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Dalbavancin for the treatment of acute bacterial skin and skin structure infections

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Abstract

Introduction—Acute bacterial skin and skin structure infections (ABSSSI) have increased in incidence and severity. The involvement of resistant organisms, particularly methicillin-resistant *Staphylococcus aureus*, presents additional challenges. The lipoglycopeptide dalbavancin has a prolonged half-life, high protein binding, and excellent tissue levels which led to its development as a once-weekly treatment for ABSSSI. In the pivotal DISCOVER 1 and DISCOVER 2 trials, dalbavancin proved non-inferior to vancomycin followed by linezolid when used sequentially for ABSSSI, forming the basis for its recent approval in the US and Europe for ABSSSI.

Areas covered—A literature search of published pharmacologic and clinical data was conducted to review the chemistry, pharmacodynamics, and pharmacokinetics of dalbavancin. We also discuss its development process, highlighting efficacy and safety data from pertinent clinical trials and the role it could play in the current clinical landscape.

Expert opinion—DISCOVER 1 and DISCOVER 2 demonstrated dalbavancin's non-inferiority to vancomycin followed by linezolid for ABSSSI and confirmed its safety and tolerability. They were among the first trials to use new, early primary efficacy endpoints, and dalbavancin was among the first agents designated a Qualified Infectious Disease Product for expedited review. Dalbavancin may prove to be a valuable option for ABSSSI patients in whom conventional therapy is limited.

Keywords

acute bacterial skin and skin structure infections; dalbavancin; gram-positive bacteria; lipoglycopeptide

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Declaration of interest

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1. Introduction

Acute bacterial skin and skin structure infections (ABSSSI) was recently defined by the FDA as a bacterial infection of the skin with a lesion size area of at least 75 cm^2, measured by redness, edema, or induration [1]. ABSSSI represent a significant burden on the healthcare system, with increasing incidence and severity in recent years. Admissions for ABSSSI in the United States exceed 860,000 annually, a 29% increase from 2000 to 2004 [2]. Annual outpatient visits for ABSSSI nearly doubled from 1997 to 2005 [3]. Between 2006 and 2010, about 34.8 million ABSSSI cases were seen in ambulatory settings, 33% in the Emergency Department [4]. Yet these figures may underestimate the true magnitude of ABSSSI; approximately 50% of people with moderately severe infections reported they would self-treat without medical care [5].

The most notable factor in the rise of ABSSSI may be the emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) [6]. From 2001 to 2009, hospitalizations for *S. aureus* ABSSSI rose from 160,811 to 358,212, a 123% increase, and *S. aureus* ABSSSI incidence doubled [7]. *S. aureus* is by far the most commonly isolated pathogen in cultures of ABSSSI, and MRSA accounts for nearly half of these isolates [8]. The empirical use of antibiotics for MRSA has mirrored the upward trajectory of ABSSSI in the past decade [3]. Though MRSA is less prevalent in Europe than in the United States, it poses a similar public health challenge [9,10].

Infectious Diseases Society of America guidelines recommend therapy with a β-lactam or clindamycin for mild/moderate, non-purulent ABSSSI and vancomycin plus piperacillin/tazobactam for severe, non-purulent ABSSSI [11]. Treatment of purulent ABSSSI should cover MRSA empirically with doxycycline or trimethoprim/sulfamethoxazole (TMP/SMX) in moderate cases and vancomycin, daptomycin, linezolid, televancin, or ceftaroline in severe cases [11]. With increasing clinical MRSA isolates with decreased susceptibility or resistance to these drugs, treatment of ABSSSI is now challenged by antibiotic resistance, toxicity, few oral options, and greater need for hospitalization and its associated costs [12-14].

Dalbavancin (Box 1), a new addition to the antimicrobial armamentarium that could meet these challenges, is a novel lipoglycopeptide approved by the FDA in May 2014 and by the European Medicines Agency (EMA) in February 2015 for ABSSSI caused by susceptible Gram-positive organisms [15,16]. This review will discuss its pharmacologic properties, data from pertinent clinical trials, and the role it could play in the current clinical landscape.

Data and other information for this review were obtained from a PubMed/MEDLINE electronic database search for English language articles from February 2002 through April 2015 that contained keywords dalbavancin, lipoglycopeptide, and skin and soft tissue infections.

2. Overview of the market

Antimicrobials available in the US for treating ABSSSI with activity against MRSA and other resistant Gram-positive pathogens include vancomycin, daptomycin, linezolid,

televancin, ceftaroline, dalbavancin, oritavancin, and tedizolid. Oritavancin and tedizolid proved non-inferior to vancomycin and linezolid, respectively, for ABSSSI and were approved by the FDA in 2014 [17,18]. Of the antimicrobials listed, only linezolid and tedizolid have oral formulations, and some have significant potential for toxicity, including renal impairment from vancomycin, bone marrow suppression, and drug interactions (e.g., selective serotonin re-uptake inhibitors) from linezolid, and myopathy from daptomycin [14,19]. While doxycycline and TMP/SMX have MRSA activity, their activity against β-hemolytic streptococci is poorly understood, limiting their use as monotherapy for ABSSSI [11].

There are several compounds in development that may have future indications for treating ABSSSI. These include the quinolones delafloxacin, avarofloxacin, finafloxacin, and nemonoxacin; the tetracycline omadacycline; the oxazolidinones radezolid and MRX-I; the defensin-mimetic Brilacidin; the pleuromutilin lefamulin; the glycopeptide-cephalosporin heterodimers TD-1702 and TD-1607; the FabI inhibitors CG-400549 and Debio 1452, as well as its pro-drug Debio 1450, and the type 2 topoisomerase inhibitor GSK2140944 [20,21].

3. Introduction to the compound

Dalbavancin is a semi-synthetic lipoglycopeptide that, like other glycopeptides, binds to the terminal D-alanyl-D-alanine peptidoglycan sequence of the Gram-positive bacterial cell wall. This forms a complex that prevents transpeptidation and subsequent transglycosylation, interfering with cross-linking and polymerization in the bacterial cell wall for a bactericidal effect [22]. As a lipoglycopeptide, dalbavancin is characterized by a long, lipophilic side chain. This side chain allows dalbavancin to dimerize and anchor in the bacterial cell membrane, increasing stabilization and interaction with bacterial peptidoglycans [22]. The *N*-acylglucosamine moiety results in a long plasma terminal half-life that makes it unique among drugs used to treat ABSSSI [22].

3.1 Chemistry

Dalbavancin is derived from the naturally occurring glycopeptide A 40926, which was isolated from *Nonomuria* spp. through a three-step procedure involving selective esterification of the *N*-acyclaminoglucuronic acid function, amidation of the peptide-carboxy group, and saponification of the sugar methyl ester [22]. Neither this process nor additional minor modifications affected the D-alanyl-D-alanine binding pocket [22].

Determination of the crystal structure of dalbavancin identified molecular features that likely enhance its antimicrobial activity [23]. Dalbavancin's structure is more closed than its parent compound, and the dimerization that occurs between dalbavancin pairs at the D-alanyl-D-alanine target site is a loose association unlike the hydrogen-bonded dimers noted with other glycopeptide antimicrobials [23]. Dalbavancin's C-terminal dimethyl-propylamine group is free and flexible, supporting the hypothesis that it enhances activity by inserting into the bacterial membrane [23]. The fatty acyl group allows nonspecific protein binding that likely contributes to dalbavancin's long plasma half-life and its ability to bind its target sites [23].

3.2 Pharmacodynamics

Dalbavancin is highly protein-bound (93%), particularly to albumin, leading to a steady-state volume of distribution ≈ 10 – 12 l and a prolonged half-life ≈ 240 h; the initial free drug concentration after a 1 g dose is approximately 21 mg/l [24]. An *in vitro* pharmacokinetic model using four *S. aureus* strains with decreasing dalbavancin concentrations to simulate a 240 h half-life noted concentration-independent killing with initial free drug concentrations of 3 – 21 mg/l [24]. Another *in vitro* study found that dalbavancin exhibited time-dependent killing against 146 staphylococci strains and was more potent than other agents [25]. An evaluation of both time-dependent and concentration-dependent pharmacodynamics of dalbavancin against *S. aureus* and *Streptococcus* spp. found that estimated susceptibility breakpoints using both AUC_{14days}/MIC and t > MIC for all isolates were well above the known dalbavancin MIC_{90}s, further supporting the use of once-weekly dosing of dalbavancin [26].

The rat granuloma pouch model demonstrated greater efficacy of dalbavancin versus vancomycin and linezolid against *S. aureus*, with > 2 log CFU/ml reduction and prevention of regrowth at 120 h with a single 10 mg/kg intravenous dose [27]. The pharmacodynamics of dalbavancin in neutropenic murine thigh and lung models demonstrated dose-dependent bactericidal activity, which correlated well with *in vivo* dalbavancin activity, supporting the use of large, infrequent doses [28].

Multiple studies have established dalbavancin's potent *in vitro* activity against a variety of Gram-positive isolates from both community and hospital settings [29-42]. *S. aureus* MIC_{90}s are typically 0.06 μg/ml, ranging from 0.06 – 0.25 μg/ml, and β-hemolytic streptococci MIC_{90}s range 0.03 – 0.25 μg/ml [29-41]. Dalbavancin is also active against coagulase-negative staphylococci, viridans group streptococci, enterococci (excluding VanA phenotype), *Corynebacterium* spp., *Bacillus* spp. *Listeria* spp., and several anaerobes [29-31,34,42,43].

Dalbavancin demonstrated superior *in vitro* activity versus comparators, including vancomycin, with dramatically lower MICs without evidence of resistance through direct selection or serial passage [29-37,43]. Dalbavancin has maintained this *in vitro* potency for over a decade without evidence of emergent resistance [38-41]. There has been no evidence to date to suggest that its long half-life would contribute to the development of resistance.

A synergy study of dalbavancin and nine antimicrobial classes did not show any antagonism [44]. The study noted synergy or partial synergy between dalbavancin and oxacillin for staphylococci, including MRSA and VISA, and enterococci [44]. Further investigation is necessary to determine the clinical utility of this synergistic effect.

3.3 Pharmacokinetics and metabolism

Like other glycopeptides, dalbavancin has poor oral absorption and requires intravenous administration, but its high protein binding and long half-life make it unique in its class [24]. Pharmacokinetic studies in a rat model noted a plasma concentration-time profile consistent with a three-compartment model, wide tissue distribution, a terminal half-life of 124 – 188 h, and excretion via both renal and non-renal routes [45].

A Phase I double-blind, randomized, placebo-controlled, single- and multiple-dose study had similar results [46]. Those in the single-dose group received 140, 350, 500, 630, 840, or 1120 mg of dalbavancin. The multiple-dose groups received a loading dose of 300, 400, 600, 800, or 1000 mg divided into two equal doses administered 12 h apart followed by six daily doses of 30, 40, 60, 80, and 100 mg, respectively. Here dalbavancin exhibited dose-proportional, linear pharmacokinetics, a steady state volume of distribution of approximately 10 l, a terminal half-life between 149 and 198 h, and 33.5% renal excretion [46]. Blister fluid concentration was concordant with plasma concentration, and serum bactericidal activity at plasma concentrations ≥ 20 mg/l, attainable with once weekly dosing, support the use of dalbavancin for ABSSSI [46,47]. Another study confirmed that dalbavancin concentrations in blister fluid over 7 days remained above the MIC_{90} values for typical ABSSSI pathogens [48]. A recent Phase I study measured total dalbavancin concentrations in plasma, bone, articular tissue, and surrounding skin at 12, 24, 72, 168, 240, and 336 h after a single 1000 mg dose [49]. The mean concentrations in skin at all time points were well above the MIC_{90} values for common ABSSSI pathogens.

A population pharmacokinetics study of dalbavancin 1000 mg intravenously on day 1 and 500 mg on day 8 demonstrated a two-compartment model with first-order elimination [50]. Body surface area (BSA) predicted central volume of distribution, and both BSA and creatinine clearance (CL_{CR}) predicted dalbavancin clearance [50]. Dalbavancin clearance was not affected by age, gender, race, serum albumin, cytochrome P450 substrates, inducers, or inhibitors, or concomitant medications [50]. Overall, pharmacokinetic studies suggest low inter-individual variability, and subtherapeutic levels have not been observed.

Dalbavancin pharmacokinetics was examined in patients with varying degrees of hepatic and renal impairment. When administered as a single dose (500 or 1000 mg) or two doses (1000 mg followed by 500 mg 1 week later), only severe renal impairment (CL_{CR} < 30 ml/min) showed a significant increase in mean $AUC_{0-\infty}$ [51]. These patients should be treated with 750 mg followed by 375 mg 1 week later; no dose adjustment is necessary for CL_{CR} ≥ 30 ml/min, hemodialysis, or any degree of hepatic impairment [51]. Of note, further studies are needed to evaluate the pharmacokinetics of dalbavancin in critically ill patients since low albumin levels and increased volume of distribution may affect serum levels and clinical efficacy.

4. Clinical efficacy

A randomized, controlled, open-label Phase II proof-of-concept trial compared dalbavancin to standard agents for treating ABSSSI in 62 adults from 2001 to 2002 [52]. Subjects received either 1100 mg of dalbavancin as a single infusion (n = 20), 1000 mg of dalbavancin intravenously followed by 500 mg intravenously 1 week later (n = 21), or a comparator (ceftriaxone, cefazolin, piperacillin/tazobactam, clindamycin, vancomycin, linezolid, or cephalexin, used individually or in combination, n = 21) for 7 to 21 days. Clinical and microbiological success rates were similar among groups, with a trend to favor the two-dose dalbavancin regimen. There were no differences in drug-related adverse events among the groups, and all regimens were well tolerated [52].

An international, multicenter, Phase III, non-inferiority study from 2003 to 2004 randomized well-matched patients with complicated ABSSSI known or suspected to involve MRSA in a 2:1, double-blind manner to receive a two-dose dalbavancin regimen (1000 mg intravenously on day 1 and 500 mg intravenously on day 8, n = 571) or linezolid (600 mg intravenously or orally every 12 h for 14 days, n = 283) [53]. Clinical success rates were ≥ 90%, and a microbiological response was > 85% in evaluable patients in both arms. Adverse events were mild and slightly higher in the linezolid arm (32.2 vs 25.4%).

DISCOVER 1 and DISCOVER 2, identically designed, Phase III, international, multicenter, randomized, double-blind, double-dummy trials demonstrated the non-inferiority of dalbavancin versus vancomycin followed by linezolid when used in a sequential manner for treatment of ABSSSI (Table 1) [54]. From 2011 to 2012, well-matched patients, many of whom were seriously ill, received either the previously described two-dose regimen of dalbavancin (n = 659) or vancomycin at a dose of 1 g (or 15 mg/kg of body weight) intravenously every 12 h for at least 3 days with the option to switch to linezolid 600 mg orally every 12 h to complete 10 to 14 days of therapy (n = 653) [54]. DISCOVER 1 included slightly more patients with major abscesses, while DISCOVER 2 included more with cellulitis, but the infected area in both far exceeded the minimum size of 75 cm^2 with median values > 300 cm^2. In the pooled analysis, 79.7% in the dalbavancin group and 79.8% in the vancomycin–linezolid group met the primary endpoint of early clinical response with cessation of spread of infection-related erythema and absence of fever at 48 to 72 h. Treatment success was also similar between groups in both studies when analyzed at the traditional endpoint and by infection type, underlying illness, infection severity, and pathogen [54].

5. Safety and tolerability

Across all studies, dalbavancin has been well tolerated with adverse events that were generally mild and similar to comparators [46,49,52-56]. The most commonly reported adverse events include nausea, diarrhea, fever, headache, oral candidiasis, and pruritis. Drug-related adverse events were rare and included one episode each of transient urticaria, mild forearm pain, cellulitis, anaphylactoid reaction, and mild leukopenia which resolved spontaneously [49,53,54]. DISCOVER 1 and DISCOVER 2 noted low rates of treatment-limiting adverse effects in both arms: 2.1% for dalbavancin and 2.0% for vancomycin–linezolid [54]. There were no significant abnormalities in hematologic or clinical chemistry parameters, and there were no drug-related deaths across the studies.

Dalbavancin does not appear to have ototoxic effects, nor does it prolong the QTc interval [56,57]. A small study found no major change in the intestinal flora and no detectable *Clostridium difficile* among healthy patients who received a single 1000 mg dose of dalbavancin [58]. There have not been any post-marketing adverse events reported to date.

6. Regulatory affairs

Dalbavancin was in development for about 15 years under four different companies [59]. Discovered by Marion Merrell Dow, it was first developed for clinical investigation by Biosearch Italia in 1999. Versicor Pharmaceuticals, Inc. partnered with Biosearch Italia and

sought to begin US trials in 2000. In 2003, these companies merged to form Vicuron Pharmaceuticals, Inc., which conducted most of the early clinical trials. Pfizer Inc. acquired Vicuron in 2005. Vicuron and dalbavancin were acquired by Durata Therapeutics, Inc. in 2009, and Durata was acquired by Actavis in November, 2014.

From 2005 to 2007, the FDA issued three approvable action letters to Pfizer [59]. The first two involved manufacturing issues, and the third entailed evolving views of non-inferiority clinical trial design. Despite complete responses to all three, Pfizer withdrew the New Drug Application for dalbavancin in 2008. In its 2010 Guidance for Industry report on ABSSSI, the FDA recommended a primary efficacy endpoint based on early assessment of efficacy at 48 – 72 h. Durata's DISCOVER 1 and DISCOVER 2 trials were among the first ABSSSI studies registered using this new guidance [54].

Under the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act, dalbavancin was designated as a Qualified Infectious Disease Product (QIDP) [60]. The QIDP designation granted dalbavancin priority review (6 months rather than 10 months) and provides additional marketing exclusivity to Durata Therapeutics/ Actavis, which currently markets dalbavancin. Dalbavancin was approved by the FDA in May 2014 and by the EMA in February 2015 for treatment of ABSSSI caused by susceptible Gram-positive bacteria in adults ≥ 18 years of age [15,16].

7. Conclusion

Dalbavancin is a recently approved, novel lipoglycopeptide which could be an important addition to the antimicrobial armamentarium. It has a well established activity against the Gram-positive organisms commonly involved in ABSSSI, including MRSA and other multi-drug-resistant pathogens, and the MIC_{90} values for these organisms have remained stable over the past decade. Dalbavancin's high-protein binding and prolonged half-life allow for easily and consistently attainable therapeutic levels. Even with extensive protein binding, the free serum levels are adequate to provide excellent tissue penetration. Several clinical trials have demonstrated its tolerability, efficacy, and non-inferiority compared to standard therapy for ABSSSI. Dalbavancin's most unique feature is its once weekly dosing, and it has been approved as a 1000 mg dose followed by 500 mg 1 week later (Table 2). This provides opportunities for increased adherence and fewer hospitalizations for complicated ABSSSI. Patients who once required hospitalization could reasonably be managed entirely as an outpatient, with one or both doses administered in the emergency department, clinic, or infusion center settings, or any combination thereof. Though convenient, dalbavancin's long half-life raises concerns about the management of adverse events, and close monitoring may be needed.

8. Expert opinion

Phase III trials found dalbavancin to be non-inferior to vancomycin when followed by linezolid and similar in efficacy to other conventional treatments for ABSSSI. From a drug development perspective, DISCOVER 1 [54] and DISCOVER 2 [54] are among the first trials to use early primary efficacy endpoints for the newly defined indication ABSSSI.

Dalbavancin was also among the first drugs to earn a QIDP designation under the GAIN Act, with expedited review and marketing incentives for Durata/Actavis. As such, dalbavancin may not only be a novel treatment option for ABSSSI, but also an important example to foster future drug development efforts.

Current evaluation of a single dose study of dalbavancin for ABSSSI, a planned Phase III trial for community-acquired pneumonia, and trials in pediatric populations will further define its therapeutic use [61]. Additional studies are needed to determine its role in bacterial bone and joint infections, hospital-acquired pneumonia, endocarditis, deep-tissue abscess, and central nervous system infections. Cost-effectiveness analyses may support the use of dalbavancin over less expensive options as it may enable outpatient treatment in patients who formerly would have been admitted to the hospital. Post-marketing surveillance will also be important for a drug with such a prolonged half-life as managing adverse events may be challenging. Additionally, direct comparison with the novel lipoglycopeptide oritavancin in clinical trials would be of interest given the shared spectrum of activity and long half-life.

The best use of dalbavancin from an antimicrobial steward-ship standpoint remains unclear. The empiric use of a drug with an 8- to 10-day half-life may not be appropriate if therapy can be tailored after 2 – 3 days based on microbiologic culture data. The inability to de-escalate may expose patients to prolonged selective pressure. It would be reasonable to reserve empirical dalbavancin for ABSSSI cases that are not amenable to culture in settings with high MRSA rates.

Dalbavancin presents an attractive alternative for patients who need prolonged intravenous antimicrobial therapy. Once weekly dosing obviates the need for an indwelling intravenous catheter and its associated risks, including infection and venous thromboembolism. Dalbavancin also provides an option for injection drug users who may be at high risk for inappropriate use of an intravenous catheter. This treatment modality is also more convenient for patients and could reduce costs associated with long courses of intravenous antibiotics, including home nursing care, admission to skilled nursing facilities, and hospitalization for related complications. It may also prove useful for patients who may not be adherent to complicated oral regimens (e.g., TMP/SMX plus cephalexin) and for those in whom conventional treatments are limited by allergy or drug toxicity.

After a long development process, dalbavancin was approved in the US in 2014 and in Europe in 2015, and stands to become a valuable therapeutic option for ABSSSI. Dalbavancin has excellent activity against bacteria most commonly implicated in ABSSSI, including multi-drug-resistant strains of *S. aureus*, and has not had any evidence of resistance to date. Reported adverse events are mild and no significant drug interactions have been noted to date. In the current era of increasing infections caused by multi-drug-resistant pathogens, dalbavancin is a safe and efficacious option for patients with ABSSSI. Future studies will hopefully define its role in other infections, including osteomyelitis and bloodstream infection.

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Box 1. Drug summary

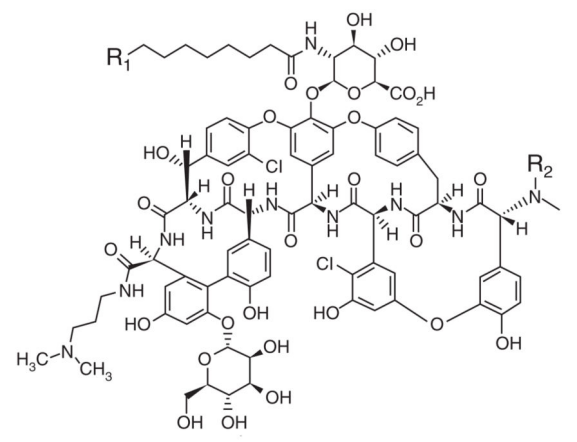
Drug name	Dalbavancin
Phase	Approved in US and Europe
Indication	Acute bacterial skin and skin structure infections
Pharmacology description/ mechanism of action	Lipoglycopeptide that disrupts bacterial cell wall formation by binding to the terminal D-alanyl-D-alanine peptidoglycan sequence in Gram-positive bacteria in a linear, concentration-dependent manner
Route of administration	Intravenous only
Chemical structure	
Pivotal trials	DISCOVER-1 [54] and DISCOVER-2 [54]

Table 1
Summary of DISCOVER 1 and DISCOVER 2 studies

Characteristic	DISCOVER 1		DISCOVER 2		DISCOVER studies	
	Dalbavancin	Vancomycin/ linezolid	Dalbavancin	Vancomycin/ linezolid	Dalbavancin	Vancomycin/ linezolid
	N = 288	N = 285	N = 371	N = 368	N = 659	N = 653
Age – years						
Mean	48.8	48.9	49.1	51.4	48.9	50.3
Range	18, 84	18, 84	18, 85	18, 84	18, 85	18, 84
Male sex n, (%)	170 (59.0)	173 (60.7)	223 (60.1)	201 (54.6)	393 (59.6)	374 (57.3)
Diabetes mellitus n, (%)	43 (14.9)	30 (10.5)	35 (9.4)	62 (16.8)	78 (11.8)	92 (14.1)
SIRS n, (%)*	175 (61.6)	175 (61.6)	157 (42.7)	161 (43.8)	332 (50.9)	336 (51.5)
Infection type n, (%)						
Major abscess	72 (25.0)	86 (30.2)	90 (24.3)	87 (23.6)	162 (24.6)	173 (26.5)
Cellulitis	156 (54.2)	147 (51.6)	198 (53.4)	202 (54.9)	354 (53.7)	349 (53.4)
Wound/surgical site infection	60 (20.8)	52 (18.2)	82 (22.1)	79 (21.5)	142 (21.5)	131 (20.1)
Infection area, median cm^2, (range)‡	333.0 (26, 3400)	367.8 (78, 3675)	313.50 (85, 5100)	362.40 (72, 3922)	324.0 (26, 5100)	366.8 (72, 3922)
Patients with a pathogen isolated at baseline, n	153	155	184	174	337	329
MRSA, n	44	39	46	28	90	67
MSSA, n	78	88	89	101	167	189
S. pyogenes, n	12	14	25	22	37	36
Primary endpoint success rates at 48 – 72 h (early clinical response, ITT population)						
Dalbavancin n/N (%)	240/288 (83.3)		285/371 (76.8)		525/659 (79.7)	
Vancomycin/linezolid n/N(%)	233/285 (81.8)		288/368 (78.3)		521/653 (79.8)	
Absolute difference in success rates (95% CI)	1.5 (−4.6, 7.9)		−1.5 (−7.4, 4.6)		−0.1 (−4.5, 4.2)	

Data from [54].

MRSA: Methicillin-resistant *Staphylococcus aureus*.

*SIRS, systemic inflammatory response syndrome, is defined as having two or more of the following: temperature < 36°C or > 38°C; heart rate > 90 beats per minute; respiratory rate > 20 breaths per minute; WBC count < 4000 cells/mm^3 or > 12,000 cells/mm^3 or > 10% band forms.

‡Area of erythema defined as longest length × widest width perpendicular to length

Table 2

Dalbavancin dosing regimen, dose adjustment, length of therapy, and cost

Dosing	1000 mg followed 1 week later by 500 mg
	For creatinine clearance less than 30 ml/min and not on hemodialysis: 750 mg followed one week later by 375 mg
	For hepatic impairment: no dose adjustment needed
Length of therapy	Two dose regimen over 2 weeks
Wholesale acquisition cost	US$1490/500 mg vial (as of 3/2/15)