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Treatment of hospitalized patients with complicated Gram-positive skin and skin structure infections: two randomized, multicentre studies of quinupristin/dalfopristin versus cefazolin, oxacillin or vancomycin

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Quinupristin/dalfopristin (Synercid), the first injectable streptogramin antibiotic available for the treatment of complicated Gram-positive skin and skin structure infections, was compared with standard comparators (cefazolin, oxacillin or vancomycin) in one USA and one international trial. These two randomized, open-label trials of virtually identical design enrolled a total of 893 patients (450 quinupristin/dalfopristin, 443 comparator). The majority of patients had erysipelas, traumatic wound infection or clean surgical wound infection. *Staphylococcus aureus* was the most frequently isolated pathogen in both treatment groups and polymicrobial infection was more common in the quinupristin/dalfopristin group than in the comparator group. The clinical success rate (cure plus improvement) in the clinically evaluable population was equivalent between the two treatment groups (68.2% quinupristin/dalfopristin, 70.7% comparator; 95% CI, –10.1, 5.1) despite a shorter mean duration of treatment for quinupristin/dalfopristin patients. In the bacteriologically evaluable population, by-patient and by-pathogen bacteriological eradication rates were somewhat lower for quinupristin/dalfopristin (65.8% and 66.6%, respectively) than for the comparator regimens (72.7% and 77.7%, respectively). The lower bacteriological response rates in the quinupristin/dalfopristin group were, in part, due to a higher rate of polymicrobial infections and a higher incidence of patients classified as clinical failure, a category which included premature discontinuation of treatment because of local venous adverse events. The bacteriological eradication rate for quinupristin/dalfopristin was higher in monomicrobial infections than in polymicrobial infections (72.6% versus 63.3%, respectively), whereas the corresponding rate for the comparator regimens was lower for monomicrobial infections than polymicrobial infections (70.8% versus 83.1%). This finding was not unexpected, since the spectrum of quinupristin/dalfopristin is focused on Gram-positive pathogens and additional antibiotics to treat Gram-negative bacteria were not required per protocol. The systemic tolerability of both treatment regimens was qualitatively similar. A higher rate of drug-related venous adverse events was reported for quinupristin/dalfopristin (66.2%) than for the comparator regimen (28.4%). Premature discontinuation of study drug was primarily due to adverse clinical events for quinupristin/dalfopristin (19.1%), whereas the most common reason for discontinuation among those receiving the comparator regimens was treatment failure (11.5%). Quinupristin/dalfopristin is an effective alternative for the treatment of hospitalized patients with complicated skin and skin structure infections due to quinupristin/dalfopristin-susceptible Gram-positive organisms, including methicillin- and erythromycin-resistant *S. aureus*.

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Introduction

Skin and skin structure infections, ranging from mild pyodermas to life-threatening full-thickness burn wounds, are frequently encountered in the care of hospitalized patients. Complicated infections of the skin and its structures, such as post-surgical wound infections, traumatic wound infections, severe carbunculosis and erysipelas are often caused by Gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus pyogenes*.[1,2] Furthermore, complicated infections of the skin often involve several bacterial species, some of which express resistance to commonly used antibiotics. Treatment of these infections usually consists of a single agent, such as penicillinase-resistant penicillin or a cephalosporin. Vancomycin is used for suspected or documented infection due to methicillin-resistant staphylococci or if a patient is allergic to β-lactam antibiotics; however, the recent appearance of vancomycin intermediate-resistant *S. aureus* indicates the need for additional options in antimicrobial selection.[3,4] Because many complicated skin and skin structure infections are extensive and indolent, surgical intervention (i.e. drainage and debridement) is an integral part of appropriate management, in addition to systemic antimicrobial therapy.[1,2]

Quinupristin/dalfopristin (Synercid), the first intravenous streptogramin, belongs to the macrolide-lincosamide-streptogramin group of antibiotics. It has excellent in-vitro activity against the Gram-positive organisms most frequently encountered in complicated skin and skin structure infections, including *S. aureus* and *S. pyogenes*.[5–7] In addition, quinupristin/dalfopristin has activity against most methicillin-, lincosamide- and erythromycin-resistant strains of coagulase-negative staphylococci and *S. aureus* (MIC_{90} 0.5 and 1 mg/L, respectively).[6] The drug is also active ($MIC_{90} \leqslant 1$ mg/L) against glycopeptide-resistant (vancomycin- and teicoplanin-resistant) *S. aureus*.[8] However, quinupristin/dalfopristin is not active *in vitro* against Gram-negative enteric bacilli or *Pseudomonas aeruginosa*. Cross-resistance has not been reported between quinupristin/dalfopristin and glycopeptide, quinolone or β-lactam antimicrobials.[6]

The purpose of the two studies presented here was to compare the efficacy, tolerance and safety of quinupristin/dalfopristin with those of standard comparators (cefazolin, oxacillin or vancomycin) in the treatment of hospitalized adult patients with complicated skin and skin structure infections caused by Gram-positive bacteria. Both studies were conducted in accordance with the published guidelines of the Infectious Diseases Society of America and the US Food and Drug Administration.[9]

Patients and methods

Study design and selection of patients

Two open-label, randomized, phase III comparative trials were undertaken. The first study was conducted between February 1995 and April 1996 at 40 centres in the continental USA and three located in Puerto Rico. The second trial was conducted from June 1995 to July 1996 at 89 centres in Australia, Belgium, France, Germany, Israel, Italy, The Netherlands, the UK, the USA and South Africa. Approximately 450 clinically evaluable patients were to be enrolled in each of the two studies. Hospitalized patients, 18 years of age and older, with presumed complicated Gram-positive skin or skin structure infections were randomly assigned using a computer-generated 'balanced block randomization' scheme to treatment with either quinupristin/dalfopristin or a comparator therapy (i.e. cefazolin, oxacillin or vancomycin).[10] The studies were not conducted using a double-blind design. This was for several reasons: the choice of the comparator could be targeted by the investigator based on local bacterial susceptibility patterns, patient history, the likelihood of the presence of oxacillin-resistant bacteria and culture results; the infusion duration and dosing intervals of the four study drugs varied; and vancomycin dosing was to be adjusted based on the results of therapeutic drug monitoring.

Adult men and non-pregnant, non-lactating women with an infection of skin and skin structures of sufficient severity to require hospitalization for at least 24 h and requiring at least 3 days of parenteral antibacterial therapy were eligible for study entry. Patients with such infections presumed to be predominantly due to Gram-positive organisms were enrolled, including those with infections following clean surgical procedures; infections resulting from partial thickness burn wounds (<5% total body area, USA trial only); erysipelas; skin or skin structure infection at central venous catheter insertion sites (with removal of catheter within 24 h following study enrolment); severe carbunculosis and traumatic wound infections. Patients were required to present with purulent/seropurulent drainage and/or at least three of the following signs: tenderness to palpation, localized erythema >1 cm from the edge of the infection, induration, fluctuance or temperature >38°C. In addition, a specimen for culture, consisting of drainage, aspirate of material, biopsy of material, catheter tip or saline swab from the suspected site of infection, was required prior to the administration of study drug.[11]

Patients were excluded if they had known underlying immunocompromising disease or immunosuppressive therapy; HIV-seropositive reaction with a CD4 count $<200/\mu L$; severe neutropenia ($<500/mm^3$); documented Type 1 hypersensitivity reaction to streptogramins or all comparator agents; Gram's stain or culture findings indicative of predominantly Gram-negative, anaerobic or mixed organisms; baseline pathogen(s) presumed to be resistant to any study drug before randomization; receipt of more than a single dose of a systemic antibacterial treatment presumed to be effective (i.e. no in-vitro resistance and not a clinical failure) within 24 h before study drug; another site of infection requiring concomitant systemic

antibacterial therapy; suspected presence of contiguous osteomyelitis or septic arthritis at study entry; baseline ALT and/or AST values over five times the upper limit of normal and/or conjugated bilirubin over three times the upper limit of normal; serum creatinine values >2.24 mg/dL and/or creatinine clearance <30 mL/min; skin and skin structure infections which require significant surgical intervention (i.e. could not be performed at the patient's bedside) after >24 h of study drug treatment; skin and skin structure infection which could be totally cured by surgical intervention; or receipt of another investigational drug within 30 days before enrolment. Patients were also excluded if they were not available for follow-up. Additional exclusion criteria which were applied for patients enrolled in the USA trial included skin and skin structure infection likely to yield mixed pathogens; infection with a causative foreign body remaining in place >24 h after initiation of study drug therapy; infection which could be cured by surgical intervention alone or was expected to require <72 h of study drug therapy; septic shock; life expectancy of <6 months; and previous participation in a quinupristin/dalfopristin trial. Each participating site received institutional review board or Ethics Committee approval, and all patients provided written informed consent before study enrolment.

Antimicrobial therapy, surgical intervention and patient evaluations

In the USA study, patients were dosed intravenously for 3–14 days with quinupristin/dalfopristin 7.5 mg/kg every 12 h (1 h infusion), oxacillin 2 g every 6 h (10–30 min infusion) or vancomycin 1 g every 12 h (1–2 h infusion). The selection of oxacillin or vancomycin was made by the investigator, based on knowledge of local bacterial susceptibility patterns, patient history and the likelihood of oxacillin-resistant bacteria. Patients with a history of β-lactam hypersensitivity who were randomized to the comparator received vancomycin. In the international trial, patients were dosed intravenously with quinupristin/dalfopristin 7.5 mg/kg every 12 h (1 h infusion), cefazolin 1 g every 8 h by iv bolus injection or rapid infusion, or vancomycin 1 g every 12 h (1–2 h infusion), each for 3–14 days. The choice of cefazolin or vancomycin was at the investigator's discretion. The vancomycin dosage regimen was adjusted by the investigator in both studies, as appropriate, for bodyweight, abnormal renal function and in response to therapeutic blood level monitoring. Concomitant systemic antibacterial agents were permitted only if the agent did not have in-vitro activity against Gram-positive pathogens; in the international study, concomitant use of a monobactam antimicrobial (aztreonam) was specifically allowed.

Surgical debridement and drainage were permitted only at the patient's bedside following the start of study drug therapy. Cleaning of wounds with water or saline solution at the initiation of therapy and soaking and cleaning with saline during the course of therapy were also allowed; however, the topical use of antiseptics and soaps for wound care was prohibited.

Clinical and microbiological assessments were performed at baseline, on day 4, within 24 h after the last study drug infusion (end-of-treatment) and 14–28 days after treatment discontinuation (test-of-cure). A Gram's stain was performed on any specimen obtained from the site of infection. To be considered a baseline pathogen, coagulase-negative staphylococci must have been recovered in pure culture from an adequate specimen, including two or more blood cultures if recovered only from the blood. All Gram-positive pathogens were tested for susceptibility to oxacillin according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines.[12,13] All organisms isolated before therapy, as well as pathogens isolated at the end of therapy or at the test-of-cure visits, were re-identified and tested by a central laboratory (SciCor Laboratories, Indianapolis, IN, USA or Bioinova, Plaisir, France) for susceptibility to study drugs and a standard panel of other antimicrobial agents.

Study evaluations

Three populations are described: (i) all-treated (all randomized patients who received at least one dose of study drug; this was the population evaluated for safety); (ii) clinically evaluable (patients with documented complicated Gram-positive skin and skin structure infection who completed the test-of-cure and/or end-of-treatment assessments, received at least 72 h and 80% of scheduled study drug and met all other protocol requirements); and (iii) bacteriologically evaluable (patients who were clinically evaluable and had at least one Gram-positive pathogen isolated from cultures obtained no earlier than 4 days before receipt of study drug and no later than the second dose of study drug).

Outcome variables

The primary efficacy variable, defined before data analysis, was the clinical response in the clinically evaluable population as determined at test-of-cure (or at the end-of-treatment, if the patient was discontinued from the study prematurely). Bacteriological efficacy variables included by-pathogen bacteriological response and by-patient bacteriological response.

Clinical response

Investigator assessments of patient outcomes were not used. All patients were evaluated with an algorithm for clinical efficacy responses (Table I). Clinical success was defined as cure or improvement. A steering committee comprised of

Table I. Assessment of clinical signs and symptoms

Response	Signs and symptoms
Cured	All signs and symptoms of infection present at baseline were absent, and no new signs or symptoms of infection. Equivalent rectal temperature was <37.5°C. Serous drainage may be present. If more than one lesion was present at baseline, all lesions were classified as cured.
Improved	In patients not cured: equivalent rectal temperature ⩽37.9°C drainage: absent or serious tenderness: absent fluctuance: absent erythema and induration: reduction of area (short axis × long axis) by ⩾50% compared with baseline assessment no new signs or symptoms of infection Note: if more than one lesion was present at baseline, all lesions were classified as improved or a combination of cured and improved
Failure	Persistence of all the signs and symptoms present at baseline, or appearance of a new sign or symptom, or worsening of a sign or symptom observed at baseline, or discontinuation for test drug ineffective, or addition of new effective antibacterial therapy in patients discontinued due to an adverse event, or requirement for a significant surgical procedure for management of the skin and skin structure infection after 24 h of study drug therapy.
Indeterminate	Inability to assess the patient's signs and symptoms due to 'lost to follow-up', or absence of information at baseline or test-of-cure, or administration of new antibiotic therapy (including topical antibacterial agents), known or presumed to be effective against baseline pathogen, during study treatment up to test-of-cure visit (in patients not classified failure), or patients who received less than 3 days of study drug.

study investigators, blinded to treatment assignment, evaluated all patients for whom evaluability or efficacy responses could not be determined with the algorithm.

Bacteriological response

The by-pathogen bacteriological response was determined for each baseline pathogen as eradication (baseline pathogen not isolated from post-treatment cultures from the original site of infection); presumed eradication (no material available for culture or inadequate specimen taken and the patient's clinical response was cure or improvement); persistence (baseline pathogen isolated from post-treatment cultures from the original site of infection); presumed persistence (no culture attempted or sample inadequate and the patient's clinical response was failure); indeterminate (no culture attempted or sample inadequate and the patient's clinical response was indeterminate). The by-patient bacteriological response was defined as follows: eradication (all baseline pathogens were eradicated); presumed eradication (all baseline pathogens had a response of presumed eradication or a combination of responses of eradication or presumed eradication); persistence (all baseline pathogens had a response of persistence or a combination of persistence and presumed persistence); presumed persistence (all baseline pathogens had a response of presumed persistence); multiple pathogens with partial eradication (at least one pathogen was classified as persistence or presumed persistence and the others were classified as eradication); or indeterminate (all baseline pathogens had a response of indeterminate).

Superinfection and colonization

Organisms recovered from post-treatment cultures but not present at baseline were categorized as superinfecting pathogens if the clinical response was failure, or as colonizing pathogens if the clinical response was cure or improvement.

Safety evaluation

Drug safety was evaluated in all patients who received at least one dose of study drug (all-treated population). To ensure consistent and accurate reporting of venous tolerability, investigators were asked to report separately

adverse clinical events and adverse venous events. Adverse events were categorized by their relationship to study drug (probable, possible, remote or none) and by their severity (mild, moderate or severe).

Statistical analysis

Both studies were powered to detect equivalence between the quinupristin/dalfopristin and comparator regimens. With the size of the clinically evaluable population enrolled, the USA study had a power of 76% and the international trial had a power of ⩾80% to detect equivalence between quinupristin/dalfopristin and the comparator regimen ($\alpha = 0.05$, two-sided). For test-of-cure evaluations, 95% two-sided confidence intervals (95% CI) were calculated for the differences between quinupristin/dalfopristin and comparator for clinical response (cure plus improvement) and bacteriological eradication (eradication plus presumed eradication) rates. Treatment-by-centre effect was tested by logistic regression analysis. The two treatments were considered equivalent if the lower limit of the 95% confidence interval for the difference exceeded a specific value (δ), determined by the higher observed success rate. Following the recommendations of the 1992 Food and Drug Administration, Division of Anti-infective Drug Products 'Points to Consider', the specified value was $\delta = 10\%$, if the larger success rate equalled or exceeded 90%; $\delta = 15\%$, if the larger success rate equalled or exceeded 80% and was less than 90%; and $\delta = 20\%$ if the larger success rate was less than 80%.

The comparability of baseline demographics and background disease between the two treatment groups was analysed descriptively. The chi-squared test or Fisher's exact test was used for analysis of selected univariate comparisons.

Logistic regression analyses were performed on the clinical success for the clinically evaluable population and on the bacteriological and clinical successes in the bacteriologically evaluable population. For quinupristin/dalfopristin patients, the mean daily dose was added to the model to assess its effect on the primary outcome criterion. For the bacteriologically evaluable population, the following explanatory variables were also used in the model: bacteraemic infection; polymicrobial infection; methicillin-resistant *S. aureus* (MRSA); *S. pyogenes*; *P. aeruginosa*; and area of induration <25 cm^2. An odds ratio (OR) of greater than one indicates a higher likelihood of success.

Results

Unless specified, the data reported represent an integrated analysis of the USA and international studies.

Study population

A total of 893 patients (450 quinupristin/dalfopristin, 443 comparator) from 10 countries were enrolled and treated (all-treated population). Of the 450 quinupristin/dalfopristin patients, 438 received quinupristin/dalfopristin alone and 12 quinupristin/dalfopristin plus aztreonam. Of the 443 patients treated with a comparator regimen, 158 received cefazolin, 134 oxacillin, 118 vancomycin, 17 vancomycin and/or cefazolin with aztreonam, nine both oxacillin and vancomycin and seven vancomycin plus cefazolin.

Demographic and medical characteristics of the clinically evaluable and all-treated populations are summarized in Tables II and III. The distribution of patients by age, gender and race was similar for the two treatment groups

Table II. Demographic characteristics (clinically evaluable and all-treated populations)

	Clinically evaluable population		All-treated population	
Demographic characteristics	quinupristin/dalfopristin ($n = 289$)	comparator ($n = 273$)	quinupristin/dalfopristin ($n = 450$)	comparator ($n = 443$)
Age (years)				
mean ± S.D.	55.3 ± 17.8	55.5 ± 17.0	53.6 ± 17.9	53.9 ± 17.7
range	19–90	20–106	19–90	18–106
18–64	179 (61.9)	177 (64.8)	297 (66.0)	299 (67.5)
⩾65	110 (38.1)	96 (35.2)	153 (34.0)	144 (32.5)
Gender [number (%)]				
male	162 (56.1)	141 (51.6)	252 (56.0)	237 (53.5)
Race [number (%)]				
Caucasian	217 (75.1)	203 (74.4)	321 (71.3)	324 (73.1)
Black	42 (14.5)	45 (16.5)	81 (18.0)	70 (15.8)
Hispanic	24 (8.3)	18 (6.6)	38 (8.4)	39 (8.8)
Oriental/other	6 (2.1)	7 (2.6)	10 (2.2)	10 (2.3)

Table III. Medical characteristics in the clinically evaluable and all-treated populations

Medical characteristics	Number (%) of patients			
	clinically evaluable		all-treated	
	quinupristin/dalfopristin ($n = 289$)	comparator ($n = 273$)	quinupristin/dalfopristin ($n = 450$)	comparator ($n = 443$)
Erysipelas	115 (39.8)	108 (39.6)	172 (38.2)	161 (36.3)
Requirement for surgery	91 (31.5)	94 (34.4)	143 (31.8)	151 (34.1)
Traumatic wound infections	76 (26.3)	61 (22.3)	114 (25.3)	120 (27.1)
Diabetes mellitus	67 (23.2)	71 (26.0)	109 (24.2)	108 (24.4)
Clean surgical infections	52 (18.0)	49 (17.9)	83 (18.4)	75 (16.9)
Peripheral vascular disease	45 (15.6)	46 (16.8)	64 (14.2)	78 (17.6)
Presence of bacteraemia	14 (4.8)	14 (5.1)	26 (5.8)	23 (5.2)
Severe carbunculosis	12 (4.2)	15 (5.5)	19 (4.2)	21 (4.7)
SSSI at central venous insertion site	5 (1.7)	3 (1.1)	7 (1.6)	5 (1.1)
Partial thickness burn wounds	3 (1.0)	1 (0.4)	4 (0.9)	2 (0.5)

Numbers and percentages may exceed the total in the study due to multiple underlying conditions.

for both populations. The majority of patients had erysipelas, traumatic wound infections and clean surgical wound infections.

Among all-treated patients, 28.2% (127 of 450) of quinupristin/dalfopristin and 23.0% (102 of 443) of comparator-treated patients had a polymicrobial infection. For clinically evaluable patients, the mean duration of treatment was consistently shorter for the quinupristin/dalfopristin group than for the comparator: 7.0 ± 3.2 days for the quinupristin/dalfopristin group versus 8.4 ± 3.4 days for the comparator recipients in the USA trial ($P < 0.001$), and 7.7 ± 3.5 days versus 8.7 ± 3.3 days, respectively, in the international study ($P = 0.005$).

Evaluability and premature discontinuation

All 893 patients in the all-treated population were evaluated for safety. Of these 893, 63% (296 quinupristin/dalfopristin, 267 comparator) had a pre-therapy pathogen isolated. Of the 893 all-treated patients, 35.8% (161 of 450) of quinupristin/dalfopristin and 38.4% (170 of 443) of comparator-treated patients were excluded from the clinically evaluable population. The major reasons for non-evaluability among these 331 patients were the lack of required efficacy data, missing efficacy visits and insufficient baseline criteria to merit study inclusion. Thus, 62.9% of patients (289 quinupristin/dalfopristin, 273 comparator) were clinically evaluable. Approximately 40% (39.3%) of patients were bacteriologically evaluable (190 quinupristin/dalfopristin, 161 comparator).

Three hundred and eight patients were prematurely discontinued from the studies (172 quinupristin/dalfopristin, 136 comparator). The most common reasons for premature discontinuation of study drug were different between the quinupristin/dalfopristin and comparator regimens: adverse clinical events in the quinupristin/dalfopristin group [86 of 172 (50%)] and treatment failures in the comparator group [51 of 136 (37.5%)].

Clinical response

The clinical success rate in the clinically evaluable populations was equivalent between the quinupristin/dalfopristin (68.2%) and the comparator (70.7%) regimens (95% CI = –10.1, 5.1) (Table IV). In the USA trial, the clinical success rate was 64.7% (88 of 136) for quinupristin/dalfopristin and 68.3% (82 of 120) for comparator-treated patients (95% CI = –15.2, 7.9), whereas in the international trial it was 71.2% (109 of 153) for quinupristin/dalfopristin and 72.5% (111 of 153) for comparator (95% CI = –11.4, 8.8). Equivalent clinical success rates were also demonstrated in the all-treated population for both treatment regimens in both studies (data not shown).

The major difference between treatments in the analysis of the clinically evaluable population was a lower rate of clinical success in the quinupristin/dalfopristin group (57.1%) compared with the comparator regimens (78.2%) in the setting of polymicrobial infection ($P = 0.012$). In contrast, in monomicrobial infections, quinupristin/dalfopristin performed as well as comparator in the USA study (63.8% versus 66.7%) and better than the comparator (79.3% versus 60.3%) in the international trial. In the USA trial, quinupristin/dalfopristin patients infected with *S. aureus* (monomicrobial or polymicrobial) had a lower clinical success rate than those receiving the comparator regimen (59.6% and 70.8%, respectively); however, quinupristin/dalfopristin-treated patients in the international study had a higher clinical success rate, similar to

Table IV. Clinical response rates (clinically evaluable population)

Response	Number (%) of patients	
	quinupristin/dalfopristin	comparator
Clinically evaluable patients	289 (100.0)	273 (100.0)
Cure	137 (47.4)	132 (48.4)
Improvement	60 (20.8)	61 (22.3)
Failure	92 (31.8)	80 (29.3)
Clinical success (cure and improvement)	197 (68.2)	193 (70.7)

Table V. By-pathogen bacteriological success rates for selected pathogens (bacteriologically evaluable population)

Pathogen	Number (%) of pathogens eradicated or presumed eradicated	
	quinupristin/dalfopristin	comparator
All pathogens	215/323 (66.6)	188/242 (77.7)[a]
Staphylococcus aureus[b]	70/109 (64.2)	75/100 (75.0)
methicillin-sensitive *S. aureus*	45/70 (64.3)	49/64 (76.6)
methicillin-resistant *S. aureus*	7/9 (77.8)	3/6 (50.0)[c]
Staphylococcus epidermidis	18/23 (78.3)	12/15 (80.0)
Other coagulase-negative staphylococci	6/8 (75.0)	7/11 (63.6)
Streptococcus pyogenes	25/30 (83.3)	10/13 (76.9)
Streptococcus agalactiae	7/9 (77.8)	13/15 (86.6)
Gram-positive cocci only	18/32 (56.3)	23/33 (69.7)
Gram-positive cocci plus Gram-negative rods	22/42 (52.4)	19/22 (86.4)[d]

[a] $P = 0.004$.
[b] $P = 0.091$; includes 18 and 23 eradicated or presumed eradicated isolates in the quinupristin/dalfopristin and comparator groups, respectively, in which methicillin sensitivity testing not done.
[c] Five of six comparator-treated patients with MRSA received vancomycin, the other patient received cefazolin.
[d] $P = 0.007$.

that of comparator patients (68.4% versus 73.1%, respectively).

The findings of the univariate analyses were further examined by logistic regression analysis. When clinical success in the bacteriologically evaluable population was analysed in a logistic regression model, quinupristin/dalfopristin patients with polymicrobial infection were less likely than all other patients to be cured or improved (OR = 0.23); however, patients with *S. pyogenes* infection treated with quinupristin/dalfopristin were more likely to have a successful outcome than all other patients (OR = 3.23).

Bacteriological response

One or more causative organisms were isolated pretherapy from 351 of 562 (62.5%) clinically evaluable patients. *S. aureus* was the most commonly isolated pathogen, including 15 methicillin-resistant isolates, followed by *S. epidermidis* and *S. pyogenes.* Of 109 quinupristin/dalfopristin-treated patients with a skin infection due to *S. aureus*, the organism was the sole pathogen in 64 (58.7%). Similarly, 66% (66 of 100) of comparator-treated patients with *S. aureus* isolated had monomicrobial infection.

The by-pathogen bacteriological eradication rate for all pathogens was lower in the quinupristin/dalfopristin group (66.6%) than in the comparator group (77.7%; $P = 0.004$) (Table V). This difference was due primarily to lower eradication rates for methicillin-sensitive *S. aureus* (64.3% and 76.6%, respectively, for quinupristin/dalfopristin and comparator). For other major pathogens, such as *S. epidermidis* and *S. pyogenes*, eradication rates were comparable between the two treatment groups. In addition, eradication rates were lower in the quinupristin/dalfopristin group than in the comparator group for polymicrobial infections (63.3% and 83.1%, respectively), but were comparable for monomicrobial infections (72.6% and 70.8%, respectively). No decrease in susceptibility (i.e. >4-fold increase

in MIC) was found among persisting pathogens for any study drug.

There were relatively few infections due to MRSA in these two trials (15 MRSA/565 pathogens; 2.7%), yet vancomycin was selected for 19.6% of patients receiving comparator.

The clinical outcomes of patients receiving quinupristin/dalfopristin and those receiving vancomycin were comparable (68.4% success quinupristin/dalfopristin versus 63.2% success vancomycin), as were the by-patient bacteriological outcomes (66.7% success quinupristin/dalfopristin versus 64.7% success vancomycin). Because patients were not randomized between quinupristin/dalfopristin and vancomycin, it was not appropriate to assess these outcomes statistically.

The by-patient bacteriological success rate in the bacteriologically evaluable population was comparable between the quinupristin/dalfopristin (65.8%; 125 of 190) and comparator regimens (72.7%, 117 of 161) (95% CI = –16.5, 2.8). Similar findings were observed for the all-treated population, in which the bacteriological success rate by patient was 46.3% for quinupristin/dalfopristin and 48.5% for the comparator regimen.

Concordance between the clinical and bacteriological responses in both treatment groups for the bacteriologically evaluable population was excellent. A total of 120 of 190 (63.2%) patients in the quinupristin/dalfopristin group and 108 of 161 (67.1%) patients in the comparator group experienced clinical success with the eradication or presumed eradication of their pre-therapy pathogen(s). Similarly, 58 quinupristin/dalfopristin and 42 comparator-treated patients were both a clinical and a bacteriological failure. A discordant response was observed in 23 patients, including clinical success with bacteriological persistence in seven quinupristin/dalfopristin-treated patients. *S. aureus* was identified as the pre-therapy pathogen in more than 50% of patients with an unsatisfactory clinical response in both treatment groups.

Superinfection

A total of 22 patients in the bacteriologically evaluable population had a pathogen isolated from a superinfection. In the quinupristin/dalfopristin group 17 patients had a total of 20 pathogens isolated, including six *S. aureus* and 10 Gram-negative bacilli. In contrast, five patients in the comparator group had a total of seven pathogens from superinfections, including one *S. aureus* and four Gram-negative bacilli. In addition, five patients in the comparator group and four patients in the quinupristin/dalfopristin group, for whom a pre-therapy pathogen was not found, experienced a subsequent superinfection.

Adverse events

Two hundred and eighty-three of 450 (62.8%) quinupristin/dalfopristin and 239 of 443 (54.0%) comparator-treated patients reported at least one adverse clinical event. The majority of adverse clinical events (>80%) in both treatment groups were of mild to moderate severity. Drug-related (possibly or probably) adverse clinical events are summarized in Table VI. The most commonly reported quinupristin/dalfopristin-related adverse clinical events were nausea, vomiting, pain and rash. Study drug was discontinued early due to an adverse clinical event more often in the quinupristin/dalfopristin group (19.1%; 86 of 450) than in the comparator group (4.7%; 21 of 443). However, study drug was prematurely stopped due to therapeutic failure more often in the comparator group (11.5%; 51 of 443) than the quinupristin/dalfopristin group (5.5%; 25 of 450).

In addition to adverse clinical events, 463 patients reported an adverse venous event (defined as atrophy, oedema, haemorrhage, hypersensitivity, inflammation, thrombophlebitis, pain). The percentage of patients reporting a drug-related adverse venous event at least once during treatment was higher in the quinupristin/

Table VI. Most frequently reported drug-related adverse events[a]

	Number of patients (%)		
Adverse event	quinupristin/dalfopristin (n = 450)	comparator (n = 443)	P value
Patients with adverse clinical events[b]	113 (25.1)	58 (13.1)	0.000
nausea	114 (6.2)	59 (2.0)	0.002
vomiting	115 (3.8)	60 (0.9)	0.007
rash	116 (3.1)	6 (1.4)	0.111
pain	117(3.1)	1 (0.2)	0.001
pruritus	12 (2.7)	10 (2.3)	0.830
Patients with adverse venous events	298 (66.2)	126 (28.4)	0.000

[a]Probable or possible drug-related events which occurred in ⩾2% of either treatment group.
[b]Excludes adverse venous events.

dalfopristin group (66.2%) than in the comparator group (28.4%); Table VI). Most patients in both treatment groups received at least one infusion of study drug via a peripheral vein: 403 of 450 quinupristin/dalfopristin patients and 417 of 443 comparator patients (89.6% versus 94.1%, respectively). Injection site pain and/or inflammation were the most frequently reported adverse venous events in both treatment groups. Approximately one-third of patients in the quinupristin/dalfopristin group reported a moderate to severe adverse venous event. The median day of onset of the first adverse venous event after initiation of study therapy was 1 day earlier in the quinupristin/dalfopristin-treated group than in the comparator-treated group: (2.0 days quinupristin/dalfopristin versus 3.0 days comparator). The discontinuation of patients due to adverse venous events was greater in the quinupristin/dalfopristin group (12%; 54 of 450) than in the comparator group (2.0%; nine of 443).

Few clinically important drug-related adverse laboratory events were detected during the surveillance period in either trial. No meaningful changes were observed in haematology parameters for quinupristin/dalfopristin- or comparator-treated patients.

Discussion

The two multicentre, phase III, randomized studies described here compared the effectiveness of quinupristin/dalfopristin with that of established comparators for treatment of Gram-positive complicated skin and skin structure infections. Because of similar study design and contemporaneous patient enrolment, the results of the two studies were pooled, for a total of 450 quinupristin/dalfopristin patients and 443 comparator patients. The distribution of patients by geographical location and the demographic characteristics of the two study groups were comparable, as were their medical histories and prognostic and risk factors. The majority of patients in both treatment groups had erysipelas, traumatic wound infection and clean surgical wound infection. Surgical intervention was required in approximately one-third of patients in both treatment groups. The only demographic difference between the patients enrolled in the two studies was that patients in the USA trial were hospitalized for treatment approximately 3–5 days later after the onset of symptoms than were patients in the international trial.

The primary efficacy criterion, defined in advance by algorithm, was the clinical response in the clinically evaluable population as measured at the test-of-cure visit (or at the end-of-therapy visit when patient discontinued for failure). Of note, patients were categorized as a clinical failure if they were taken off study drug because of an adverse event and required continuation of antibiotic therapy for treatment of skin infection. Furthermore, in the bacteriologically evaluable population, patients who were defined as a clinical failure, but did not have a culture taken at the efficacy assessment visit, were classified as presumed persistence for the bacteriological response.

The clinical response to quinupristin/dalfopristin was equivalent to that for the established comparators in these two studies. In the integrated analysis, the clinical success rate in the clinically evaluable population was 68.2% in the quinupristin/dalfopristin group and 70.7% for the comparator regimen, thereby demonstrating equivalence despite a shorter mean duration of treatment for quinupristin/dalfopristin patients.

Clinical success was not influenced by medical history or risk factor, except that the clinical success rate was higher in comparator-treated patients in both trials with polymicrobial infection. The finding may have been due to isolation of greater numbers of Gram-negative bacilli in the quinupristin/dalfopristin group which are not within the spectrum of activity of quinupristin/dalfopristin. In monomicrobial infections, quinupristin/dalfopristin performed as well as comparator in the USA study (63.8% versus 66.7%) and better than the comparator (79.3% versus 60.3%) in the international trial.

In both trials, the by-pathogen bacteriological eradication rate for all pathogens was lower for quinupristin/dalfopristin than the comparator regimen (66.6% and 77.7%, respectively), reflecting the lower eradication rates for the primary pathogen methicillin-sensitive *S. aureus.* These findings were observed for both monomicrobial and polymicrobial infections in the USA trial, but only for polymicrobial infections in the international trial.

In the integrated analysis, by-patient bacteriological response was comparable across the two treatment groups. However, the by-patient bacteriological success rate was higher for the comparator regimen versus quinupristin/dalfopristin (75.9% versus 63%) in the USA trial, but comparable in the international study (69.5% and 68.9%, respectively).

The studies, conducted here for registration purposes, prohibited the use of concomitant antibiotic therapy with activity against both Gram-negative and Gram-positive bacteria. It has long been appreciated that such trials do not reflect clinical practice, in which the use of a concomitant antibiotic with Gram-negative activity would not be restricted by protocol. The lower by-patient bacteriological success rate in the USA trial is partly explained by the higher incidence of polymicrobial infection in the quinupristin/dalfopristin group, as well as by the large number of presumed bacteriological failures, so classified as a consequence of more premature discontinuations for adverse venous events and need for continuation of antibiotic therapy.

Other potential reasons for the outcome differences seen in these trials relate to the selection of comparator and their open-label design. Investigators were required to call a central, automated randomization system by telephone and were instructed to administer either quinupristin/

dalfopristin or their choice of comparator (i.e. oxacillin or vancomycin in the USA study, or cefazolin or vancomycin in the international study) depending upon patient history, knowledge of local epidemiology and the availability of culture results. Because of this intervention on the part of the investigator, it was not possible to stratify patient randomization between quinupristin/dalfopristin and the individual drugs used as comparators. This may have led to a potential bias in favour of the comparator arm, according to the amount of knowledge of a patient's condition at the time of randomization. For example, in the international trial, a patient with a possible polymicrobial infection could have been treated with cefazolin instead of vancomycin. Furthermore, the use of a new antibiotic in an open-label study is problematic, since investigators may discontinue therapy in a patient responding slowly to treatment with the investigational agent, yet they may be more comfortable continuing treatment with an approved antibiotic with which they are more familiar following years of clinical practice.

Tan *et al.*[14] compared the efficacy of two broad-spectrum agents, piperacillin–tazobactam and ticarcillin–clavulanate, in a double-blind, randomized trial for complicated skin infections in hospitalized patients. *S. aureus* and streptococcal species were the most frequently isolated pathogens; 60% of patients had a polymicrobial infection. Despite the broad-spectrum activity of these two antimicrobial agents, approximately one-quarter of all patients was a clinical failure: 24.0% for piperacillin–tazobactam and 23.0% for ticarcillin–clavulanate. The clinical success rates reported in the Tan study are very similar to those reported in these two trials with quinupristin/dalfopristin, thus emphasizing the difficulty in successfully treating these infections.

The incidence of drug-related adverse clinical events was greater following administration of the streptogramin than the comparator regimens. This difference was predominantly due to a higher incidence of nausea and/or vomiting, rash and pain in the quinupristin/dalfopristin group. In addition, quinupristin/dalfopristin was associated with more infusion-related adverse venous events (i.e. inflammation and pain at the infusion site) than was the comparator regimen. Although a higher percentage of quinupristin/dalfopristin patients (38.2%) than comparator patients (30.7%) were discontinued prematurely from study treatment, comparator patients were more often discontinued for therapeutic failure of the study drug and quinupristin/dalfopristin patients for a venous or clinical adverse event.

In conclusion, the efficacy of quinupristin/dalfopristin in the treatment of complicated skin and skin structure infection in hospitalized patients was demonstrated in the two studies separately, as well as in the integrated analysis. Quinupristin/dalfopristin performed better in monomicrobial Gram-positive infections than in polymicrobial infections, a finding consistent with the targeted Gram-positive spectrum of the antibiotic. A higher frequency of adverse venous events associated with quinupristin/dalfopristin use often necessitated premature discontinuation, and was, in part, responsible for the higher than expected rate of clinical and presumed bacteriological failure. The majority of patients received quinupristin/dalfopristin via a peripheral catheter; it is probable that venous tolerability would improve with increased infusion volume, or the use of central venous access or a peripherally inserted central venous catheter.[15] In conjunction with surgical intervention, quinupristin/dalfopristin is an effective treatment for patients with complicated skin and skin structure infections caused by quinupristin/dalfopristin-susceptible Gram-positive bacteria, including methicillin- and erythromycin-resistant *S. aureus.*

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