ORIGINAL ARTICLE

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D., for the SOLO I Investigators*

From Duke University Medical Center, Durham, NC (G.R.C.); Sunrise Hospital and Medical Center, Las Vegas (H.K.); Sharp Chula Vista Medical Center, Chula Vista (P.M., W.O.), and Sharp Grossmont Hospital, San Diego (J.S.O.) — both in California; MV Hospital and Research Center, Lucknow (S. Gupta), and Inamdar Multispecialty Hospital, Pune (A. Porwal) — both in India; Orlando Health, Orlando, FL (P.G.); and South Jersey Infectious Disease, Somers Point (C.L.), and the Medicines Company, Parsippany (A. Perez, S. Good, H.J., G.M.) — both in New Jersey. Address reprint requests to Dr. Corey at Duke University Medical Center, 310 Trent Dr., Box 90519, Durham, NC 27708, or at g.corey@duke.edu.

*A complete list of the investigators in the SOLO I trial is provided in the Supplementary Appendix, available at NEJM.org.

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ABSTRACT

BACKGROUND

Oritavancin is a lipoglycopeptide with bactericidal activity against gram-positive bacteria. Its concentration-dependent activity and prolonged half-life allow for single-dose treatment.

METHODS

We conducted a randomized, double-blind trial in which adults with acute bacterial skin and skin-structure infections received either a single intravenous dose of 1200 mg of oritavancin or a regimen of intravenous vancomycin twice daily for 7 to 10 days. Three efficacy end points were tested for noninferiority. The primary composite end point was defined as cessation of spreading or reduction in lesion size, absence of fever, and no need for administration of a rescue antibiotic 48 to 72 hours after administration of oritavancin. Secondary end points were clinical cure 7 to 14 days after the end of treatment, as determined by a study investigator, and a reduction in lesion size of 20% or more 48 to 72 hours after administration of oritavancin.

RESULTS

The modified intention-to-treat population comprised 475 patients who received oritavancin and 479 patients who received vancomycin. All three efficacy end points met the prespecified noninferiority margin of 10 percentage points for oritavancin versus vancomycin: primary end point, 82.3% versus 78.9% (95% confidence interval [CI] for the difference, –1.6 to 8.4 percentage points); investigator-assessed clinical cure, 79.6% versus 80.0% (95% CI for the difference, –5.5 to 4.7 percentage points); and proportion of patients with a reduction in lesion area of 20% or more, 86.9% versus 82.9% (95% CI for the difference, –0.5 to 8.6 percentage points). Efficacy outcomes measured according to type of pathogen, including methicillin-resistant *Staphylococcus aureus*, were similar in the two treatment groups. The overall frequency of adverse events was also similar, although nausea was more common among those treated with oritavancin.

CONCLUSIONS

A single dose of oritavancin was noninferior to twice-daily vancomycin administered for 7 to 10 days for the treatment of acute bacterial skin and skin-structure infections caused by gram-positive pathogens. (Funded by the Medicines Company; SOLO I ClinicalTrials.gov number, NCT01252719.)

The economic burden of acute bacterial skin and skin-structure infections remains substantial[1] and is driven by the high costs of hospitalization[2,3] and by treatment with agents that require dosing once or twice daily for a duration of 7 to 10 days or more.[2,4-12] Treatment of these infections often requires agents that are active against methicillin-resistant *Staphylococcus aureus* (MRSA), which continues to be an important causative pathogen in many countries.[13,14] Even treatment in an outpatient setting cannot overcome the disadvantage of multiple administrations, incomplete adherence to medication regimens,[15] and the complexity of monitoring therapeutic drug levels.[16]

Oritavancin is a lipoglycopeptide antibiotic with three mechanisms of action[17-19] that result in concentration-dependent bactericidal activity[20] against clinically relevant gram-positive pathogens.[21-23] Oritavancin has a prolonged terminal half-life[24] and is excreted unchanged in both urine and feces. No dose adjustment is required on the basis of age or renal function or for patients with moderate hepatic impairment.[24,25] In two previous phase 3 trials of oritavancin for the treatment of acute bacterial skin and skin-structure infections, in which oritavancin was administered once daily for 3 to 7 days, the data accrued failed to provide substantial evidence of efficacy overall and in the subgroup of patients infected with MRSA. Since the pharmacokinetic–pharmacodynamic profile of oritavancin allows for single-dose treatment,[26,27] the phase 3 study presented here (SOLO I) was designed to evaluate the efficacy and safety of a single dose of oritavancin as compared with a regimen of twice-daily vancomycin for 7 to 10 days in adults with acute bacterial skin and skin-structure infections.

Methods

Study Design

SOLO I was an international, randomized, double-blind study designed to compare the efficacy and safety of a single intravenous dose of oritavancin with intravenous dosing of vancomycin for 7 to 10 days in adults with acute bacterial skin and skin-structure infections (wound infection, cellulitis, or major cutaneous abscess). The study design was consistent with current guidelines[28-30] for eligibility criteria, end points, assessment methods, and noninferiority margins. The protocol was approved by the institutional review board or ethics committee at each participating site, and all patients provided written informed consent. (The protocol is available with the full text of this article at NEJM.org.) The study was conducted from January 2011 through November 2012. Participants underwent randomization in a 1:1 ratio to receive either a single intravenous dose of 1200 mg of oritavancin followed by intravenously administered placebo or an intravenous dose of vancomycin (1 g, or 15 mg per kilogram of body weight) every 12 hours for 7 to 10 days.

Randomization was stratified according to geographic region, study site, and presence or absence of diabetes mellitus. Enrollment of patients with major cutaneous abscesses was capped at 30%.

Clinical evaluations were performed at the following time points: 48 to 72 hours after the initiation of the study treatment (early clinical evaluation), day 7 to day 10 (end of therapy) or, in the case of early discontinuation, the day the patient stopped receiving the study drug or was switched to a nonstudy drug for primary acute bacterial skin and skin-structure infection; 10 days after the initiation of the study drug; and 7 to 14 days after the end-of-therapy visit (post-therapy evaluation). A follow-up period of 60 days was specified for analysis of safety in order to evaluate the potential effect of the prolonged half-life of oritavancin. Safety data were reviewed by an external independent data and safety monitoring committee, once after 120 patients had been treated and again after 250 patients had been treated. (Definitions of the analysis populations are provided in Fig. 1.)

The Medicines Company designed and conducted the study and prepared the statistical analysis plan. Analyses were performed and data interpreted by the Medicines Company in conjunction with the authors. An author who is an employee of the sponsor prepared the first draft of the manuscript. All the authors reviewed and edited the manuscript and made the decision to submit the manuscript for publication. All the authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of study conduct to the protocol.

Eligibility Criteria

Eligible patients were at least 18 years of age and had received a diagnosis of acute bacterial skin and skin-structure infection that was thought or proven to be caused by a gram-positive pathogen

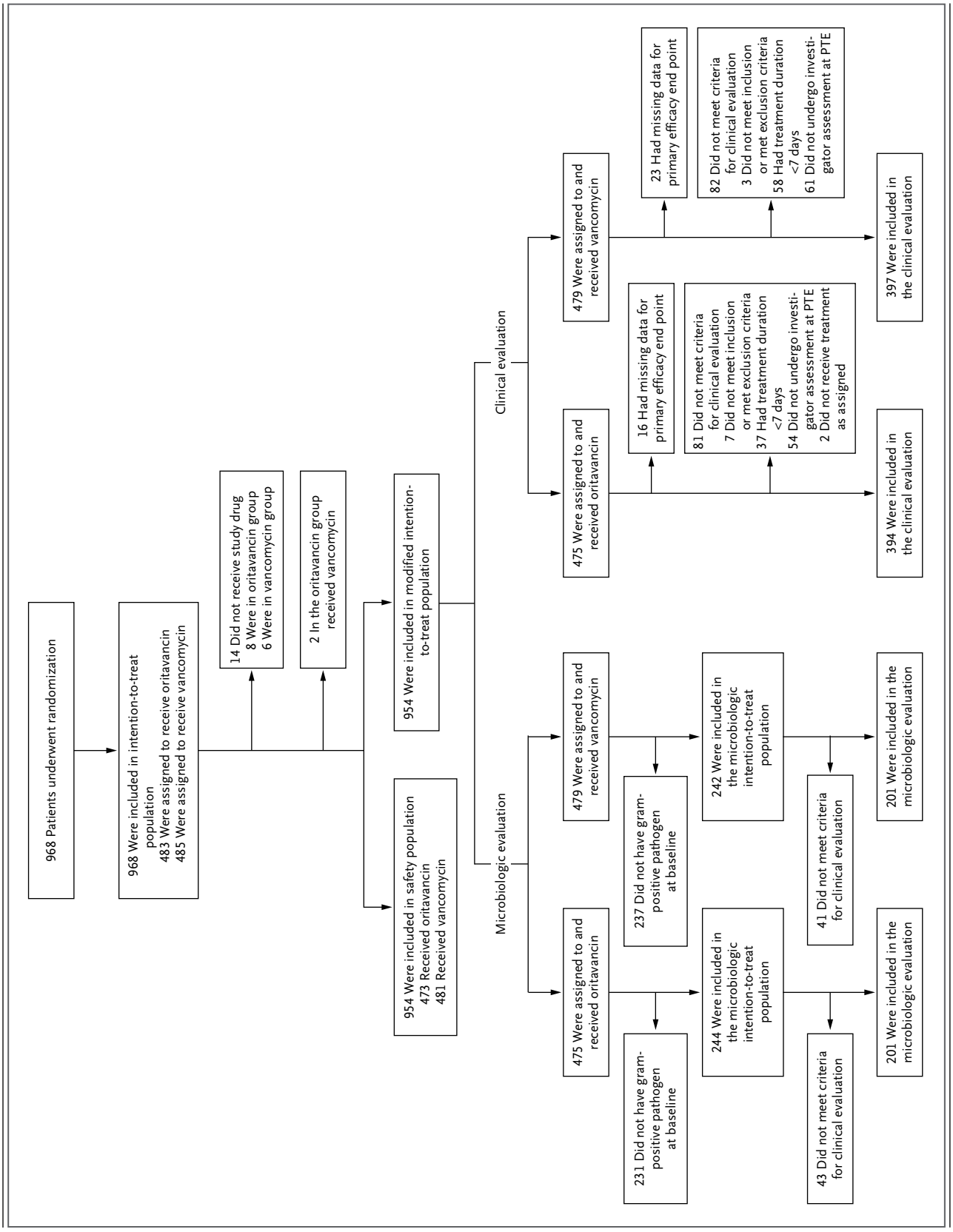

Figure 1 (facing page). Study-Group Assignments and Analysis Populations.

The intention-to-treat population included all patients who underwent randomization. The modified intention-to-treat population was the primary population for all the efficacy analyses and included all patients who underwent randomization and received either oritavancin or vancomycin. The safety population was the primary population for all safety analyses and consisted of all patients who received the assigned study drug. Treatment classification was based on the actual treatment received. The population that underwent clinical evaluation consisted of all patients in the modified intention-to-treat population who met the criteria for study inclusion, received the full-course of study treatment (for a minimum of 7 days), and underwent an assessment for clinical cure at the post-therapy evaluation (PTE) by the site investigator. Analysis of data for this population was used to confirm the efficacy analyses. The population that underwent microbiologic evaluation consisted of all patients in the modified intention-to-treat population in whom a gram-positive pathogen known to cause acute bacterial skin and skin-structure infections was detected at baseline and who could be evaluated clinically. This population was used for secondary efficacy analyses. Two patients who were randomly assigned to receive oritavancin inadvertently received vancomycin. Patients who did not meet the criteria for clinical evaluation may be included in more than one category.

and that required at least 7 days of intravenous therapy. The diagnosis of acute bacterial skin and skin-structure infection required the presence of wound infection (either traumatic or surgical in origin), cellulitis, erysipelas, or a major cutaneous abscess, with each lesion surrounded by erythema, edema, or an induration of at least 75 cm^2. Signs and symptoms of systemic inflammation also had to be present. (Further details regarding the eligibility criteria are available in the Methods section in the Supplementary Appendix, available at NEJM.org.)

EFFICACY ASSESSMENTS

The primary efficacy end point and the end point approved by the Food and Drug Administration was a composite outcome at the time of the early clinical evaluation that comprised the cessation of spreading or a reduction in the size of the baseline lesion, the absence of fever, and the absence of a need for rescue antibiotic medication. The key secondary end point was clinical cure as assessed by a study investigator at the post-therapy evaluation, as required by the European Medicines Agency. Another important secondary efficacy end point was a decrease in lesion area of 20% or more from baseline to the early clinical evaluation. Outcomes were analyzed for the modified intention-to-treat population, all patients who could be evaluated clinically, patients in the intention-to-treat population who could be evaluated microbiologically, and all patients who could be evaluated both clinically and microbiologically (Fig. 1). Further explanation of the efficacy end points, including the definition of treatment failure, can be found in Section 2.3 in the Supplementary Appendix.

SAFETY ASSESSMENTS

Safety was assessed by monitoring vital signs, performing electrocardiography (ECG), measuring serum chemical and hematologic values, and recording adverse events and serious adverse events in the safety population. Adverse events that developed during treatment were defined as events with an onset or worsening severity at the time of or after the administration of the first dose of the study drug through the safety follow-up visit on day 60.

STATISTICAL ANALYSIS

We calculated that a sample of 960 patients (480 per treatment group) would provide at least 90% power to test the noninferiority of oritavancin as compared with vancomycin with respect to the primary efficacy end point; a noninferiority margin of 10 percentage points was used at a one-sided alpha level of 0.025, with an assumed rate of 75% for the primary efficacy outcome in both treatment groups. This sample size would also provide at least 90% power to test noninferiority with respect to clinical cure as assessed by investigators at the post-therapy evaluation, with the use of a noninferiority margin of 10 percentage points at a one-sided alpha level of 0.025 and an assumed rate of 65% for clinical cure in both the oritavancin and vancomycin groups.

For the primary efficacy assessment performed at the early clinical evaluation, the investigator's assessment of clinical cure at the post-therapy evaluation, and the determination of whether there was a decrease in lesion area by 20% or more from baseline to the early clinical evaluation, a two-sided 95% confidence interval for the difference in rates between the two treatment groups was derived with the use of a two-group, large-sample normal approximation test of pro-

portions. If the lower bound of the two-sided 95% confidence interval for the between-group difference (oritavancin vs. vancomycin) was above –10 percentage points, noninferiority of oritavancin was claimed at a one-sided alpha level of 0.025. A hierarchical ordering of statistical testing was used, with the primary efficacy end point at the early clinical evaluation tested first, followed by testing of investigator-assessed clinical cure at the post-therapy evaluation; a decrease in the lesion area of 20% or more from baseline to the early clinical evaluation was tested last.

The noninferiority margin of 10 percentage points for the primary efficacy end point and for the end point of a decrease in lesion area of 20% or more from baseline was based on studies showing that a treatment effect of 18% for sulfonamides as compared with ultraviolet light can be estimated for the main component of the primary efficacy end point — cessation of lesion spread.[28,31,32] This noninferiority margin is justified on the basis of the belief that the control effect of vancomycin is at least as large as that for sulfonamides as compared with ultraviolet light and on the assumption that the control effect on the end point of a decrease in lesion area of 20% or more from baseline in the present study would be similar to the effect on the cessation of lesion spread in the earlier studies. Justification of the noninferiority margin of 10 percentage points for the clinical cure rate was based on analyses conducted by Spellberg et al.[33]

The analysis of the primary and secondary efficacy end points was performed in the modified intention-to-treat population. Patients with missing assessments were considered to have had treatment failure with respect to the primary and secondary efficacy end points. For additional end points, 95% confidence intervals were provided for descriptive purposes only. For safety

Table 1. Demographic and Baseline Clinical Characteristics of the Study Participants (Modified Intention-to-Treat Population).*

Characteristic	Oritavancin (N = 475)	Vancomycin (N = 479)
Age — yr		
Mean	46.2±14.20	44.3±14.50
Median	46.0	45.0
Range	18–89	18–93
Age ≥65 yr — no. (%)	47 (9.9)	38 (7.9)
Male sex — no. (%)	301 (63.4)	301 (62.8)
Race — no. (%)†		
White	274 (57.7)	275 (57.4)
Black	43 (9.1)	40 (8.4)
Asian	153 (32.2)	154 (32.2)
Other	5 (1.1)	10 (2.1)
Body weight — kg		
Mean	81.9±24.44	82.7±26.52
Median	77.2	78.2
Range	35–200	37–220
BMI‡		
Mean	28.7±8.33	28.8±8.67
Median	27.1	26.9
Range	15.2–74.2	13.8–83.8
Value — no. (%)		
<25	162 (34.1)	175 (36.5)
25 to <30	158 (33.3)	138 (28.8)
≥30	155 (32.6)	166 (34.7)

Table 1. (Continued.)

Characteristic	Oritavancin (N=475)	Vancomycin (N=479)
Infection type		
Wound — no. (%)	92 (19.4)	105 (21.9)
Wound with MRSA infection confirmed — no./total no. (%)	23/104 (22.1)	20/100 (20.0)
Cellulitis— no. (%)	243 (51.2)	233 (48.6)
Cellulitis with MRSA infection confirmed — no./total no. (%)	20/104 (19.2)	23/100 (23.0)
Abscess — no. (%)	140 (29.5)	141 (29.4)
Abscess with MRSA infection confirmed — no./total no. (%)	61/104 (58.7)	57/100 (57.0)
Diabetes mellitus — no. (%)	93 (19.6)	95 (19.8)
Temperature ≥38.0°C — no./total no. (%)	68/474 (14.3)	79/478 (16.5)
White-cell count >12,000 per mm^3 — no./total no. (%)	104/434 (24.0)	85/430 (19.8)
Lesion area — cm^2		
Median	248.0	225.6
Range	47–3249	75–3417
Lesion area ≥75 cm^2 — no./total no. (%)	473/475 (99.6)	478/478 (100.0)
Receipt of permitted medications — no. (%)		
Aztreonam	52 (10.9)	47 (9.8)
Metronidazole	15 (3.2)	17 (3.5)
Positive infection-site culture — no./total no. (%)	290/475 (61.1)	290/479 (60.5)
Any gram-positive pathogen	279/290 (96.2)	277/290 (95.5)
S. aureus	218/279 (78.1)	210/277 (75.8)
Positive blood culture — no. (%)	18 (3.8)	9 (1.9)
S. aureus	9	0
Positive infection-site and blood cultures for MRSA	104	100

* Plus–minus values are means ±SD. There were no significant between-group differences except for age (P=0.04, calculated with the use of the Kruskal–Wallis test) and a positive blood culture for *Staphylococcus aureus* (P=0.002, calculated with the use of Fisher's exact test). Percentages may not add up to 100 because of rounding. MRSA denotes methicillin-resistant *S. aureus*.
† Race was self-reported.
‡ BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters).

assessments, descriptive analyses were performed in the safety population for all safety variables according to treatment group. Methods of microbiologic assessment are outlined in the Methods section of the Supplementary Appendix.

RESULTS

STUDY POPULATION

Figure 1 shows the numbers of patients who were screened, randomly assigned to a treatment group, and included in the primary analysis. In the modified intention-to-treat population, the oritavancin and vancomycin groups had similar demographic and clinical characteristics (Table 1). The mean age of the patients was 45 years, and 8.9% were at least 65 years of age. The patients were predominantly white and male. Infection types were balanced in the oritavancin and vancomycin groups, with approximately 50% of patients having cellulitis, 30% having abscess, and 20% having wound infection. The median size of the infection area at baseline was 248.0 cm^2 in the oritavancin group and 225.6 cm^2 in the vancomycin group. A pathogen was isolated from approximately 60% of patients in both treatment

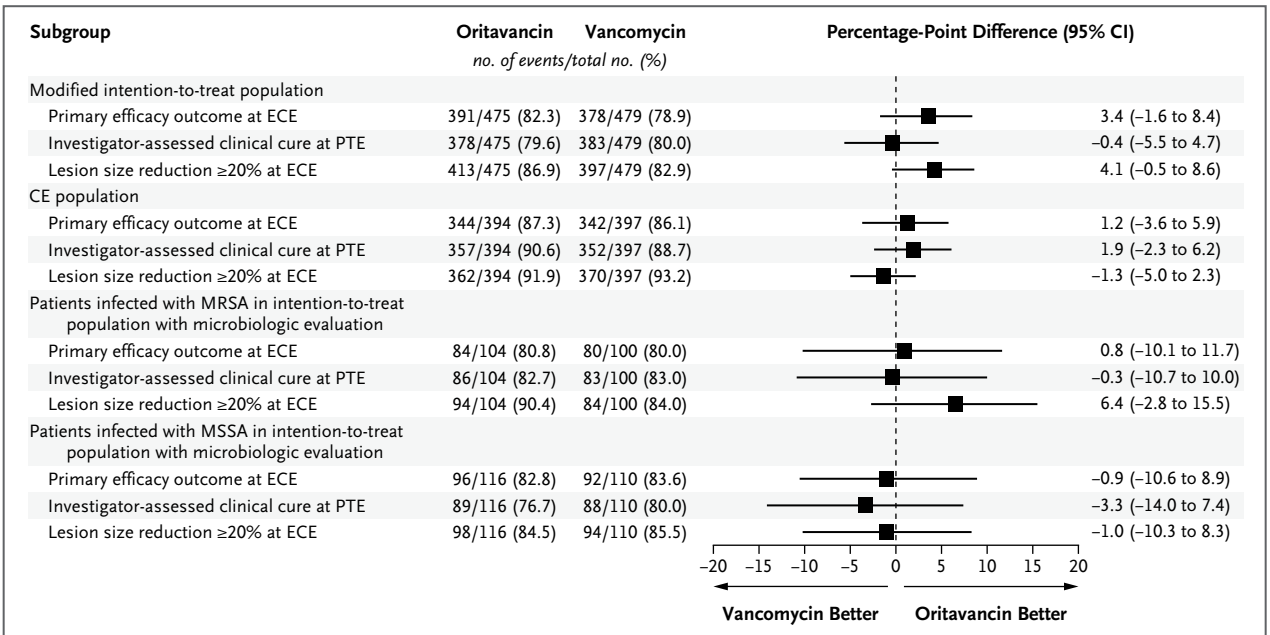

Figure 2. Primary and Secondary Efficacy End Points According to Analysis Population and MRSA Subgroup.

CE denotes clinical evaluation, ECE early clinical evaluation, MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-susceptible *S. aureus*, and PTE post-therapy evaluation.

groups at baseline; 96% of these patients had a gram-positive pathogen known to cause acute bacterial skin and skin-structure infections. *S. aureus* was the most common pathogen, and MRSA was recovered in 204 patients.

CLINICAL OUTCOMES

The efficacy of a single 1200-mg intravenous dose of oritavancin was similar to that of vancomycin administered twice daily for 7 to 10 days, at both the early clinical evaluation and the post-therapy evaluation. The primary composite end point at the early clinical evaluation (82.3% with oritavancin and 78.9% with vancomycin), the end point of clinical cure at post-therapy evaluation as assessed by a study investigator (79.6% and 80.0%, respectively), and the end point of a reduction in lesion size of 20% or more at early clinical evaluation (86.9% and 82.9%, respectively) met the prespecified noninferiority margin, since the lower limit of the 95% confidence interval for the between-group difference (oritavancin vs. vancomycin) was above –10 percentage points (Fig. 2).

The efficacy rates for oritavancin and vancomycin with respect to the primary end point (early clinical evaluation) were similar when analyzed according to body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), presence or absence of diabetes, age, presence or absence of MRSA infection, sex, race, or lesion type (Fig. S1 in the Supplementary Appendix). On the basis of the results of pharmacokinetic analyses, demographic characteristics, including age, race, and sex, had no significant effect on the pharmacokinetic activity of oritavancin. Approximately 34% of patients had a BMI of more than 30, and there were no significant differences between these patients and those with a BMI of 30 or lower with regard to the primary efficacy end point in the oritavancin and vancomycin treatment groups at the early clinical evaluation or with regard to a reduction in lesion size of more than 20% or to investigator-assessed clinical cure at the post-therapy evaluation.

The number of patients in whom there was treatment failure and the reasons for failure at both the early clinical evaluation and the post-therapy evaluation were balanced between the two treatment groups (Tables S2 and S3 in the Supplementary Appendix). Overall, 11.6% of patients in the oritavancin group (55 of 475) and 12.7% of patients in the vancomycin group (61 of 479) were classified as having treatment failure

Table 2. Primary Efficacy Outcome at Early Clinical Evaluation According to Pathogen Detected at Baseline (Intention-to-Treat Population Who Could Be Evaluated Microbiologically).*

Pathogen	Oritavancin (N=244)	Vancomycin (N=242)	Difference (95% CI)†
	no./total no. (%)		*percentage points*
Detection of at least one pathogen	201/244 (82.4)	196/242 (81.0)	1.4 (–5.5 to 8.3)
Staphylococcus aureus	180/220 (81.8)	172/210 (81.9)	–0.1 (–7.4 to 7.2)
MRSA	84/104 (80.8)	80/100 (80.0)	0.8 (–10.1 to 11.7)
MSSA	96/116 (82.8)	92/110 (83.6)	–0.9 (–10.6 to 8.9)
Streptococcus species	25/31 (80.6)	31/38 (81.6)	–0.9 (–19.5 to 17.6)
S. anginosus group‡	12/13 (92.3)	14/16 (87.5)	
S. agalactiae	6/7 (85.7)	8/8 (100.0)	
S. pyogenes	5/8 (62.5)	5/10 (50.0)	
S. dysgalactiae	2/3 (66.7)	3/3 (100.0)	
Enterococcus faecalis	6/7 (85.7)	4/5 (80.0)	

* The pathogens listed are gram-positive pathogens known to cause acute bacterial skin and skin-structure infections, whether isolated from an infection site-culture or a blood culture. The pathogens listed include only those detected in both treatment groups. Patients with multiple pathogens were counted once in the rows for each pathogen. MSSA denotes methicillin-susceptible *S. aureus*.

† Differences and 95% confidence intervals are shown only for speciated pathogens identified from 10 or more patients in each treatment group.

‡ This group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*.

because of missing data for the end point of investigator-assessed clinical cure. For the majority of these patients (98.3%), treatment was considered to be a failure because the patients did not undergo the post-therapy evaluation. Results in the modified intention-to-treat population were consistent with those in the population of patients who could be evaluated clinically (Fig. 1, and Table S4 in the Supplementary Appendix). Results of sensitivity analyses in which different methods were used to handle missing data are presented in Table S5 in the Supplementary Appendix.

In the subpopulation of patients with MRSA infection, similar efficacy was observed in the two treatment groups for the primary and secondary end points (Fig. 2). These efficacy results for patients infected with MRSA were consistent with those in the population of patients who could be evaluated microbiologically (Table S6 in the Supplementary Appendix).

Results for the primary end point according to the infecting pathogen at baseline are presented in Table 2. The efficacy of oritavancin against these isolates was similar to that of vancomycin.

The mean (±SD) total daily vancomycin dose in the safety population was 2.3±0.94 g, and the mean duration of vancomycin therapy was 8.1±2.43 days. The mean vancomycin level in patients with a measurable trough level (before administration of the fourth dose) was 15.4 μg per milliliter, and the median level 11.1 μg per milliliter.

SAFETY AND SIDE-EFFECT PROFILE

The incidence of adverse events that developed during treatment, regardless of the relationship of the event to the study drug, was similar in the oritavancin and vancomycin groups (Table 3), and most of the events were mild. The most frequently reported adverse events in the oritavancin group were nausea (11.0%, vs. 8.9% in the vancomycin group), headache (7.2% vs. 7.9%), vomiting (4.9% vs. 3.7%), and diarrhea (4.9% vs. 3.5%) (Table 3). The proportion of patients with an adverse event that led to discontinuation of the study drug was lower in the oritavancin group. The incidence of abnormalities on tests of liver function was 2.3% in the oritavancin group and 1.0% in the vancomycin group. No symptomatic adverse events related to liver function were reported, there were no reports of serious elevations in levels of metabolites related to liver func-

Table 3. Patients with Adverse Events (Safety Population).*

Adverse Event	Oritavancin (N=473)	Vancomycin (N=481)
	no. of patients (%)	
At least 1 adverse event that developed during treatment	284 (60.0)	307 (63.8)
Related to study drug	108 (22.8)	151 (31.4)
Leading to discontinuation of study drug	18 (3.8)	28 (5.8)
Serious adverse event†	35 (7.4)	35 (7.3)
Related to study drug	3 (0.6)	3 (0.6)
Leading to discontinuation of study drug	11 (2.3)	13 (2.7)
Death	1 (0.2)	2 (0.4)
Most frequently reported adverse events‡		
Nausea	52 (11.0)	43 (8.9)
Headache	34 (7.2)	38 (7.9)
Pruritus	16 (3.4)	44 (9.1)
Infusion-site reaction	19 (4.0)	34 (7.1)
Infusion-site extravasation	18 (3.8)	23 (4.8)
Vomiting	23 (4.9)	18 (3.7)
Constipation	19 (4.0)	21 (4.4)
Diarrhea	23 (4.9)	17 (3.5)
Cellulitis	20 (4.2)	17 (3.5)
Pyrexia	15 (3.2)	20 (4.2)
Dizziness	15 (3.2)	15 (3.1)
Insomnia	14 (3.0)	13 (2.7)
Chills	10 (2.1)	12 (2.5)
Urticaria	7 (1.5)	15 (3.1)
Pruritus, generalized	11 (2.3)	9 (1.9)
Subcutaneous abscess	9 (1.9)	11 (2.3)
Abscess on limb	13 (2.7)	5 (1.0)
Infusion-site phlebitis	8 (1.7)	10 (2.1)
Alanine aminotransferase elevation	11 (2.3)	5 (1.0)
Fatigue	10 (2.1)	6 (1.2)

* A study investigator determined whether there was a causal relationship between an adverse event and the study drug.
† All serious adverse events are listed, not only those that developed during treatment.
‡ Listed are the adverse events that occurred in more than 2% of the patients in either study group during treatment.

tion, and none of the patients discontinued the study drug as a result of these adverse events. There was no case in which a patient's hepatic profile met the criteria of Hy's law (a serum alanine or aspartate aminotransferase level that is more than three times the upper limit of the normal range and a serum total bilirubin level that is more than two times the upper limit of the normal range in the absence of initial findings of cholestasis, with no other explanation for the combination of elevated aminotransferase and total bilirubin levels).[34,35] In the oritavancin group, the only adverse event that developed during treatment and led to discontinuation in more than one patient was cellulitis (in two patients). In the vancomycin group, adverse events that developed during treatment and led to discontinuation of the study drug were hypersensitivity (in five patients), cellulitis (in three patients), and sepsis, bacterial skin infection, drug hypersensitivity, pruritus, and rash (in two patients for each condition).

The frequency of serious adverse events was similar in the two groups (7.4% with oritavancin and 7.3% with vancomycin), as was the distribution of serious adverse events (Table 3, and Table S13 in the Supplementary Appendix). Three patients died during the study: in the oritavancin group, one patient died from sepsis and septic shock, and in the vancomycin group, one patient died from sepsis and one from advanced dementia with parkinsonism.

The incidence of laboratory abnormalities was balanced between the treatment groups. No significant between-group difference in vital signs or ECG findings was identified.

DISCUSSION

Currently available therapeutic options for the treatment of acute bacterial skin and skin-structure infections require repeat administrations that may result in extended hospitalization and can result in substantial costs to the health care system. A single-dose treatment for acute bacterial skin and skin-structure infections that results in an early and sustained clinical response could have the potential to reduce the complications associated with multiple intravenous administrations in patients with these infections, improve adherence to treatment, improve quality of life, and reduce the utilization of health care resources.[16]

In this phase 3 study (SOLO I) involving adults with acute bacterial skin and skin-structure infections, treatment with a single dose of oritavancin met the primary and secondary efficacy end points and had an adverse-event pro-

file that was similar to that of the active comparator, vancomycin, which was administered twice daily for 7 to 10 days. Oritavancin was noninferior to vancomycin on the basis of both the early clinical evaluation of efficacy (reduction in lesion size, assessed 48 to 72 hours after the initiation of treatment) and the post-therapy evaluation of efficacy (clinical cure, assessed by the site investigator 7 to 14 days after the end of treatment). These early and late assessments of efficacy were concordant (Table S11 in the Supplementary Appendix). In addition, oritavancin showed efficacy against infection with *S. aureus*, and MRSA in particular, irrespective of the end point and the analysis population.

Treatment-failure rates were balanced between the two groups, and the reasons for failure were similar in the groups. The main reason for failure at the post-therapy evaluation was missing data, and this problem was largely due to a missed follow-up visit. The results of sensitivity analyses (performed in the modified intention-to-treat population and in the population of patients who could be evaluated clinically) in which missing data were either excluded or imputed as indicating successful treatment were consistent with the results of the primary analyses, for both the early clinical evaluation and the post-therapy evaluation.

The frequency, distribution, and severity of adverse events that emerged during treatment were similar in the oritavancin and vancomycin groups. Discontinuation of the study treatment because of such events were uncommon. In addition, no clinically significant between-group differences in clinical laboratory values were observed. The prolonged half-life of oritavancin[24] was not associated with any untoward safety issues during the study, which included a follow-up assessment on day 60.

The severity of the baseline infection was underscored both by the need for at least 7 days of intravenous therapy, as determined by the site investigator, and the median lesion area, including surrounding erythema, edema, and induration of approximately 235 cm^2. The fact that approximately 20% of the patients in the study had diabetes mellitus also attests to the complicated nature of the baseline infections.

The oritavancin regimen, in which 1200 mg is administered in a single dose, may ensure adherence to treatment, reduce or eliminate hospital stays, and reduce the utilization of health care resources.[16] The results presented here, which show the efficacy of a single dose of oritavancin without obvious consequences for safety, as compared with 7 to 10 days of treatment with intravenous vancomycin, should provide an impetus to determine the costs of outpatient care for patients with acute bacterial skin and skin-structure infections.

There are several limitations of the SOLO I study. Whereas the extended half-life of oritavancin provides the physician with a single infusion option for treatment, it also raises concern about extended illness, should a serious reaction to this antibiotic occur. The evidence to date suggests that oritavancin has a safety profile that is similar to the profile for vancomycin, and the 60-day follow-up assessment in our study, involving nearly 500 patients treated with oritavancin, did not identify any such prolonged adverse events; however, experience with this treatment is limited. Similarly, the inability to "step down" to a beta-lactam antibiotic once the possibility of MRSA infection has been ruled out has the potential to result in increased microbial resistance. Further evaluation of this possibility will be important. Whether patients treated with a single infusion can be discharged and followed on an outpatient basis remains to be determined. Several questions must be answered; for example, is there a risk that outpatient follow-up will delay the diagnosis of serious, deep infections such as necrotizing fasciitis and bacteremia? Serious infections such as bacteremia, which were once considered manageable only in a hospital setting, have since shown the potential to be effectively managed on an outpatient basis once the patient's condition has stabilized.[36] Also, studies are needed to determine whether treatment with oritavancin is effective for other infections, such as bacteremia, osteomyelitis, and prosthetic-joint infections.

In conclusion, treatment with a single dose of oritavancin was noninferior to 7 to 10 days of vancomycin in adults with acute bacterial skin and skin-structure infections caused by gram-positive pathogens, including MRSA. No significant differences in safety between the two treatment regimens were observed.

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