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# New Lipoglycopeptides

## A Comparative Review of Dalbavancin, Oritavancin and Telavancin

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## Abstract

Dalbavancin, oritavancin and telavancin are semisynthetic lipoglycopeptides that demonstrate promise for the treatment of patients with infections caused by multi-drug-resistant Gram-positive pathogens. Each of these agents contains a heptapeptide core, common to all glycopeptides, which enables them to inhibit transglycosylation and transpeptidation (cell wall synthesis). Modifications to the heptapeptide core result in different *in vitro* activities for the three semisynthetic lipoglycopeptides. All three lipoglycopeptides contain lipophilic side chains, which prolong their half-life, help to anchor the agents to the cell membrane and increase their activity against Gram-positive cocci. In addition to inhibiting cell wall synthesis, telavancin and oritavancin are also able to disrupt bacterial membrane integrity and increase membrane permeability; oritavancin also inhibits RNA synthesis. Enterococci exhibiting the VanA phenotype (resistance to both vancomycin and teicoplanin) are resistant to both dalbavancin and telavancin, while oritavancin retains activity. Dalbavancin, oritavancin and telavancin exhibit activity against VanB vancomycin-resistant enterococci. All three lipoglycopeptides demonstrate potent *in vitro* activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* regardless of their susceptibility to meticillin, as well as *Streptococcus* spp. Both dalbavancin and telavancin are active against vancomycin-intermediate *S. aureus* (VISA), but display poor activity versus vancomycin-resistant *S. aureus* (VRSA). Oritavancin is active against both VISA and VRSA. Telavancin displays greater activity against *Clostridium* spp. than dalbavancin, oritavancin or vancomycin.

The half-life of dalbavancin ranges from 147 to 258 hours, which allows for once-weekly dosing, the half-life of oritavancin of 393 hours may allow for one dose per treatment course, while telavancin requires daily administration. Dalbavancin and telavancin exhibit concentration-dependent activity and AUC/MIC (area under the concentration-time curve to minimum inhibitory concentration ratio) is the pharmacodynamic parameter that best describes their activities. Oritavancin's activity is also considered concentration-dependent *in vitro*, while *in vivo* its activity has been described by both concentration and time-dependent models; however, AUC/MIC is the pharmacodynamic parameter that best describes its activity.

Clinical trials involving patients with complicated skin and skin structure infections (cSSSIs) have demonstrated that all three agents are as efficacious

as comparators. The most common adverse effects reported with dalbavancin use included nausea, diarrhoea and constipation, while injection site reactions, fever and diarrhoea were commonly observed with oritavancin therapy. Patients administered telavancin frequently reported nausea, taste disturbance and insomnia. To date, no drug-drug interactions have been identified for dalbavancin, oritavancin or telavancin. All three of these agents are promising alternatives for the treatment of cSSSIs in cases where more economical options such as vancomycin have been ineffective, in cases of reduced vancomycin susceptibility or resistance, or where vancomycin use has been associated with adverse events.

The problem of multi-drug-resistant (MDR) Gram-positive pathogens is not a new one and cases of methicillin-resistant *Staphylococcus aureus* (MRSA) appeared in the literature as early as the 1960s.<sup>[1]</sup> However, it was not until the 1980s that MRSA truly became widespread.<sup>[2]</sup> The steep rise of MRSA in hospital isolates during that decade resulted in a sharp increase in vancomycin use.<sup>[3]</sup> Today, healthcare-associated MRSA is a worldwide concern and the percentage of *S. aureus* isolates resistant to methicillin exceeds 60% in some intensive care units.<sup>[4]</sup> Certain countries, including the US, are also experiencing a significant increase in the number of community-associated MRSA infections in otherwise healthy individuals.<sup>[1,5]</sup> Compounding the problem is the emergence of vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA) and vancomycin-resistant enterococci (VRE), which have added a greater sense of urgency to the search for novel antibacterials with activity against such isolates.<sup>[2]</sup>

For decades, vancomycin was viewed by many as the 'gold standard' for the treatment of MRSA infections.<sup>[6]</sup> Although active against the vast majority of MRSA infections, vancomycin is plagued by issues of poor penetration into certain tissues (e.g. lung) and slow bactericidal activity.<sup>[4]</sup> In addition, the minimum inhibitory concentration (MIC) of vancomycin for Gram-positive pathogens such as MRSA has been reported to be increasing by some studies, and increasing numbers of therapeutic failures have also been published.<sup>[4]</sup> The rampant spread of MRSA and the inherent limitations of vancomycin therapy highlight the need for novel, rapidly bactericidal agents to combat MRSA infections.

Dalbavancin, oritavancin and telavancin are semisynthetic lipoglycopeptides that demonstrate promise for the treatment of patients with infections caused by MDR Gram-positive pathogens. All three lipoglycopeptides target Gram-positive bacteria through a bactericidal mechanism of action.<sup>[4,6,7]</sup> These agents are active against MDR strains of staphylococci, enterococci and streptococci, although neither dalbavancin nor telavancin are active against VRE exhibiting the VanA phenotype.<sup>[3,8-10]</sup> When compared with vancomycin, dalbavancin, oritavancin and telavancin all have lower MIC values for the aforementioned pathogens and their long half-lives allow for once-daily dosing for telavancin, once-weekly dosing for dalbavancin and potentially one dose per treatment course for oritavancin.<sup>[2,10]</sup>

This article reviews the data available on the chemistry, mechanisms of action and resistance, microbiology, pharmacokinetics, pharmacodynamics, clinical trials, adverse effects, drug interactions, and the role in therapy of dalbavancin, oritavancin and telavancin.

## 1. Chemistry

### 1.1 Glycopeptides

All glycopeptides contain a common heptapeptide core, which enables them to inhibit cell wall synthesis by impeding transglycosylation and transpeptidation through binding to the C-terminal D-alanyl-D-alanine (D-Ala-D-Ala) of growing peptidoglycan chains. Modifications made to the common heptapeptide core structure result in differential activities amongst semisynthetic

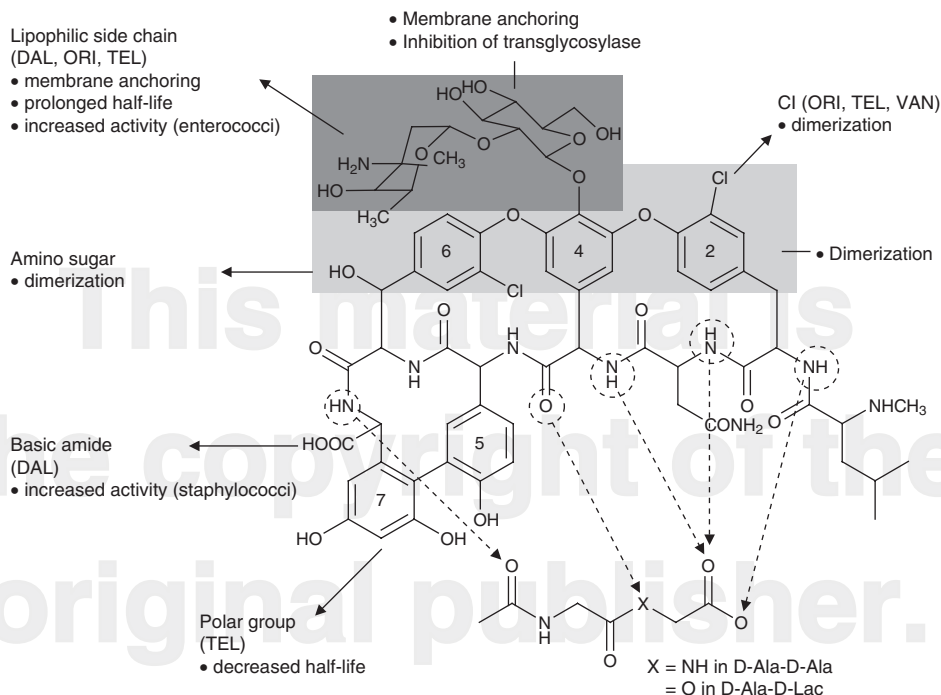


**Fig. 1.** Structure activity relationships of the glycopeptides. **DAL** = dalbavancin; **ORI** = oritavancin; **TEL** = telavancin; **VAN** = vancomycin.

lipoglycopeptide antibacterials and define the spectra of activity of these agents (figure 1).<sup>[2,11,12]</sup>

### 1.2 Dalbavancin

Dalbavancin is a semisynthetic lipoglycopeptide derived from the teicoplanin-like antibiotic A-40926 (figure 2).<sup>[3,12-14]</sup> A-40926 is an agent produced naturally by the actinomycete *Nonomura* spp.,<sup>[2,3,12,14,15]</sup> and dalbavancin is synthesized from A-40926 in a three-step procedure.<sup>[3,14]</sup> An important step in the synthesis of dalbavancin is the amidation of the peptide carboxyl group in the teicoplanin structure with a 3,3 dimethylamino-propylamide group, resulting in improved potency of dalbavancin against staphylococci, including coagulase-negative staphylococci (CoNS).<sup>[2,14,15]</sup> Dalbavancin also differs from teicoplanin by its lack of the acetylglucosamine group, and the presence of a chlorine atom and a terminal methylamino group.<sup>[2,15]</sup> The removal of the acetylglucosamine group was an intentional effort to improve the activity of dalbavancin against

VanA enterococci; but despite this alteration, this pathogen remained resistant to dalbavancin.<sup>[2,14]</sup> Additionally, dalbavancin has an acylaminoglucuronate instead of an acylglucosamine on ring 4.<sup>[2]</sup> The long lipophilic side chain in dalbavancin serves a dual purpose by both extending the half-life, which allows for once-weekly dosing, as well as anchoring the compound to the membrane, which enhances its antimicrobial activity by improving its affinity for the terminal D-Ala-D-Ala (figures 1 and 2).<sup>[2,14,15]</sup>

### 1.3 Oritavancin

Oritavancin is a synthetic derivative of the naturally occurring glycopeptide chloroeremomycin (figure 2).<sup>[10,16]</sup> Chloroeremomycin belongs to the eremomycin class, which differs from vancomycin by the addition of a 4-epi-vancosamine monosaccharide to the amino acid residue in ring 6 and the substitution of the vancosamine by a 4-epi-vancosamine portion.<sup>[16-18]</sup> In addition, oritavancin differs from chloroeremomycin by



**Fig. 2.** Chemical structures of dalbavancin, oritavancin, telavancin and vancomycin.

the addition of an N-alkyl-*p*-chlorophenylbenzyl substituent on the disaccharide sugar.<sup>[9,16]</sup> This structural alteration imparts improved activity against both vancomycin-susceptible enterococci (VSE) and VRE, including VanA enterococci.<sup>[10,16,17]</sup> The lipophilic side chain in oritavancin anchors the compound to the cell membrane through hydrophobic interactions and it stabilizes the oritavancin dimer (figure 1).<sup>[9]</sup> The formation of dimers is achieved by interactions involving the disaccharides attached to ring 4, the 4-epi-vancosamine on ring 6 as well as the chlorine on ring 2.<sup>[16]</sup> The dimers formed improve the ability of oritavancin to bind to its target, including D-alanyl-D-lactate (D-Ala-D-Lac) seen in VanA enterococci.<sup>[10]</sup>

#### 1.4 Telavancin

Telavancin, a semisynthetic derivative of vancomycin, differs from the parent compound by the addition of a hydrophobic and a hydrophilic group to the vancomycin structure (figures 1 and 2).<sup>[8,19]</sup> The hydrophilic (phosphomethyl) aminomethyl moiety is present at the 4' position of ring 7.<sup>[8,19]</sup> The hydrophobic decylaminoethyl moiety is attached to the vancosamine sugar and it is the reason for the classification of telavancin as a lipoglycopeptide.<sup>[2,8,19]</sup> The decylaminoethyl lipophilic chain imparts to telavancin the ability to bind to cell membranes, a feature which improves the antibacterials' binding affinity for the D-Ala-D-Ala target site.<sup>[19]</sup> The lipophilic side chain is also responsible for the activity of telavancin against both MRSA phenotypes and non-VanA enterococci.<sup>[2,4]</sup> The length of the lipophilic side chain is important, as increasing the chain length increases the activity of the agent against enterococci but reduces its activity against MRSA.<sup>[2,20]</sup> A 13-carbon chain is optimal for maximal activity versus enterococci, thus it is clear that the 10-carbon lipophilic side chain found in telavancin is a compromise between ideal enterococci and MRSA activity.<sup>[2]</sup> The liposaccharide moiety in telavancin inhibits peptidoglycan production through inhibition of transglycosylases, while the presence of a chlorine atom on ring 2 further increases the binding af-

finity of telavancin for its target binding site.<sup>[20]</sup> The negatively charged hydrophilic group present improves the ability of telavancin to distribute into tissues, as well as promoting the clearance of the drug and also reducing any potential nephrotoxic effects.<sup>[2,20]</sup>

## 2. Mechanism of Action

The mechanism of action common to all members of the glycopeptide class is the inhibition of bacterial cell wall synthesis.<sup>[2,21]</sup> Glycopeptides bind to the terminal D-Ala-D-Ala in growing peptidoglycan chains, and through this binding hinder polymerization and cross-linking ultimately resulting in the destabilization of the cell wall, with bacterial cell death occurring presumably due to osmotic insult.<sup>[2]</sup> The chemical structures of the different lipoglycopeptide agents impart additional mechanisms of action to certain members of the group, including oritavancin and telavancin (figure 1). A feature common to the newer lipoglycopeptides is the presence of lipid side chains, which anchor the molecule to the cell membrane and thereby concentrate the drug at its site of action, dramatically increasing their potency relative to their parent glycopeptide.<sup>[2,14,22]</sup> In addition, it has been proposed that the lipid side chains may act as detergent-like molecules and cause partial destabilization of the cell membrane and loss of membrane potential.<sup>[2,22]</sup>

### 2.1 Dalbavancin

Dalbavancin inhibits cell wall synthesis in Gram-positive bacteria through the formation of a stable complex between its heptapeptide backbone and the D-Ala-D-Ala portion of cell wall precursors.<sup>[2,3,14]</sup> This complex prevents the transglycosylase and transpeptidase enzymes from polymerizing and cross-linking the peptidoglycan, and as a result the peptidoglycan chain growth is arrested.<sup>[14]</sup> In addition, it appears that the lipophilic side chain of dalbavancin enhances the antibacterial's binding affinity for its D-Ala-D-Ala target site through the formation of dimers and membrane anchoring, leading to a superior

potency than its parent glycopeptide.<sup>[2,14]</sup> Dimerization aids the process by maintaining the binding pocket in the optimal position for cooperative binding, while membrane anchoring helps by focusing dalbavancin closer to its target.<sup>[14]</sup> The role of the lipid side chain in destabilization of cell membranes has not been demonstrated for dalbavancin.

## 2.2 Oritavancin

Oritavancin inhibits cell wall synthesis by complexing with the terminal D-Ala-D-Ala of a nascent peptidoglycan chain and also to the pentaglycine bridge, thus inhibiting transglycosylation and transpeptidation.<sup>[23,24]</sup> Unlike other glycopeptides, oritavancin is able to bind to depsipeptides including D-Ala-D-Lac, which facilitates its inhibition of cell wall synthesis even in organisms exhibiting VanA-type resistance.<sup>[23,24]</sup> Oritavancin forms homodimers prior to binding to D-Ala-D-Ala or D-Ala-D-Lac, which increases its binding affinity for the target site.<sup>[23,25]</sup> The *p*-chloro-phenylbenzyl side chain of oritavancin interacts with the cell membrane, exerting two beneficial effects.<sup>[23]</sup> This binding acts to maintain the antibacterial in a prime position for peptidoglycan interactions and it also imparts oritavancin with the ability to disrupt the bacterial membrane potential and thus increase membrane permeability.<sup>[22,23]</sup> Oritavancin has been shown to dissipate membrane potential in both stationary and exponential phase growing bacteria, which is rare and may carry clinical implications in terms of its activity against slowly growing organisms and biofilms.<sup>[22]</sup> The dual mechanism of action could also theoretically increase effectiveness and reduce the risk of resistance selection.<sup>[22]</sup> In addition to the aforementioned mechanisms, it has also been hypothesized that oritavancin inhibits RNA synthesis.<sup>[22]</sup>

## 2.3 Telavancin

Telavancin exhibits a dual mechanism of action against Gram-positive bacteria. As with other glycopeptides, telavancin binds to terminal D-Ala-D-Ala residues and inhibits cell wall synthesis.<sup>[2,19]</sup> Due to its ability to bind to bac-

terial cell membranes, telavancin is ten times more active than vancomycin at inhibiting both the transglycosylation and the synthesis of peptidoglycan.<sup>[2,19]</sup> Like oritavancin, telavancin also alters cell membrane permeability and dissipates membrane potential.<sup>[2,19]</sup> This second mechanism of action may promote or be the lone reason for its rapid bactericidal activity.<sup>[19]</sup>

## 3. Mechanisms of Resistance

Numerous mechanisms of resistance have been elucidated for glycopeptides, which account for resistance or reduced susceptibility to vancomycin.<sup>[26,27]</sup> A number of glycopeptide-resistant phenotypes have been found, and these include VanA, VanB, VanC, VanD, VanE and VanG types.<sup>[27]</sup> VanA is the most common type and is responsible for high-level resistance to both vancomycin and teicoplanin.<sup>[27]</sup> These mechanisms of resistance arise via alteration of peptidoglycan precursors such that pentapeptides normally terminating in D-Ala-D-Ala are revised to terminate in D-Ala-D-Lac or D-alanine-D-serine.<sup>[27]</sup> This change results in the loss of one of five hydrogen bonds between the pentapeptide core of the glycopeptide and its target, and thus reduces the affinity of the antibacterial for its target.<sup>[27]</sup> In the case of an alteration to D-Ala-D-Lac, the affinity of the glycopeptide for the target may be reduced up to 1000-fold.<sup>[2,27]</sup> Expression of the *vanA* and *vanB* operons is inducible and expression is driven by glycopeptides. Vancomycin activates both the *vanA* and *vanB* operons, while teicoplanin, oritavancin, dalbavancin and telavancin are only activators of the *vanA* operon (table I).<sup>[27]</sup> As a result, teicoplanin, oritavancin, dalbavancin and telavancin retain activity against strains that express VanB.<sup>[27]</sup>

VanA-type, and to a lesser extent VanB-type, acquired resistance is common among enterococci due to their ability to easily acquire and exchange genetic material.<sup>[24]</sup> Interspecies gene transfer is also possible and clinically important as it has been reported that the Michigan and Pennsylvania clinical VRSA isolates resulted from an *in vivo* transfer of the *vanA* transposon from *Enterococcus faecalis* (it can also occur with

**Table 1.** *In vitro* activity of dalbavancin, oritavancin, telavancin and vancomycin against Gram-positive organisms<sup>[2,24,28-48]</sup>

| Bacteria                                     | Dalbavancin       |      |             | Oritavancin       |       |               | Telavancin        |      |            | Vancomycin        |     |            |
|----------------------------------------------|-------------------|------|-------------|-------------------|-------|---------------|-------------------|------|------------|-------------------|-----|------------|
|                                              | MIC <sub>50</sub> | MIC  | range       | MIC <sub>50</sub> | MIC   | range         | MIC <sub>50</sub> | MIC  | range      | MIC <sub>50</sub> | MIC | range      |
| <i>Staphylococcus aureus</i> (MS)            | 0.06              | 0.06 | ≤0.008–0.5  | 0.06              | 0.12  | ≤0.004–2      | 0.25              | 0.5  | ≤0.015–2   | 1                 | 1   | 0.25–2     |
| <i>S. aureus</i> (MR)                        | 0.06              | 0.06 | ≤0.008–0.5  | 0.06              | 0.25  | ≤0.004–4      | 0.25              | 0.5  | ≤0.06–2    | 1                 | 2   | 0.25–2     |
| <i>Staphylococcus epidermidis</i> (MS)       | ≤0.03             | 0.06 | 0.015–0.25  | 0.25              | 0.5   | 0.008–1       | 0.25              | 1    | 0.12–1     | 2                 | 2   | 1–2        |
| <i>S. epidermidis</i> (MR)                   | 0.06              | 0.06 | 0.015–1     | 0.5               | 0.5   | ≤0.004–4      | 0.5               | 1    | 0.25–2     | 2                 | 4   | 1–4        |
| <i>Streptococcus pyogenes</i> (group A)      | 0.015             | 0.03 | ≤0.002–0.06 | 0.12              | 0.25  | 0.008–0.5     | 0.03              | 0.06 | 0.03–0.12  | 0.5               | 1   | 0.5–1      |
| <i>Streptococcus agalactiae</i> (group B)    | 0.06              | 0.12 | 0.008–0.25  | N/A               | 0.12  | 0.03–0.5      | 0.06              | 0.06 | 0.002–0.25 | 0.25              | 0.5 | 0.25–0.5   |
| Other β-haemolytic <i>Streptococcus</i> spp. | ≤0.008            | 0.06 | ≤0.002–0.25 | N/A               | 0.5   | 0.001–1       | 0.03              | 0.06 | 0.002–0.25 | 0.25              | 0.5 | 0.25–1     |
| <i>Streptococcus pneumoniae</i> (PS)         | 0.015             | 0.03 | ≤0.008–0.06 | 0.002             | 0.004 | ≤0.0005–0.25  | 0.015             | 0.03 | 0.008–0.06 | 0.25              | 0.5 | 0.06–1     |
| <i>S. pneumoniae</i> (PI)                    | 0.015             | 0.03 | ≤0.008–0.06 | 0.004             | 0.008 | ≤0.0005–0.5   | 0.015             | 0.03 | 0.008–0.12 | 0.5               | 1   | 0.25–1     |
| <i>S. pneumoniae</i> (PR)                    | 0.015             | 0.03 | ≤0.008–0.25 | 0.004             | 0.008 | ≤0.0005–0.015 | 0.015             | 0.03 | 0.008–0.12 | 0.25              | 0.5 | 0.06–2     |
| <i>Enterococcus faecalis</i> (VS)            | 0.03              | 0.06 | 0.015–4     | 0.03              | 0.06  | ≤0.0005–0.5   | 0.25              | 0.5  | ≤0.015–4   | 1                 | 2   | 0.5–4      |
| <i>E. faecalis</i> (VR)                      | 4                 | 32   | 0.015–>32   | 0.5               | 1     | 0.015–4       | 8                 | 8    | 0.25–32    | 512               | 512 | 8 to >512  |
| <i>Enterococcus faecium</i> (VS)             | 0.06              | 0.12 | ≤0.015–4    | 0.015             | 0.015 | ≤0.0005–0.06  | 0.12              | 0.25 | ≤0.015–2   | 0.5               | 1   | 0.5–2      |
| <i>E. faecium</i> (VR)                       | 8                 | 32   | 0.03–>32    | 0.06              | 0.25  | ≤0.0005–4     | 2                 | 4    | 0.5–16     | 512               | 512 | 8 to >512  |
| <i>E. faecium</i> (VanA)                     | 16                | 32   | 0.03–>32    | N/A               | 0.25  | 0.004–2       | 4                 | 8    | ≤0.015–16  | 512               | 512 | 64 to >512 |
| <i>E. faecium</i> (VanB)                     | 0.03              | 0.12 | 0.03–0.12   | N/A               | 0.03  | 0.004–0.06    | 0.5               | 2    | 0.06–4     | 32                | 64  | 4 to >512  |
| <i>Clostridium</i> spp.                      | 0.03              | 2    | ≤0.015–8    | 0.25              | 1     | 0.06–1        | 0.25              | 0.25 | 0.12–0.5   | 0.5               | 1   | 0.25–8     |

MIC<sub>50</sub> = minimum concentration to inhibit growth of 50% of isolates; MIC<sub>90</sub> = minimum concentration to inhibit growth of 90% of isolates; MR = methicillin resistant; MS = methicillin susceptible; N/A = not available; PI = penicillin intermediate (MIC 0.12–1 mg/L); PR = penicillin resistant (MIC ≥2 mg/L); PS = penicillin susceptible (MIC ≤0.06 mg/L); VR = vancomycin resistant (MIC ≥32 mg/L); VS = vancomycin susceptible (MIC ≤4 mg/L).

*Enterococcus faecium*) to MRSA.<sup>[24]</sup> In addition, VanA and VanB have rarely been identified in other Gram-positive bacteria, including *Corynebacterium* spp., *Arcanobacterium haemolyticum*, *Lactococcus* spp., *Streptococcus bovis* and anaerobes.<sup>[2]</sup> VanC is typically associated with the intrinsically vancomycin-resistant *Enterococcus casseliflavus* and *Enterococcus gallinarum*. VanC is constitutively expressed and confers low-level resistance to vancomycin but not teicoplanin. The relatively higher potency of the newer lipoglycopeptides may well overcome this low-level resistance, the clinical relevance of which is not known. VanD, E, G and L are rare genotypes of glycopeptide resistance infrequently encountered in clinical practice. The activity of the new lipoglycopeptides against these strains is not well known.

Resistance to vancomycin in the Mu50 strain of *S. aureus* may be attributed to a thickening of the cell wall, accelerated peptidoglycan synthesis and reduced peptidoglycan cross-linking.<sup>[49]</sup> Changes in teichoic acids of the cell wall may also be important in this mechanism of resistance.<sup>[2]</sup> Reduced susceptibility or resistance to vancomycin in VISA strains results from an excess of D-Ala-D-Ala residues, which bind the antibacterial and thus prevent it from reaching its target.<sup>[49]</sup> Intrinsic resistance to glycopeptides in uncommon pathogens including *Pediococcus*, *Leuconostoc* and *Lactobacillus* spp. is mediated by a D-alanine:D-lactate ligase that constitutively produces peptidoglycan precursors that end in D-Ala-D-Lac.

### 3.1 Dalbavancin-Resistance Selection

Resistance to dalbavancin occurs as a result of the aforementioned change in peptidoglycan precursors from *vanA*-expressed D-Ala-D-Ala to D-Ala-D-Lac.<sup>[3]</sup> The presence of the *vanB* operon does not confer resistance to dalbavancin, since the latter is not an inducer of the *vanB* operon. There has been no single-step, high-level dalbavancin resistance (frequency  $<10^{-10}$ ) detected when *Staphylococcus haemolyticus* and *S. aureus* were plated on agar containing 10 mg/L of dalbavancin.<sup>[2,14]</sup> The lack of single-step dalbavancin resistance was also demonstrated in MRSA and

VISA isolates when incubated at 0.5, 1, 2, 4 and 8 times the MIC of dalbavancin.<sup>[14]</sup> Following 24 serial passages of *S. aureus* and *S. haemolyticus* at sub-MIC concentrations of dalbavancin, the dalbavancin MICs increased 2-fold for *S. aureus* and 4-fold for *S. haemolyticus*; however, the reason for this increase is not yet known.<sup>[14]</sup> Upon examination of the subcultures of colonies from different passage steps, it was shown that there was little variability in the dalbavancin MIC distribution, whereas the vancomycin MICs displayed heterogeneity.<sup>[2]</sup> These preliminary data suggest that the selection of dalbavancin resistance among staphylococci is slower than that with vancomycin.<sup>[2]</sup>

### 3.2 Oritavancin-Resistance Selection

Although clinically isolated VanA, VanB and VanC enterococci are susceptible to oritavancin, it has been demonstrated *in vitro* that moderate-level resistance to oritavancin can occur in enterococci isolates exhibiting the VanA or VanB phenotypes.<sup>[26]</sup> However, resistance in isolates harbouring the *vanB* operon were only observed when the operon was altered such that it became inducible by teicoplanin or constitutively expressed.<sup>[26]</sup> Isolates producing peptidoglycan precursors terminating in D-Lac may exhibit resistance to oritavancin if all precursors terminating in D-Ala are eliminated.<sup>[26]</sup> This has been achieved *in vitro* by increasing resistance gene expression or reducing D-Ala-D-Ala production.<sup>[26]</sup> Such changes resulted in a moderate-level resistance to oritavancin (MIC  $\leq 16$  mg/L).<sup>[26,27]</sup> The expression of the *vanZ* gene of the *vanA* gene cluster also resulted in resistance to oritavancin, with an increase to an MIC of 8 mg/L through an unknown mechanism.<sup>[26]</sup> Thus far it has not been possible to select for high-level oritavancin resistance in the laboratory and there have been no cases of resistance to this lipoglycopeptide drug among clinically isolated pathogens.<sup>[16,23]</sup>

### 3.3 Telavancin-Resistance Selection

*In vitro*, telavancin has been reported to have a low incidence of spontaneous resistance development among enterococci and staphylococci.<sup>[50]</sup>

It has been demonstrated that the frequency of spontaneous resistance to telavancin was  $<4.0 \times 10^{-11}$  to  $<2.9 \times 10^{-10}$  at  $2 \times \text{MIC}$  for MRSA and VISA, which was lower than the spontaneous mutation frequencies obtained with comparators.<sup>[50]</sup>

#### 4. Microbiology

Table I presents the *in vitro* activities of dalbavancin, oritavancin, telavancin and vancomycin against key Gram-positive pathogens. The values in the table are modal MICs cited in the literature for each of the agents. All MICs reported in table I adhered to recognized laboratory standards (Clinical and Laboratory Standards Institute [CLSI]). Dalbavancin, oritavancin and telavancin all demonstrate potent *in vitro* activity against *S. aureus* and *Staphylococcus epidermidis*, regardless of the microorganism's susceptibility or resistance to meticillin. All three of these semisynthetic lipoglycopeptides are also active against *Streptococcus* spp. and VSE. The spectrum of activity of all three of these agents is exclusive to Gram-positive bacteria, which is to be expected considering the large size of these molecules.

##### 4.1 Dalbavancin

Dalbavancin demonstrates *in vitro* activity against clinically significant Gram-positive pathogens, including meticillin-susceptible *S. aureus* (MSSA), MRSA, meticillin-susceptible *S. epidermidis* (MSSE), meticillin-resistant *S. epidermidis* (MRSE) and enterococci, but lacks activity against VanA-type enterococci.<sup>[28-33]</sup> Dalbavancin MICs for *Staphylococcus* spp. are significantly lower than that of vancomycin, with both MIC for 50% of isolates ( $\text{MIC}_{50}$ ) and 90% of isolates ( $\text{MIC}_{90}$ ) values for *S. aureus* being 0.06 mg/L, regardless of meticillin resistance or susceptibility of the organism.<sup>[28-33]</sup> Dalbavancin has been reported to be active against VISA ( $\text{MIC}_{50}$  and  $\text{MIC}_{90}$  of 0.25 and 2 mg/L, respectively) but shows poor activity versus VRSA (modal MIC  $>16$  mg/L). Activity against *Streptococcus pneumoniae* is also potent ( $\text{MIC}_{50}$  and  $\text{MIC}_{90}$  of 0.015 and 0.03 mg/L, respectively) and

is unaffected by the presence of penicillin resistance amongst the isolates.<sup>[28,32,33]</sup> As previously mentioned, dalbavancin lacks activity against VanA-type enterococci, but maintains activity against the VanB phenotype (table I). The activity of dalbavancin against *Clostridium* spp. ( $\text{MIC}_{90}$  2 mg/L) is comparable with vancomycin.

##### 4.2 Oritavancin

Oritavancin exhibits potent activity against MSSA, MRSA, MSSE and MRSE (table I).<sup>[34,51-56]</sup> Oritavancin has been reported to be active against VISA ( $\text{MIC}_{50}$  and  $\text{MIC}_{90}$  both 1 mg/L) as well as VRSA (modal MIC 0.5 mg/L).<sup>[52,53]</sup> Compared with other glycopeptides, oritavancin has the lowest MIC for *S. pneumoniae*, including the penicillin-resistant phenotype ( $\text{MIC}_{50}$  0.004 mg/L).<sup>[34,51-54]</sup> Unlike dalbavancin and telavancin, oritavancin continues to be active against VanA VRE (table I). Compared with vancomycin, oritavancin demonstrates significantly reduced MICs for all the clinically significant aerobic Gram-positive pathogens listed in table I. Oritavancin displays similar activity to vancomycin against *Clostridium* spp. The MICs reported for oritavancin represent studies using 0.002% polysorbate-80 (P-80) as per CLSI methods.<sup>[51]</sup> Older oritavancin susceptibility studies, which lacked the addition of P-80, underestimated the potency of oritavancin because the agent was adsorbed to the plasticware used in the determinations (use of P-80 minimizes adsorption and reflects more accurate estimates of activity).<sup>[51]</sup>

##### 4.3 Telavancin

As with dalbavancin, telavancin exhibits potent activity against MSSA, MRSA, MSSE and MRSE (table I).<sup>[50,57-64]</sup> Telavancin is active against VISA ( $\text{MIC}_{50}$  and  $\text{MIC}_{90}$  both 1 mg/L) but is not very active against VRSA (modal MIC 4 mg/L). Similar to oritavancin and dalbavancin, telavancin also exhibits consistently low MIC for *S. pneumoniae*, with no variability in MIC between the penicillin-susceptible, -intermediate and -resistant phenotypes. While telavancin maintains activity against enterococci, it is poorly

active against VanA VRE but has modest activity against VanB VRE (table I). Telavancin displays the lowest MICs (MIC<sub>90</sub> 0.25 mg/L) of the lipoglycopeptides detailed in table I against *Clostridium* spp.

## 5. Pharmacokinetics

The pharmacokinetic and pharmacodynamic parameters of dalbavancin, oritavancin, telavancin and vancomycin are summarized in table II.

### 5.1 Dalbavancin

Dalbavancin follows linear, dose-proportional pharmacokinetics when administered to healthy volunteers in single doses ranging from 140 to 1120 mg.<sup>[2,66]</sup> Like other glycopeptides, dalbavancin is poorly absorbed when administered orally, necessitating intravenous administration.<sup>[2]</sup> The standard dose of dalbavancin is 1000 mg administered on day 1 and 500 mg administered 1 week later.<sup>[3]</sup> Following a single 1000 mg dose of dalbavancin in healthy adults, the maximum concentration in plasma (C<sub>max</sub>) achieved was 278.3–301 mg/L and the mean area under the concentration-time curve (AUC) was 23 843 mg • h/L.<sup>[2,3]</sup> The terminal elimination half-life of dalbavancin ranges from 147 to 258 hours, allowing the once-weekly dosing that maintains the serum plasma concentrations of dalbavancin above the MIC of common pathogens for 7 days (table II).<sup>[2]</sup> The long-half life of dalbavancin is a result of its extensive protein binding (93–98%), as well as its retention within cells.<sup>[2,14]</sup> Despite a small percentage of the administered drug being free or non-protein

bound, this is enough for the drug to exert its bactericidal activity due to its high capacity but low affinity for protein binding.<sup>[14]</sup> Dalbavancin is not a substrate for the cytochrome P450 (CYP) isoenzymes, nor does it induce or inhibit their activity.<sup>[2]</sup>

In healthy volunteers, dalbavancin blister fluid penetration ratios were 0.60 and correlated with plasma concentrations of the drug.<sup>[2,66]</sup> These blister fluid concentrations remained above 30.3 mg/L, which exceeded the MIC for Gram-positive pathogens. Dalbavancin achieves higher blister fluid concentrations than both telavancin and oritavancin (60% vs 40% and 19%, respectively).<sup>[2]</sup> In rats, it has been demonstrated that following a dose of radio-labelled dalbavancin, the drug distributed extensively throughout the body and into 40 different biological fluids and tissues, with the highest concentrations of the drug found in kidney and liver.<sup>[14,67]</sup> No retention of drug in any particular tissue occurred.<sup>[2,67]</sup> The elimination of dalbavancin occurs by both renal and non-renal routes, with up to 42% of the administered dose excreted in urine.<sup>[2]</sup> Following population pharmacokinetic analysis, it was determined that the mean clearance of dalbavancin is 0.0571 L/h. It has been demonstrated that no dosage adjustments are necessary for dalbavancin in patients with mild and moderate renal or hepatic impairment, or in patients with end-stage renal disease requiring haemodialysis.<sup>[3]</sup> Dose adjustments are required for patients with severe renal impairment, defined as creatinine clearance <30 mL/min, although specific recommendations are currently unavailable.<sup>[3]</sup> Gender, age, race and serum albumin have been demonstrated to not be influential factors in dalbavancin pharmacokinetics.<sup>[14]</sup>

**Table II.** Pharmacokinetic parameters for glycopeptides at usual human doses (data obtained from healthy volunteers)<sup>[2,24,43,65]</sup>

| Parameter               | Dalbavancin<br>(1 g day 1, 500 mg day 8) | Telavancin<br>(10 mg/kg od) | Oritavancin<br>(3 mg/kg od) | Vancomycin<br>(15 mg/kg bid) |
|-------------------------|------------------------------------------|-----------------------------|-----------------------------|------------------------------|
| C <sub>max</sub> (mg/L) | 312                                      | 88                          | 29                          | 20–50                        |
| AUC (mg • h/L)          | 27 103                                   | 858                         | 146                         | 260                          |
| Vd (L/kg)               | 0.11                                     | 0.1                         | 0.65–1.92                   | 0.3                          |
| Protein binding (%)     | 93–98                                    | 90–93                       | 86–90                       | 10–55                        |
| Terminal half-life (h)  | 147–258                                  | 7–9                         | 393                         | 4–8                          |

**AUC**=area under the concentration-time curve; **bid**=twice daily; **C<sub>max</sub>**=peak concentration reached in plasma/serum; **od**=once daily; **Vd**=volume of distribution.

## 5.2 Oritavancin

Oritavancin administered intravenously exhibits linear pharmacokinetics for doses ranging from 0.02 to 10 mg/kg.<sup>[65,68]</sup> It also displays a high degree of protein binding (86–90%), and tissue distribution studies conducted in animals have reported that the liver, kidney, spleen and lungs take up significant amounts of the administered dose (59–64%, 2.7%, 1.8% and 1.7%, respectively).<sup>[2]</sup> Based on population pharmacokinetics, oritavancin has a terminal half-life of 393 hours, which when combined with its high degree of plasma protein binding, allows for once-a-day dosing (or potentially one dose per entire treatment regimen) [table II].<sup>[65]</sup> Oritavancin displays a complex, multi-exponential elimination phase and its distribution is most commonly characterized by a three-compartment model.<sup>[18,65]</sup> In human trials, <5% of the administered dose was recovered in urine and <1% in faeces.<sup>[27,54]</sup> Oritavancin is not metabolized in animals and, although limited data are available, the negligible amounts of drug recovered in faeces support the notion that oritavancin is not metabolized hepatically in humans.<sup>[27]</sup> Despite a reduction in both the AUC and  $C_{\max}$  among subjects with Class B Child-Pugh scores, no dosage adjustment is currently recommended for patients with mild-to-moderate hepatic dysfunction.<sup>[2]</sup> It is unlikely that dosage adjustments will be necessary for patients with renal dysfunction as only a small amount of drug was recovered in the urine.<sup>[27]</sup>

*In vitro* studies using macrophages obtained from mice and humans have demonstrated that oritavancin accumulates extensively in these cells.<sup>[69]</sup> This unique feature of oritavancin is important, as it may enable oritavancin to be active against pathogens that are able to survive within lysosomes.<sup>[69]</sup> In a human blister fluid model, oritavancin demonstrated modest penetration, with blister fluid oritavancin concentrations approximately 19% of the plasma drug concentrations, which is lower than that of both dalbavancin and telavancin.<sup>[54]</sup> Oritavancin penetration into the CSF fluid was 1–5% of the serum oritavancin concentration, as determined by a rabbit meningitis model.<sup>[70]</sup>

## 5.3 Telavancin

Telavancin, like other members of the glycopeptide class, has poor oral bioavailability and thus is administered over 30–120 minutes by an intravenous infusion.<sup>[2,71]</sup> From dose-escalation studies it has been determined that for dosages ranging from 7.5 to 15 mg/kg/day, telavancin follows linear pharmacokinetics.<sup>[2,71]</sup> The half-life of telavancin in serum is 7–9 hours, which allows for once-daily dosing with minimal accumulation (table II).<sup>[2,8]</sup> The volume of distribution of telavancin in healthy adults following a single 10 mg/kg dose is 0.115 L/kg, 0.105 L/kg after a 12.5 mg/kg dose and 0.119 L/kg following a 7.5 mg/kg dose.<sup>[8]</sup> Similar to dalbavancin and oritavancin, telavancin demonstrates a higher degree of plasma protein binding than vancomycin (93% vs 50%).<sup>[2]</sup> Despite the high degree of protein binding, the protein-binding association constant of telavancin is considered to be weak, as the agent's activity is not greatly altered by the presence or absence of serum.<sup>[2]</sup> Telavancin achieves good penetration into skin blister fluid, with the AUC in blister fluid approximately 40% of that in plasma following three daily doses of telavancin 7.5 mg/kg.<sup>[72]</sup> This feature has been demonstrated to maintain telavancin concentrations in blister fluid above the MIC for common skin and skin structure pathogens such as *S. aureus* and *Streptococcus* spp.<sup>[2,72]</sup> Telavancin also displays good penetration into pulmonary epithelial lining fluid (ELF) as well as alveolar macrophages, with the mean AUC of ELF approximately equal to the AUC of unbound drug in plasma (mean  $AUC_{\text{ELF}}/\text{free } AUC_{\text{plasma}} = 1.01 \pm 0.96$ ).<sup>[4,73]</sup> The activity of telavancin *in vitro* is not affected by the presence of pulmonary surfactant. In an animal model of meningitis it has been shown that 1% of the unbound drug enters un-inflamed meninges, while 2% penetrates when inflammation is present.<sup>[4,74]</sup>

The primary mode of elimination of telavancin from the body is via the renal route, with up to 70% of the dose excreted in the urine as unchanged drug.<sup>[4]</sup> The half-life of the drug in patients with renal dysfunction is extended compared with that reported in healthy individuals,

and increases with increasing renal dysfunction, thus making dosage adjustments necessary.<sup>[8]</sup> While patients with mild renal dysfunction can receive the full dose of the drug, the dose of telavancin for patients with creatinine clearance ranging from 30 to 50 mL/min should be 75% of the dose administered to healthy adults, whereas patients with end-stage renal disease should be administered the full dose (10 mg/kg) every 48 hours, rather than every 24 hours as in healthy volunteers.<sup>[2,8]</sup> Provided that the patient has normal renal function, advanced age alone does not warrant a telavancin dosage adjustment, despite a larger volume of distribution and longer half-life in this population.<sup>[4,50]</sup> Similarly, patients with moderate liver dysfunction displayed similar pharmacokinetic parameters for telavancin as healthy patients.<sup>[4]</sup> Telavancin is not an inhibitor, inducer or a substrate for CYP isoenzymes.<sup>[2]</sup>

## 6. Pharmacodynamics

Vancomycin, the best known member of the glycopeptide class, is slowly bactericidal, achieving a 3 log<sub>10</sub> bacterial reduction over 24 hours.<sup>[2,75]</sup> Newer lipoglycopeptide agents produce a more rapid bactericidal effect, with telavancin requiring only 8 hours to yield a 3 log<sub>10</sub> decrease in colony-forming units (cfu)/mL and oritavancin requiring 15 minutes to 2 hours to achieve 99.9% killing of tested strains of MSSA, MRSA and VRSA.<sup>[2,76]</sup> AUC/MIC is the best predictor of vancomycin efficacy.<sup>[2,4,75]</sup>

### 6.1 Dalbavancin

Dalbavancin exhibits concentration-dependent bactericidal activity, resulting in increased activity with increasing drug concentration.<sup>[2,35,77-79]</sup> It has been demonstrated in a murine thigh infection model that higher doses of dalbavancin administered less frequently resulted in greater bacterial kill than more frequent administration of smaller doses.<sup>[14,77]</sup> This finding was reinforced by a rat granuloma pouch infection model demonstrating that high doses of dalbavancin produced greater reduction in MRSA bacterial load.<sup>[78]</sup> The pharmacodynamic

parameters that correlate well with dalbavancin activity are AUC/MIC and C<sub>max</sub>/MIC.<sup>[2,79]</sup> Of these two parameters, AUC/MIC is considered the primary parameter: it has been demonstrated in an *in vitro* pharmacodynamic model simulating free dalbavancin concentrations versus *S. aureus* isolates, including MSSA, MRSA and VISA, that AUC/MIC had a better correlation with bactericidal activity than C<sub>max</sub>/MIC.<sup>[2,14,79]</sup> This study demonstrated that in order to achieve bactericidal activity, a total AUC/MIC ratio of 214–331 was necessary, whereas ratios of 36–100 yielded bacteriostatic effects.<sup>[14,79]</sup> A free AUC/MIC ratio (fAUC/MIC) of 4 and free C<sub>max</sub>/MIC ratio (fC<sub>max</sub>/MIC) of 0.6 correlate well with activity.<sup>[2]</sup> Dalbavancin has long-acting bactericidal activity following a single dose, an uncommon feature that may carry clinical implications. It was demonstrated that one large (10 mg/kg) dose of dalbavancin prevented *S. aureus* regrowth for 120 hours, whereas it took four doses of vancomycin to produce the same effect, despite the similar *in vitro* activity of the agents against the studied isolates.<sup>[14,79]</sup>

In order to elucidate the presence of synergy or antagonism resulting from combinations of dalbavancin with other antimicrobials, the *in vitro* activity of dalbavancin in combination with each of clindamycin, daptomycin, gentamicin, levofloxacin, linezolid, oxacillin, quinupristin/dalfopristin and rifampicin (rifampin) was studied.<sup>[2,35]</sup> All but one of the pairs tested exhibited indifference in activity when combined, with the exception of the dalbavancin and oxacillin combination, which resulted in a synergistic action against MRSA, methicillin-resistant CoNS and VISA.<sup>[35]</sup> This synergistic action resulted in a ≥4-fold reduction in the MIC for both agents.<sup>[14,35]</sup> While official breakpoints are yet to be determined by the FDA in the US, the manufacturer of dalbavancin has put forward a provisional set of breakpoints, which place susceptibility for staphylococci at ≤1 mg/L and ≤2 mg/L for streptococci.<sup>[2]</sup>

### 6.2 Oritavancin

Oritavancin consistently exhibits concentration-dependent bactericidal activity *in vitro*

against numerous Gram-positive pathogens including MSSA, MRSA, VRSA, VISA, VSE, and VanA and VanB VRE.<sup>[76]</sup> The activity of oritavancin *in vivo* is more complex, as there are studies supporting both concentration- and time-dependent activity of oritavancin in animal models of infection. A number of *in vivo* studies conducted in animals have demonstrated that administering a larger dose of oritavancin less often resulted in a greater reduction in bacterial load compared with administering a smaller dose more frequently, a feature consistent with concentration-dependent activity.<sup>[23]</sup> Using a neutropenic mouse thigh infection model it was determined that the pharmacodynamic parameter that best correlated with the efficacy of oritavancin *in vivo* was free oritavancin  $C_{\max}/\text{MIC}$  ( $r^2=0.93$ ).<sup>[36]</sup> In another study, a model of *E. faecalis* endocarditis in rabbits did not exhibit an increase in activity as  $C_{\max}$  or AUC increased, which left the authors to conclude that oritavancin displayed time-dependent activity.<sup>[37]</sup>

Human clinical pharmacodynamic data are limited to information collected during a phase II trial of 86 patients with *S. aureus* bacteraemia.<sup>[38]</sup> The authors of the study discovered that  $\text{AUC}_{0-24}/\text{MIC}$ ,  $C_{\max}/\text{MIC}$  and  $fT>\text{MIC}$  (free-drug % time  $>\text{MIC}$ ) all had a statistically significant correlation with clinical response and microbiological efficacy of oritavancin.<sup>[38]</sup> It was determined that the probability of microbiological success was higher in patients whose  $fT>\text{MIC}$  was  $\geq 22\%$  (93% chance of success) than in patients below this threshold (76% chance of success).<sup>[38]</sup> It was also discovered that the patients who were successfully treated had higher average drug exposure as well as higher  $\text{AUC}/\text{MIC}$  and  $C_{\max}/\text{MIC}$  parameters than the patients who experienced microbiological failure. However, it should be noted that the oritavancin MIC values of the infecting pathogens in that study were determined in the absence of P-80 (see section 4.2); as such,  $T>\text{MIC}$  may not be the pharmacokinetic/pharmacodynamic parameter most predictive of efficacy, since  $T>\text{MIC}$  approached 100% in all patients, irrespective of cure or failure.

Compared with dalbavancin and telavancin, oritavancin more frequently demonstrated *in vitro* synergistic activity with different classes of antimicrobials. *In vitro* studies have demonstrated a synergistic effect against *E. faecium* when oritavancin was combined with ampicillin, quinupristin/dalfopristin or gentamicin, and synergy against *E. faecalis* by an oritavancin-ciprofloxacin combination.<sup>[39,40]</sup> Oritavancin and daptomycin displayed synergy against VanA *E. faecium* and VanB *E. faecalis* phenotypes, and oritavancin in combination with rifampicin, moxifloxacin, linezolid or gentamicin demonstrated synergy against various *S. aureus* isolates.<sup>[39]</sup> No antagonism has been observed when oritavancin was combined with other antimicrobial agents *in vitro*. Oritavancin exhibits a post-antibiotic effect (PAE) *in vitro* against MRSA and vancomycin-resistant *E. faecium*.<sup>[18]</sup> The length of PAE, like the activity, is concentration dependent and has been found to be significantly shorter in staphylococci than in enterococci.<sup>[39,40]</sup> Through *in vitro* studies, the PAE of oritavancin against VRE has been determined to be 23 hours at ten times the MIC, whereas that time decreased to 12.2 hours in human serum at ten times the MIC.

### 6.3 Telavancin

Telavancin displays concentration-dependent bactericidal activity and, similar to oritavancin, it also displays a prolonged PAE.<sup>[2,41,42]</sup> The PAE ranged from 4 to 6 hours for most Gram-positive bacteria, which is at least four times longer than the PAE observed with vancomycin.<sup>[4,8,41]</sup> A murine neutropenic thigh model of infection demonstrated that the parameter that best predicts the efficacy of telavancin is the  $f\text{AUC}/\text{MIC}$  ratio.<sup>[20,42]</sup> If protein binding is not accounted for, both  $\text{AUC}/\text{MIC}$  and time above MIC provide equally good predictions of telavancin activity.<sup>[20,42]</sup> This conclusion is supported by results of other studies, which have also found that increasing the  $\text{AUC}/\text{MIC}$  ratio resulted in greater killing and a longer delay in the regrowth of bacteria.<sup>[20,42,43]</sup> An  $\text{AUC}/\text{MIC}$  ratio of 50, corresponding to a human dosage of 10 mg/kg once

daily and a minimum concentration in plasma of 5 mg/L, was the lowest concentration that resulted in no bacterial growth at 24 hours, while maximal activity was observed at total AUC/MIC of 404.<sup>[4]</sup> The following breakpoints (susceptible in mg/L) for telavancin are available: *S. aureus* (including meticillin-resistant isolates)  $\leq 1$ ; *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group  $\leq 0.12$ ; and *E. faecalis* (vancomycin-susceptible isolates only)  $\leq 1$ .

In order to elucidate any potential synergy, antagonism or indifference resulting from combinations of telavancin with other antimicrobial agents, a checkerboard methodology was employed to yield a fractional inhibitory concentration index (FICI).<sup>[2]</sup> Synergy was defined as FICI  $\leq 0.5$ , indifference  $>0.5-4$  and antagonism as FICI  $>4$ .<sup>[2]</sup> The study considered combinations of telavancin with ciprofloxacin, cefepime, imipenem and piperacillin/tazobactam against MRSA (oxacillin), MRSA (daptomycin-non-susceptible), VISA (Mu50), Michigan VRSA, *S. agalactiae*, erythromycin-resistant *S. pyogenes*, *E. faecalis* (vancomycin susceptible) and *E. faecium* exhibiting the VanA phenotype.<sup>[2]</sup> The results of the study demonstrated the absence of antagonism with any of the studied combinations and synergy with telavancin combined with cefepime or piperacillin/tazobactam against VISA and VRSA isolates.<sup>[2]</sup>

## 7. Clinical Trials

### 7.1 Dalbavancin

The clinical efficacy of dalbavancin has been evaluated in complicated and uncomplicated skin and skin structure infections (cSSSIs and uSSSIs) and catheter-related bloodstream infections (CR-BSIs) in two phase II and three phase III trials (table III).<sup>[2,44-46]</sup>

#### 7.1.1 Phase II Clinical Trials

The first of the two phase II clinical trials conducted with dalbavancin compared success rates (defined as cure or improvement), in a total of 62 adult patients with cSSSIs of known or suspected Gram-positive origin.<sup>[2,14,44]</sup> In this

randomized, controlled, open-label, multicentre study, patients were randomly assigned to receive one of three possible regimens: (i) a single intravenous dose of dalbavancin (1100 mg); (ii) two intravenous doses of dalbavancin (1000 mg on day 1 and 500 mg 1 week later); or (iii) a cephalosporin, clindamycin, piperacillin/tazobactam, linezolid or vancomycin, either in combination or on their own.<sup>[2,44]</sup> The duration of administration of comparator agents ranged from 7 to 21 days and conversion to oral therapy was approved if deemed appropriate.<sup>[14,44]</sup> Forty-one of the 62 isolates (66.1%) obtained from patients at baseline were Gram-positive pathogens, with *S. aureus* accounting for 83% of all Gram-positive isolates.<sup>[2,44]</sup> At the test-of-cure visit conducted upon study completion, it was demonstrated that 94.1% (16/17) of clinically evaluable patients treated with two doses of dalbavancin achieved clinical success, compared with 61.5% (8/13) of patients treated with a single dalbavancin dose and 76.2% (16/21) of patients treated with a comparator agent.<sup>[2,14,44]</sup> Microbiological eradication of *S. aureus* was successfully attained by 50% (5/10, single dalbavancin dose), 90% (9/10, two doses of dalbavancin) and 60% (6/10, comparator agent) of the affected patients, whereas 67% (2/3), 80% (4/5) and 71% (5/7) of patients with streptococcal infections at baseline achieved eradication.<sup>[2,44]</sup> The incidence of adverse effects was similar among all the groups evaluated.

Following the results from the previous phase II trial assessing the use of dalbavancin in cSSSIs, the manufacturers of dalbavancin decided to study its safety and efficacy in CR-BSIs.<sup>[14]</sup> This randomized, controlled, open-label, multicentre trial assessed 75 adult patients with Gram-positive bacteraemia of known or suspected catheter-related origin.<sup>[14,45]</sup> Study participants were randomized to receive either intravenous dalbavancin (1000 mg on day 1 and 500 mg 1 week later) or intravenous vancomycin (1000 mg twice daily for 14 days, adjusted according to serum vancomycin concentrations).<sup>[2,45]</sup> The most common bacteria isolated at baseline were CoNS (48%, 26/54), followed by *S. aureus* (43%, 23/54) and MRSA (26%, 14/54).<sup>[2,14,45]</sup> Patients randomized to the dalbavancin group attained a

**Table III.** Summary of selected clinical trials of dalbavancin, oritavancin and telavancin in various infections

| Inflection type<br>(name of trial)       | Study design/therapy administered                                                                                                                                                                                                                                                                                                                                                                                     | Results                                                                                                                                                                                                                                                                                                                                                                                          | References |
|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| <b>Dalbavancin</b>                       |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                  |            |
| cSSSI                                    | Phase II, randomized, controlled, open-label, multicentre trial of 62 adult patients with cSSSIs<br>Patients were randomized into 3 groups: dalbavancin 1100 mg IV as a single dose (group 1), dalbavancin 1000 mg IV on day 1 and 500 mg IV on day 8 (group 2) or comparator agent (a cephalosporin, clindamycin, linezolid, piperacillin/tazobactam or vancomycin, alone or in combination) [group 3] for 7–21 days | Clinical success, defined as clinical cure or improvement, was achieved by 61.5% of clinically evaluable patients treated with a single dalbavancin dose, 94.1% of patients treated with two doses of dalbavancin and 76.2% of patients receiving a comparator agent at the test-of-cure visit (no statistical information provided)                                                             | 2,14,44    |
| CR-BSI                                   | Phase II, randomized, controlled, open-label, multicentre trial assessing 75 adult patients with Gram-positive bacteraemia of catheter-related origin<br>Patients randomized to either dalbavancin group (1000 mg IV on day 1 and 500 mg on day 8) or vancomycin group (1000 mg IV administered every 12 hours for 14 days; dose adjusted according to serum concentrations)                                          | Overall success rate of 87% in the dalbavancin arm, while the vancomycin group achieved a 50% success rate ( $p < 0.05$ ). Complete eradication of isolated pathogen was achieved in 100% of the patients treated with dalbavancin and 80% of patients treated with vancomycin. Clinical success achieved in 92.2% and 45% of the patients treated with dalbavancin and vancomycin, respectively | 2,14,45    |
| cSSSIs                                   | Phase III, randomized, double-blind, multicentre trial in 854 adult patients<br>Patients randomized to dalbavancin (1000 mg IV on day 1 and 500 mg on day 8) and linezolid (600 mg IV/PO every 12 hours for 14 days)                                                                                                                                                                                                  | Clinical efficacy was achieved at test-of-cure visits by dalbavancin (88.9%) and linezolid regimens (91.2%). Microbiological eradication rates were 89.5% for dalbavancin and 87.5% for linezolid                                                                                                                                                                                                | 2,14,46    |
| uSSSIs                                   | Phase III clinical trial in 156 adult patients with cSSSIs<br>Patients randomized to IV dalbavancin or cefazolin                                                                                                                                                                                                                                                                                                      | Clinical response 89.1% in both treatment arms. Using intention-to-treat analysis, 76% of patients treated with dalbavancin and 75.8% of patients treated with cefazolin achieved clinical response                                                                                                                                                                                              | 2,7        |
| cSSSIs                                   | Phase III, randomized, open-label clinical trial of 156 patients with cSSSIs with known or suspected MRSA<br>Patients were randomized to either dalbavancin or vancomycin (no additional information available)                                                                                                                                                                                                       | Clinical response 89.9% of dalbavancin and 86.7% of vancomycin-treated patients (95% CI –13.0, 19.4). Response rates in the intention-to-treat arm were 86% for dalbavancin and 65.3% for vancomycin (95% CI 4.3, 37.0)                                                                                                                                                                          | 2,7        |
| <b>Oritavancin</b>                       |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                  |            |
| Gram-positive bacteraemia                | Phase II, open-label trial of 27 patients assessing the best oritavancin regimen for Gram-positive bacteraemia<br>Regimens included a loading dose/daily maintenance dose and were administered for 7–10 days. Regimens studied were 3/2, 4/3 and 5/4 mg/kg                                                                                                                                                           | Only 10 patients from the 5/4 mg/kg regimen group met prespecified study criteria for assessment of bacterial eradication. Nine of the 10 (90%) patients had a favourable response documented at 5 days post-therapy                                                                                                                                                                             | 23         |
| <i>Staphylococcus aureus</i> bacteraemia | Phase II, open-label, non-inferiority trial<br>Patients randomized to oritavancin (5, 6.5, 8 and 10 mg/kg/day) and vancomycin for MRSA bacteraemia (15 mg/kg/dose administered twice daily) or a $\beta$ -lactam for MSSA bacteraemia. Treatment duration was 10–14 days (number of patients treated was not available)                                                                                               | Bacteriological cure at 5–12 days post-therapy was achieved by 83%, 71%, 67% and 80% of the patients in the oritavancin 5, 6.5, 8 and 10 mg/kg/day groups, respectively. Bacteriological eradication was 70% (p-values not available) in the comparator group                                                                                                                                    | 23         |
| cSSSIs                                   | Phase II, randomized, double-blind, multicentre trial involving 302 patients<br>Patients randomized to receive either oritavancin 200 mg/day for 3–7 days, oritavancin single dose of 1200 mg or oritavancin infrequent dose 800 mg day 1 and 400 mg day 5                                                                                                                                                            | Of the clinically evaluable patients ( $n = 228$ ), clinical cure rates were 72.4% in the oritavancin 200 mg/day for 3–7 days group, 81.5% in the oritavancin 1200 mg single dose group and 77.5% in the oritavancin infrequent dose 800 mg day 1 and 400 mg day 5 group. Clinical cure                                                                                                          | 80         |

Continued next page

Table III. Contd

| Infection type (name of trial)                                                                                                                                                                                                                                                                                                                                                                            | Study design/therapy administered                                                                                                                                                                                                                                                                                                                                                                                                                  | Results                                                                                                                                                                                                                                                                                                                                                                                              | References |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| cSSSIs                                                                                                                                                                                                                                                                                                                                                                                                    | Phase III, randomized, double-blind, multicentre non-inferiority trial of 517 patients                                                                                                                                                                                                                                                                                                                                                             | rates in patients with MRSA were 78.3–87.0% and were not significantly different (p-values not available)                                                                                                                                                                                                                                                                                            | 23,24      |
|                                                                                                                                                                                                                                                                                                                                                                                                           | Patients randomized to oritavancin or vancomycin plus oral cephalixin. Patients in the oritavancin arm received either 1.5 or 3 mg/kg of oritavancin daily for 3–7 days, after which they were switched to oral placebo. Patients in the vancomycin arm received twice daily vancomycin (15 mg/kg/dose IV) for 3–7 days, after which they were switched to oral cephalixin 500–1000 mg twice daily. The total duration of treatment was 10–14 days | Of the clinically evaluable patients, 76% from the oritavancin group and 80% from the vancomycin/cephalexin group achieved the primary endpoint of clinical success (cure or improvement in patient's condition). Clinical success in patients with MRSA was achieved in 74% of patients who received oritavancin and 80% of patients who received the comparator treatment (p-values not available) |            |
| cSSSIs                                                                                                                                                                                                                                                                                                                                                                                                    | Phase III, randomized, double-blind, multicentre non-inferiority trial involving 1267 patients                                                                                                                                                                                                                                                                                                                                                     | From 1000 clinically evaluable patients, oritavancin was non-inferior to the comparator treatment, as 79% of the patients treated with oritavancin achieved clinical cure, compared with 76% of patients in the comparator group                                                                                                                                                                     | 23,24      |
| Telavancin                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                      |            |
| cSSSIs (FAST)                                                                                                                                                                                                                                                                                                                                                                                             | Phase II, randomized, controlled, double-blind, multicentre trial of 167 adult patients                                                                                                                                                                                                                                                                                                                                                            | Clinical cure rate was 79% with telavancin and 80% for standard therapy. For the subset of patients infected with MRSA, clinical cure rates of 82 and 69% were demonstrated for the telavancin and standard therapy group, respectively (p = 1.0)                                                                                                                                                    | 2,4,47     |
| cSSSIs (FAST-2)                                                                                                                                                                                                                                                                                                                                                                                           | Patients randomized in a 1 : 1 ratio to receive either IV telavancin (7.5 mg/day) or standard IV therapy. Standard therapy consisted of one of vancomycin (1 g administered ever 12 hours), nafcillin, oxacillin (both administered 2 g every 6 hours) or cloxacillin (0.5–1 g administered every 6 hours) for 4–14 days                                                                                                                           | Clinical cure (in clinically evaluable patients) was 96% with telavancin and 90% in the standard therapy group (p = 0.42)                                                                                                                                                                                                                                                                            | 2,4,48     |
| cSSSIs (ATLAS-1 and ATLAS-2)                                                                                                                                                                                                                                                                                                                                                                              | Phase II, randomized, double-blind, multicentre trial of 195 adult patients with cSSSIs                                                                                                                                                                                                                                                                                                                                                            | Overall response rate of 88.6% was achieved by telavancin therapy and 86.2% with vancomycin therapy. In patients who had MRSA isolated at baseline, 90.6% of those treated with telavancin achieved clinical cure, compared with 86.4% in the vancomycin group                                                                                                                                       | 2,4,81     |
| HAP (ATTAIN-1 and ATTAIN-2)                                                                                                                                                                                                                                                                                                                                                                               | Patients randomized to receive a 7- to 14-day treatment of either telavancin (10 mg/kg/day) or vancomycin (1 g administered every 12 hours)                                                                                                                                                                                                                                                                                                        | At test-of-cure visits, clinical cure rates for pneumonia caused by a single Gram-positive pathogen were 85% for those who received telavancin and 76% for vancomycin-treated patients (95% CI 0.3, 17.5). For MRSA HAP, 82% of the telavancin-treated group achieved clinical cure, compared with 74% in the vancomycin group (95% CI –3.5, 19.3)                                                   | 4          |
|                                                                                                                                                                                                                                                                                                                                                                                                           | Two identical phase III, randomized, double-blind clinical trials comparing telavancin and vancomycin in HAP                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                      |            |
|                                                                                                                                                                                                                                                                                                                                                                                                           | Patients randomized to receive either IV vancomycin (1 g every 12 hours) or telavancin (10 mg/kg/day) for 7–21 days                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                      |            |
| <b>CR-BSI</b> = catheter-related bloodstream infection; <b>cSSSIs</b> = complicated skin and skin structure infections; <b>HAP</b> = hospital-acquired pneumonia; <b>IV</b> = intravenous; <b>MRSA</b> = methicillin-resistant <i>S. aureus</i> ; <b>MSSA</b> = methicillin-susceptible <i>S. aureus</i> ; <b>PO</b> = orally/by mouth; <b>uSSSIs</b> = uncomplicated skin and skin structure infections. |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                      |            |

significantly higher overall success rate – defined as a combination of clinical and microbiological response – than those in the vancomycin group (87% vs 50%;  $p < 0.05$ ).<sup>[2,45]</sup> Complete eradication of the isolated pathogen was achieved in 100% (14/14) of the dalbavancin subjects and 80% (16/20) of the vancomycin subjects at the test-of-cure visit.<sup>[14,45]</sup> Clinical success in which patients had no further need for antibacterial therapy was achieved in 92.9% (13/14) of dalbavancin patients and 45% (9/20) of vancomycin patients.<sup>[2,45]</sup> The occurrence of adverse effects was similar between the dalbavancin and the vancomycin groups.

### 7.1.2 Phase III Clinical Trials

In 2003 and 2004 the safety and efficacy of dalbavancin in the treatment of cSSSIs was evaluated in a randomized, double-blind, multi-centre phase III trial involving 854 adult patients.<sup>[14,46]</sup> The study compared the safety and efficacy of once-weekly intravenous dalbavancin therapy (1000 mg on day 1 and 500 mg on day 8) against twice-daily linezolid therapy (600 mg orally or intravenous administered every 12 hours for 14 days) in the treatment of cSSSIs of known or suspected Gram-positive origin.<sup>[14,46]</sup> Out of the Gram-positive isolates collected at baseline, 89% (492/550) were *S. aureus* and 51% (278/550) were MRSA.<sup>[2,14,46]</sup> Microbiological success in the study was defined as eradication or presumed eradication of the organism isolated at baseline and the rate of microbiological success among the clinically evaluable population at the test-of-cure visit was similar between the dalbavancin and linezolid groups (89.5% and 87.5%, respectively).<sup>[14,46]</sup> The clinical efficacy of the two treatments was comparable as well, with 88.9% of the clinically evaluable patients who received dalbavancin achieving the goal at the test-of cure visit, compared with 91.2% of the clinically evaluable patients in the linezolid group (95% CI –7.28, –12.5).<sup>[7,46]</sup> The rates of adverse effects were also similar between the dalbavancin and linezolid groups.<sup>[2,46]</sup> This non-inferiority trial demonstrated that two doses of dalbavancin are equally effective as 14 days of twice-daily linezolid therapy in the treatment of cSSSIs.<sup>[7,14,46]</sup>

A second phase III trial was conducted to compare dalbavancin and intravenous cefazolin in the treatment of uSSSIs.<sup>[2,7]</sup> The large trial included 565 patients who received either intravenous dalbavancin or intravenous cefazolin followed by oral cephalexin as treatment for uSSSIs.<sup>[2,7]</sup> Clinical response was the primary endpoint of the trial, and in the clinically evaluable patients the same percentage of subjects from each group (89.1%) achieved the primary endpoint.<sup>[7]</sup> When intention-to-treat analysis was conducted, the results demonstrated that 76% of dalbavancin-treated patients and 75.8% of the cefazolin-treated patients (95% CI –7.7, 8.2) achieved the primary endpoint.<sup>[2,7]</sup>

The third phase III trial conducted on dalbavancin focused on the agent's efficacy in the treatment of cSSSIs. The randomized, open-label clinical trial enrolled 156 patients with cSSSIs where the cause was known or suspected to be MRSA.<sup>[2,7]</sup> Patients enrolled in the study were randomized to receive either vancomycin or dalbavancin, and the response rates were then compared between the groups.<sup>[2,7]</sup> Of the evaluable patients in the dalbavancin treatment arm, 89.9% exhibited a response following treatment, compared with 86.7% of evaluable patients treated with vancomycin.<sup>[2,7]</sup> Following intention-to-treat analysis, the dalbavancin response rate was 86%, while that of vancomycin was 65.3% (95% CI 4.3, 37.0).<sup>[2,7]</sup> The results of this trial were presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in 2005 but never formally published.

## 7.2 Oritavancin

To date, the results of three phase II and two phase III clinical trials evaluating the safety and efficacy of oritavancin in bacteraemia and cSSSIs have been released (table III).

### 7.2.1 Phase II Trials

Two phase II open-label trials have been conducted to evaluate the use of oritavancin in bacteraemia of Gram-positive origin.<sup>[80]</sup> The first of the trials was a non-controlled trial, which assessed three different dosage regimens of oritavancin

in 27 patients with Gram-positive bacteraemia.<sup>[80]</sup> All of the dosage regimens consisted of a loading dose/daily maintenance dose combination administered for 7–10 days.<sup>[80]</sup> Five patients received the 3/2 mg/kg regimen, another five received the 4/3 mg/kg regimen and 17 received the 5/4 mg/kg regimen.<sup>[80]</sup> The primary endpoint of bacterial eradication was assessed in ten of the patients from the 5/4 mg/kg regimen who met certain pre-specified criteria.<sup>[80]</sup> From the ten patients analysed, nine (90%) patients exhibited a favourable bacteriological response at 5 days following the end of therapy.<sup>[80]</sup> The findings of this trial were presented at ICAAC 2001 but never formally published. The second trial compared oritavancin and vancomycin in *S. aureus* bacteraemia in a randomized, open-label, non-inferiority trial.<sup>[80]</sup> Oritavancin administered in doses ranging from 5–10 mg/kg/day for 10–14 days was compared with a 15 mg/kg/dose of vancomycin administered twice daily for patients found to be infected with MRSA or a  $\beta$ -lactam for those patients with MSSA bacteraemia.<sup>[80]</sup> Bacteriological cure and clinical improvement at 5–12 days following the completion of therapy formed the primary endpoint of the trial.<sup>[80]</sup> Results from 84 patients were evaluated and demonstrated that regardless of the dose of oritavancin administered, the new lipoglycopeptide was not inferior to the comparator treatment.<sup>[80]</sup> The percentage of patients achieving the primary endpoint in the oritavancin group did not vary with dosage increases, as patients dosed at 5, 6.5, 8 and 10 mg/kg/day reported 83%, 71%, 67% and 80% success rates, respectively.<sup>[80]</sup> The rate of success in the comparator arm of the study was 70%.<sup>[80]</sup> The findings of this trial were presented at ICAAC 2004 but never formally published.

A phase II, randomized, double-blind, multicentre trial involving 302 patients with cSSSIs randomized the subjects to receive either (i) oritavancin 200 mg daily for 3–7 days; (ii) an oritavancin single dose of 1200 mg; or (iii) an oritavancin infrequent dose of 800 mg on day 1 and 400 mg on day 5.<sup>[80]</sup> Of the clinically evaluable patients ( $n=228$ ), clinical cure rates were 72.4% in the first group, 81.5% in the second group and 77.5% in the third group. Clinical cure rates in

patients with MRSA ranged from 78.3% to 87.0% and were not significantly different ( $p$ -values not available). The results of the study demonstrated that single and infrequent doses of oritavancin are as efficacious as daily oritavancin dosing for cSSSIs.

### 7.2.2 Phase III Trials

Results of the two phase III clinical trials assessing the safety and efficacy of oritavancin in cSSSIs were presented at ICAAC in 2001 and 2003 but are presently not formally published.<sup>[54,80]</sup> The first trial was a non-inferiority, double-blind, randomized, multicentre trial involving 517 patients with cSSSIs of Gram-positive origin.<sup>[54,80]</sup> The patients involved in the study were randomized to either the oritavancin group or the vancomycin group.<sup>[54,80]</sup> The patients in the oritavancin group received oritavancin 1.5 or 3 mg/kg/day for 3–7 days, after which time they were switched to an oral placebo.<sup>[54,80]</sup> The vancomycin group received twice daily vancomycin doses (15 mg/kg/dose) for 3–7 days and then oral cephalexin 500–1000 mg, which was also dosed twice daily.<sup>[54,80]</sup> The duration of intravenously administered therapy in both treatment arms was designed to be between 3 and 7 days, but in cases where clinical response was not achieved, it was allowed to continue for up to 14 days.<sup>[80]</sup> The duration of therapy for both groups was 10–14 days and the primary endpoint of the study was clinical success, which was defined as either clinical cure or improvement in the patient's condition.<sup>[54,80]</sup> For the 384 clinically evaluable patients, 76% in the oritavancin group achieved clinical success (regardless of dosage received), compared with 80% in the comparator group.<sup>[54,80]</sup> For the subset of patients infected with MRSA, 74% of the patients receiving oritavancin and 80% of the patients who received vancomycin achieved clinical success.<sup>[80]</sup> Overall, the results of the study demonstrated that oritavancin at both 1.5 and 3 mg/kg/day was not inferior to vancomycin in the treatment of cSSSI.<sup>[54,80]</sup> The findings of this study have yet to be formally published.

The design of the second phase III trial assessing the efficacy and safety of telavancin

in cSSSIs had a similar design to the first (randomized, double-blind, multicentre, non-inferiority).<sup>[54,80]</sup> A total of 1267 patients were randomized to receive either oritavancin 200 mg (300 mg for patients >110 kg) once daily for 3–7 days, which was then followed by oral placebo, or twice-daily doses of vancomycin (15 mg/kg/dose) followed by cephalexin 1000 mg administered orally twice daily for a total treatment time of 10–14 days.<sup>[54,80]</sup> The investigators assessed the results from 1000 clinically evaluable patients and found that 79% of oritavancin-treated patients and 76% of the vancomycin-treated patients achieved clinical cure.<sup>[54,80]</sup> Similar to the findings of the previous study, the results of this trial also demonstrated non-inferiority between oritavancin and vancomycin in achieving clinical cure in patients with cSSSIs.<sup>[54,80]</sup> It was also noted that the average length of treatment was significantly shorter for patients treated with oritavancin than for patients treated with vancomycin (5.3 vs 10.9 days, respectively;  $p < 0.0001$ ).<sup>[80]</sup> The findings of this study have yet to be formally published.

The Medicines Company is currently in dialogue with the FDA regarding plans for a phase III programme and anticipates the start of the programme in the fourth quarter of 2009 with an expected enrolment period of 1–2 years.

### 7.3 Telavancin

The safety and clinical efficacy of telavancin was assessed in patients with cSSSIs and hospital-acquired pneumonia (HAP) in two phase II trials – FAST (telavancin vs standard therapy for treatment of complicated skin and soft-tissue infections due to Gram-positive bacteria) and FAST-2 (telavancin vs standard therapy for treatment of complicated skin and skin structure infections caused by Gram-positive bacteria) – and four phase III trials – ATLAS-1 (assessment of telavancin in complicated skin and skin structure infections), ATLAS-2, ATTAIn-1 (telavancin for the treatment of HAP caused by MRSA and MSSA) and ATTAIn-2 (telavancin for the treatment of HAP in severely ill and older patients) [table III].<sup>[47,48,81]</sup>

#### 7.3.1 Phase II Clinical Trials

FAST and FAST-2 are two phase II clinical trials that evaluated the efficacy of telavancin in the treatment of cSSSIs.<sup>[2]</sup> The FAST study was a randomized, double-blind, multicentre trial that took place in the US and South Africa.<sup>[4,47]</sup> FAST randomized 167 adult patients in a 1:1 ratio to receive either intravenous telavancin 7.5 mg/day or standard intravenous therapy consisting of one of (i) vancomycin (1 g every 12 hours), (ii) nafcillin or oxacillin (2 g every 6 hours) or (iii) cloxacillin (0.5–1 g every 6 hours) for 4–14 days.<sup>[2,47]</sup> Overall, the clinical cure rates – defined as “resolution of clinically significant signs and symptoms associated with the skin and soft-tissue infection present at study admission or improvement to the extent that the infectious process had been controlled and required no further antimicrobial therapy” – between the two groups were similar, with 80% of standard therapy patients and 79% of the telavancin patients achieving clinical cure.<sup>[4]</sup> Patients who had an *S. aureus* infection at baseline had similar cure rates regardless of their group allocation (80% for the telavancin group and 77% for the standard therapy group).<sup>[2,47]</sup> When the subset of patients with MRSA cSSSIs was analysed, telavancin produced higher cure rates (82%, 18/22) than the standard therapy group (69%, 18/26), but the difference was not statistically significant.<sup>[2,47]</sup> Up to 84% (16/19) of patients with an infection caused by MRSA achieved microbiological eradication when treated with telavancin, whereas 74% (14/19) achieved this on the standard therapy regimens ( $p = 0.53$ ).<sup>[2,47]</sup> Fewer patients in the telavancin group experienced serious adverse effects than the standard group (4 vs 7 events), although the proportion of discontinuations due to adverse effects was similar between the groups, at 5%.<sup>[2,47]</sup> The authors of the FAST study concluded that treatment of cSSSIs with telavancin was as effective as that with standard therapy, but noted that higher response rates were documented with telavancin treatment in patients with MRSA infections.<sup>[4,47]</sup>

The FAST-2 trial had a similar design to the FAST trial in that it was also a randomized, double-blind trial conducted in the US and South

Africa.<sup>[4,48]</sup> The FAST-2 trial included 195 adult patients who were randomly assigned to receive either intravenous telavancin 10 mg/kg once daily or standard intravenous therapy consisting of one of (i) nafcillin or oxacillin (2 g every 6 hours), (ii) cloxacillin (0.5–1 g every 6 hours) or (iii) vancomycin (1 g every 12 hours) for 4–14 days.<sup>[2,48]</sup> Of the microbiologically evaluable patients identified to have an *S. aureus* infection at baseline, 96% of the telavancin group and 90% of the standard therapy group achieved clinical cure ( $p=0.36$ ).<sup>[2,48]</sup> Identical clinical cure rates were established for the telavancin and comparator groups (96% vs 90%, respectively) in patients identified to be infected with MRSA at baseline ( $p=0.42$ ).<sup>[2,48]</sup> For both *S. aureus* and MRSA cSSIs, telavancin demonstrated a superior ability to achieve microbiological eradication compared with standard therapy (92% vs 78% [ $p=0.07$ ] for *S. aureus* infections and 92% vs 68% [ $p=0.04$ ] for MRSA infections).<sup>[2,48]</sup> The rate of occurrence of serious adverse effects was similar between the groups, (6% for telavancin vs 4% for standard therapy), as was the discontinuation of therapy due to adverse effects, with 6% withdrawing from the telavancin group and 3% from the standard therapy group.<sup>[2,48]</sup> The conclusion of the study was that telavancin 10 mg/kg/day was as effective as standard intravenous therapy for the treatment of cSSIs.<sup>[4,48]</sup>

### 7.3.2 Phase III Clinical Trials

ATLAS-1 and ATLAS-2, completed in late 2006, were two parallel, multicentre, double-blind, active-controlled non-inferiority phase III trials that assessed the safety and efficacy of telavancin in patients with cSSIs.<sup>[2,4,81]</sup> Patients included in the study had a suspected or confirmed Gram-positive pathogen as the cause of their cSSI and were randomized to receive either intravenous vancomycin (1 g every 12 hours, with dosage adjustments permitted based on serum concentrations) or intravenous telavancin (10 mg/kg/day) for 7–14 days.<sup>[2,4,81]</sup> The two trials combined recruited 1867 patients, who received at least one dose of the medications, and approximately 80% of these patients were clinically evaluable.<sup>[2,81]</sup> Both ATLAS-1 and ATLAS-2

reported numerically higher microbiological and clinical response rates among patients receiving telavancin, but the difference in overall response rates was not statistically significant.<sup>[2]</sup> The combined results of the ATLAS trials found that the overall response rate, defined as clinical cure and microbiological eradication, was 88.6% (467/527) for the telavancin group and 86.2% (462/536) for the vancomycin group, and that out of all the patients who had a pathogen identified at baseline, 89.8% of the telavancin group and 87.3% of the vancomycin group achieved microbiological eradication.<sup>[2,4,81]</sup> When the subset of patients with MRSA infection was analysed, 90.6% (252/278) of the telavancin group achieved cure compared with 86.4% (260/301) in the vancomycin group ( $p=0.60$ ), with 89.9% of telavancin and 85.4% of vancomycin MRSA patients achieving microbiological eradication.<sup>[2,4,81]</sup> More patients in the telavancin group than the comparator group experienced adverse effects (735/929 [79%] vs 676/938 [72%]), the majority of which were mild and reversible, and included nausea and vomiting.<sup>[2,81]</sup> The rate of serious adverse effects was 7% for the telavancin-treated patients and 4% for the comparator group (no statistics provided).<sup>[2,81]</sup> The conclusion drawn by the authors of the ATLAS studies was that telavancin 10 mg/kg/day was as effective as twice-daily vancomycin in the treatment of cSSIs.<sup>[4,81]</sup>

The ATTAIN trials were two large, randomized, double-blinded phase III trials that assessed the safety and efficacy of telavancin in adult patients for the treatment of HAP.<sup>[4]</sup> The studies included two arms, with one group randomized to receive intravenous telavancin (10 mg/kg/day) and the other to intravenous vancomycin (1 g every 12 hours) for 7–21 days.<sup>[4]</sup> Clinical cure rates (definition not available) evaluated at test-of-cure visits conducted 7–14 days after the end of treatment demonstrated that patients whose pneumonia was caused by a single Gram-positive pathogen had statistically significantly higher cure rates if they received telavancin than if vancomycin was administered (85% [139/164] vs 76% [125/165]; 8.9% difference; 95% CI 0.3, 17.5).<sup>[4]</sup> When patients with MRSA HAP were evaluated, the telavancin arm achieved

numerically higher cure rates than the vancomycin group (82% [72/88] vs 74% [86/116]), but the difference was not statistically significant (95% CI -3.5, 19.3).<sup>[4]</sup> Similar cure rates were also demonstrated in patients in whom MSSA was the causative pathogen (88% vs 75%).<sup>[4]</sup> Upon examination of results obtained from older and severely ill patients, telavancin was deemed to be equally effective as vancomycin in treating HAP, with cure rates in patients with APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of  $\geq 20$  reaching 68% in the telavancin group and 57% in the vancomycin group (95% CI -9.4, 27.5).<sup>[4]</sup> In patients over the age of 65 years, clinical cure rates of 81% were achieved with telavancin treatment compared with 76% when vancomycin was administered.<sup>[4]</sup> The results of the ATTAIN trials have not yet been formally published.

## 8. Adverse Effects

### 8.1 Dalbavancin

In all clinical trials conducted to date, dalbavancin has been well-tolerated by patients, with the most frequent adverse events (AEs) reported being of mild to moderate intensity.<sup>[2,3,7,13,14,44-46]</sup> There have been no deaths attributed to dalbavancin therapy. Results from a phase I dose-escalation trial demonstrated that the most common AEs reported by patients receiving dalbavancin were pyrexia (50%), headache (25%) and nausea (6%).<sup>[7,14]</sup> The AEs of pyrexia and headache were also commonly reported in the placebo group, with 38% of patients reported to have experienced episodes of pyrexia and 31% reporting headaches.<sup>[7,14]</sup> Auditory toxicity and vestibular dysfunction were not detected at any point during the trial.<sup>[7,14]</sup> This study also did not identify the presence of any dose-limiting toxicities to dalbavancin therapy, which suggests that doses higher than 1120 mg (single dose) or 1600 mg (cumulative dose) that were used in the study could potentially be used clinically.<sup>[14]</sup> The pooled results of two phase II and three phase III trials conducted for the use of dalbavancin in various infections consistently demonstrated that

the most common AEs experienced by patients receiving dalbavancin therapy were gastrointestinal in nature and of mild to moderate intensity.<sup>[14]</sup> These common gastrointestinal AEs include nausea, diarrhoea and constipation, the rates of which were similar to the comparator treatments.<sup>[14]</sup> The only serious AE that was determined to be related or probably related to dalbavancin treatment was mild leukopenia, which resolved spontaneously.<sup>[14]</sup> In addition, the studies did not identify any detrimental effects to the auditory, cutaneous, cardiac (QT interval effects included), nervous, renal or vestibular systems resulting from dalbavancin treatment.<sup>[14]</sup> Overall, the rate of discontinuation of treatment due to AEs was low for dalbavancin and similar to the comparator agents studied (3.5% vs 3.8%, respectively).<sup>[14]</sup> Nine deaths were reported in patients assigned to dalbavancin groups.<sup>[14]</sup> A small trial of 12 patients (6 men, 6 women) followed patients for 60 days after administration of a single dose of dalbavancin 1000 mg in order to identify any potential effects of therapy on normal intestinal flora.<sup>[13]</sup> The treatment had little effect on the number of *Escherichia coli* and enterococci recovered, and no change in the number of clostridia, bacteroides or lactobacilli was identified.<sup>[13]</sup> *Clostridium difficile* was not recovered from any of the patients at any point during the study.<sup>[13]</sup>

### 8.2 Oritavancin

Results from three phase II, two phase III and two pharmacokinetic studies concluded that, overall, oritavancin is well tolerated and that the rate of AEs reported were similar to the comparators used in the trials.<sup>[23,24,27,80]</sup> One of the two pharmacokinetic studies elucidated the presence of asymptomatic elevations in liver transaminases (5/11 patients), with four of the patients experiencing enzyme elevations less than three times the upper limit of normal and all of which were normalized by the end of the study.<sup>[27]</sup> The fifth patient reported consumption of alcohol during the study, which could have affected the elevated liver enzyme findings in that individual.<sup>[27]</sup> The other pharmacokinetic study reported that patients most commonly reported

mild and general AEs including pain, headache, dry skin and rhinitis.<sup>[24,27]</sup> In addition, two volunteers, one from each study arm, also reported injection-site thrombosis and muscle spasms.<sup>[24]</sup> In phase II trials, the most commonly reported AEs included phlebitis at the injection site (19%), fever (19%), diarrhoea (17%) and hypotension (16%), with the patients exposed to the comparator agent experiencing a similar rate of these AEs as well.<sup>[23]</sup> A phase III trial of 517 adults concluded that the common AEs of phlebitis, nausea and vomiting were experienced by a similar percentage of patients, regardless of whether they had been allocated to the oritavancin or the vancomycin group.<sup>[23]</sup> More patients in the oritavancin group experienced tremor and local oedema than in the comparator group.<sup>[24]</sup> This study also found that more patients from the comparator group discontinued treatment due to AEs than in the oritavancin group (4.8% vs 1.8%, respectively;  $p=0.003$ ).<sup>[24,27]</sup> The second phase III trial ( $n=1246$ ) concluded that patients administered oritavancin had significantly fewer AEs than those treated with vancomycin.<sup>[23]</sup> *In vitro* studies have elucidated that oritavancin accumulates to a great extent inside macrophages and specifically within lysosomes, with intracellular concentrations being as much as 350-fold higher than that found extracellularly.<sup>[24]</sup> It has also been demonstrated that at clinically significant drug concentrations, oritavancin exposure resulted in morphological alterations in the lysosomes of macrophages and fibroblast cells.<sup>[24]</sup> Biochemical changes in the form of intracellular accumulation of cholesterol and phospholipids, which were respectively reversible and partially reversible, were also detected, pointing to a potential disorder in mixed-lipid storage.<sup>[23,24]</sup> The effects of these observations have yet to be studied *in vivo* in order to fully elucidate the potential clinical implications of such findings.

### 8.3 Telavancin

Phase I clinical trials of telavancin in healthy adults found that the most common AEs associated with telavancin treatment were taste disturbance (75% vs 14% placebo) and headache

(40% vs 29% placebo).<sup>[20]</sup> Taste disturbances were only reported at telavancin doses  $\geq 10$  mg/kg/day, and were mild and reversible without treatment.<sup>[20]</sup> Headaches were reported throughout the range of doses studied (0.25–10 mg/kg).<sup>[20]</sup> Other reported AEs included dizziness, nausea and rash in two subjects.<sup>[20]</sup> At telavancin doses  $\geq 10$  mg/kg, the investigators noticed a change in corrected QT (QTc) interval in the subjects studied, which prompted a second phase I trial assessing QTc changes with telavancin 7.5 and 15 mg/kg.<sup>[20]</sup> The study randomized 160 patients to receive one of telavancin (7.5 or 15 mg/kg), moxifloxacin or placebo daily for 3 days.<sup>[20]</sup> The placebo-controlled results demonstrated that the mean QTc change from baseline with telavancin treatment was  $<5$  msec regardless of dose administered, while that with moxifloxacin was 9.2 msec.<sup>[20]</sup> None of the subjects had QTc exceeding 500 msec and no one experienced any cardiovascular AE.<sup>[20]</sup> The results of safety evaluations of telavancin in the FAST clinical trial demonstrated that the AEs that occurred more often in the telavancin than in the standard therapy group were nausea (15% vs 13%), psychiatric disorder (12% vs 10%), headache (11% vs 10%), vomiting (10% vs 4%), dyspnoea (8% vs 1%), paraesthesia (5% vs 0%) and constipation (4% vs 0%).<sup>[47]</sup> Out of these, dyspnoea, vomiting and paraesthesia AEs were determined to be unrelated to telavancin treatment. Seven patients in the telavancin group and two in the standard therapy group experienced reversible elevations in serum creatinine levels.<sup>[47]</sup> It was also noted that mild decreases in thrombocytes and microalbuminuria were documented more frequently in patients receiving telavancin.<sup>[47]</sup> Compared with values collected at baseline, the patients who received telavancin had a 6.4 msec longer mean increase in QTc interval than those receiving standard therapy.<sup>[47]</sup>

The results of the FAST-2 trial paint a similar picture of the telavancin AE profile, reporting that nausea, taste disturbance, insomnia and headache were more frequent in patients receiving telavancin.<sup>[48]</sup> Two patients in the telavancin group were removed from the study due to the development of skin rashes of moderate intensity, although there were no cases of red man

syndrome.<sup>[48]</sup> Increases in serum creatinine were reported in five patients receiving telavancin, one of which admitted concomitant use of ibuprofen and diclofenac.<sup>[48]</sup> Analysis of ECGs revealed that compared with baseline values the QTc interval was 12.5 msec longer in the telavancin arm than in the standard therapy group, although no cardiovascular AEs were reported as a result of this prolongation.<sup>[48]</sup> The ATLAS studies also reported that mild nausea, taste disturbance, vomiting and foamy urine were more common in patients receiving telavancin.<sup>[81]</sup> One patient in the telavancin group reported mild and reversible hearing loss.<sup>[81]</sup> Serum creatinine increased in varying degrees in 12.6% of the telavancin group and 4.4% of the vancomycin group, and in all cases was reversible.<sup>[81]</sup> The rate of outlier QTc prolongation was equal in the telavancin and vancomycin treatment groups, with 1% of patients from each treatment arm experiencing a QTc prolongation >60 msec or >500 msec.<sup>[81]</sup> The mean QTc interval change was not reported and no cardiac AE resulted from QTc prolongation.<sup>[81]</sup>

## 9. Drug Interactions

To date, no drug-drug interactions have been identified for dalbavancin, oritavancin or telavancin.<sup>[2,27]</sup> Whereas dalbavancin and telavancin are renally eliminated and do not appear to affect the activity of CYP isoenzymes,<sup>[2,27]</sup> oritavancin was found to be a weak nonspecific inhibitor of human cytochromes.<sup>[82]</sup> It has been suggested that oritavancin cytochrome inhibition is reversible and likely to be clinically irrelevant.<sup>[82]</sup> More studies need to be conducted to determine the effects that CYP inhibitors, inducers and competitive substrates would have on any of the three aforementioned glycopeptides, as well as whether renal toxicity could result from a combination of any of these three agents with renally eliminated medications.<sup>[2,27]</sup>

## 10. Role in Therapy

Dalbavancin, oritavancin and telavancin all demonstrate bactericidal activity against MSSA, MRSA, MSSE, MRSE and penicillin-resistant

*S. pneumoniae*. Oritavancin is unique in that it maintains its activity against VanA enterococci. Dalbavancin and oritavancin both maintain activity against VanB enterococci, whereas telavancin only displays modest activity against these isolates. Clinically, dalbavancin, oritavancin and telavancin may be used for the treatment of resistant Gram-positive pathogens such as MRSA in patients with infections unresponsive to vancomycin, reduced susceptibility or resistance to vancomycin, or for those patients intolerant of vancomycin adverse effects.

The focus of clinical trials involving dalbavancin has been its use in cSSSIs. The results of these trials have consistently demonstrated that dalbavancin is as effective as standard therapy for the treatment of cSSSIs.<sup>[2,44,46]</sup> These studies support the notion that the primary approved indication for dalbavancin is likely to be for the treatment of cSSSIs caused by resistant Gram-positive pathogens such as MRSA. Considering the long half-life of 147–258 hours, which allows for once-weekly dosing, dalbavancin may also be considered as an option for the outpatient treatment of cSSSIs.<sup>[2]</sup> Despite an anticipated high acquisition cost, use of dalbavancin could substantially decrease healthcare resources (e.g. daily drug and administration costs) as well as improve adherence and convenience of therapy. Two different studies have also demonstrated that dalbavancin is efficacious in CR-BSIs and in cSSSIs.<sup>[2,45]</sup> In patients who are candidates for outpatient antibacterial therapy, dalbavancin could represent a safe, efficacious and economic option for the treatment of CR-BSIs.

Oritavancin has been studied in both bacteraemia of Gram-positive origin and in cSSSIs, and was demonstrated to be equally effective as standard therapy.<sup>[23,24]</sup> It is likely that the role of oritavancin, once it reaches the market, will be as an alternative to vancomycin for the treatment of cSSSIs and/or MRSA bacteraemia. The safety and efficacy of single and infrequent doses of oritavancin, which would be predicted to optimize its pharmacodynamic activity based on preclinical pharmacokinetic/pharmacodynamic studies, remains to be demonstrated in phase III studies of cSSSI. A single-dose treatment regimen

for oritavancin, like dalbavancin, would probably produce resource savings if used as out-patient therapy. While not examined in clinical trials, oritavancin may also have a role in the treatment of bacteraemia and other infections where enterococci, and particularly VRE, are the causative pathogens. The rationale for this is that oritavancin is the only glycopeptide that exhibits potent activity against both VanA and VanB harbouring enterococci. The multiple mechanisms of action of oritavancin may limit the development of resistant strains.

The efficacy of telavancin has been studied in both cSSSIs and HAP in humans, and has been found to be as effective as standard treatment in both of these indications.<sup>[4,47,48,81]</sup> As with oritavancin, the role of telavancin in the treatment of cSSSIs is likely to be as an alternative to vancomycin. The role of telavancin in the treatment of pneumonia due to MRSA needs to be further studied and may represent an important new treatment. The dual mechanism of action of telavancin is likely to limit the development of resistant strains.

## 11. Current Status

Dalbavancin is presently in late phase III clinical trials. The agent was not granted FDA approval in late 2008 and thus its current status is unclear. Pfizer is presently pursuing the sale of dalbavancin to another pharmaceutical company. Oritavancin is presently in phase III clinical trials. This agent was not granted FDA approval in late 2008 and thus its current status is unclear. A new phase III clinical trial is underway worldwide. The parent company, Targanta, was recently purchased by the Medicine Company. Astellas Pharma received (September 2009) FDA approval of telavancin in the US for the treatment of adults with cSSSIs, including those caused by MRSA. The company launched the agent in the fourth quarter of 2009. Approval is also pending in Europe.

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