

## Origin, structure, and activity *in vitro* and *in vivo* of dalbavancin

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**Dalbavancin is a novel semi-synthetic lipoglycopeptide that was designed to improve upon the natural glycopeptides currently available, vancomycin and teicoplanin. Chemical modification of natural glycopeptides has produced compounds with more potent antimicrobial activity and longer  $t_{1/2}$ , while maintaining an excellent safety profile. Dalbavancin, prepared from a teicoplanin-like glycopeptide, has better activity, *in vitro* and in animal infection models, than vancomycin and teicoplanin. In particular, dalbavancin has excellent activity against staphylococci, including coagulase-negatives. A unique feature of dalbavancin is its pharmacokinetics, characterized by a long elimination  $t_{1/2}$  in humans which makes a once-weekly dosing regimen feasible. Dalbavancin recently completed Phase 3 clinical trials in skin and skin structure infection.**

Keywords: glycopeptides, structure–activity relationships, Gram-positive, staphylococci

### Introduction

Owing to the continued development of antimicrobial resistance in Gram-positive bacteria, there is a need for new, effective and well-tolerated agents. Resistance to recently introduced agents such as quinupristin/dalfopristin, linezolid, new quinolones and telithromycin has been reported.<sup>1,2</sup> A 2000 survey showed that 36%, 34% and 54% of *Staphylococcus aureus* isolates from hospitals in the USA, Europe and the Western Pacific, respectively, were methicillin-resistant (MRSA).<sup>3</sup> Furthermore, community-acquired MRSA has recently emerged worldwide.<sup>4</sup> Additional challenges for the treatment of Gram-positive infections include widespread penicillin resistance, increasing resistance to macrolides in *Streptococcus pneumoniae* and increasing incidence of glycopeptide-resistant enterococci.<sup>1</sup>

Glycopeptides are a large class of naturally occurring antimicrobial agents, of which only vancomycin and teicoplanin are currently commercially available (Figure 1). Glycopeptides are active against Gram-positive bacteria and are widely used in hospitals, in particular to treat infections caused by methicillin-resistant staphylococci.<sup>5</sup>

Glycopeptides interfere with formation of the bacterial cell wall by binding to the terminal D-alanyl-D-alanine of nascent peptidoglycan chains. The formation of a complex between the glycopeptide and the muramyl-stem peptides of the peptidoglycan chains prevents transpeptidation and, indirectly, transglycosylation, thus interfering with cross-linking and polymerization.<sup>6</sup>

With the exception of the enterococci, clinically relevant resistance to glycopeptides is uncommon, although reduced susceptibility, particularly to teicoplanin, has been observed in

coagulase-negative staphylococci (CoNS), beginning about 15 years ago.<sup>7</sup> A limited number of glycopeptide-intermediate *S. aureus* (GISA) strains have appeared globally in recent years<sup>8</sup> and, more recently, two vancomycin-resistant strains (VRSA) have been identified in the USA.<sup>9,10</sup>

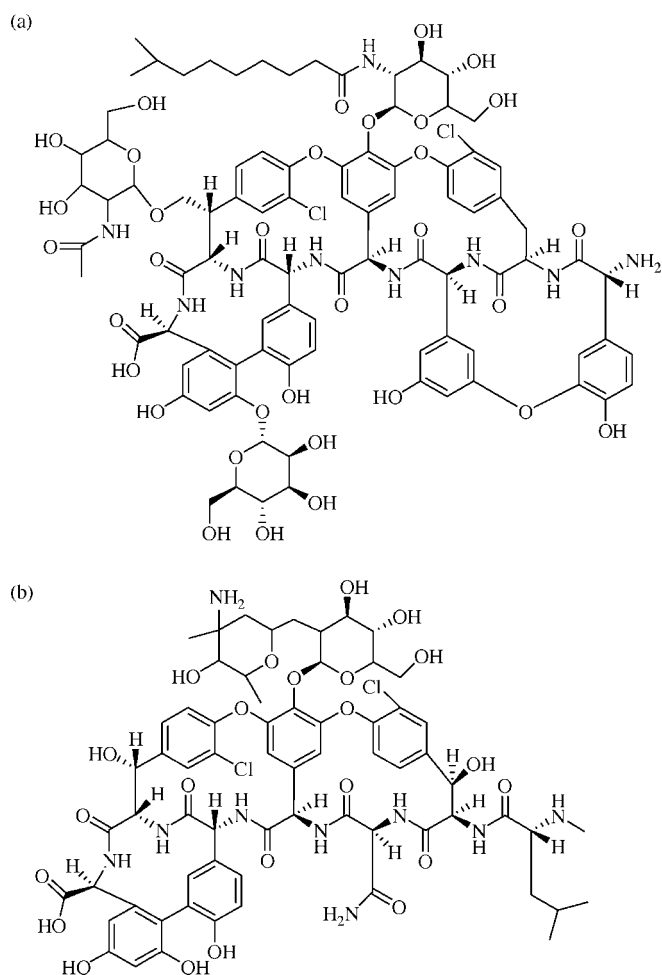
Although vancomycin was introduced more than 40 years ago, it is still the only glycopeptide available in the USA, and teicoplanin is the only other member of the class available in other countries. Disadvantages of vancomycin include the requirement for twice daily intravenous (iv) doses, infusion over a 1 h period to avoid infusion-related effects, drug level monitoring and dosage adjustments for diminished renal function.<sup>11</sup> It therefore appeared attractive and plausible to design a second-generation glycopeptide with improved characteristics.

A chemical programme was aimed at improving the antimicrobial properties of teicoplanin-like glycopeptides by using molecular modelling and molecular dynamic simulation studies based on structure–activity relationships of previous semi-synthetic derivatives of teicoplanin and vancomycin.<sup>12</sup>

### Structure–activity relationships in glycopeptides and synthesis of dalbavancin

The naturally produced glycopeptides are highly modified linear heptapeptides that have five invariant amino acids. The primary structural elements of differentiation are amino acids 1 and 3. Glycopeptides are classified, depending on the aliphatic or aromatic nature of these two amino acids, into four main classes.<sup>13</sup> Other important elements of differentiation are the number, structure and position of the sugars, the number and position of

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**Figure 1.** Structures of (a) teicoplanin and (b) vancomycin.

the chlorine atoms, and the number and position of methyl and hydroxyl groups.<sup>13</sup>

The peptide backbone of the glycopeptides forms the D-alanyl-D-alanine binding site, which is an absolute requirement for antimicrobial activity of the natural glycopeptides.<sup>13</sup> Thus, derivatization was aimed at modifying the functional groups of a teicoplanin-like antibiotic, A 40926, without directly affecting the binding pocket. Antimicrobial potency and physicochemical properties are influenced by the structure and position of the sugar and acyl-sugar moieties.

Structure–activity relationship studies of vancomycin and teicoplanin derivatives provided data for the rational design of a molecule with improved antimicrobial activity and pharmacokinetic properties.<sup>12</sup> In teicoplanin-type glycopeptides, conversion of the carboxy group into an ester, amide or hydrazide has previously been shown to improve antimicrobial potency,<sup>14</sup> in particular, derivatization of the carboxy terminus of the peptide improves activity against CoNS. The relative activity of these derivatives depends largely on their ionic characters.<sup>13</sup> The N-acylglucosamine is responsible for the long plasma  $t_{1/2}$  of teicoplanin-like antibiotics, as well as activity against VanB and VanC enterococci.

Some glycopeptides, particularly those possessing a lipophilic chain linked to mono- or disaccharide moieties positioned at the

top of the molecule (Figure 1) tend to dimerize to different degrees.<sup>15</sup> The lipophilic side chain may also be anchored in the bacterial cell membrane, which could stabilize the putative dimer in a position favourable for simultaneous interaction with two pentapeptide stems of the nascent peptidoglycans.<sup>15</sup>

The teicoplanin-like glycopeptide A 40926 was the starting point for the studies that led to dalbavancin.<sup>12</sup> A 40926 was isolated from *Nonomuria* sp. using affinity chromatography with sepharose-D-alanyl-D-alanine resin and eluting the adsorbed glycopeptide with 1% aqueous ammonia.<sup>16</sup> A 40926 is structurally related to teicoplanin (Figures 1 and 2). Differences from teicoplanin include the absence of the acetylglucosamine in the benzylic position, the presence of an acylaminoglucuronic acid on amino acid 4 in place of acylglucosamine, and the presence of a terminal methylamino group. A 40926 also differs from teicoplanin in the position of a chlorine atom and the length of the lipophilic side chain. A 40926 generally has similar activity to teicoplanin; however, it is less active against CoNS.<sup>17,18</sup> The  $t_{1/2}$  of A 40926 is longer than that of teicoplanin.<sup>17</sup> Modifications of A 40926 included removal or substitution of sugars, and derivatization of functional groups such as the carboxy group of amino acid 7 (the C-terminus of the peptide), the N-terminus of the peptide and different hydroxy groups. All modifications were at sites that did not directly affect the D-alanyl-D-alanine binding pocket.<sup>12,13</sup>

Dalbavancin, 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O-[2-deoxy-2-[(10-methyl-1-oxoundecanoyl)amino]- $\beta$ -D-glucopyranosyl]-38-[[[3-(dimethylamino)propyl]amino]carbonyl]-42-O- $\alpha$ -D-mannopyranosyl-N15-N-methyl-ristomycin A aglycon (synonyms: MDL 63,397, BI 397, A-A1 and VER 001), was prepared following a three-step procedure (Figure 2). First, the N-acylaminoglucuronic acid function was selectively esterified by incubation in methanol in the presence of sulphuric acid at 0–5°C for 24 h. Second, the peptide-carboxy group was amidated with 3-(dimethylamino)-1-propylamine in dimethylsulphoxide in the presence of benzotriazolyloxy-*tris*-pyrrolidinophosphonium-hexafluoro-phosphate. Finally, the sugar methyl ester was saponified with 15% sodium hydroxide.

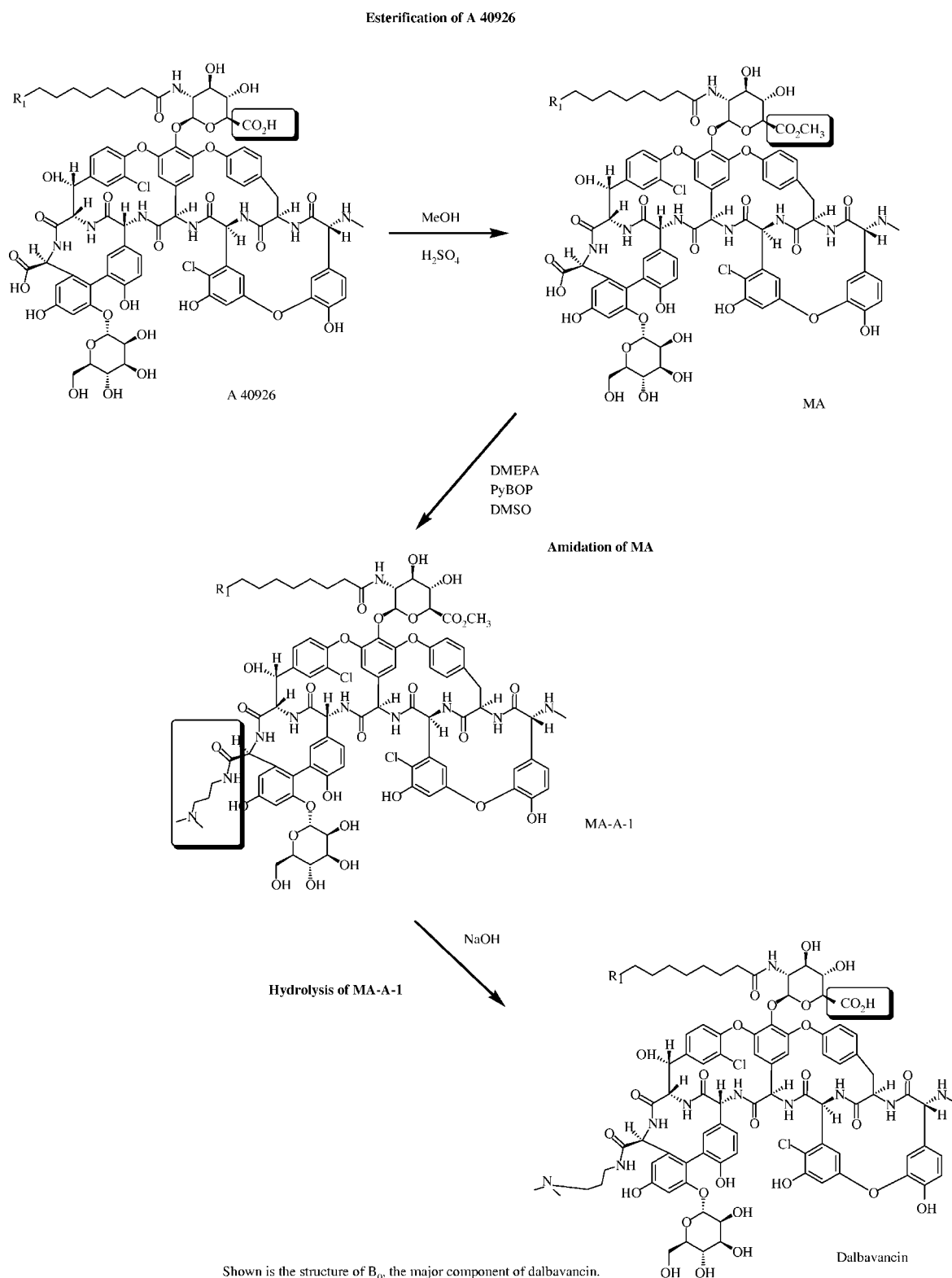
### *In vitro* activity of dalbavancin

Dalbavancin has a similar spectrum of *in vitro* activity to the other glycopeptides, but it is more potent than vancomycin or teicoplanin.<sup>10,19–23</sup> The monoamide (dimethylaminopropyl) substituent at the peptide carboxy group is responsible for increased potency against staphylococci, particularly CoNS.

In a recent survey of more than 1100 MRSA clinical isolates, the MIC<sub>50</sub> of dalbavancin was 0.06 mg/L, compared with 1 and 0.5 mg/L, respectively, for vancomycin and teicoplanin (Table 1).<sup>23</sup> Similarly, dalbavancin was more active against methicillin-resistant CoNS (MIC<sub>90</sub> 0.06 mg/L, versus 2 and 4 mg/L for vancomycin and teicoplanin, respectively). Dalbavancin is also active against isolates with reduced susceptibility to vancomycin and teicoplanin (GISA) with MICs of 0.06–1 mg/L.<sup>24</sup> Recently, dalbavancin was shown to be active (MIC 0.5 mg/L) against one of the two VRSA strains isolated in the USA (VRSA-Hershey).<sup>10</sup>

Against streptococci, dalbavancin is as active as teicoplanin and more active than vancomycin.<sup>19,20,23</sup> Dalbavancin MICs for penicillin-resistant isolates of *S. pneumoniae* and viridans-group

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**Figure 2.** Synthesis of dalbavancin.

**Table 1.** *In vitro* activity of dalbavancin and other glycopeptides against antibiotic-resistant Gram-positive bacteria

|                                                                         | Dalbavancin                 |                             | Vancomycin                  |                             | Teicoplanin                 |                             |
|-------------------------------------------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                                                                         | MIC <sub>50</sub><br>(mg/L) | MIC <sub>90</sub><br>(mg/L) | MIC <sub>50</sub><br>(mg/L) | MIC <sub>90</sub><br>(mg/L) | MIC <sub>50</sub><br>(mg/L) | MIC <sub>90</sub><br>(mg/L) |
| MRSA ( <i>n</i> = 1177)                                                 | 0.06                        | 0.06                        | 1                           | 2                           | 0.5                         | 2                           |
| Methicillin-resistant CoNS ( <i>n</i> = 617)                            | 0.03                        | 0.06                        | 1                           | 2                           | 2                           | 4                           |
| Penicillin-non-susceptible <i>S. pneumoniae</i> ( <i>n</i> = 400)       | ≤ 0.015                     | 0.03                        | 0.25                        | 0.5                         | –                           | –                           |
| Penicillin-non-susceptible viridans group streptococci ( <i>n</i> = 30) | ≤ 0.015                     | 0.03                        | 0.5                         | 0.5                         | –                           | –                           |

Data from Streit *et al.*<sup>23</sup>

streptococci, in comparison with vancomycin, are shown in Table 1. In the 2002 survey, MIC<sub>90</sub>s of dalbavancin for different groups of streptococci (a total of almost 2000 isolates), ranged from 0.03 to 0.06 mg/L.<sup>23</sup>

Dalbavancin, like teicoplanin, is more active than vancomycin against vancomycin-susceptible enterococci and is active against VanB and VanC enterococci.<sup>19</sup> Dalbavancin is for the most part inactive against VanA enterococci; in this it differs from some other new-generation glycopeptides (oritavancin, TD-6424) that have a second mechanism of action, direct inhibition of transglycosylation of the peptidoglycan.<sup>25–27</sup> This second mechanism appears to be responsible for their activity against VanA enterococci. Dalbavancin is more potent against staphylococci than either of these compounds.<sup>27–29</sup> Dalbavancin appears to undergo dimerization and its lipophilic side chain is hypothesized to anchor in the membrane.<sup>12</sup> These attributes might increase the affinity of dalbavancin for its target, resulting in improved antimicrobial activity.

Dalbavancin is bactericidal for staphylococci, in the presence or absence of serum, at concentrations that are achieved and maintained *in vivo* and its activity *in vivo* is consistent with this observation.<sup>30</sup>

### Efficacy of dalbavancin in animal infection models

In all species studied, dalbavancin has a long elimination *t*<sub>1/2</sub>. A consistent finding in animal infection studies is that dalbavancin is efficacious at lower and/or less frequent doses than comparators, including teicoplanin, vancomycin, linezolid and penicillin.<sup>19,31–33</sup> Animal models included: acute disseminated infections in mice (immunocompetent and neutropenic) with staphylococci (including MRSA), streptococci and enterococci; granuloma pouch infection in rats, including *S. aureus*; pneumococcal pneumonia in immunocompetent and neutropenic rats; staphylococcal endocarditis in rats and rabbits, and *S. aureus* foreign body infection in rabbits. Test organisms included staphylococci [methicillin-susceptible *S. aureus* (MSSA), MRSA, GISA, *Staphylococcus epidermidis*], streptococci (*Streptococcus pyogenes*, penicillin-susceptible and -resistant *S. pneumoniae*) and *Enterococcus faecalis*. Data from some of the disseminated infection, lobar pneumonia and rat endocarditis experiments are summarized in Tables 2 and 3.

The efficacy of dalbavancin at infrequent doses is related to its pharmacokinetics as well as its intrinsic activity. Experiments with the granuloma pouch model demonstrated reduction in

bacterial load and prolonged suppression of the regrowth of organisms including MRSA.<sup>33</sup> These results were important in predicting that weekly treatment of human infections was feasible.<sup>34</sup>

### Studies in humans

In clinical trials, the *t*<sub>1/2</sub> of dalbavancin in humans was shown to be approximately 1 week and the concentration 1 week after a first 1000 mg dose (or 1 week after a second 500 mg dose given on day 8) averaged approximately 30 mg/L,<sup>35,36</sup> well above concentrations expected on the basis of *in vitro* studies to be bactericidal for most target organisms. Additionally, concentrations of at least 50 mg/L are present for most of the dosing interval. Bactericidal concentrations of dalbavancin were present in the serum of volunteers for up to 7 days following a dalbavancin dose of 500 mg.<sup>35</sup>

In a recently completed Phase 2 clinical trial, dalbavancin (1000 mg iv, followed 1 week later by 500 mg iv) was well tolerated and demonstrated 94% clinical success in the treatment of Gram-positive skin and skin structure infections (SSSI), compared with 76% in the comparator arm.<sup>36</sup> MICs of dalbavancin for the clinical isolates from this trial were comparable to pre-

**Table 2.** Comparative efficacy of dalbavancin against disseminated infections in mice

| Organism                | Antibiotic              | ED <sub>50</sub> <sup>a</sup> (mg/kg) |
|-------------------------|-------------------------|---------------------------------------|
| Immunocompetent mice    |                         |                                       |
| <i>S. aureus</i> (MSSA) | dalbavancin             | 0.08                                  |
|                         | vancomycin              | 1.12                                  |
|                         | teicoplanin             | 0.20                                  |
| <i>S. pyogenes</i>      | dalbavancin             | 0.06                                  |
|                         | teicoplanin             | 0.18                                  |
| <i>S. pneumoniae</i>    | dalbavancin             | 0.56                                  |
|                         | vancomycin <sup>b</sup> | 0.79                                  |
|                         | teicoplanin             | 0.4                                   |
| Neutropenic mice        |                         |                                       |
| <i>S. epidermidis</i>   | dalbavancin             | 0.38                                  |
|                         | vancomycin <sup>b</sup> | 7.07                                  |
|                         | teicoplanin             | 10.7                                  |

Some of these data previously reported by Candiani *et al.*<sup>19</sup><sup>a</sup>Extrapolated dose that protects 50% of the mice.<sup>b</sup>Vancomycin administered twice, other agents once.

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**Table 3.** Efficacy of dalbavancin in pneumonia and endocarditis in rats

|                                                            | Dosage regimen<br>(mg/kg, route, frequency) | Survivors/total | Number of sterile<br>organs/total <sup>a</sup> | Mean (S.D.)<br>log <sub>10</sub> cfu/g of organs <sup>a</sup> |
|------------------------------------------------------------|---------------------------------------------|-----------------|------------------------------------------------|---------------------------------------------------------------|
| Lobar pneumonia: penicillin-resistant <i>S. pneumoniae</i> |                                             |                 |                                                |                                                               |
| pre-treatment                                              | –                                           | –               | 0/10                                           | 8.8 (0.3)                                                     |
| untreated                                                  | –                                           | 4/11            | 0/4                                            | 7.7 (0.9)                                                     |
| dalbavancin                                                | 10 iv once                                  | 8/11            | 4/8                                            | 2.8 (0.9)                                                     |
| penicillin                                                 | 80 000 IU/kg im bid                         | 7/11            | 0/8                                            | 6.7 (1.4)                                                     |
| Endocarditis: <i>S. aureus</i> (MRSA)                      |                                             |                 |                                                |                                                               |
| pre-treatment                                              | –                                           | –               | 0/6                                            | 7.3 (1.0)                                                     |
| untreated                                                  | –                                           | 0/12            | 0/12                                           | 9.7 (0.3)                                                     |
| dalbavancin                                                | 10 iv qd <sup>b</sup>                       | 11/11           | 4/11                                           | 3.7 (2.2)                                                     |
| vancomycin                                                 | 100 im bid                                  | 8/10            | 2/10                                           | 4.1 (2.2)                                                     |
| teicoplanin                                                | 20 iv bid <sup>b</sup>                      | 6/8             | 0/8                                            | 6.1 (2.1)                                                     |

iv, intravenous; im, intramuscular; bid, twice daily, qd, once daily. Data from Candiani *et al.*<sup>19</sup>

<sup>a</sup>Lungs for pneumonia, heart for endocarditis.

<sup>b</sup>First dose was a doubled loading dose.

viously observed MICs for isolates from other sources. Phase 3 clinical trials to confirm the efficacy of dalbavancin in the treatment of patients with uncomplicated and complicated SSSI were recently completed. Dalbavancin has also shown clinical efficacy in a Phase 2 study of catheter-related bacteraemia.<sup>37</sup>

## Conclusions

Dalbavancin, a second-generation lipoglycopeptide antibiotic, was synthesized during a programme to design a derivative with enhanced antibacterial potency and prolonged pharmacokinetics. Dalbavancin, like earlier glycopeptides, is active against important resistant organisms such as methicillin-resistant staphylococci and penicillin-resistant streptococci. An advantage of dalbavancin over vancomycin and teicoplanin is its greater potency and more consistent activity against all species of staphylococci. The most innovative feature of dalbavancin is its pharmacokinetics. Its long  $t_{1/2}$  is largely responsible for its efficacy in animal infection models at lower and/or less frequent doses than comparators. The long  $t_{1/2}$  has enabled clinical efficacy studies using once-weekly dosing (two doses over 2 weeks). Clinical studies have shown that once-weekly treatment is effective in treating infections caused by Gram-positive bacteria.

## Transparency declarations

Both authors are or have been employees of Vicuron Pharmaceuticals.

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