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Dalbavancin

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Contents

Abstract

▲ Dalbavancin is a semisynthetic glycopeptide antibacterial agent that is active against Gram-positive bacteria associated with complicated skin and skin structure infections (cSSSIs). It is administered as a two-dose regimen intravenously infused over 30 minutes once weekly.

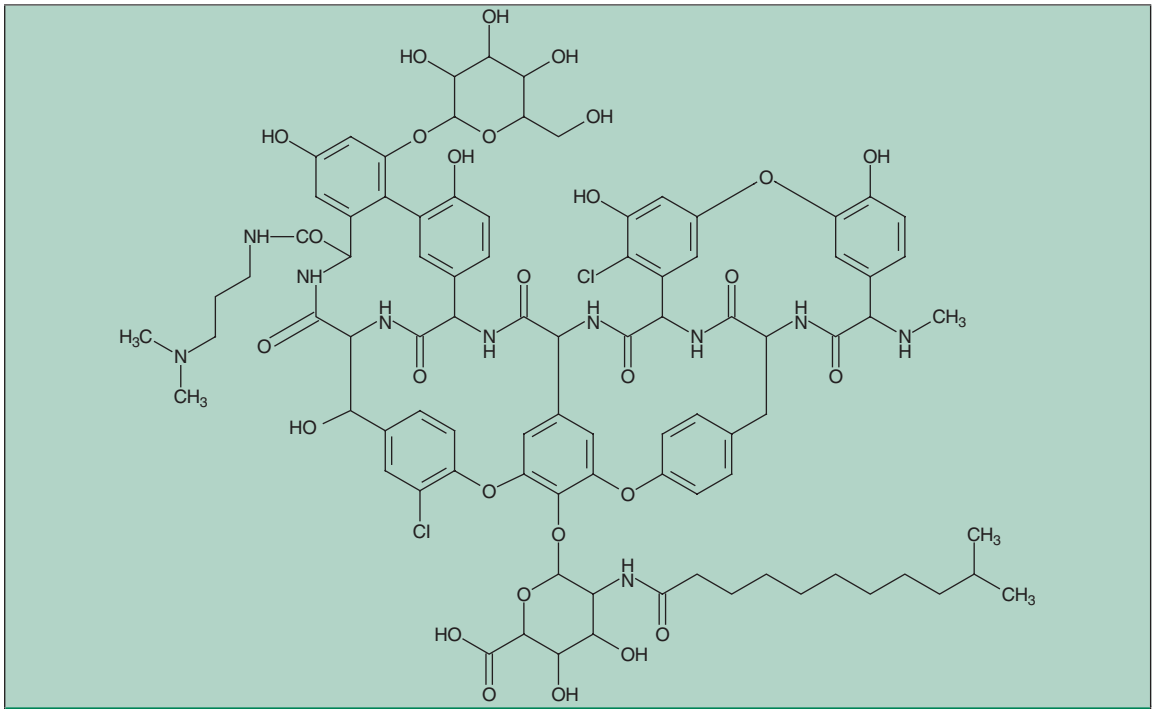
▲ The efficacy of dalbavancin (1000 mg on day 1 and 500 mg on day 8) has been examined in two randomized controlled trials in adults with cSSSIs. In each study, the primary efficacy measure was clinical success at the test-of-cure or follow-up visit in clinically evaluable patients.

▲ In a randomized, controlled, double-blind, multinational, phase III trial, dalbavancin was noninferior to linezolid, with clinical success rates of 88.9% and 91.2%.

▲ In a randomized, open-label, multicentre, phase II trial, clinical success rates were 94% with dalbavancin and 76% with comparator antibacterials.

▲ Dalbavancin was generally well tolerated by adult patients with cSSSIs, with most adverse events being of mild or moderate severity.

Features and properties of dalbavancin	
Indication	
Complicated skin and skin structure infections in adults	
Mechanism of action	
Glycopeptide antibacterial: inhibits peptidoglycan synthesis	
Dosage and administration in clinical studies	
Dose	1000 mg day 1; 500 mg day 8
Frequency of administration	Once weekly; two doses
Administration	30-minute intravenous infusion
Pharmacokinetic profile in healthy volunteers (1000 mg day 1; 500 mg day 8)	
Peak plasma concentration	278.3 mg/L (day 1) 166.3 mg/L (day 8)
Area under the plasma concentration-time curve on day 8	10 577 mg • h/L
Apparent steady-state volume of distribution	18.3 L
Terminal elimination half-life	321 h
Apparent plasma clearance rate	0.0466 L/h
Most common (≥5%) treatment-related adverse events	
Nausea, diarrhoea	



Skin and skin structure infections (SSSIs) are often caused by Gram-positive bacteria, such as staphylococci and β-haemolytic streptococci,[1] and encompass a range of conditions such as cellulitis, impetigo, ulcers and abscesses.[2] If an SSSI involves the deeper layers of soft tissue and/or surgery is required, then it is usually considered a complicated SSSI (cSSSI).

While minor SSSIs are easy to treat with agents such as penicillin, oral cephalosporins, clindamycin or macrolides, resistant strains of Gram-positive pathogens (e.g. meticillin [methicillin]/oxacillin-resistant *Staphylococcus aureus* [MRSA] and macrolide-resistant *Streptococcus pyogenes*) can make treatment more problematic.[2]

Most community-acquired strains of MRSA are susceptible to tetracycline or trimethoprim/sulfamethoxazole (cotrimoxazole) treatment; however, patients hospitalized with severe or progressive SSSIs due to MRSA may require treatment with a glycopeptide antibacterial, linezolid or daptomycin.[2] Glycopeptide antibacterials and linezolid are recommended in MRSA SSSIs where there is a high risk of bacteraemia.[3]

Dalbavancin is a novel glycopeptide antibacterial agent with a once-weekly, two-dose administration schedule that is active against Gram-positive bacteria, including MRSA. This review examines the pharmacological profile of dalbavancin and its clinical efficacy and tolerability in patients with cSSSIs.

1. Pharmacodynamic Profile

Mechanism of Action

Dalbavancin is a semisynthetic glycopeptide, derived from the natural glycopeptide A40926.[4] Glycopeptide antibacterials inhibit late stages of peptidoglycan synthesis and interfere with bacterial cell wall synthesis.[4,5] Dalbavancin binds to the D-Ala-D-Ala terminus of pentapeptide peptidoglycan

precursors, thereby inhibiting cell wall peptidoglycan crosslinking.[4,6]

Antibacterial Activity

This section focuses on the antibacterial activity of dalbavancin against the microorganisms associated with cSSSIs specified in the proposed prescribing information (*S. aureus* [including MRSA isolates], *S. pyogenes* and *S. agalactiae* [i.e. β-haemolytic streptococci]).[7]

In Vitro Activity

The *in vitro* activity of dalbavancin was examined by determining the minimum inhibitory concentration (MIC) in Mueller-Hinton broth. Where more than 6–10 isolates were tested, the MIC necessary to inhibit 50% (MIC_{50}), 90% (MIC_{90}) or 100% (MIC_{100}) of the target bacterial strains were commonly reported; in some studies, the minimum bactericidal concentration (MBC) was also determined.

Susceptibility breakpoints for dalbavancin have not yet been established, although susceptibility breakpoints for staphylococci (MIC ≤1 mg/L) and streptococci (MIC ≤2 mg/L) have been proposed by the manufacturer of dalbavancin.[8] Studies were conducted on isolates obtained worldwide,[9,10] from Europe and North America,[11] Latin America[5] and the US;[8,12,13] the origin of isolates in other studies was not reported.[14-16]

- Dalbavancin is bactericidal[4] and has demonstrated *in vitro* activity against a wide range of Gram-positive pathogens.[17]
- Dalbavancin has good *in vitro* activity against *S. aureus*, including MRSA isolates. MIC_{50}, MIC_{90} and MIC_{100} values against 43–2441 methicillin/oxacillin-susceptible *S. aureus* (MSSA) isolates were 0.03–0.125, 0.06–0.125 and 0.5 mg/L, respectively, with corresponding values against 29–1177 MRSA isolates of 0.03–0.125, 0.06–0.125 and 0.25 mg/L.[5,8,9,11,13-15] In one study, 100% of 762 oxacillin-susceptible and 1009 oxacillin-resistant *S. aureus* isolates were susceptible to dalbavancin.[8] MIC_{50} and MIC_{90} values against 20 *S. aureus* clinical isolates were 0.06 and 0.12 mg/L.[18] A vancomycin- and teicoplanin-susceptible strain of *S. aureus* had MIC and MBC values of 0.5 mg/L;[19] MIC and MBC values for another MSSA strain were ≤0.13–0.25 and 2 mg/L and for another MRSA isolate were 0.25–0.5 and 16–32 mg/L.[20]
- Serum diminishes the *in vitro* activity of dalbavancin. For example, in media containing 50% human serum, MIC and MBC values for dalbavancin were 1–4 and 2–8 mg/L for MSSA, compared with 0.06–0.25 and 0.06–0.5 mg/L in media without serum.[16] Against MRSA, MIC and MBC values were both 4–16 mg/L with serum, compared with 0.12–0.25 and 0.25–8 mg/L without serum.[16] Against glycopeptide-intermediate-resistant *S. aureus*, MIC and MBC values were 16–32 and 32 mg/L with serum, compared with 1–2 and 1–4 mg/L without serum.[16]
- The MBC of dalbavancin was 2.04 and 1.61 mg/L against two MRSA test strains incubated with 50% human serum obtained from healthy volunteers who had received intravenous dalbavancin.[21] Serum samples from those who had received a single dalbavancin dose of ≥500 mg, or multiple doses of the drug, showed bactericidal activity 7 days after antibacterial administration.
- Dalbavancin did not show complete cross-resistance with vancomycin against staphylococci. For example, dalbavancin had MIC values of 0.06–32 mg/L against 12 vancomycin-resistant isolates derived *in vitro* from the 'Hershey' strain of *S. aureus*,[12] and an MIC value of 4 mg/L against a vancomycin- and teicoplanin-resistant strain of *S. aureus* and a teicoplanin-resistant derivative of this strain.[19] In addition, the MBC of the vancomycin- and teicoplanin-resistant isolate was also 4 mg/L.[19] Moreover, MIC_{50} and MIC_{90} values against ten vancomycin-intermediate-resistant staphylococcal isolates were 0.06 and 1 mg/L.[10]
- A time-kill experiment revealed that dalbavancin was bactericidal (99.9% killing) after 24 hours against six strains of staphylococci (including MSSA, MRSA and meticillin-susceptible and meticillin-resistant coagulase-negative staphylococci) at a concentration 4-fold higher than the MIC.[15]
- Dalbavancin had good *in vitro* activity against β-haemolytic streptococci, such as *S. pyogenes* and

S. agalactiae. MIC_{50} and MIC_{90} values were ≤0.008–0.06 mg/L and 0.016–0.125 mg/L (22–342 isolates).[5,8,9,11,13,14] The MIC for dalbavancin against ten streptococcal clinical isolates was ≤0.016 mg/L.[22]

- Dalbavancin also demonstrated *in vitro* activity against vancomycin-susceptible *Enterococcus faecalis* (MIC_{50} 0.03 mg/L and MIC_{90} 0.06 mg/L; 586 isolates),[9] vancomycin-susceptible *E. faecium* (MIC_{50} 0.06 mg/L and MIC_{90} 0.12 mg/L; 29–77 isolates)[9,10] [including isolates resistant to quinupristin/dalfopristin],[9] ampicillin-susceptible *E. faecalis* (MIC_{50} 0.06 mg/L; 4 isolates),[18] and coagulase-negative staphylococci such as *S. epidermis* (MIC_{50} 0.03–0.06 mg/L and MIC_{90} 0.06–0.12 mg/L, 27–1231 isolates).[5,11,13,18]

Activity In Animal Models

- In the rat granuloma pouch infection model,[20] single 2.5, 5 and 10 mg/kg intravenous doses of dalbavancin reduced MSSA levels in the rat granuloma pouch; the 10 mg/kg dose reduced MSSA levels to below the limits of detection at 24 hours with no regrowth detected for at least 96 hours.[20] In comparison, controls had an increase in MSSA levels. Against MRSA, dalbavancin reduced bacterial levels in a dose-dependent manner; dalbavancin 10 mg/kg reduced bacterial levels by 2–3 log_{10} cfu/mL and prevented regrowth for at least 96 hours.[20]

Pharmacodynamic/Pharmacokinetic Relationship

Glycopeptide antibacterials are generally considered to have time-dependent bactericidal activity, although as well as the period of time that serum concentrations remain above the MIC, the pharmacodynamic/pharmacokinetic parameters of maximum plasma concentration (C_{max}) : MIC ratio and area under the concentration-time curve from time zero to 24 hours (AUC_{24}) : MIC ratio have been correlated with efficacy in *in vitro* studies and animal models.[17,23,24]

- The pharmacodynamic activity of dalbavancin against *S. pneumoniae* and *S. aureus* was examined *in vivo* using murine thigh or lung infection models.[23] To achieve a bacteriostatic effect, mean free-drug AUC_{24} : MIC ratios of 17 and 265 were required against five isolates each of *S. pneumoniae* and *S. aureus*, with a <2-fold higher AUC_{24} : MIC target needed for a bactericidal effect (1 or 2 log reduction in bacterial counts), suggesting that *in vivo* efficacy of dalbavancin against *S. aureus* requires a higher drug concentration than that needed for *in vitro* activity, whereas the *in vitro* and *in vivo* efficacy against *S. pneumoniae* was similar.
- In a study simulating initial free dalbavancin concentrations of up to 21 mg/L over 240 hours against strains of *S. aureus*,[24] the AUC_{24} : MIC ratio for a bacteriostatic effect ranged from 36 to 100 (for endpoints taken at 24–240 hours), whereas a bactericidal effect (2 log reduction in bacterial counts) occurred at an AUC_{24} : MIC ratio of 214–331 over the same time frame. Initial dalbavancin concentrations of 15 and 21 mg/L resulted in three vancomycin-susceptible isolates being undetectable by 48–96 hours, and one vancomycin-intermediate isolate being undetectable at 144 and 96 hours.
- In contrast to the rat granuloma pouch infection model,[20] and murine thigh and lung infection models,[23] results from the *in vitro* pharmacokinetic system indicated that dalbavancin has a non-concentration-related effect against strains of *S. aureus*. Further studies are required to confirm the relationship between the concentration of dalbavancin and its effect *in vitro* and *in vivo*.

Potential For Resistance

- When plates containing dalbavancin 10 mg/L were used to culture *S. aureus*, no single-step high-level resistance was observed.[16] There was a 2-fold increase in the MIC against *S. aureus* (from 0.25 to 0.5 mg/L) after 24 passages at sub-MIC concentrations. There was also little distribution variability in the MICs of colonies isolated from the passage steps.[16] In an analysis of three phase III clinical studies, no strains with an increased dalbavancin MIC emerged from persistent isolates.[25]

2. Pharmacokinetic Profile

The pharmacokinetics of dalbavancin (administered as an intravenous infusion over 30 minutes) have been examined in healthy volunteers,[21,26-28] patients with renal[29] or hepatic[28,30] impairment, and patients with SSSIs.[22] In addition, adults with SSSIs (n = 502) or catheter-related bloodstream infections (n = 30) from three clinical trials were included in a population pharmacokinetic analysis[6] in which almost 80% of patients received dalbavancin 1000 mg on day 1 and 500 mg on day 8, with the remainder receiving dalbavancin 650 mg on day 1 followed by dalbavancin 65 mg/day for up to 13 days, or a single 1000 or 1100 mg dose of the drug.[6] Four studies are available as abstracts and/or posters[26,28-30] and four studies are fully published.[6,21,22,27]

Absorption and Distribution

- Linear, dose-proportional pharmacokinetics were observed in healthy volunteers (n = 21) given single doses of dalbavancin 140–1120 mg.[21] C_{max} was attained after completion of the 30-minute dalbavancin infusion.[21] In six healthy adults receiving a single 1000 mg dose of dalbavancin, mean C_{max} was 301 mg/L and mean AUC was 23 843 mg • h/L.[26]
- In healthy adults (n = 9), C_{max} was 278.3 mg/L following a 1000 mg loading dose, and 166.3 mg/L after a 500 mg maintenance dose on day 8; the 8- and 15-day AUC was 10 577 and 20 473 mg • h/L, and the AUC extrapolated to infinity (AUC_{∞}) was 33 851 mg • h/L.[28]
- Plasma dalbavancin concentrations were maintained above the relevant MIC_{90} values (see section 1) for at least 12 days in patients with SSSIs who received intravenous dalbavancin 1000 mg on day 1 and 500 mg on day 8.[22] Mean plasma dalbavancin concentrations were 30.4, 21.2 and 9.0 mg/L on days 8, 20 and 34, respectively.[22] Concentrations of ≈10 mg/L are thought to be bactericidal against *S. aureus*.[17]
- The mean volume of distribution at steady state (V_{ss}) in healthy volunteers receiving dalbavancin 1000 mg on day 1 and 500 mg on day 8 was 18.3 L.[28] In the population pharmacokinetic analysis,[6] the estimated V_{ss} was 15.7 L, the central volume of distribution was 4.15 L and the peripheral volume of distribution was 11.4 L.[6]
- Intravenous administration of dalbavancin 1000 mg achieved skin penetration of ≈60% in healthy volunteers who had blisters induced with cantharidin ointment; mean blister fluid AUC was 6438 mg • h/L and mean plasma AUC was 10 806 mg • h/L.[27] Blister fluid concentrations of dalbavancin remained above 30.3 mg/L through to day 7 (study end), exceeding the MIC_{90} values (section 1) for target bacteria, including drug-resistant strains of staphylococci and streptococci.[27]
- Dalbavancin is ≈93% plasma protein bound.[31] While no information is available on dalbavancin accumulation in humans, in rats, dalbavancin was not retained by any particular organ or component of blood or tissue.[32]

Metabolism and Elimination

- Little information on the metabolism of dalbavancin is available, but it has been reported that a minor metabolite (hydroxy-dalbavancin; 8−12% of the administered dose) has been observed in human urine.
- Dalbavancin is eliminated by both renal and non-renal routes with ≈42% of the dose excreted unchanged in the urine in healthy volunteers.[26] Total clearance (CL) after a single dose of dalbavancin 1000 mg was 0.0181 L/h.[26] After dalbavancin 1000 mg on day 1 and 500 mg on day 8, CL was 0.0466 L/h.[28] In the population pharmacokinetic analysis, estimated mean CL was 0.0571 L/h.[6]
- Mean faecal dalbavancin concentrations of 6.8–73.4 mg/kg (day 5) and 7.4–26.4 mg/kg (day 14) were obtained from 12 healthy volunteers after a single 1000 mg dose of dalbavancin, but the drug did not appear to have a significant effect on normal human intestinal microflora.[33]
- The clearance of dalbavancin appeared to be unaffected by the concomitant administration of cytochrome P450 substrates, inhibitors or inducers, and other medications including paracetamol (aceta-

minophen), aztreonam, fentanyl, metronidazole, furosemide (frusemide), proton pump inhibitors, midazolam or simvastatin.[6]

- During the first 24–48 hours of the distribution phase, a steep decline in the plasma concentration was observed in healthy volunteers followed by a slow terminal phase.[26] The terminal elimination half-life ($t_{1/2}\beta$) of dalbavancin after administration of a single dose was very long (149–257 hours);[21,26] after doses on days 1 and 8 it was 321 hours.[28] The estimated mean $t_{1/2}\beta$ in the population pharmacokinetic analysis was 8.5 days.[6]

Special Patient Populations

- Compared with healthy volunteers, the pharmacokinetics of dalbavancin were not altered to a clinically significant extent in patients with mild (Child-Pugh Class A),[28,30] moderate (Child-Pugh Class B)[28,30] or severe (Child-Pugh Class C)[28] hepatic impairment; thus, dosage adjustment is not required in patients with hepatic impairment.
- In addition, the pharmacokinetics of dalbavancin were similar in patients with mild renal impairment (creatine clearance 3–4.8 L/h [50–80 mL/min]) to those in healthy volunteers, requiring no dosage adjustment.[29]

3. Clinical Efficacy

The clinical efficacy of dalbavancin in adults with an SSSI has been evaluated in a randomized, open-label, active-comparator-controlled, multicentre, dose-ranging, phase II trial,[22] and a randomized, double-blind, multinational, phase III, noninferiority trial comparing dalbavancin with linezolid.[34]

Both studies included patients with SSSIs suspected or known to be caused by Gram-positive pathogens.[22,34] The phase II trial included patients with infections involving deep soft tissues and/or that required significant surgical intervention (e.g. major abscess, infected ulcer, major burn, deep/extensive cellulitis); >90% of patients in this trial had deep or complicated infections.[22]

The phase III trial included patients with cSSSI, defined as deeper soft tissue infections, infections requiring surgical intervention (e.g. major abscess, major burn, traumatic/surgical wound infection, deep SSSI, such as extensive/ulcerating cellulitis) or infections known or thought to be caused by MRSA.[34]

Patients in both trials also had to have at least two signs and/or symptoms of SSSI, such as erythema, drainage, heat, fluctuance, pain or tenderness to palpation, or swelling.[22,34] In the phase III study,[34] patients were also required to show systemic infection or some other complicating factor necessitating parenteral therapy. Exclusion criteria included septic arthritis or osteomyelitis,[22,34] infections that would need more than two surgical interventions during the study period[34] and any conditions needing antimicrobial treatment that could interfere with the investigation.[34]

In the phase II trial,[22] dalbavancin was administered intravenously as either a two-dose regimen (1000 mg day 1 and 500 mg on day 8 [n = 21; intent-to-treat (ITT) population]) or a single 1100 mg dose (n = 20; ITT). Comparator regimens (n = 21; ITT) in the dose-ranging study were determined by the investigators prior to randomization; the standard-of-care comparators included ceftriaxone, cefazolin, piperacillin plus tazobactam, clindamycin, vancomycin, linezolid or cefalexin.[22] Only descriptive analyses were conducted in this study.

In the phase III trial,[34] dalbavancin was administered in a two-dose regimen as an intravenous infusion; 1000 mg on day 1 and 500 mg on day 8 (n = 571; ITT). If certain criteria were met (temperature reduction or clinical improvement at the infection site after at least 24 hours of parenteral treatment), patients were switched to an oral placebo. Linezolid 600 mg was administered intravenously every 12 hours (n = 283; ITT); patients were eligible to receive oral linezolid (600 mg every 12 hours) after a minimum of 24 hours of intravenous treatment.[34]

To maintain blinding, patients receiving dalbavancin were given intravenous placebo infusions of 5% dextrose or saline every 12 hours until a switch

to oral placebo was made.[34] Similarly, on day 8 every patient received an intravenous infusion of either dalbavancin 500 mg, linezolid 600 mg or placebo. In addition, the oral placebo or linezolid regimens were continued if patients were already receiving them.[34]

Aztreonam,[22,34] metronidazole[22,34] or ceftazidime[22] was administered if mixed infections were suspected.

The primary endpoint in both studies was the clinical success rate at the follow-up[22] or test-of-cure (TOC)[34] visit in clinically evaluable patients (n = 51[22] and n = 434 [dalbavancin] or 226 [linezolid][34]). Clinical success was a clinical response to treatment such that additional antibacterial therapy was not necessary.[22,34] In the phase II trial,[22] clinical success was the combined clinical response categories of cure and improvement.

In the phase III trial, dalbavancin was deemed noninferior to linezolid if the lower limit of the 97.5% confidence interval (CI) for the between-group difference in the clinical success rate did not exceed −12.5%.[34] The follow-up visit was on day 24 of the single-dose treatment arm and on day 34 of the two-dose treatment arm.[22] The TOC[34] visit was ≈14 days after the end of treatment.

Secondary endpoints included microbiological success (eradication or presumed eradication of all Gram-positive pathogens)[22,34] and overall success (combined clinical and microbiological success)[34] at the follow-up[22] or TOC[34] visit.

In the phase II study,[22] Gram-positive pathogens were isolated in 66% of patients at baseline, most of whom had a single Gram-positive pathogen isolated. *S. aureus* was detected in 83%, including MRSA in 32%, of patients from whom pathogens were isolated (more than one pathogen was detected in some patients).[22]

Similarly, in the phase III study,[34] 550 patients (64%) had one or more Gram-positive pathogens isolated. *S. aureus* was the predominant pathogen in 89.5% of these patients and 56.5% of these *S. aureus* isolates were MRSA (50.5% of all patients who had pathogens identified at baseline).[34] Other pathogens isolated in the trials included group B streptococci, *S. pyogenes* and other *Streptococcus* spp.[22,34]

Phase II Trial

- In the phase II study,[22] a numerically higher proportion of patients treated with the two-dose regimen of dalbavancin had successful clinical responses at the follow-up visit (primary endpoint) compared with those who were treated with the active comparators (94% vs 76%); patients receiving a single dose of dalbavancin had a clinical success rate of 62%.
- The microbiological success rate at the follow-up visit was 92% in dalbavancin two-dose recipients versus 71% with other active comparators in microbiologically evaluable patients; in the dalbavancin single-dose treatment arm, 58% of patients had microbiological success.[22]
- A successful clinical response in those infected with MRSA was observed in four of five patients receiving two-doses of dalbavancin, three of six patients receiving a single-dose of dalbavancin and one of two patients receiving a comparator regimen.[22]

Phase III Trial

- Dalbavancin was at least as effective as linezolid in achieving clinical success. Clinical success (primary endpoint) was observed in 88.9% of dalbavancin recipients versus 91.2% of those receiving linezolid.[34] The lower limit of the 97.5% CI for the between-group difference in clinical success rate was −7.28%, establishing the noninferiority of dalbavancin to linezolid.
- The microbiological and overall success rates in the treatment groups were 89.5% and 88.4% (dalbavancin) and 87.5% and 86.8% (linezolid).[34]
- Of the pathogens isolated at baseline, at least 85% were eradicated regardless of the treatment used; specifically, 91% and 89% of MRSA had been eradicated by dalbavancin and linezolid at the TOC visit.[34] A recurrence of the pathogen(s) isolated at baseline occurred in a small proportion of patients (1% and 4% of patients receiving dalbavancin and

linezolid) and persistence of the original pathogen(s) occurred in ≤2% of patients by the TOC visit; the emergence of new pathogens was rare (<1% of patients).[34]

- In a separate analysis (published as an abstract)[35] of evaluable patients infected with community-acquired MRSA at baseline (n = 128), there was no significant difference between dalbavancin and linezolid recipients in the clinical (95.3% vs 90.7%; 95% CI −5.2, 14.4) or microbiological (92.9% vs 93.0%; 95% CI −9.4, 9.3) success rates.

4. Tolerability

This section focuses on tolerability data from the phase II[22] and III[34] trials (see section 3 for design details). No statistical analyses were reported.

- Dalbavancin was generally well tolerated in patients with cSSSIs and most adverse events were mild or moderate in severity.[22,34] The tolerability profile of dalbavancin was similar to that of linezolid.[34]
- Adverse events were reported by 56% of dalbavancin and 61% of linezolid recipients in the phase III study,[34] with 25.4% and 32.2% of patients experiencing adverse events considered to be probably or possibly related to treatment; 90% of patients in the phase II trial reported at least one adverse event, but most were of mild or moderate severity.
- Among dalbavancin recipients in the phase III trial, the most common adverse events considered probably or possibly related to treatment included nausea and diarrhoea (figure 1).[34] Infusion-site reactions occurred in 2.8% of dalbavancin recipients and 3.9% of linezolid recipients.

In the phase II trial, 11 (55%) patients receiving one dose of dalbavancin, 10 (48%) of those receiving two doses of dalbavancin and 12 recipients of comparator regimens experienced possibly or probably drug-related adverse events.[22]

- Serious adverse events considered to be related to the study drug occurred in one dalbavancin recipient (mild leukopenia) and two linezolid recipients (moderate thrombocytopenia and severe pancytopenia) in the phase III trial.[34] No serious drug-related adverse events were reported in the phase II trial.[22]
- Adverse events leading to discontinuation of therapy occurred in 3.9% and 3.2% of dalbavancin and linezolid recipients in the phase III trial;[34] one patient withdrew from the phase II trial as a result of a drug-related adverse event.[22] In the the phase III trial, four patients died in total (two in each treatment arm); however, all deaths were thought to be unrelated to treatment.[34]
- Clinically significant laboratory abnormalities were not observed in the phase II trial[22] and were were infrequent in the phase III trial.[34] Examination of particular abnormalities experienced by patients in the phase III trial did not suggest any cause for concern.[34]

5. Dosage and Administration

In clinical trials, dalbavancin was administered intravenously as an infusion over 30 minutes.[22,34]

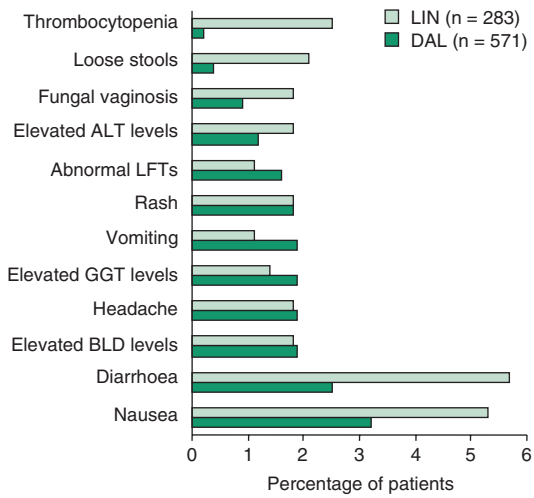


Fig. 1. Tolerability of dalbavancin (DAL) and linezolid (LIN) in patients with complicated skin and skin structure infections. Results are from a randomized, double-blind, multicentre, phase III trial.[34] Adverse events considered probably or possibly related to treatment that were reported by ≥2% of patients after intravenous administration of either DAL 1000 mg on day 1 followed by DAL 500 mg on day 8 or intravenous LIN 600 mg twice daily for a minimum of 24 hours followed by oral LIN 600 mg twice daily. To maintain blinding, DAL recipients were given intravenous placebo infusions every 12 hours until switched to oral placebo. No statistical analyses were reported. **BLD** = blood lactate dehydrogenase; **GGT** = γ-glutamyltransferase; **LFTs** = liver function tests.

The dosage used in the phase III trial was 1000 mg on day 1 and 500 mg on day 8 (section 3).[34]

6. Dalbavancin: Current Status

Dalbavancin has been investigated for the treatment of adults with cSSSIs caused by susceptible organisms including *S. aureus* (including MRSA), *S. pyogenes* and *S. agalactiae*.

Intravenously administered dalbavancin was noninferior to linezolid in a well designed phase III trial. In both this trial and a phase II trial, clinical success rates with dalbavancin were >88%. Dalbavancin was generally well tolerated and had a tolerability profile similar to that of linezolid.

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