Once-daily oral omadacycline versus twice-daily oral linezolid for acute bacterial skin and skin structure infections (OASIS-2): a phase 3, double-blind, multicentre, randomised, controlled, non-inferiority trial

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See Online for appendix

Summary

Background Pathogen resistance and safety concerns limit oral antibiotic options for the treatment of acute bacterial skin and skin structure infections (ABSSSI). We aimed to compare the efficacy and safety of once-daily oral omadacycline, an aminomethylcycline antibiotic, versus twice-daily oral linezolid for treatment of ABSSSI.

Methods In this phase 3, double-blind, randomised, non-inferiority study, eligible adults with ABSSSI at 33 sites in the USA were randomly assigned (1:1) to receive omadacycline (450 mg orally every 24 h over the first 48 h then 300 mg orally every 24 h) or linezolid (600 mg orally every 12 h) for 7–14 days. Randomisation was done via an interactive response system using a computer-generated schedule, and stratified by type of infection (wound infection, cellulitis or erysipelas, or major abscess) and receipt (yes or no) of allowed previous antibacterial treatment. Investigators, funders, and patients were masked to treatment assignments. Primary endpoints were early clinical response, 48–72 h after first dose, in the modified intention-to-treat (mITT) population (randomised patients without solely Gram-negative ABSSSI pathogens at baseline), and investigator-assessed clinical response at post-treatment evaluation, 7–14 days after the last dose, in the mITT population and clinically evaluable population (ie, mITT patients who had a qualifying infection as per study-entry criteria, received study drug, did not receive a confounding antibiotic, and had an assessment of outcome during the protocol-defined window). The safety population included randomised patients who received any amount of study drug. We set a non-inferiority margin of 10%. This study is registered with ClinicalTrials.gov, NCT02877927, and is complete.

Findings Between Aug 11, 2016, and June 6, 2017, 861 participants were assessed for eligibility. 735 participants were randomly assigned, of whom 368 received omadacycline and 367 received linezolid. Omadacycline (315 [88%] of 360) was non-inferior to linezolid (297 [83%] of 360) for early clinical response (percentage-point difference 5·0, 95% CI –0·2 to 10·3) in the mITT population. For investigator-assessed clinical response at post-treatment evaluation, omadacycline was non-inferior to linezolid in the mITT (303 [84%] of 360 *vs* 291 [81%] of 360; percentage-point difference 3·3, 95% CI –2·2 to 9·0) and clinically evaluable (278 [98%] of 284 *vs* 279 [96%] of 292; 2·3, –0·5 to 5·8) populations. Mild to moderate nausea and vomiting were the most frequent treatment-emergent adverse events in omadacycline (111 [30%] of 368 and 62 [17%] of 368, respectively) and linezolid (28 [8%] of 367 and 11 [3%] of 367, respectively) groups.

Interpretation Once-daily oral omadacycline was non-inferior to twice-daily oral linezolid in adults with ABSSSI, and was safe and well tolerated. Oral-only omadacycline represents a new treatment option for ABSSSI, with potential for reduction in hospital admissions and cost savings.

Funding Paratek Pharmaceuticals.

Introduction

Skin and skin structure infections impose a substantial burden on health-care systems and society.[1,2] In the USA, the number of adults admitted to hospital for skin infections increased by an estimated 17% between 2005 and 2011.[2] In both the USA and Europe, acute bacterial skin and skin structure infections (ABSSSI) are estimated to result in more than 800 000 hospitalisations annually.[3] In the USA, adults aged 45–64 years who are admitted to hospital for ABSSSI treatment will face an estimated mean cost of US$7253 (SD 114), and stay in hospital for a median of 4 days (range 3–5).[4] The major drivers of cost are room and pharmacy fees.[5,6] Considerable benefits and cost savings could be gained from reducing the length of stay in hospital or avoiding hospitalisation altogether, particularly among non-diabetic patients with community-acquired ABSSSI who have low complication and mortality rates.[5,7]

Research in context

Evidence before this study

To explore recommended oral antibiotic treatment options for acute bacterial skin and skin structure infections (ABSSSI), we searched PubMed using the terms "skin and skin structure infections" AND "oral antibiotic treatment" AND "treatment guidelines" for articles published up to March 14, 2019, with no language or date restrictions. This search yielded only one relevant published treatment guideline: the Infectious Diseases Society of America (IDSA) 2014 guidance for treatment of skin and skin structure infections (SSTIs). Therefore, we modified the search terms to include "antibiotic treatment" rather than "oral antibiotic treatment". Among the publications identified by this modified search was a 2013 review of developments since the 2005 IDSA SSTI guidelines, which concluded that the increasing prevalence of community-acquired meticillin-resistant *Staphylococcus aureus* (MRSA) has led organisations, including the IDSA, to recommend empiric coverage of community-acquired MRSA for patients with ABSSSI. The review noted that, although community-acquired MRSA is resistant to available oral β-lactams and to many fluoroquinolones and macrolides, most strains remain susceptible to tetracyclines. However, the few prospective randomised trials that have investigated older tetracyclines include patients with uncomplicated infections. Newer intravenous therapy options with expanded MRSA coverage are discussed in the 2013 review, which also looks at investigational drugs that were in development at the time, including omadacycline, an aminomethylcycline antibiotic derived from the tetracycline class. The OPTIC phase 3 study (NCT02531438) showed that once-daily intravenous-to-oral omadacycline was non-inferior in efficacy, and similar in safety and tolerability, to once-daily moxifloxacin for the treatment of adults with community-acquired bacterial pneumonia. The OASIS-1 study (NCT02378480) showed that once-daily intravenous-to-oral omadacycline was non-inferior in efficacy, and similar in safety and tolerability, to twice-daily intravenous-to-oral linezolid for the treatment of adults with ABSSSI.

Added value of this study

The present study extends the findings of OASIS-1, indicating that an oral-only, once-daily regimen of omadacycline is an effective and safe alternative to twice-daily, oral linezolid for treating serious ABSSSI. Omadacycline is a new treatment option in an era of rising antibiotic resistance that circumvents common resistance mechanisms to tetracyclines, and offers the convenience of once-daily oral dosing. Strengths of this study include the enrolment of patients with substantial (ie, well above the minimum size criteria for inclusion and definition of ABSSSI of 75 cm^2) skin infections (ie, wound infection, cellulitis or erysipelas, or major abscess), with large lesions (median 322 cm^2 [IQR 198–495] for omadacycline and 294 cm^2 [190–462] for linezolid groups), and high rates of identified bacterial pathogens.

Implications of all the available evidence

Early clinical response (at 48–72 h) and post-therapy success were observed with this omadacycline regimen for serious ABSSSI of various infection types with large lesions and caused by common skin pathogens. The data suggest that an oral-only, once-daily omadacycline treatment regimen has consistent efficacy, providing physicians with a new potential treatment option for outpatient management of ABSSSI. Considering the substantial burdens for patients and health-care systems associated with the management of serious ABSSSI, administration of oral-only omadacycline could reduce the proportion of patients who are admitted to hospital solely for infusion therapy to treat ABSSSI, as well as reducing the related treatment costs.

Staphylococcus aureus and streptococci are the most frequently identified causes of ABSSSI, with *S aureus* being most common in purulent infections with abscess.[8,9] The prevalence of meticillin-resistant *S aureus* (MRSA) infection is high, accounting for nearly half of all ABSSSI isolates in the USA and 10–50% of isolates in Europe.[1,10–12] Increases in antibiotic resistance—most notably the emergence of community-onset MRSA infections—and the absence of culture data for many skin infections complicate therapy decisions.[10]

Although antimicrobial agents effective against *S aureus* (including MRSA) and streptococci are available, prospective randomised data are minimal for older antibiotics, including tetracyclines, and trials have typically included patients with uncomplicated skin infections.[9,13–15] Real-world concerns surrounding ABSSSI treatment options include high and increasing rates of resistance to older antibiotics, including β-lactams, co-trimoxazole, clindamycin, and older tetracyclines;[16–19] uncertainty around optimal dosing of older agents (eg, co-trimoxazole);[18] adverse events[18,20–22] (eg, tendinopathy with fluoroquinolones,[22] *Clostridioides difficile* infection with multiple classes,[23] and photosensitivity and tooth discolouration with available tetracyclines);[18] and drug–drug interactions (eg, linezolid and antidepressants).[20] Therefore, the development of new oral antibiotics that could be used to treat patients when these concerns arise would facilitate ABSSSI management in outpatient settings, and thus the avoidance of hospitalisation, for patients and prescribers.

Omadacycline is a once-daily aminomethylcycline antibiotic derived from minocycline that circumvents the efflux and ribosomal protection mechanisms of tetracycline-specific resistance, restoring activity in vitro and in vivo against common community-acquired skin pathogens, including staphylococci (eg, meticillin-susceptible *S aureus* [MSSA] and MRSA), streptococci, *Enterococcus* species, and many Gram-negative bacilli.[24–26]

The OASIS-1 study[27] showed that once-daily intravenous-to-oral omadacycline was non-inferior in efficacy and similar in safety to twice-daily intravenous-to-oral linezolid for the treatment of adults with ABSSSI known or suspected to be caused by Gram-positive pathogens. The OASIS-2 study reported here evaluated the efficacy and safety of oral-only omadacycline dosing compared with linezolid.

Methods

Study design

OASIS-2 was a phase 3, double-blind, double-dummy, randomised, non-inferiority study done at 33 sites in the USA between Aug 11, 2016, and June 6, 2017. The study was done in accordance with Good Clinical Practice guidelines and provisions of the Declaration of Helsinki. The institutional review board or ethics committee at each participating site approved the protocol and amendments. The Article conforms to CONSORT reporting guidelines for randomised trials. The protocol is available online.

For more on the **protocol** see https://paratekpharma.com/media/1576/ptk0796-absi-16301-protocol-v30r.pdf

Patients

Adults aged 18 years or older with a qualifying skin or skin structure infection (wound infection, cellulitis or erysipelas, or major abscess) were eligible for study inclusion. Qualifying infections were at least 75 cm² in total surface area of contiguous involved tissue exhibiting erythema, oedema, induration, or all three. The method of lesion measurement was standardised across study sites (appendix p 6). Major abscesses were limited to a maximum of 30% of patients, as per US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance for trial design.[28–30] Eligible patients also required evidence of a systemic response to infection (ie, leukocytosis, leucopenia, bandaemia, lymphangitis, lymphadenopathy, fever, or hypothermia).

Patients were excluded if they had received a potentially effective systemic or topical antibacterial treatment within 72 h before the first dose of study drug, except for a single dose of a short-acting antibiotic (which was allowed in a maximum of 25% of patients). An allowed short-acting antibiotic was defined as a non-oxazolidinone antibacterial with a standard dosing regimen more frequent than once per day; a full list is available in the protocol. Also excluded were patients with infections expected to require more than 14 days of treatment or associated with chronic (>3 months) skin lesions, ulcers, or wounds. Substantial liver or renal insufficiency, immunocompromised patients, and inability to tolerate oral medication were other exclusion criteria. Complete eligibility criteria are provided in the appendix (pp 3–5).

Each patient provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either omadacycline or linezolid. Linezolid was chosen as a comparator because it is an oral monotherapy approved for the treatment of skin and skin structure infections that covers MRSA, has a well characterised safety profile, and has contemporary data for efficacy in ABSSSI.[20,31,32] Randomisation was done via an interactive response system using a computer-generated schedule (internet-based central block randomisation [block size of six]), and stratified by type of infection (wound infection, cellulitis or erysipelas, or major abscess) and receipt (yes or no) of allowed previous antibacterial treatment. Study site personnel confirmed patient eligibility and contacted the interactive response system, which randomly assigned a treatment corresponding to the next available number in the respective stratum of the computer-generated randomisation schedule. The interactive response system instructed the study site personnel as to which study drug kit to administer. The investigators, funders, and patients were masked to treatment assignments, with patients receiving the same number of active drug and comparator-matched placebo tablets, which were identical in appearance. All patients received doses twice per day; in the omadacycline group, only one of the daily doses contained active omadacycline. All patients fasted for one of two daily doses, which corresponded (as the odd-numbered dose) to the dose that would be either omadacycline or its matched placebo. Fasting was required for administration of the odd-numbered doses because of the effects of food consumption on the bioavailability of oral omadacycline. Study site personnel monitored medication compliance through medication return and patient-completed diaries.

Procedures

Patients received two once-daily 450 mg doses of oral omadacycline (days 1 and 2) then once-daily 300 mg oral omadacycline, or twice-daily 600 mg oral linezolid, for a total treatment period of 7–14 days (appendix p 8).

At the screening visit, samples were collected from the site of infection (biopsy or similar deep specimen of the advancing margin of the involved area) for Gram stain and culture, and blood samples for culture were collected within 24 h before the first dose of study drug (appendix p 6). Blood samples for haematology (including coagulation) and serum chemistry were tested at a central laboratory. Blood samples collected before study drug dosing were also tested at the study site laboratory to assess patient eligibility.

The investigator measured the size of the primary ABSSSI lesion at screening; at visits on study days 2, 3, and 7; at the end of treatment visit within 2 days after the last dose of study drug; and at the post-treatment evaluation at 7–14 days after the last dose of study drug.

Safety was assessed based on adverse events, vital signs, electrocardiograms (ECG), and laboratory results.

Outcomes

Two independent primary efficacy analyses were done for this study, each to comply with recommendations and

guidelines from the US FDA and EMA, respectively.[28–30] The US FDA primary efficacy endpoint was early clinical response in the modified intention-to-treat (mITT) population, which included all randomised patients without solely Gram-negative ABSSSI pathogens at baseline (because linezolid is not active against Gram-negative bacteria).[20] Clinical success for early clinical response was defined as survival with at least 20% reduction in lesion size 48–72 h after the first dose of study drug without rescue antibacterial therapy. Early clinical response was determined based on investigator measurements of the primary lesion size. If more than one assessment of lesion size was done during the time window, the most recent assessment was used. A post-hoc analysis of early clinical response in the clinically evaluable early clinical response population was also done.

The EMA primary efficacy endpoint was the investigator assessment of clinical response at post-treatment evaluation (derived from the end of treatment visit and post-treatment evaluation 7–14 days after the last dose of study drug) in the mITT and clinically evaluable populations. The clinically evaluable population included mITT patients who had a qualifying infection as per study-entry criteria, received study drug, did not receive a confounding antibiotic, and had an assessment of outcome during the protocol-defined window. Clinical success was defined as the infection being sufficiently resolved such that further antibacterial therapy was not needed at both end of treatment and post-treatment evaluations. Investigator-assessed clinical response also was assessed at the end of treatment visit as a secondary endpoint.

Additional, preplanned microbiological responses (defined in the appendix, p 7) were assessed at the end of treatment and post-treatment evaluation visits in the microbiological mITT and microbiologically evaluable populations to support clinical findings. The microbiological mITT population consisted of mITT patients with at least one Gram-positive causative bacterial pathogen identified from a blood culture or from a culture of a microbiological sample obtained from the primary ABSSSI site at baseline. The microbiologically evaluable population consisted of clinically evaluable patients who had at least one Gram-positive causative pathogen at baseline. Safety (including all-cause mortality within 30 days after the first dose of the study drug) and pharmacokinetic outcomes were also assessed. The safety population included randomly assigned patients who received any amount of study drug. Pharmacokinetic analyses will be presented in a separate paper.

Statistical analysis

A non-inferiority margin of 10% was used for both primary outcomes of early clinical response and investigator-assessed clinical response at post-treatment evaluation, based on historical data for treatment effect of antibiotics in ABSSSI and guidance from the US FDA and EMA.[28–30] A two-sided 95% CI for the difference in the proportion of patients achieving early clinical response in the mITT population was calculated using the unadjusted method of Miettinen and Nurminen.[33] Non-inferiority of omadacycline to linezolid was concluded for early clinical response if the lower limit of the 95% CI for the treatment difference was greater than –10%. Two-sided 95% CIs for the difference in the investigator-assessed clinical response at post-treatment evaluation of the proportion of patients achieving clinical response in the mITT and clinically evaluable populations were calculated using the adjusted (for the randomisation stratification factors) method of Miettinen and Nurminen.[33] Non-inferiority of omadacycline to linezolid was concluded for investigator-assessed clinical response at post-treatment evaluation if the lower limit of the 95% CI for the treatment difference was greater than –10% for both the mITT and clinically evaluable populations. Because the two primary endpoints were analysed independently, no adjustment for multiplicity was made. Unadjusted 95% CIs are provided for additional efficacy endpoints as descriptive statistics.

Assuming the proportion of patients achieving clinical response of 79% in both treatment groups,[31] 90% power, and a one-sided α of 0·025,[31] and using the method of Farrington and Manning,[34] 704 patients were required in the ITT population to show non-inferiority for early clinical response. Assuming investigator-assessed clinical response at post-treatment evaluation proportions of 85% (mITT) and 90% (clinically evaluable) based on OASIS-1,[31] 704 and 564 patients (assuming an 80% evaluability rate), respectively, provided more than 90% power to show non-inferiority for investigator-assessed clinical response at post-treatment evaluation.

Missing data for early clinical response, investigator-assessed clinical response, and microbiological responses were classified as indeterminate responses and counted as clinical failures in analyses of the mITT and microbiological mITT populations (patients with indeterminate responses were excluded from the clinically evaluable and microbiologically evaluable populations).

Sensitivity analyses were done to assess the effect of missing data on early clinical response. A multiple imputation analysis using Markov chain Monte Carlo full-data imputation was done: 50 datasets were created, with type of infection, previous receipt of antibiotics, infection resulting from intravenous drug use, and baseline lesion area included as predictive variables. In another analysis, all patients with an indeterminate response in both treatment groups were considered as early clinical response successes. Finally, a tipping point analysis was done, in which an indeterminate response was considered a clinical failure in the omadacycline group and a clinical success in the linezolid group. Statistical analyses were done using SAS, version 9.4.

This study is registered with ClinicalTrials.gov, number NCT02877927.

Role of the funding source
The funder did the study and prepared the statistical analysis plan. Data analyses and interpretation were by the funder in conjunction with the authors. All 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. Medical writers, paid by the funder, assisted with preparation of the Article. All authors reviewed and edited the Article and made the decision to submit the Article for publication.

Results

Of 861 patients assessed for eligibility, 735 were randomly assigned (ITT population) across the 33 sites in the USA. The most common reasons patients did not meet study eligibility criteria were absence of evidence of a systemic response to infection (21 [17%] of 126) and existence of a confounding concomitant condition (32 [25%] of 126). All 735 ITT patients received at least one dose of study drug (safety population; figure 1). 15 patients in the ITT population had Gram-negative bacteria as the sole causative pathogen at baseline, leaving 720 patients in the mITT population (360 in each group).

Overall, most patients were male (462 [63%] of 735), white (668 [91%] of 735), and intravenous drug users (526 [72%] of 735; table 1). In the mITT population, median lesion sizes (omadacycline, 322 cm² [IQR 198–495]; linezolid, 294 cm² [190–462]) at baseline were well above the 75 cm² eligibility threshold. 545 (76%) of 720 infections occurred on a limb and 494 (69%) were reported by patients to be a result of intravenous drug use. 296 (82%) of 360 patients in the omadacycline group and 285 (79%) of 360 patients in the linezolid group had a surgical procedure at the primary ABSSSI infection site before first treatment (within 30 days before screening for surgical wound infections and within 7 days for all others). 59 (16%) of 360 patients in the omadacycline group and 54 (15%) of 360 patients in the linezolid group had a surgical procedure after first treatment (within 24 h and no later than 48 h after the start of study drug). Six (2%) of 360 patients in the omadacycline group and eight (2%) of 360 patients in the linezolid group received a single dose of a protocol-allowed, short-acting antibiotic within 72 h before the first dose of study drug.

At least one Gram-positive ABSSSI pathogen was identified at baseline in 563 (78%) of 720 patients in the mITT population (figure 1): within this microbiological mITT population, *S aureus* was the predominant pathogen in both treatment groups, with MRSA accounting for just under 40% of infections in both groups (table 1). Most infections in the microbiological mITT population were monomicrobial (table 1). Two (<1%) of 360 patients in the omadacycline group and eight (2%) of 360 patients in the linezolid group had bacteraemia.

The proportions of patients who completed the study were similar between the treatment groups (624 [85%] of 735 patients overall in the ITT population; omadacycline group 314 [85%] of 368, linezolid group 310 [85%] of 367), and study treatment was completed by 328 (89%) of 368 patients in the omadacycline group and 315 (86%) of 367 patients in the linezolid group. 75 (10%) of 735 patients were lost to follow-up, the most common reason for study discontinuation. The proportions of patients who were compliant with dosing (98% in each group had compliance of ≥80%; omadacycline 360 [98%] of 368, linezolid 358 [98%] of 367) and fasting (98% in each group had compliance of ≥80%; omadacycline predose 362 [98%] and post dose 361 [98%] of 368, linezolid predose 361 [98%] and post dose was 360 [98%] of 367) were similar between groups. Mean treatment exposures were 8·2 days (SD 2·8) for omadacycline and 8·0 days (3·0) for linezolid, with similar distribution of total duration of treatment (7–10 days; 286 [78%] of 368 for omadacycline, 278 [76%] of 367 for linezolid).

Omadacycline showed non-inferiority compared with linezolid for the US FDA primary endpoint of early clinical response in the mITT population: 315 (88%) of 360 patients in the omadacycline group versus 297 (83%) of 360 patients in the linezolid group (percentage-point difference 5·0, 95% CI –0·2 to 10·3; figure 2; appendix p 10). Patients assessed as clinical failure represented similar percentages within the omadacycline (26 [7%] of 360) and linezolid (32 [9%] of 360) groups; indeterminates (missing data) represented 19 (5%) of 360 patients in the omadacycline group and 31 (9%) of 360 patients in the linezolid group. In sensitivity analyses assessing the influence of missing data, including a multiple imputation analysis, omadacycline remained non-inferior to linezolid (appendix p 11). In a post-hoc analysis of the clinically evaluable population, omadacycline was non-inferior to linezolid for early clinical response (figure 2; appendix p 10).

Omadacycline was also non-inferior to linezolid for the EMA primary endpoint of investigator-assessed clinical response at post-treatment evaluation in both the mITT population and clinically evaluable population (figure 2; appendix p 10). In the mITT population, clinical success at investigator-assessed clinical response post-treatment evaluation was reported in 303 (84%) of 360 patients in the omadacycline group and 291 (81%) of 360 patients in the linezolid group (percentage-point difference 3·3, 95% CI –2·2 to 9·0). In the clinically evaluable population, clinical success at investigator-assessed clinical response post-treatment evaluation was reported in 278 (98%) of 284 patients in the omadacycline group and in 279 (96%) of 292 patients in the linezolid group (2·3, –0·5 to 5·8). Patients assessed as clinical failures represented low percentages within the omadacycline and linezolid groups (12 [3%] of 360 *vs* 21 [6%] of 360, respectively, in mITT population; six [2%] of 284 *vs* 13 [4%] of 292, respectively, in clinically evaluable population); indeterminates represented 45 (13%) of 360 patients and 48 (13%) of 360 patients, respectively, of the omadacycline and linezolid groups in the mITT population.

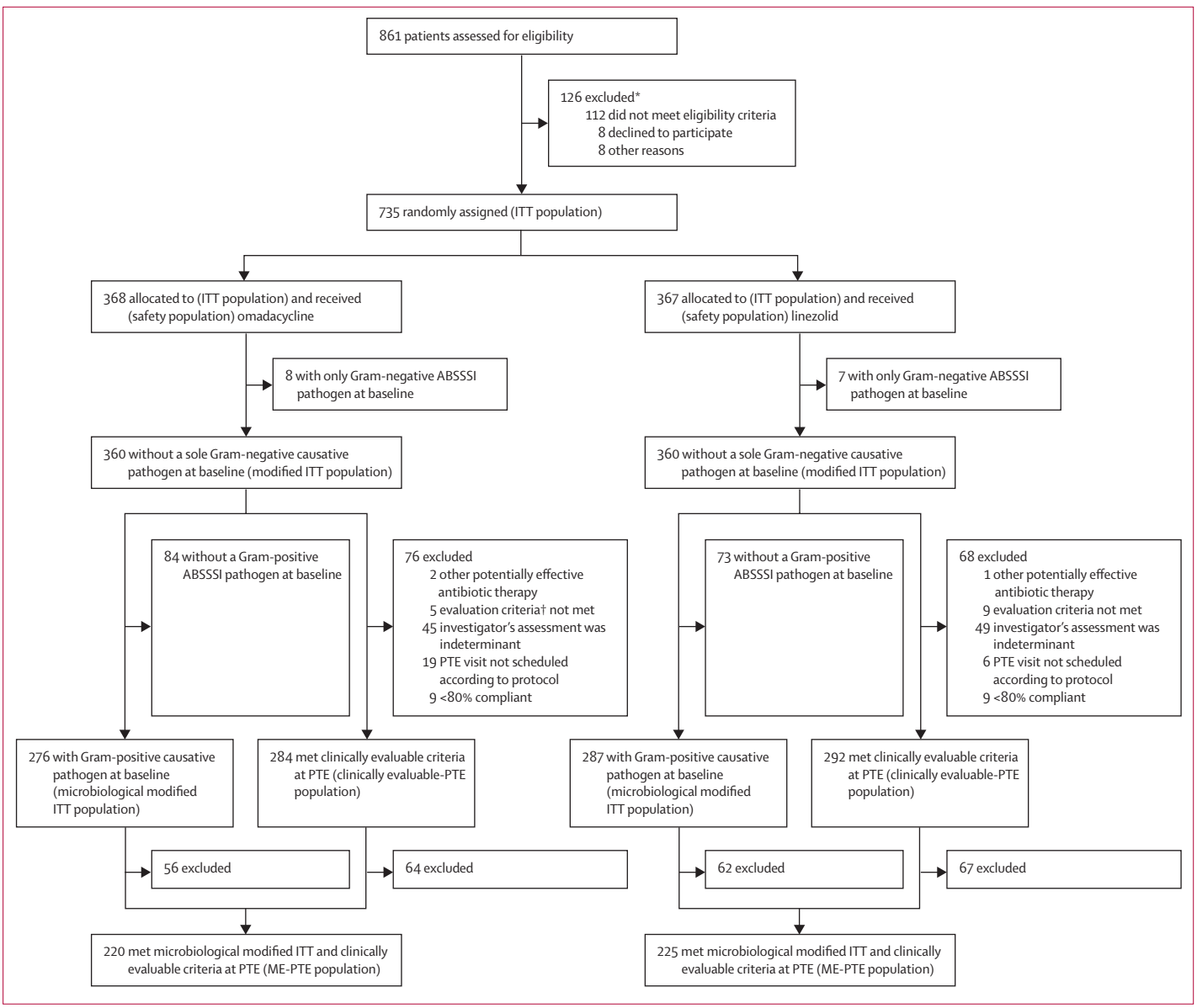

Figure 1: **Trial profile**
*Patients excluded from a population for more than one reason are counted only once in the total number of patients excluded from the population. †Did not receive the minimal number of study drug doses to assess outcome. ABSSSI=acute bacterial skin and skin structure infections. ITT=intention-to-treat. ME=microbiologically evaluable. PTE=post-treatment evaluation.

A subgroup analysis in the mITT population showed that the proportion of patients achieving early clinical response success was similar in patients who were intravenous drug users versus patients who were not intravenous drug users (227 [89%] of 254 *vs* 88 [83%] of 106, respectively, in the omadacycline group; 206 [86%] of 240 *vs* 91 [76%] of 120, respectively, in the linezolid group). Similar results were seen for clinical success at post-treatment evaluation in intravenous drug users versus patients who were not intravenous drug users in the mITT population (209 [82%] of 254 *vs* 94 [89%] of 106, respectively, in the omadacycline group; 192 [80%] of 240 *vs* 99 [83%] of 120, respectively, in the linezolid group).

Similar efficacy between treatment groups was also observed within subgroups based on infection type (figure 2) and lesion size (appendix p 12). Clinical response based on previous antibiotic use, lesion size, and concomitant use of non-steroidal anti-inflammatory drugs, as well as microbiological response rates at end of treatment and post-treatment evaluation in the microbiological mITT and microbiologically evaluable populations, are provided in the appendix (p 12).

	Omadacycline* (n=368)	Linezolid* (N=367)
Age, years	41 (32–53)	46 (33–53)
Sex		
Female	126 (34%)	147 (40%)
Male	242 (66%)	220 (60%)
Race		
White	327 (89%)	341 (93%)
Black or African American	22 (6%)	13 (4%)
Asian	3 (1%)	5 (1%)
American Indian or Alaska Native	7 (2%)	3 (1%)
Other	9 (2%)	5 (1%)
Body-mass index, kg/m²	27 (23–31)	27 (24–31)
Comorbid conditions (≥15% cutoff)		
Intravenous drug use	268 (73%)	258 (70%)
Tobacco use	147 (40%)	146 (40%)
Hepatitis C	116 (32%)	129 (35%)
Anxiety	76 (21%)	78 (21%)
Depression	69 (19%)	62 (17%)
Hypertension	58 (16%)	59 (16%)
Infection type†		
Wound infection	210 (58%)	214 (59%)
Cellulitis or erysipelas	86 (24%)	84 (23%)
Major abscess	64 (18%)	62 (17%)
Lesion area, cm²†	322 (198–495)	294 (190–462)
Lymphadenopathy proximal to primary lesion†	314 (87%)	293 (81%)
Lymphangitis proximal to primary lesion†	67 (19%)	69 (19%)
White blood cells ≥10 000 cells per µL or ≤4000 cells per µL‡	113 (32%)	133 (38%)
Temperature >38°C†	16 (4%)	10 (3%)
Gram-positive aerobes§¶	270 (98%)	278 (97%)
Staphylococcus aureus||	220 (80%)	233 (81%)
MSSA||	120 (44%)	130 (45%)
MRSA||	104 (38%)	107 (37%)
Streptococcus pyogenes	29 (11%)	16 (6%)
Streptococcus anginosis group**	57 (21%)	45 (16%)
Enterococcus faecalis	7 (3%)	10 (4%)
Gram-positive anaerobes§	17 (6%)	17 (6%)
Gram-negative aerobes§††	24 (9%)	30 (11%)
Gram-negative anaerobes§††	11 (4%)	12 (4%)
Monomicrobial Gram-positive infection§	184 (67%)	212 (74%)
Polymicrobial Gram-positive infection§	60 (22%)	37 (13%)
Polymicrobial mixed Gram-positive and Gram-negative infection§	32 (12%)	38 (13%)

Data are median (IQR) or n (%). ABSSSI=acute bacterial skin and skin structure infection. MRSA=meticillin-resistant *S aureus*. MSSA=meticillin-susceptible *S aureus*. *Safety population. †Modified intention-to-treat population; n=360 in each group. ‡Modified intention-to-treat population with a white blood cell measurement at baseline; n=352 in each group. §Patients with more than one isolated pathogen of a specific pathogen type (eg, Gram-positive aerobes) were counted only once in the overall count of that pathogen type. ¶Microbiological modified intention-to-treat population; n=276 in the omadacycline group and n=287 in the linezolid group. ||Patients with both MRSA and MSSA isolates were counted only once in the overall count of *S aureus*. **Includes *S anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*. ††Gram-negative pathogens were part of mixed infections because the presence of monomicrobial or polymicrobial infection with Gram-negative pathogens only at baseline was an exclusion criterion from the modified intention-to-treat analysis.

Table 1: **Baseline characteristics**

In both treatment groups, the median lesion size was reduced from baseline by approximately 60% on day 3 (median lesion sizes on day 3 were 110·0 cm³ [IQR 71·3–202·9] in the omadacycline group and 108·0 cm² [65·5–185·5] in the linezolid group), approximately 88% on day 7 (median lesion sizes on day 7 were 34·1 cm² [19·3–63·0] in the omadacycline group and 34·5 cm² [16·3–60·2] in the linezolid group), and approximately 98% at end of treatment (median lesion sizes at end of treatment were 6·0 cm² [0·0–20·7] in the omadacycline group and 7·0 cm² [0·0–20·0] in the linezolid group; appendix p 10). All local signs of infection present at baseline were absent in 88 (26%) of 336 patients and 90 (28%) of 325 patients with assessments in the omadacycline and linezolid groups, respectively, at end of treatment, and in 215 (68%) of 318 and 215 (68%) of 317 patients in each group, respectively, at post-treatment evaluation. Of patients who did not have complete resolution at post-treatment evaluation, most cases (ie, 93 [92%] of 101 in the omadacycline group, and 83 [81%] of 102 in the linezolid group) were determined to be an investigator-assessed clinical response success at post-treatment evaluation: these cases had mild residual or minimal signs and symptoms of ABSSSI at post-treatment evaluation that did not require further systemic antimicrobial therapy. Three patients (two receiving omadacycline and one receiving linezolid) were admitted to hospital during the study for management of the ABSSSI.

Omadacycline showed similar clinical efficacy to linezolid in patients with infections caused by the most frequent ABSSSI pathogens, including MRSA (table 2). The proportions of patients achieving investigator-assessed clinical response at post-treatment evaluation were also generally similar in omadacycline and linezolid groups among patients with monomicrobial Gram-positive infections (155 [84%] of 184 *vs* 167 [79%] of 212, respectively), polymicrobial Gram-positive infections (49 [82%] of 60 *vs* 26 [70%] of 37, respectively), and polymicrobial mixed (Gram-positive and Gram-negative) infections (25 [78%] of 32 *vs* 31 [82%] of 38, respectively). Early clinical response success among the small subgroup with bacteraemia occurred in one (50%) of two patients on omadacycline and six (75%)of eight patients on linezolid.

At least one treatment-emergent adverse event occurred in 197 (54%) of 368 patients who received omadacycline and 137 (37%) of 367 patients who received linezolid (table 3). Among the ten patients with serious treatment-emergent adverse events (table 3), most were associated with worsening of the underlying ABSSSI or other infection. The only death occurred in the linezolid group (opiate overdose after post-treatment evaluation); this death occurred approximately 2 months after the patient completed the study (ie, not during the 30-day all-cause mortality window). No deaths occurred in the omadacycline group. Premature discontinuation of study drug due to serious treatment-emergent adverse events

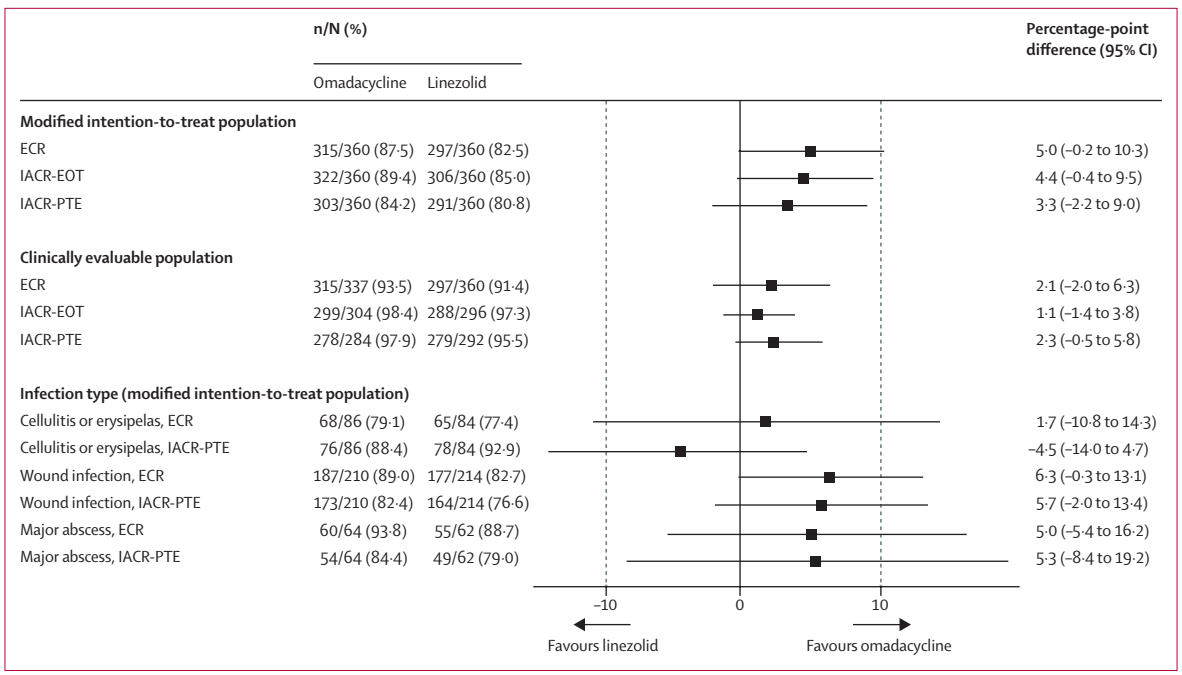

Figure 2: **Forest plot of primary and secondary endpoints**
ECR in the clinically evaluable population, as well as ECR and IACR-PTE in infection type subgroups, were exploratory endpoints. The 95% CI is based on the Miettinen and Nurminen method without stratification,[31] except the analyses for IACR-PTE in the modified intention-to-treat and clinically evaluable populations, which were adjusted for the randomisation stratification factors. ECR=early clinical response. IACR=investigator-assessed clinical response. PTE=post-treatment evaluation. EOT=end of treatment.

occurred in three patients in the omadacycline group and two patients in the linezolid group. All treatment-emergent adverse events and serious treatment-emergent adverse events recorded during the study are provided in the appendix (pp 13–17).

Nausea and vomiting were more frequent with omadacycline than with linezolid (table 3), and generally occurred during the loading-dose phase on days 1 or 2 (appendix p 18). Nausea and vomiting treatment-emergent adverse events were transient, mild to moderate in intensity (appendix pp 13–16), and resulted in study drug discontinuation in only one patient (moderate nausea and vomiting; omadacycline group). Anti-emetic medications were used in 58 (16%) of 368 patients for nausea and 39 (11%) patients for vomiting in the omadacycline group, and in 12 (3%) of 367 patients for nausea and four (1%) patients for vomiting in the linezolid group. Diarrhoea occurred with similar frequency in both groups (table 3), with no reports of *C difficile* infection.

Neither group experienced clinically relevant changes in vital signs or ECG or laboratory parameters (data not shown). In the omadacycline group, abnormal alanine aminotransferase (ALT) values at baseline were more frequent than in the linezolid group (111 [30%] of 368 *vs* 75 [20%] of 367, respectively). Liver chemistry results were similar between groups. Among patients with normal baseline ALT values, the proportion who had maximum post-baseline changes of greater than three times the upper limit of normal was similar in the omadacycline and linezolid treatment groups (three [1%] of 257 *vs* 13 [4%] of 292, respectively). No patient met Hy's law criteria.[35]

	Omadacycline (n=276)	Linezolid (n=287)
*Staphylococcus aureus**	182/220 (83%)	186/233 (80%)
MSSA*	97/120 (81%)	103/130 (79%)
MRSA*	89/104 (86%)	85/107 (79%)
Streptococcus anginosus group†	49/57 (86%)	33/45 (73%)
S anginosus	24/27 (89%)	16/20 (80%)
Streptococcus intermedius	18/23 (78%)	16/24 (67%)
Streptococcus pyogenes	20/29 (69%)	9/16 (56%)
Enterococcus faecalis (VSE)	7/7 (100%)	7/10 (70%)

Data are n/N (%). MRSA=meticillin-resistant *S aureus*. MSSA=meticillin-susceptible *S aureus*. VSE=vancomycin-susceptible enterococci. *Patients with both MRSA and MSSA isolates were counted only once in the overall count of *S aureus*. †Includes *S anginosus*, *S intermedius*, and *Streptococcus constellatus*.

Table 2: **Clinical response at post-treatment evaluation in the microbiological modified intention-to-treat population, by baseline pathogen (occurring in at least ten patients)**

Discussion

In this trial, once-daily oral omadacycline was non-inferior to twice-daily oral linezolid in the treatment of ABSSSI. This non-inferiority result was robust, showing consistency across primary and secondary clinical

	Omadacycline (N=368)	Linezolid (N=367)
Any treatment-emergent adverse event*	197 (54%)	137 (37%)
Treatment-related treatment-emergent adverse event	139 (38%)	52 (14%)
Serious treatment-emergent adverse event†	5 (1%)	5 (1%)
Treatment discontinuation for treatment-emergent adverse events‡	6 (2%)	3 (1%)
Death§	0	1 (<1%)
Treatment-emergent adverse event in >2% in either group		
Nausea¶	111 (30%)	28 (8%)
Vomiting	62 (17%)	11 (3%)
Wound infection	22 (6%)	17 (5%)
Alanine aminotransferase increased	19 (5%)	11 (3%)
Aspartate aminotransferase increased	17 (5%)	12 (3%)
Diarrhoea‖	15 (4%)	10 (3%)
Headache	13 (4%)	8 (2%)
Cellulitis	12 (3%)	9 (3%)
Abdominal pain, upper	10 (3%)	4 (1%)
Subcutaneous abscess	6 (2%)	8 (2%)

Data are number of patients (%). *All treatment-emergent adverse events are presented by maximum severity in the appendix (pp 13–16). †All serious treatment-emergent adverse events are presented in the appendix (p 17). ‡Six patients treated with omadacycline (one each for subcutaneous abscess, staphylococcal bacteraemia, infection [secondary acute bacterial skin and skin structure infection wound], cellulitis [worsening], pregnancy, and one for haematemesis, nausea, and vomiting) and three treated with linezolid (one each for rash, angio-oedema, and wound infection [secondary, worsening]) discontinued study drug because of a treatment-emergent adverse event. §One death occurred in the linezolid group due to an opiate overdose after post-treatment evaluation; this occurred approximately 2 months after the patient completed the study (ie, not during the 30-day all-cause mortality window). ¶Omadacycline 75% mild, 25% moderate; linezolid 86% mild, 14% moderate. ‖No reports of *Clostridioides difficile* infection in either treatment group.

Table 3: **Adverse events (safety population)**

efficacy endpoints specified by both US FDA and EMA guidance, subtypes of ABSSSI (wound infection, cellulitis or erysipelas, and major abscess), lesion sizes, and bacterial pathogens, including MRSA. The efficacy observed in OASIS-2 is similar to that observed in the OASIS-1 study;[27] it confirms the efficacy of the omadacycline oral-only formulation in the treatment of ABSSSI.

Given the similar study designs of OASIS-1 and OASIS-2, the proportions of patients treated with omadacycline achieving early clinical response and clinical success at post-treatment evaluation in the mITT populations in OASIS-1 (85% and 86%, respectively) and OASIS-2 (88% and 84%, respectively) suggest that initial treatment of ABSSSI with either intravenous or oral omadacycline is likely to result in high proportions of clinical success. The high early clinical response, early lesion size reduction, and low number of subsequent hospitalisations in OASIS-2 suggest that omadacycline treatment for ABSSSI can occur in the community without the need for hospitalisation or intravenous antibiotic administration. Unlike other kinds of infections, many patients with skin and skin structure infections are younger than 65 years; thus, outpatient management of ABSSSI can have important consequences for occupational productivity at the workplace and educational achievements in school.[2,3,7,10]

Although both omadacycline and linezolid were generally well tolerated in the present study, the incidence of at least one treatment-emergent adverse event was higher in patients receiving omadacycline than in those receiving linezolid and was primarily attributed to higher frequencies of nausea and vomiting associated with the loading-dose phase on days 1 or 2. Nausea and vomiting were the most common treatment-emergent adverse events and are well described tetracycline and oxazolidinone class effects;[36,37] all episodes were mild to moderate, and only one patient treated with omadacycline discontinued study drug for this reason. The reason for nausea and vomiting during the loading-dose phase of oral omadacycline has not been established, but might be related to local gastrointestinal irritation, given the lower occurrence of nausea and vomiting observed with the intravenous formulation.[27] The proportions of patients with diarrhoea were similar between the omadacycline and linezolid groups, and there were no reported cases of *C difficile* infection.

The strengths of this study include its design, which enabled enrolment of patients with common ABSSSI infection types of substantial lesion size. In addition, we were able to identify a high proportion of the causative pathogens. A limitation was that the study was underpowered to conclude non-inferiority by infection type and in clinically important subgroups (eg, large lesion sizes). Additional limitations include exclusion of certain skin infection types under current regulatory guidance for ABSSSI trials (eg, chronic wound infections) and the study-mandated therapy duration, which limits the ability to inform on the usefulness of shorter therapy durations (eg, <7 days). The majority of patients received 7–10 days of therapy, and given the large lesions observed

in the study, the therapy duration was consistent with the guideline-recommended 7–14 days.[19] This study was done entirely in the USA and included a high percentage of intravenous drug users. Intravenous drug use is a risk factor for ABSSSI, and is commonly seen in the patient populations of contemporary ABSSSI trials.[27,32,38] In addition, the pathogens isolated and the efficacy of the drugs were similar between patients who were intravenous drug users and those who were not, and are similar to pathogens identified in other ABSSSI studies that have global enrolment.[27,32,38,39] Additional real-world data would be beneficial for understanding the utility of omadacycline treatment for ABSSSI in a broader range of patients than presented here, including those with comorbidities that were exclusion criteria.

In conclusion, an oral-only omadacycline regimen was non-inferior to oral linezolid for the treatment of adults with ABSSSI. Omadacycline had a similar safety profile to linezolid. Considering the substantial burdens associated with initial inpatient management of skin infections, oral omadacycline is a new once-daily option to treat ABSSSI that might be considered as an alternative to linezolid.

Contributors

WO'R ran the study at eStudySite; made intellectual input into the protocol, study plan, analysis and Article; reviewed the study results and statistical results; finalised the Article on the basis of comments from other authors; and, as chief medical officer of three research sites that participated in the study, oversaw and supervised the conduct and practice of this study. CC ran the study at eStudySite, was a principal investigator, and reviewed the study results and statistical results. ES was a principal investigator and helped in data collection, data analysis, data interpretation, and draft review. AS made intellectual input into the protocol and study plan, reviewed the study results, and co-wrote the Article. LG-R wrote the protocol; made intellectual input into the protocol, study plan, analysis and Article; reviewed the study results; co-wrote the Article; and finalised the Article on the basis of comments from other authors. AFD designed the statistical plan, supervised the statistical analysis, wrote the statistical section of the protocol, reviewed the study results and statistical results, and reviewed the Article. PBE contributed to writing the protocol; edited the statistical plan, made intellectual input into the protocol, study plan, analysis and Article; reviewed the study results and statistical results, led the interpretation of microbiological results; and edited the Article. AM wrote the protocol; made intellectual input into the protocol, study plan, analysis, and Article; and reviewed the study results. JNS made intellectual input into the protocol, study plan, analysis and Article; reviewed the study results and statistical results; led the microbiological aspects of the study, including interpretation of the results; co-wrote the Article; and finalised the Article on the basis of comments from other authors. ET wrote the protocol; made intellectual input into the protocol, study plan, analysis, and Article; reviewed the study results; and co-wrote the Article. PCM made intellectual input into the study plan, analysis and Article; reviewed the study results; and co-wrote the Article. EL wrote the protocol; made intellectual input into the protocol, study plan, analysis, and Article; reviewed the study results; and co-wrote the Article.

Declaration of interests

WO'R reports being a subinvestigator of OASIS-1; his employer (eStudySite) received funds to do the study; being a subinvestigator on a phase 2 uncomplicated UTI trial; being a Paratek Pharmaceuticals advisory board member; being a subinvestigator for Revive I and Revive II trials, for which he received consultation fees and for which his employer received funding; being a Motif advisory board member, for which he received travel and consultation fees; being a subinvestigator and consultant for Basilea, for which he received consultation fees and his employer received funding; being a subinvestigator and consultant for The Medicines Company, for which he received consultation fees and his employer received funding; being a subinvestigator and consultant for GlaxoSmithKline, for which he received consultation fees and his employer received funding; being a subinvestigator and consultant for Debiopharm, for which he received consultation fees and his employer received funding; being a consultant and subinvestigator for Cellceutix, for which he received consultation fees and his employer received funding. CC reports receiving other funding for work as a principal investigator of OASIS-2 (her employer [eStudySite] received funds to do the study); compensation for work as subinvestigator for Motif, Basilea, GlaxoSmithKline, and Debiopharm. AFD reports personal fees from Paratek Pharmaceuticals during the study; and personal fees from Contrafect, Nabriva, Union Therapeutics, Iterum, Utility Therapeutics, Zavante, Wockhardt, Tetraphase, Cempra, and Achaogen outside the submitted work. PBE reports personal fees from Paratek Pharmaceuticals during the study; and personal fees from Nabriva Therapeutics, Spero Therapeutics, Utility Therapeutics, and InClin outside the submitted work. AM, AS, ET, LG-R, EL, PCM, and JNS are employees and shareholders of Paratek Pharmaceuticals. ES declares no competing interests.

Data sharing

To review the data used in these analyses, please see the appendix and https://clinicaltrials.gov/ct2/show/results/NCT02877927?term=NCT02877927&rank=1&view=results.

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