The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 5, 2014 VOL. 370 NO. 23

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.

ABSTRACT

BACKGROUND

Dalbavancin, a lipoglycopeptide antibiotic agent that is active against gram-positive pathogens, has a long plasma half-life, allowing for once-weekly dosing. DISCOVER 1 and DISCOVER 2 were identically designed noninferiority trials of dalbavancin for the treatment of acute bacterial skin and skin-structure infection.

METHODS

We randomly assigned patients to receive dalbavancin intravenously on days 1 and 8 or vancomycin intravenously for at least 3 days with the option to switch to oral linezolid to complete 10 to 14 days of therapy. The primary end point, early clinical response, required the cessation of spread of infection-related erythema and the absence of fever at 48 to 72 hours. Secondary end points at the end of therapy included clinical status and investigator's assessment of outcome.

RESULTS

Analysis of the primary end point showed noninferiority of dalbavancin in both DISCOVER 1 and DISCOVER 2. In the pooled analysis, 525 of 659 patients (79.7%) in the dalbavancin group and 521 of 653 (79.8%) in the vancomycin–linezolid group had an early clinical response indicating treatment success (weighted difference, −0.1 percentage point; 95% confidence interval, −4.5 to 4.2). The outcomes were similar in the analyses by study and the pooled analyses of clinical status at the end of therapy and the investigator's assessment of outcome. For patients infected with *Staphylococcus aureus*, including methicillin-resistant *S. aureus*, clinical success was seen in 90.6% of the patients treated with dalbavancin and 93.8% of those treated with vancomycin–linezolid. Adverse events and study days with an adverse event were less frequent in the dalbavancin group than in the vancomycin–linezolid group. The most common treatment-related adverse events in either group were nausea, diarrhea, and pruritus.

CONCLUSIONS

Once-weekly intravenous dalbavancin was not inferior to twice-daily intravenous vancomycin followed by oral linezolid for the treatment of acute bacterial skin and skin-structure infection. (Funded by Durata Therapeutics; DISCOVER 1 and DISCOVER 2 ClinicalTrials.gov numbers, NCT01339091 and NCT01431339.)

From the Division of Infectious Diseases and Geographic Medicine, Tufts Medical Center and Tufts University School of Medicine, Boston (H.W.B.); the Department of Microbiology, Leeds Teaching Hospital and University of Leeds, Old Medical School, Leeds, United Kingdom (M.W.); Talbot Advisors, Anna Maria, FL (G.H.T.); Durata Therapeutics, Branford, CT (S.P., M.W.D.); and InClin, San Mateo, CA (A.F.D.). Address reprint requests to Dr. Boucher at Tufts Medical Center, 800 Washington St., Box 238, Boston, MA 02111, or at hboucher@tuftsmedicalcenter.org.

N Engl J Med 2014;370:2169-79.
DOI: 10.1056/NEJMoa1310480

Acute bacterial skin and skin-structure infections are among the most common reasons for the hospitalization of adults in the United States today.[1] These infections are caused most often by *Staphylococcus aureus* and streptococci.[2] Methicillin-resistant *S. aureus* (MRSA) accounts for many of these infections and presents a particular treatment challenge because current therapies are limited by toxicity, resistance, or the lack of an oral formulation.[3] Associated medical costs are substantial.[4]

Dalbavancin (Durata Therapeutics) is a lipoglycopeptide antibiotic agent with in vitro and in vivo activity against gram-positive pathogens, including a minimal inhibitory concentration (MIC) required to inhibit the growth of 90% of the isolates (MIC_{90}) for *S. aureus* of 0.06 μg per milliliter. Dalbavancin has a terminal half-life of 2 weeks, related in part to 93% protein binding, and is more efficacious in animal models when administered as larger, less frequent doses, as compared with smaller, more frequent doses. Phase 1 trials of once-weekly dosing showed mean total and calculated free plasma concentrations that were above the *S. aureus* bactericidal concentration for 7 to 14 days.[5-7] Efficacy was shown in a "registrational" development program (i.e., one designed and conducted to support regulatory review and approval for marketing) that included four trials involving 1086 patients with skin infection.[5,8,9]

The role of antibiotic treatment, in addition to incision and drainage, in the treatment of small cutaneous abscesses is an unresolved question that is under active investigation. Assessment of the antibiotic effect in the treatment of large abscesses and cellulitis has been challenging, given the need for placebo-controlled data on which to base a noninferiority margin for registrational clinical trials. Recent guidance from the Food and Drug Administration (FDA) requires that the area of the skin infection be larger than historical standards and that abscesses be of substantial size and complexity.[10] Central to this updated guidance was a focus on identifying a quantifiable, reproducible efficacy end point that showed sensitivity to drug effect, thereby providing justification for a noninferiority margin.[10] Historical studies by Snodgrass and Anderson comparing antibiotic treatment with the standard of care were cited by the FDA as a demonstration of a treatment effect over placebo with the use of both absence of fever and stabilization in the size of the infected area during therapy as end points.[11,12]

On the basis of the treatment effect of 19 to 27% that was observed in these studies for the cessation of lesion spread and for fever resolution, a noninferiority margin of 10 percentage points for the primary efficacy outcome was deemed appropriate. The trials discussed here were designed to test the efficacy of dalbavancin with the use of this new primary end point and to assess its association with the historical standard of investigator-assessed response to treatment. Both the primary and secondary end points conform to the FDA guidance and were agreed on with the FDA as part of a Special Protocol Assessment.

METHODS

TRIAL DESIGN

DISCOVER 1 and DISCOVER 2 were double-blind, double-dummy, international, multicenter, randomized trials conducted from 2011 through 2012 at 54 and 86 investigative sites, respectively. The institutional review board or ethics committee at each study site approved the protocols, available with the full text of this article at NEJM.org. All the patients provided written informed consent before participation. The identical design of the two trials allowed pooling of the data to enhance information regarding adverse events and efficacy variables of interest.

The diagnosis of acute bacterial skin and skin-structure infection required the presence of cellulitis, a major abscess, or a wound infection, each associated with at least 75 cm^2 of erythema. Eligible patients were adults who were thought to require at least 3 days of intravenous therapy who had one or more systemic signs of infection within 24 hours before randomization, including an elevated body temperature (>38°C), a white-cell count of more than 12,000 cells per cubic millimeter, or more than 10% band forms on the white-cell differential count. In addition to erythema, at least two of the following local signs were required: purulent drainage or discharge, fluctuance, heat or localized warmth, tenderness on palpation, and swelling or induration. Patients who had received antibiotic treatment within 14 days before randomization were excluded.

The studies were designed by all the authors and conducted according to the respective study protocols by the sponsor (Durata Therapeutics) in collaboration with the investigators. The sponsor collected the data, monitored the study conduct, and performed the statistical analyses. All the

authors had access to the data, assume responsibility for the integrity and completeness of the reported data and analyses, and vouch for the fidelity of this report to the study protocols. The first draft of the manuscript was prepared by the first author, with input from all the authors. All the authors participated in revisions to the manuscript.

RANDOMIZATION, TREATMENT, AND MONITORING

Patients were assigned by means of a telephone randomization system to a treatment group in a 1:1 ratio, with a block size of four. Randomization was stratified according to infection type and presence or absence of fever such that no more than 30% of the enrolled patients had a major abscess and at least 25% had fever.

Patients received either dalbavancin at a dose of 1 g given intravenously over a period of 30 minutes on day 1, followed by 500 mg given intravenously over a period of 30 minutes on day 8, or vancomycin at a dose of 1 g (or 15 mg per kilogram of body weight) given intravenously over a period of 120 minutes every 12 hours for at least 3 days, with an option to switch to oral linezolid, at a dose of 600 mg every 12 hours, to complete 10 to 14 days of therapy. The decision to use vancomycin at a fixed dose rather than at a weight-based dose was made by clinicians at the individual study sites on the basis of their local standard of care. The comparator regimen was selected because of its efficacy and routine use in clinical practice.[13]

The vancomycin dose could be adjusted, according to the local standard of care, by a pharmacist who was aware of the study-drug assignment. The protocol recommended adjusting the dose of either vancomycin or dalbavancin according to the ideal body weight for patients with renal insufficiency. Patients in the dalbavancin group received a placebo infusion every 12 hours, plus an oral placebo if there was a switch to oral therapy. Study-drug treatment was continued for 10 to 14 days in each group. Patients could receive inpatient treatment, outpatient treatment, or both, according to the investigator's judgment and appropriate logistic arrangements at the study site.

ASSESSMENTS

End Points

The primary end point was measured at 48 to 72 hours of therapy. A successful outcome (i.e., early clinical response indicating treatment success) was defined as both cessation of spread of the erythema associated with the infection (i.e., no increase in the surface area as compared with baseline) and a temperature of 37.6°C or lower at three consecutive readings performed 6 hours apart. Treatment success or failure was determined on the basis of the above criteria after the treatment was completed and therefore did not influence treatment decisions by the investigator during the trial. Patients with missing data for surface area of infection or temperature (i.e., those for whom treatment success could not be determined) were considered to have treatment failure in the primary intention-to-treat analysis. Secondary end points (including clinical status at the end of therapy, determined programmatically, and clinical response at the end of therapy, as assessed by the investigator), criteria for treatment failure, and planned sensitivity analyses are described in the Methods section in the Supplementary Appendix, available at NEJM.org.

Safety

Adverse events and serious adverse events were recorded throughout the study period. Adverse events emerging during treatment were those with an onset or worsening severity at or after administration of the first dose of the study drug through the long-term follow-up visit (day 70). Additional features of the study design are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size for each study was calculated with the use of the Farrington–Manning method. Assuming a point estimate for early clinical response of 85% in each treatment group, a one-sided alpha level of 0.025, and a noninferiority margin of 10 percentage points, we calculated that a total sample of 556 patients would be required in order to provide the study with 90% power.

The primary analysis of the early end point was based on the intention-to-treat population, which consisted of all the patients who underwent randomization. All the patients in the intention-to-treat population who received at least one dose of a study drug constituted the safety population. The patients in the clinical per-protocol population met all the inclusion criteria and none of the exclusion criteria, received the correct study drug, and met minimum dosing requirements. The patients in the microbiologic per-protocol popula-

tion were the subset of patients in the clinical per-protocol population who had at least one gram-positive pathogen isolated at baseline.

For each study, the 95% confidence interval for the difference in success rates (dalbavancin minus vancomycin–linezolid), with adjustment for the stratification factor at randomization of the presence or absence of fever at baseline, was computed with the use of the method of Miettinen and Nurminen.[14] For the pooled analysis, the weighted difference in success rates was calculated, and the 95% confidence interval, adjusted for study, was computed with the use of the same method. The analysis of clinical status at the end of therapy in the clinical per-protocol population included an adjustment in the confidence interval for both the presence or absence of fever and infection type. A determination of noninferiority for the primary end point required that the lower limit of the 95% confidence interval be greater than –10 percentage points; the 95% confidence intervals for the other assessments are provided for descriptive purposes. No adjustments were made for multiple comparisons.

For adverse events, post hoc exploratory analyses of differences between the treatment groups were conducted with the use of the Cochran–Mantel–Haenszel test, with adjustment for study, or with the use of a Poisson regression for the total number of adverse events. Two-sided P values are reported as descriptive statistics. Additional statistical methods are described in the Supplementary Appendix.

RESULTS

PATIENTS

Of the 1312 patients who underwent randomization, 9 did not receive the study drug, so 1303 patients were included in the safety population: 652 patients in the dalbavancin group and 651 in the vancomycin–linezolid group (Fig. 1). The clinical per-protocol population included 570 patients in the dalbavancin group and 545 in the vancomycin–linezolid group.

The treatment groups were well balanced according to age, sex, and race (Table 1, and Table S1 in the Supplementary Appendix). Approximately 15% of the patients had a history of recent or current intravenous drug use, and 13% had diabetes mellitus. Major abscess was slightly more frequent in DISCOVER 1, as was cellulitis in DISCOVER 2.

More than 85% of the patients had a baseline temperature of more than 38°C; the median size of the infected area was 351 cm² in DISCOVER 1 and 336 cm² in DISCOVER 2, well above the protocol-mandated minimum size of 75 cm². The criteria for the systemic inflammatory response syndrome were met in 62% of the patients in DISCOVER 1 and 43% of those in DISCOVER 2.

A total of 608 of 659 patients (92.3%) in the dalbavancin group and 601 of 653 (92.0%) in the vancomycin–linezolid group completed the study treatment. Patients receiving dalbavancin were more likely than those receiving vancomycin–linezolid to have a shorter duration of blinded treatment. Fewer patients in the dalbavancin group received 14 days of therapy, as compared with those in the vancomycin–linezolid group (31.0% vs. 38.4%, P=0.008), with more patients in the dalbavancin group receiving 10 days of therapy (20.8% vs. 15.3%, P=0.01). Approximately 25% of the patients received all their treatment as an outpatient.

OUTCOME

In DISCOVER 1, an early clinical response indicating treatment success was documented in 240 of 288 patients (83.3%) in the dalbavancin group and 233 of 285 (81.8%) in the vancomycin–linezolid group (difference, 1.5 percentage points; 95% confidence interval [CI], –4.6 to 7.9) (Table 2). In DISCOVER 2, an early clinical response indicating treatment success occurred in 285 of 371 patients (76.8%) in the dalbavancin group and 288 of 368 (78.3%) in the vancomycin–linezolid group (difference, –1.5 percentage points; 95% CI, –7.4 to 4.6). Since the lower limit of each 95% confidence interval was greater than –10 percentage points, dalbavancin was determined to be noninferior to vancomycin–linezolid in each trial.

In the pooled analysis, 525 of 659 patients (79.7%) in the dalbavancin group and 521 of 653 (79.8%) in the vancomycin–linezolid group had a successful outcome at 48 to 72 hours (weighted difference, –0.1 percentage point; 95% CI, –4.5 to 4.2). The reasons for treatment failure were similar with each regimen, and missing temperature data (e.g., the temperature was not recorded or was taken at a time outside the protocol-specified time window) accounted for the largest proportion of failures (Table S2 in the Supplementary Appendix).

In a prespecified sensitivity analysis, dalbavancin and vancomycin–linezolid had similar success

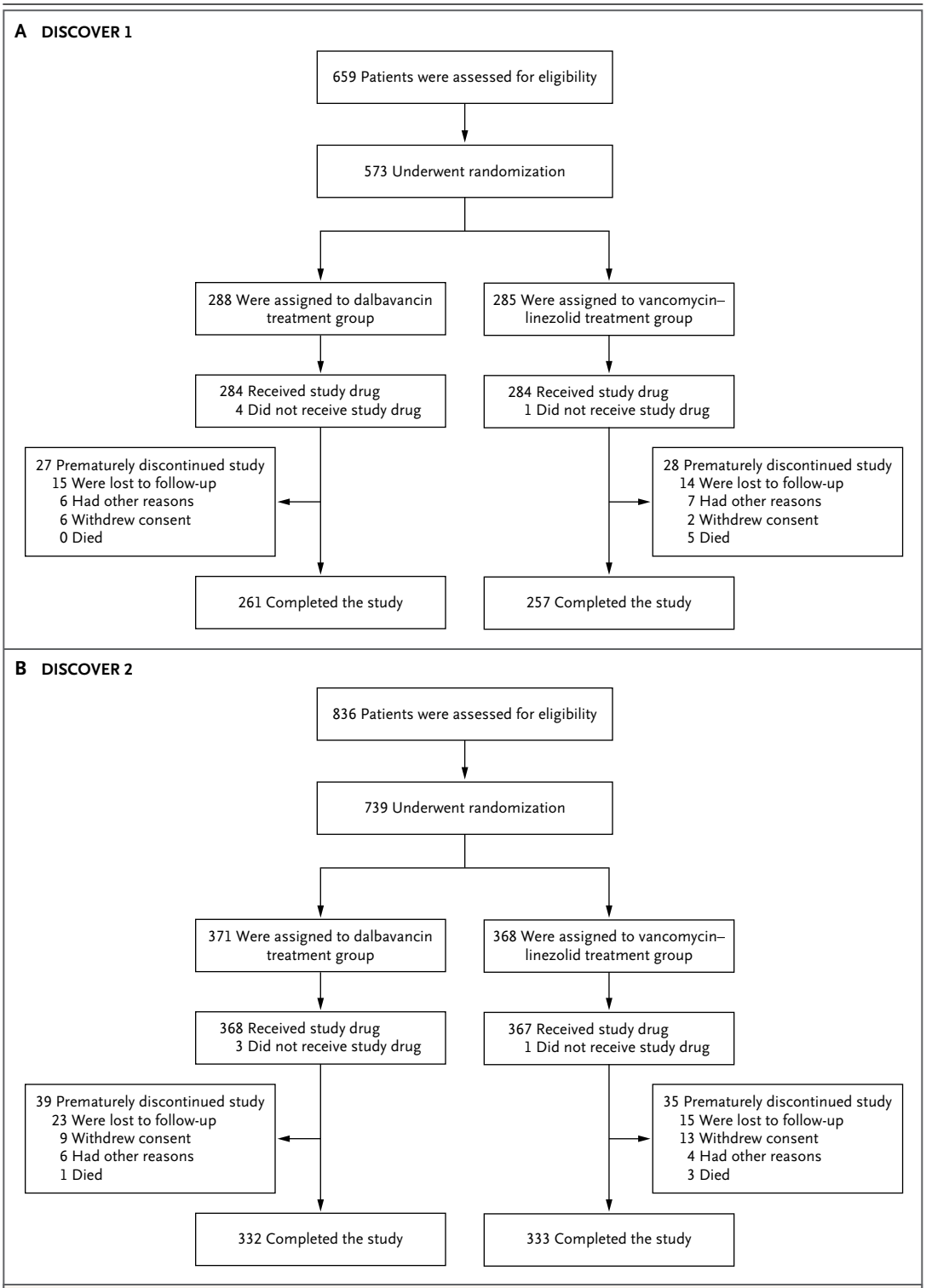

Figure 1. Screening, Randomization, and Completion of Treatment in the Trials.

rates with respect to a reduction in the size of the infected area of 20% or more at 48 to 72 hours (584 of 659 patients [88.6%] and 575 of 653 [88.1%], respectively). A number of additional prespecified sensitivity analyses examined the effect of missing temperature data and had

Table 1. Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	DISCOVER 1		DISCOVER 2		Both Trials	
	Dalbavancin (N=288)	Vancomycin–Linezolid (N=285)	Dalbavancin (N=371)	Vancomycin–Linezolid (N=368)	Dalbavancin (N=659)	Vancomycin–Linezolid (N=653)
Age — yr						
Mean	48.8	48.9	49.1	51.4	48.9	50.3
Range	18–84	18–84	18–85	18–84	18–85	18–84
Male sex — no. (%)	170 (59.0)	173 (60.7)	223 (60.1)	201 (54.6)	393 (59.6)	374 (57.3)
Race or ethnic group — no. (%)†						
White	264 (91.7)	259 (90.9)	328 (88.4)	320 (87.0)	592 (89.8)	579 (88.7)
Black	16 (5.6)	19 (6.7)	13 (3.5)	17 (4.6)	29 (4.4)	36 (5.5)
Other	8 (2.8)	7 (2.5)	30 (8.1)	31 (8.4)	38 (5.8)	38 (5.8)
Region of enrollment — no. (%)						
United States or Canada	123 (42.7)	121 (42.5)	115 (31.0)	114 (31.0)	238 (36.1)	235 (36.0)
Europe, South Africa, or Asia	165 (57.3)	164 (57.5)	256 (69.0)	254 (69.0)	421 (63.9)	418 (64.0)
Diabetes mellitus — no. (%)	43 (14.9)	30 (10.5)	35 (9.4)	62 (16.8)	78 (11.8)	92 (14.1)
Intravenous drug use — no. (%)	36 (12.5)	51 (17.9)	58 (15.6)	56 (15.2)	94 (14.3)	107 (16.4)
Infection type — no. (%)						
Major abscess	72 (25.0)	86 (30.2)	90 (24.3)	87 (23.6)	162 (24.6)	173 (26.5)
Cellulitis	156 (54.2)	147 (51.6)	198 (53.4)	202 (54.9)	354 (53.7)	349 (53.4)
Wound or surgical-site infection	60 (20.8)	52 (18.2)	82 (22.1)	79 (21.5)	142 (21.5)	131 (20.1)
Temperature ≥38°C — no./total no. (%)	243/284 (85.6)	242/284 (85.2)	306/365 (83.8)	310/365 (84.9)	549/649 (84.6)	552/649 (85.0)
White-cell count >12,000 per mm^3 — no./total no. (%)	98/259 (37.8)	104/254 (40.9)	149/368 (40.5)	146/367 (39.8)	247/627(39.4)	250/621 (40.3)
White-cell bands ≥10% — no./total no. (%)	63/238 (26.5)	66/244 (27.0)	48/241 (19.9)	42/234 (17.9)	111/479 (23.2)	108/478 (22.6)
SIRS — no./total no. (%)‡	175/284 (61.6)	175/284 (61.6)	157/368 (42.7)	161/368 (43.8)	332/652 (50.9)	336/652 (51.5)
Infection area — cm^2§						
Median	333	368	314	362	324	367
Range	26–3400	78–3675	85–5100	72–3922	26–5100	72–3922

* There were no significant differences in baseline characteristics between the treatment groups except for the proportion of patients with diabetes mellitus in DISCOVER 2 (P=0.003).
† Race or ethnic group was self-reported. Other included Asian, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, and other.
‡ The systemic inflammatory response syndrome (SIRS) was defined as the presence of two or more of the following: temperature below 36°C or above 38°C, heart rate of more than 90 beats per minute, respiratory rate of more than 20 breaths per minute, and white-cell count below 4000 per cubic millimeter or above 12,000 per cubic millimeter or with more than 10% band forms.
§ The area of erythema was defined as the longest length times the widest width that was perpendicular to length.

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Dalbavancin	Vancomycin–Linezolid	Absolute Difference (95% CI)
	number/total number (percent)		*percentage points*
Primary end point			
DISCOVER 1	240/288 (83.3)	233/285 (81.8)	1.5 (–4.6 to 7.9)
DISCOVER 2	285/371 (76.8)	288/368 (78.3)	–1.5 (–7.4 to 4.6)
Both trials	525/659 (79.7)	521/653 (79.8)	–0.1 (–4.5 to 4.2)
Sensitivity analysis			
DISCOVER 1	259/288 (89.9)	259/285 (90.9)	–1.0 (–5.7 to 4.0)
DISCOVER 2	325/371 (87.6)	316/368 (85.9)	1.7 (–3.2 to 6.7)
Both trials	584/659 (88.6)	575/653 (88.1)	0.6 (–2.9 to 4.1)
Secondary end point			
Clinical status	517/570 (90.7)	502/545 (92.1)	–1.5 (–4.8 to 1.9)
Sensitivity analysis of clinical status†	533/570 (93.5)	517/545 (94.9)	–1.4 (–4.2 to 1.4)
Investigator's assessment of outcome	547/570 (96.0)	527/545 (96.7)	–0.7 (–3.0 to 1.5)

* The primary end point was the success rate at 48 to 72 hours after the initiation of therapy (i.e., early clinical response) in the intention-to-treat population. The sensitivity analysis of the primary end point was the success rate, defined as a reduction in the infection area of at least 20% at 48 to 72 hours after the initiation of therapy, in the intention-to-treat population. The secondary end points were evaluated in a pooled analysis and included success rates at the end of therapy in the clinical per-protocol population. For the pooled analysis, the weighted difference in success rates was calculated.
† The degree of fluctuance or localized heat or warmth had to be improved from baseline.

similar results. Among patients with bacteremia at baseline who had a follow-up blood culture, 23 of 23 patients (100%) in the dalbavancin group and 12 of 14 (85.7%) in the vancomycin–linezolid group had negative blood cultures at the end of therapy.

Clinical status indicating treatment success at the end of treatment in the clinical per-protocol population was documented in a similar proportion of patients in each group (Table S3 in the Supplementary Appendix). The most common reason for failure was a lack of complete resolution of skin warmth at the infection site, which was seen more frequently in the dalbavancin group than in the vancomycin–linezolid group in DISCOVER 1 and at similar rates in the two treatment groups in DISCOVER 2. Analyses in the intention-to-treat population had similar results. The rate of clinical response indicating treatment success according to the investigator's assessment at the end of therapy was numerically higher than the programmatically determined clinical-status outcomes, with similar rates of success in each treatment group.

Treatment outcomes in the two groups were similar when analyzed according to infection type, underlying illness, and severity of infection (Table 3, and Table S4 in the Supplementary Appendix); outcomes in the individual studies were similar to those in the pooled analysis. In a pooled analysis of clinical status at day 14 in the clinical per-protocol population, success was seen in 90.7% of patients in the dalbavancin group and 92.1% of those in the vancomycin–linezolid group. Resolution of pain occurred at similar rates in each treatment group (Table S5 in the Supplementary Appendix).

The MIC_{90} of dalbavancin was 0.06 μg per milliliter for the 511 *S. aureus* isolates and 0.06 μg per milliliter for the 77 *Streptococcus pyogenes* isolates in the two studies combined; all *S. aureus* isolates had a vancomycin MIC of 1 μg per milliliter or less. In the pooled analysis of monomicrobial *S. aureus* infections in the microbiologic per-protocol population, 90.6% of the patients treated with dalbavancin and 93.8% of those treated with vancomycin–linezolid had a successful clinical outcome. Dalbavancin therapy was associated with a successful clinical outcome in 89.2% of patients with MRSA infection and in 91.5% of those with methicillin-susceptible *S. aureus* infection (Table S4 in the Supplementary Ap-

Table 3. Additional Secondary Analyses of Treatment Success.*

Variable	Dalbavancin (N=652)	Vancomycin–Linezolid (N=651)
	number/total number (percent)	
Clinical response according to infection type		
Cellulitis		
At 48–72 hr	281/354 (79.4)	269/349 (77.1)
At end of therapy	294/324 (90.7)	276/301 (91.7)
Major abscess		
At 48–72 hr	133/163 (81.6)	149/173 (86.1)
At end of therapy	125/133 (94.0)	133/139 (95.7)
Traumatic wound or surgical-site infection		
At 48–72 hr	111/142 (78.2)	103/131 (78.6)
At end of therapy	98/113 (86.7)	93/105 (88.6)
Investigator-assessed clinical response at end of therapy according to baseline pathogen†		
Staphylococcus aureus	187/191 (97.9)	171/177 (96.6)
Methicillin-resistant *S. aureus*	72/74 (97.3)	49/50 (98.0)
Streptococcus pyogenes	19/19 (100.0)	12/13 (92.3)
Clinical response at end of therapy according to diabetes mellitus status at baseline		
Diabetes mellitus	60/71 (84.5)	67/76 (88.2)
No diabetes mellitus	457/499 (91.6)	435/469 (92.7)
Clinical response at end of therapy according to SIRS status at baseline		
SIRS	257/296 (86.8)	263/290 (90.7)
No SIRS	260/274 (94.9)	239/255 (93.7)

* The success rates at 48 to 72 hours were assessed in the intention-to-treat population, and the success rates at the end of therapy were assessed in the clinical per-protocol population of patients.

† The success rates at the end of therapy were assessed in the subgroup of patients with monomicrobial infection in the microbiologic per-protocol population.

pendix). Successful outcomes according to the investigator's assessment for all these pathogens were numerically higher than the programmatically determined outcomes, but the rates were similar in the two treatment groups.

SAFETY

Adverse events were reported in fewer patients treated with dalbavancin than in those treated with vancomycin–linezolid (Table 4). The total number of adverse events reported per patient in the dalbavancin group was also lower, resulting in fewer days with an adverse event in the dalbavancin group than in the vancomycin–linezolid group. Most adverse events were thought to be unrelated to the study treatment and were mild; adverse events were assessed by the investigator, who was unaware of the treatment assignment. An adverse event led to the discontinuation of the study treatment in 2.1% of the patients in the dalbavancin group and 2.0% of those in the vancomycin–linezolid group.

The most common treatment-related adverse events in the dalbavancin and vancomycin–linezolid groups were nausea (in 2.5% and 2.9% of patients, respectively), diarrhea (in 0.8% and 2.5%; P=0.02), and pruritus (in 0.6% and 2.3%; P=0.01); these events, plus headache, were also the most common adverse events due to any cause (treatment-related or not) (Table S6 in the Supplementary Appendix). An infusion site–related reaction was seen in 9 patients (1.4%) in the dalbavancin group and 11 (1.7%) in the vancomycin–linezolid group; flushing was seen in 1 patient (0.2%) and

Table 4. Adverse Events.

Variable	Dalbavancin (N=652)	Vancomycin–Linezolid (N=651)	P Value*
Any adverse event			
Any event — no. of patients (%)	214 (32.8)	247 (37.9)	0.05
Total no. of events	540	645	0.05
Treatment-related adverse event†			
Any event — no. of patients (%)	80 (12.3)	89 (13.7)	0.45
Total no. of events	139	183	0.02
Serious adverse event — no. of patients (%)			
Any event	17 (2.6)	26 (4.0)	0.16
Treatment-related event†	2 (0.3)	4 (0.6)	0.41
Death — no. (%)‡	1 (0.2)	7 (1.1)	0.03
Treatment-limiting adverse event — no. of patients (%)§	14 (2.1)	13 (2.0)	0.85
Most common treatment-related adverse event — no. of patients (%)¶			
Nausea	16 (2.5)	19 (2.9)	0.62
Diarrhea	5 (0.8)	16 (2.5)	0.02
Pruritus	4 (0.6)	15 (2.3)	0.01

* The P value was calculated with the use of the Cochran–Mantel–Haenszel test, with adjustment for study. The P values for the total number of adverse events and total number of drug-related adverse events were calculated by means of Poisson regression.
† The investigator, who was unaware of the treatment assignment, assessed whether the adverse event was related to treatment.
‡ One patient in the dalbavancin group died at day 32 from sepsis and a prior fracture. In the vancomycin–linezolid group, two patients died from cardiopulmonary failure and one each from pulmonary emboli, congestive heart failure, acute heart failure, and systemic lupus erythematosus; one patient died suddenly.
§ Treatment-limiting adverse events were those that led to the premature discontinuation of the study drug.
¶ The most common adverse events were defined as those that occurred in more than 2% of the patients in either treatment group. A patient may have had more than one event.

4 patients (0.6%), respectively. The majority of infusion-related adverse events in patients in the dalbavancin group did not occur on administration day 1 or 8 but were related to the presence of the indwelling catheter that was required for placebo infusions in the trial.

The median durations of adverse events were 4.0 days (range, 1 to 101) in patients receiving dalbavancin and 3.0 days (range, 1 to 86) in those receiving vancomycin–linezolid; the mean (±SD) durations were 8.7±12.7 days and 8.7±12.6 days, respectively. Adverse events at 28 days or later after the initiation of treatment occurred in 40 of 652 patients (6.1%) in the dalbavancin group and in 59 of 651 (9.1%) in the vancomycin–linezolid group. Representative laboratory values obtained from testing performed according to the protocol are shown in Table S7 in the Supplementary Appendix.

A serious adverse event was reported in 17 of 652 patients (2.6%) in the dalbavancin group and in 26 of 651 (4.0%) in the vancomycin–linezolid group (P=0.16) (Table S8 in the Supplementary Appendix). Treatment-related serious adverse events were cellulitis and anaphylactoid reaction in 1 patient each in the dalbavancin group and cellulitis, gastrointestinal disorder, toxic nephropathy, and acute renal failure in 1 patient each in the vancomycin–linezolid group. One patient (0.2%) in the dalbavancin group died, as compared with 7 (1.1%) in the vancomycin–linezolid group (P=0.03).

DISCUSSION

Our results show that for the treatment of acute bacterial skin and skin-structure infection, the efficacy of dalbavancin administered once weekly

was not inferior to that of a conventional twice-daily antibiotic regimen. Our trial both met the early primary end point of cessation of the spread of infection and the absence of fever and also showed a consistent treatment effect regarding a reduction in the area of infection of 20% or more. Findings were consistent at the new early time point and the traditional later time points. Similarly, results were robust in patients with major abscess, cellulitis, or wound infection; in those with *S. aureus*, including MRSA, or *Strep. pyogenes* infection; and in those treated as an outpatient. Patients included in the study were ill enough to require intravenous therapy and hospital referral or admission and had a high rate of fever with a larger median area of skin infection than that in patients included in two registrational trials of acute bacterial skin and skin-structure infection.[15,16] Approximately 50% of the patients in our study met the criteria for the systemic inflammatory response syndrome.

Patients treated with dalbavancin had fewer adverse events than those treated with vancomycin–linezolid. The duration of treatment-related adverse events was similar for the two regimens. Late-onset events, a potential concern for a drug with a long half-life, were infrequent and were observed at a similar rate in the two treatment groups. Infusion-related reactions related to dalbavancin administered over a period of 30 minutes were not more frequent than those associated with vancomycin administered over a period of 120 minutes. Although the safety profile observed in these studies is consistent with the profile in previous clinical trials,[5,9] the true rate of adverse events, especially rare ones, can be established only after more extensive clinical use.

Our trial had limitations. The new regulatory end point mandates assessment of the primary efficacy end point at an early time point. The analyses of traditional secondary end points confirmed those of the primary end point. Some differences between the clinical-status assessment and the investigator's overall assessment resulted from the evaluation of the subjective signs of skin infection, particularly warmth, fluctuance, and induration. The regulatory definitions of major abscess, cellulitis, and wound infection may not align with practice-based criteria. In addition, adherence to the twice-daily vancomycin–linezolid regimen in the context of a clinical trial may be greater than the adherence observed in typical clinical practice.

In conclusion, the results of these trials showed the noninferiority of dalbavancin administered once weekly as compared with vancomycin–linezolid administered twice daily for the treatment of acute bacterial skin and skin-structure infection in seriously ill patients.

Supported by Durata Therapeutics.

Dr. Boucher reports receiving fees for serving on advisory boards from Basilea Pharmaceutica, Durata Therapeutics, Merck, Paratek Pharmaceuticals, Rib-X Pharmaceuticals, Theravance, and Hospira/TheraDoc and fees for serving on an adjudication committee from Merck. Dr. Wilcox reports receiving consulting fees from Actelion Pharmaceuticals, Astellas Pharma, AstraZeneca, Cerexa, Merck, Nabriva Therapeutics, Novacta Biosystems, Novartis, Optimer Pharmaceuticals, Pfizer, Roche, Sanofi Pasteur, Summit, the Medicines Company, VHsquared, Abbott Laboratories, bioMérieux, and the European Tissue Symposium, lecture fees from Astellas Pharma, AstraZeneca, Cerexa, Merck, and Pfizer, lecture fees through his institution from Alere, and grant support from Actelion Pharmaceuticals, Astellas Pharma, Cerexa, Merck, Summit, Abbott Laboratories, bioMérieux, Da Volterra, and the European Tissue Symposium. Dr. Talbot reports receiving fees through Talbot Advisors for serving on advisory boards from Actelion Pharmaceuticals, Astellas Pharma, Cubist Pharmaceuticals, Durata Therapeutics, FAB Pharma, GlaxoSmithKline, and Kalyra Pharmaceuticals, fees for serving on the board of directors of Nabriva Therapeutics, fees for serving on an independent data monitoring committee from Pfizer, consulting fees from Achaogen, Actelion Pharmaceuticals, Basilea Pharmaceutica, Cempra Pharmaceuticals, Cerexa, Durata Therapeutics, FAB Pharma, FujiFilm Pharmaceuticals, Johnson & Johnson, Kalidex Pharmaceuticals, Merada Pharmaceuticals, Nabriva Therapeutics, Paratek Pharmaceuticals, Sanofi, Sentinella, Shionogi, and Theravance, lecture fees from Bayer and Merck, and owning stock or stock options in Achaogen, Calixa Therapeutics, Cempra Pharmaceuticals, Cerexa, Durata Therapeutics, Kalyra Pharmaceuticals, and Nabriva Therapeutics. Drs. Puttagunta and Dunne report being employees of Durata Therapeutics and owning stock in Pfizer and Durata Therapeutics. Dr. Das reports receiving consulting fees through her employer from Achaogen, Durata Therapeutics, Trius Therapeutics, Cempra Pharmaceuticals, Cerexa, Nabriva Therapeutics, Paratek Pharmaceuticals, and Cubist Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Jenkins TC, Knepper BC, Sabel AL, et al. Decreased antibiotic utilization after implementation of a guideline for inpatient cellulitis and cutaneous abscess. Arch Intern Med 2011;171:1072-9.
2. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52(3):e18-e55. [Erratum, Clin Infect Dis 2011;53:319.]
3. Daum RS. Skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*. N Engl J Med 2007;357:380-90. [Erratum, N Engl J Med 2007;357:1357.]
4. Jenkins TC, Sabel AL, Sarcone EE, Price CS, Mehler PS, Burman WJ. Skin

and soft-tissue infections requiring hospitalization at an academic medical center: opportunities for antimicrobial stewardship. Clin Infect Dis 2010;51:895-903.
5. Jauregui LE, Babazadeh S, Seltzer E, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. Clin Infect Dis 2005;41:1407-15.
6. Dorr MB, Jabes D, Cavaleri M, et al. Human pharmacokinetics and rationale for once-weekly dosing of dalbavancin, a semi-synthetic glycopeptide. J Antimicrob Chemother 2005;55:Suppl 2:ii25-ii30.
7. Nord CE, Rasmanis G, Wahlund E. Effect of dalbavancin on the normal intestinal microflora. J Antimicrob Chemother 2006;58:627-31.
8. Raad I, Darouiche R, Vazquez J, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. Clin Infect Dis 2005;40:374-80.
9. Seltzer E, Dorr MB, Goldstein BP, Perry M, Dowell JA, Henkel T. Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. Clin Infect Dis 2003;37:1298-303.
10. Guidance for industry: acute bacterial skin and skin structure infections: developing drugs for treatment. Silver Spring, MD: Food and Drug Administration, 2010.
11. Snodgrass WR, Anderson T. Sulphanilamide in the treatment of erysipelas. Br Med J 1937;2:1156-9.
12. Idem. Prontosil in erysipelas. Br Med J 1937;2:101-4.
13. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 2009;49:325-7. [Erratum, Clin Infect Dis 2009;49:1465.]
14. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.
15. Corey GR, Wilcox MH, Talbot GH, Thye D, Friedland D, Baculik T. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65:Suppl 4:iv41-iv51.
16. Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA 2013;309:559-69.