Dalbavancin (Zeven), a Novel Glycopeptide For Resistant Gram-Positive Organisms

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INTRODUCTION
Severe infections associated with gram-positive organisms such as Staphylococcus aureus contribute to significant morbidity and mortality. The prevalence and resistance of MRSA has confirmed the increasing prevalence and resistance of MRSA in the community. The currently available options to treat resistant gram-positive infections include vancomycin (Vancocin, ViroPharma), linezolid (Zyvox, Pfizer), quinupristin–dalfopristin (Synercid, Monarch), daptomycin (Cubicin, Cubist), and tigecycline (Tygacil, Wyeth). In light of the developing resistance and toxicities associated with antimicrobial agents, it is imperative to continue the search for other “magic bullets” to control gram-positive pathogens. Dalbavancin (Zeven, Vicuron/Pfizer), a novel, second-generation glycopeptide, is similar to vancomycin and teicoplanin (Targocid, Sanofi-Aventis). It is being studied in phase 3 clinical trials for the treatment of gram-positive infections.

PHARMACOLOGY

Dalbavancin is a bactericidal, dimethyl amino-propylamide derivative of the glycopeptide A40926. Glycopeptides inhibit the bacterial cell wall by binding to the C terminal of the d-alanyl-d-alanine moiety of peptidoglycan, and they block enzymes involved in the final steps of peptidoglycan synthesis and cell wall formation. Osmotic shock, causing cell rupture, results from the damaged cell wall, which cannot maintain the osmotic gradient between the bacterial cell and its environment; consequently, the bacteria die.

Dalbavancin’s long lipophilic side chain is attached to the basic glycopeptide backbone (Figure 1). This side chain confirms stabilization and anchors the agent, ensuring prolonged interaction with peptidoglycan. This increased inter-
action with the bacterial cell wall contributes to dalbavancin’s pharmacokinetic and pharmacodynamic properties, specifically its extended half-life.

**PHARMACOKINETICS**

Leighton et al. evaluated multiple daily doses of dalbavancin, ranging from a loading dose of 300 to 1,000 mg, followed by 30 to 100 mg, administered via a 30-minute intravenous (IV) infusion. The peak concentration (C_max) and area-under-the-curve (AUC_{0–24}) concentration increased proportionally and linearly in relation to the dose. The half-life ranged from 185 to 213 hours, supporting once-weekly administration. In the single-dose part of this trial, the volume of distribution (V_d) ranged from 7 to 13 liters.

In another study of human volunteers, Dorr et al. reported similar pharmacokinetic parameters. The average terminal elimination half-life of dalbavancin was 170 ± 18.6 hours (seven days), and the V_d was 9.7 ± 2 liters.

Studies have shown that dalbavancin is highly protein-bound to albumin (93%), in contrast to vancomycin (30%–55%) and linezolid (31%). In addition, dalbavancin achieved up to 60% penetration into the blister fluid following a 1,000-mg single IV dose in human healthy volunteers, suggesting good tissue penetration.

Dalbavancin does not seem to undergo hepatic biotransformation with the cytochrome CYP 450 enzyme system. Approximately 40% of the drug is excreted unchanged in the urine, indicating that it follows primarily nonrenal clearance. Therefore, dose adjustments in patients with renal disease do not seem to be necessary.

Data are limited in terms of hepatic impairment and dose adjustments. In one trial, Pope and Roecker noted no differences in the terminal half-life between patients with mild, moderate, and severe liver disease and participants with normal hepatic function.

**PHARMACODYNAMICS**

Dalbavancin’s concentration in the macrophages is predictive of its intra-cellular penetration. In mouse models of thigh infection, large, infrequent doses were more efficacious than multiple doses. Dalbavancin demonstrated concentration-dependent killing because the ratio of C_max to minimum inhibitory concentration (MIC), and the AUC/MIC ratio were more predictive of bactericidal activity rather than the time above the MIC. Other analyses revealed similar results of concentration-dependent eradication by dalbavancin; in contrast, vancomycin causes time-dependent, concentration-independent killing.

**ANTIMICROBIAL ACTIVITY IN VITRO**

**Gram-Positive Organisms**

Dalbavancin is active against methicillin-susceptible S. aureus (MSSA), MRSA, vancomycin-intermediate S. aureus (VISA), vancomycin-resistant S. aureus (VRSA), and linezolid-resistant S. aureus. In vitro, dalbavancin also inhibits methicillin-susceptible coagulase-negative streptococci (MSCNS), methicillin-resistant CNS (MRSCNS), and vancomycin-intermediate CNS (VICNS).

Dalbavancin has in vitro activity against streptococci that are both susceptible and resistant to erythromycin and penicillin.

In tests of vancomycin-susceptible and vancomycin-resistant enterococci (VRE) in vitro, dalbavancin displayed activity against susceptible and resistant strains that possessed vanB and vanC genes but not vanA phenotypes of VRE.

Goldstein BP, et al. Goldstein and colleagues tested the bactericidal activity of dalbavancin in vitro against S. aureus (MSSA, MRSA, VISA), S. pyogenes, E. faecalis, and E. faecium isolates from various hospitals in the U.S. In every case, dalbavancin had lower MICs and minimum bactericidal concentrations (MBCs) than vancomycin and teicoplanin (Table 1).

The potential for the development of staphylococci resistance was tested by direct selection and serial passages of microorganisms through various concentrations of dalbavancin, including 0.5x, 1x, 2x, 4x, and 8x the initial broth microdilution MIC. After retesting isolates that were grown on drug-free media for three days, the investigators found that MICs were equal to or within one doubling dilution of the original MICs. This suggests that both tests failed to produce mutants with decreased susceptibility to dalbavancin.

**Table 1** Minimum Inhibitory Concentration (MIC) and Minimal Bacterial Concentration (MBC) of Dalbavancin, Vancomycin, and Teicoplanin

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Dalbavancin</th>
<th>Vancomycin</th>
<th>Teicoplanin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (mcg/mL)</td>
<td>MBC (mcg/mL)</td>
<td>MIC (mcg/mL)</td>
</tr>
<tr>
<td>MSSA</td>
<td>0.06</td>
<td>0.06–1</td>
<td>1</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.06</td>
<td>0.06–0.5</td>
<td>1</td>
</tr>
<tr>
<td>VISA</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>MRCNS</td>
<td>0.03–0.12</td>
<td>0.03–0.25</td>
<td>1–4</td>
</tr>
<tr>
<td>Streptococcus pyogenes (erythromycin-susceptible)</td>
<td>0.008</td>
<td>0.008–0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>S. pyogenes (erythromycin-resistant)</td>
<td>0.008</td>
<td>0.008</td>
<td>0.5</td>
</tr>
<tr>
<td>Enterococcus faecalis (vancomycin-susceptible)</td>
<td>0.03–0.06</td>
<td>4–8</td>
<td>0.25</td>
</tr>
<tr>
<td>E. faecium (vancomycin-susceptible)</td>
<td>0.015–0.03</td>
<td>2</td>
<td>&lt;0.12–0.25</td>
</tr>
</tbody>
</table>

MSSA = methicillin-susceptible S. aureus; MRSA = methicillin-resistant S. aureus; VISA = vancomycin-intermediate S. aureus; VISA = vancomycin-intermediate CNS (VICNS); MRSCNS = methicillin-resistant coagulase-negative staphylococci.
**Drug Forecast**

Biedenbach et al., 2007

In a susceptibility study, Biedenbach and associates tested dalbavancin’s efficacy against staphylococci and beta-hemolytic streptococci isolates that had been collected from medical centers in the U.S. Altogether, 2,490 isolates were valid for analysis, including 1,009 MRSA strains, 762 MSSA strains, 182 MRNC strains, 58 MSCNS strains, and 479 S. pyogenes strains. The specimens were collected from SSTIs (41%), bloodstream infections (28%), respiratory tract infections (21%) and unknown sources of infection (10%). The drug’s MICs against MSSA and MRSA were 0.12 mcg/mL and 0.19 mcg/mL, respectively. The potency of dalbavancin was eight to 16 times greater than that of vancomycin against Staphylococcus spp.

All coagulase-negative strains were inhibited at concentrations ranging from 0.125 to 0.19 mcg/mL, compared with a vancomycin concentration of 2 mcg/mL.

Dalbavancin was 16 times more potent than vancomycin against Streptococcus spp. (MIC, 0.047 mcg/mL).

Lin et al., 2005 and Mushtaq et al., 2004

Another in vitro study confirmed that the potency of dalbavancin against susceptible and resistant S. aureus, CNS, and Viridans streptococci was up to 16 times superior to that of vancomycin. In a separate study, pneumococcal species were found to be highly susceptible to dalbavancin (MIC, 0.06 mcg/mL), compared with vancomycin (MIC, 0.5 mcg/mL).

Streit et al., 2004

The bactericidal activity of dalbavancin was assessed against, 6,339 clinical isolates, including strains from the U.S. and Europe. Most of the isolates were resistant organisms (39%, MRSA; 10%, VRE; and 28%, penicillin-resistant pneumococci). More than 99% of the MICs for dalbavancin were below 1 mcg/mL.

Dalbavancin was also potent against vancomycin-susceptible enterococci, including E. faecalis (MIC, 0.06 mcg/mL) and E. faecium (MIC, 0.12 mcg/mL). However, dalbavancin displayed decreased susceptibility against VRE (MIC, from less than 0.015 to more than 32 mcg/mL). The drug was highly active against penicillin-resistant pneumococci (MIC ≤ 0.06 mcg/mL).

In this study, dalbavancin was also active against other gram-positive bacteria, including Streptococcus bovis (MIC ≤ 0.06 mcg/mL), Bacillus spp. (MIC ≤ 0.25 mcg/mL), Corynebacterium spp. (MIC ≤ 0.025 mcg/mL) and Listeria spp. (MIC ≤ 0.12 mcg/mL).

Goldstein ETJ, 2006

Goldstein and associates studied the efficacy of dalbavancin in eradicating anaerobic gram-positive isolates from patients with diabetic foot infections. Overall, dalbavancin was active against all 120 anaerobic isolates, including Clostridium perfringens and other clostridia, Peptostreptococcus asaccharolyticus, Finegoldiella magna, Anaerococcus prevotii, Peptostreptococcus anaerobius, Peptostreptococcus harei, Peptostreptococcus vaginalis, Micromonas micros, and Anaerococcus tetradus with MICs of 0.125 mcg/mL or less.

**Gram-Negative Organisms**

Jones ETJ, 2001

Dalbavancin was intrinsically inactive against gram-negative bacteria. Like other glycopeptides, it possessed minimal activity against Haemophilus influenzae; Citrobacter, Acinetobacter, and Enterobacter spp.; Klebsiella pneumoniae; Escherichia coli; and Pseudomonas aeruginosa.

**EFFICACY IN VIVO**

Seltzer ETJ, 2003

In a multicenter, randomized, controlled, open-label, phase 2 clinical trial, dalbavancin was evaluated in patients with SSTIs caused by gram-positive organisms. Sixty-two subjects were assigned to one of the three regimens:

- a single IV infusion of dalbavancin 1,100 mg (n = 20)
- an initial infusion of dalbavancin 1,000 mg, followed by 500 mg a week later (n = 21)
- a comparative standard-of-care antibiotic, including ceftazidime (Rocephin, cefazolin, piperacillin/tazobactam (Zosyn, Wyeth), clindamycin, vancomycin, linezolid, and cephalaxin (Keflex, Middle Brook/Advancis/Dista) (n = 21)

If gram-negative or anaerobic organisms were suspected or identified, additional coverage with aztreonam (Azactam, Elan), ceftazidime (Fortaz, GlaxoSmithKline), or metronidazole (Flagyl, Pfizer) was added.

The primary efficacy endpoint was a clinical response, including cure, improvement, or failure at the follow-up visit: day 24 for a single dose of dalbavancin, day 34 for the two doses of dalbavancin, and day 14 after the last dose of the comparator regimen.

Gram-positive pathogens isolated at the baseline exam included S. aureus; MRSA; S. pyogenes; beta-hemolytic (not-typable) streptococci; group B, C, G streptococci; Viridans streptococci; and Peptostreptococcus spp.

The MIC of dalbavancin against 25 baseline pathogens was 0.12 mcg/mL, including 0.12 mcg/mL for 24 isolates and 0.25 mcg/mL for one isolate.

Overall success rates in the clinically evaluable group at the follow-up visit were 62% for patients receiving the single dose, 94% for those receiving the two-dose regimen, and 76% for the comparator group. Clinical success in the intent-to-treat population was 60% for the single dose, 91% for two doses, and 76% for the comparator regimen, respectively.

At the follow-up visit, the rate of S. aureus eradication, including MSSA and MRSA, was higher with two doses of dalbavancin (90%) than with the single dose (50%) or the comparator (60%) regimen. Clinical success rates in eradicating MRSA were 80% for the two-dose dalbavancin regimen and 50% for the single-dose and comparator groups.

Jauregui ETJ, 2005

In a multicenter, phase 3, non-inferiority, randomized, double-blind trial, dalbavancin was compared with linezolid therapy for suspected or confirmed complicated SSTIs. The dalbavancin patients received an initial IV infusion of 1,000 mg, followed by a 500-mg infusion on the eighth day. Linezolid was given as 600 mg IV or orally every 12 hours for 14 days.

Aztreonam or metronidazole was used empirically for gram-negative infections. Overall, 571 patients were assigned to the dalbavancin group, and 283 patients received linezolid. Most patients were men (61%), with a mean age of 47 years, and Caucasian (68%). Mainly, SSTIs were spontaneous in nature (50%), associated...
with trauma (25%), postsurgical infections (10%), bites (6%), or other causes (6%). Primary types of infections were abscesses (30%) and cellulitis (27%). The pathogens isolated included *S. aureus* (89%), *S. pyogenes* (5%), *S. agalactiae* (4%), *Viridans* streptococci (4%), and group C and G streptococci (1%-3%).

The primary efficacy endpoint was clinical success at the test-of-cure (TOC) visit at 14 ± 2 days (i.e., 12 to 16 days) after the completion of treatment with study medications. Clinical cure was also assessed at end-of-therapy visit within three days after completion of treatment with antibiotics. Of the 854 treated patients in this study, 82% were clinically evaluable at the end of therapy and 77% were evaluable at the TOC visit. At the TOC visit, 88.9% of the patients receiving dalbavancin and 91.2% of the linezolid-treated patients achieved clinical success, thereby showing the non-inferiority of dalbavancin.

Additional results of end-of-therapy and TOC visits, as well as clinical and microbiologic success rates, are presented in Table 2. Overall, both dalbavancin and linezolid were considered to have eradicated at least 85% of the baseline pathogens at these visits.

Raad et al., 2005

The efficacy of dalbavancin in patients with catheter-related bloodstream infections was compared with vancomycin in a prospective, phase 2, randomized, controlled, open-label trial. The study enrolled participants with signs and symptoms of bacteremia, including fever and chills that were possibly or definitely related to bloodstream infections.

An IV infusion of dalbavancin at a loading dose of 1,000 mg was followed by a 500-mg dose in eight days; the vancomycin dose was 1,000 mg twice daily for 14 days.

The primary outcome was efficacy at the TOC assessment, which included clinical and microbiological cures. The secondary outcome was the rate of cure at the end of treatment. At the investigator's discretion, gram-negative coverage with aztreonam or ceftazidime and anaerobic coverage with metronidazole were added. The catheters were removed in all instances if a catheter-related bloodstream infection was suspected.

Sixty-seven patients were analyzed at the end of the study; evaluable results for the TOC visit were presented for 14 dalbavancin patients (42%) and for 20 vancomycin patients (59%). The most common pathogens identified after culture were *S. aureus* (43%), including MRSA (26%), CNS (48%), and *E. faecalis* (9%).

The microbiologically assessed intent-to-treat population at the end of treatment revealed an overall success rate of 91.3% with dalbavancin and 64.3% with vancomycin. At the TOC visit, overall success rates were 87% for dalbavancin and 50% for vancomycin (*P < 0.05*). At the end of therapy and at the TOC visit, results for the evaluable population of patients revealed similar success rates favoring dalbavancin.

**SAFETY PROFILE**

In the phase 1, single-dose and multiple-dose–ranging study by Leighton et al., dalbavancin was well tolerated with no evidence of dose-limiting toxicities.

The most common adverse effects were pyrexia (50%), headache (25%), and nausea (6%). However, patients receiving placebo also reported pyrexia (38%) and headache (31%). No auditory changes were reported among the volunteers.

In assessments of the drug’s safety, adverse events probably or possibly related to therapy were reported by 25.4% of the dalbavancin patients and by 32.2% of the linezolid patients. These adverse events were generally mild or moderate in intensity and were comparable in both groups (Table 3). Treatment-related adverse effects that were considered serious included mild leukopenia, which resolved spontaneously in the patients who were given dalbavancin, and moderate thrombocytopenia in the linezolid-treated patients.

In the comparative trial of catheter-related bloodstream infections by Raad et al. (Table 4), adverse events were relatively mild with both dalbavancin and vancomycin. Common adverse effects included hypotension, hypokalemia, diarrhea, constipation, anemia, and fever.

### Table 2 Clinical, Microbiological, and Overall Success with Dalbavancin and Linezolid

<table>
<thead>
<tr>
<th></th>
<th>Clinical Success (%)</th>
<th>Microbiological Success (%)</th>
<th>Overall Success (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-of-therapy visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>92.3</td>
<td>87.5</td>
<td>87.5</td>
</tr>
<tr>
<td>Linezolid</td>
<td>94.2</td>
<td>90.2</td>
<td>88.4</td>
</tr>
<tr>
<td><strong>Test-of-cure visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>88.9</td>
<td>89.5</td>
<td>88.4</td>
</tr>
<tr>
<td>Linezolid</td>
<td>91.2</td>
<td>87.5</td>
<td>86.8</td>
</tr>
</tbody>
</table>

*p Overall success = clinical and microbiological success combined.

### Table 3 Adverse Drug Events in a Dose-Ranging Study of Dalbavancin and Linezolid

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Dalbavancin (%)</th>
<th>Linezolid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Headache</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Loose stools</td>
<td>0.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Fungal vaginitis</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase</td>
<td>1.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Rash</td>
<td>1.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

CONCLUSION

Dalbavancin is a unique second-generation glycopeptide with in vitro activity against gram-positive organisms, including resistant organisms such as MRSA and some VRE strains. It is not active against gram-negative pathogens or VanA genes containing Enterococcus spp. A New Drug Application for dalbavancin was filed with the FDA in 2005, and the medication is currently being studied for the treatment of gram-positive complicated and uncomplicated SSTIs in phase 3 trials and for catheter-related bacteria in phase 2 clinical trials. An approval letter was issued in 2006. With its long half-life of six to 10 days, dalbavancin can be administered as a once-weekly IV infusion; this feature is especially beneficial for the long-term treatment required in some gram-positive infections. Reported adverse events have been mild and comparable to those associated with other gram-positive antimicrobial agents such as vancomycin and linezolid. To date, no renal adjustments or CYP 450 drug interactions have been reported for dalbavancin, and no nephrotic or ototoxic concerns exist with dalbavancin treatment, as is the case with vancomycin.

Clinically, laboratory drug level monitoring is not required for dalbavancin, a considerable advantage over vancomycin. So far, dalbavancin is an effective and well-tolerated antimicrobial option for gram-positive infections. Additional clinical research is needed to place this antibiotic agent among other powerful weapons against gram-positive resistant organisms.

REFERENCES

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Table 4 Adverse Drug Events in a Study of Catheter-Related Bloodstream Infections with Dalbavancin and Vancomycin

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Dalbavancin (%)</th>
<th>Vancomycin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>21.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>18.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>18.2</td>
<td>11.8</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>12.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21.2</td>
<td>11.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>18.2</td>
<td>11.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.1</td>
<td>20.6</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>3</td>
<td>0.3</td>
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</table>


