, validation, writing—original draft, writing—review & editing.

Acknowledgments. Medical writing and editorial support were provided by Agnella Izzo Matic, PhD, CMPP (AIM Biomedical, LLC), funded by Paratek Pharmaceuticals, Inc.

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

Previous publication. Portions of these data were previously presented at ATS 2025, San Francisco, CA, 18–21 May 2025.

Financial support. This work was supported by Paratek Pharmaceuticals, Inc. 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 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.

Potential conflicts of interest. K. L. W. has received research grants and/or consulting honoraria from Insmed, AN2 Therapeutics, Spero, Renovion, and Paratek Pharmaceuticals, Inc. P. A. F. reports grant support and consulting for Paratek Pharmaceuticals, Inc. R. K. performs contracted testing for Insmed, AN2 Therapeutics, Spero, Mannkind, and Paratek Pharmaceuticals, Inc; and has received research funding from Paratek Pharmaceuticals, Inc. A. S., A. M., D. H. D., A. W. S., and D. M. A. are employees and shareholders of Paratek Pharmaceuticals, Inc. C. S., A. F. D., S. C., and S. V. are consultants to Paratek Pharmaceuticals, Inc.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed

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