Review: Clinical Trial Outcomes

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CLINICAL INVESTIGATION

Dalbavancin: re-enforcing the arsenal against Gram-positive bacteria causing skin and skin structure infections

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Dalbavancin is a new lipoglycopeptide awaiting approval for the treatment of patients with skin and skin structure infections (SSSIs). It has a long half-life that allows weekly administration and pharmacokinetic properties that do not require dose adjustment for any level of hepatic impairment. Lower doses are probably required for patients with creatinine clearance <30 ml/min. In Phase II and III randomized-controlled trials, dalbavancin was as effective as comparator antibiotics for the treatment of patients with SSSIs. In addition, it was associated with fewer total and serious adverse events. This review focuses on the randomized-controlled trials comparing dalbavancin with other antibiotics for the treatment of patients with SSSIs and discusses issues that need to be addressed in the future.

Keywords: clinical trial • enterococci • glycopeptides • *Staphylococcus aureus* • wound

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The dawn of the 21st century reserved physicians an unpleasant, although expected, issue: infections due to bacteria resistant to multiple and in some cases even all available antibiotics [1,2]. The response to the call by international or state organizations for the development of new antibiotics was not satisfactory. A few new antibiotics have been developed and even fewer have been introduced in Phase II or III clinical studies. Five new antibiotics active against multidrug-resistant (MDR) bacteria received approval by the US FDA or the European Medicines Agency during the last decade: daptomycin (2003), tigecycline (2005), doripenem (2007), telavancin (2009) and ceftaroline (2010).

Although the development of new treatment options against Gram-negative bacteria was not very successful, resulting in the revival of old antibiotics such as colistin [3,4] and fosfomycin [5–7], or the development and exploitation of all pharmacodynamic and pharmacokinetic properties of antibiotics [8,9], the issue for Gram-positive bacteria was more promising. New compounds have been developed and later introduced and tested in clinical trials [10,11]. Among them, dalbavancin, a teicoplanin derivative with a long half-life, has been studied in clinical trials and its developers asked approval from the FDA and European Medicines Agency for skin and skin structure infections (SSSIs) in 2007. However, the FDA asked for more data and the developing company decided to withdraw all marketing applications in order to conduct further trials according to the requirements of the regulatory agencies. Durata Therapeutics (Chicago, Il, USA), the developer of dalbavancin, announced the preliminary top-line results of two new international double-blind (DB), randomized-controlled clinical trials (RCTs) claiming the noninferiority of dalbavancin over comparative antibiotics for the treatment of patients with SSSIs. Following a brief report on the microbiology, mechanism of action and pharmacokinetic properties of dalbavancin, this review will focus on the effectiveness and safety of dalbavancin for the treatment of patients with SSSIs due to Gram-positive bacteria.

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Mechanism of action

Dalbavancin is a bactericidal lipoglycopeptide derived chemically from the teicoplanin-like compound A-40926, which is produced by the actinomycete *Nonomuria spp.* [12]. As in all glycopeptides, dalbavancin forms a complex with the C-terminal D-alanyl-D-alanine end of the growing peptidoglycan chains, thus inhibiting bacterial cell-wall biosynthesis [13]. Moreover, it is hypothesized that dalbavancin can dimerize and anchor its lipophilic side chain in the bacterial membranes, which improves dalbavancin's stabilization and increases the affinity for its targets and its antimicrobial potency [12,14]. This probably explains dalbavancin's higher *in vitro* bactericidal activity over other antibiotics with similar antimicrobial spectrum against MDR Gram-positive organisms.

Microbiology

Dalbavancin is bactericidal *in vitro* against a variety of Gram-positive bacteria. In addition, it has been shown to be more potent than teicoplanin, vancomycin, linezolid, daptomycin and quinupristin–dalfopristin in earlier as well as contemporary studies. Most recently, dalbavancin's potency was assessed in the 2011 SENTRY Antimicrobial Surveillance Program among 1555 isolates, including methicillin resistant *Staphylococcus aureus* (MRSA; 50.4%), coagulase-negative *staphylococci*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pyogenes*, *Streptococcus agalactiae* and viridans group *streptococci* [15]. Dalbavancin (minimum inhibitory concentration for 90% inhibition [MIC_{90}]: 0.06 μg/ml) was eight- and 16-fold more potent than daptomycin and vancomycin, respectively, against *S. aureus*. Methicillin-sensitive *S. aureus* (MSSA) strains and MRSA had the same MIC_{90} results. Coagulase-negative *staphylococci* were slightly more sensitive to dalbavancin (MIC_{50}: ≤0.03 μg/ml). The highest staphylococcal MIC observed was 0.25 μg/ml. β-hemolytic *streptococci* and viridans group *streptococci* had MIC results ranging from ≤0.03–0.25 μg/ml (MIC_{90}: 0.06–0.12 μg/ml). Enterococci showed elevated MIC results for dalbavancin. VanA phenotype-resistant *E. faecalis* or *E. faecium* had MIC values at ≥1 μg/ml; VanB strains were susceptible to dalbavancin (MIC: ≤0.25 μg/ml). All dalbavancin quantitative values were consistent with earlier surveillance data (2006–2009) [15]. Evidence of MIC creep during these periods was not observed [15]. Similar findings were reported for pathogens isolated from European and Canadian hospitals and in SENTRY 2012 [16–18]. Data from clinical studies showed that the MIC_{90} of dalbavancin for both *S. aureus* and streptococci were <0.06 μg/ml; none of the isolated organisms after treatment with dalbavancin was found to have a twofold increase in MIC relative to baseline [19].

In a study that evaluated MIC values of dalbavancin, daptomycin, linezolid, tigecycline and ceftobiprole among MRSA isolates according to vancomycin MICs (>1 or <1 μg/ml), dalbavancin had the lower MIC values than all other antibiotics, regardless of the vancomycin MIC [18,20]. Finally, dalbavancin was also active against vancomycin-resistant, glycopeptide-intermediate and linezolid-resistant *S. aureus* strains [21]. It is not known why dalbavancin is not active against VanA producing enterococci but it is active against VanA producing staphylococci. In addition, dalbavancin was also potent against penicillin-sensitive and penicillin-resistant *S. pneumoniae* [22].

Pharmacokinetics

The pharmacokinetics of dalbavancin has been studied in healthy volunteers, as well as patients with SSSIs and subjects with renal and hepatic impairment. Dalbavancin is not absorbed by the gastrointestinal tract. The maximum concentrations are achieved immediately following the end of intravenous (iv.) infusion [23]. A three-compartment model (two distributional phases – α and β – followed by a terminal elimination phase) can be used to describe the pharmacokinetics of dalbavancin. *In vivo* rat and rabbit models suggested an effective extended interval dosing [24]. In a Phase I trial, 52 healthy volunteers received dalbavancin in single parenteral doses ranging from 140 to 1120 mg. A rapid decline in the plasma dalbavancin concentration in the first 24–48 h was observed, representing an initial distribution phase, followed by a longer elimination phase with a terminal half-life measuring from 123 to 210 h. Sustained plasma levels of >20 μg/ml for 8 days were observed in these subjects following a 1000-mg dose [25]. Following the administration of single iv. doses of dalbavancin 140–1120 mg, dalbavancin exhibits linear, dose-dependent pharmacokinetics in healthy adults [25,26]. Its long half-life of 170–210 h is attributed to the high total protein binding of dalbavancin (estimated to be around 93%) and possibly to retention within cells [23,27].

In rat models, the maximal tissue levels are achieved within 24 h. Liver and kidneys retain the highest concentrations. Most tissues continued to retain concentrations greater than that in plasma on day 3; liver, kidneys, skin, fat and skeletal muscle continued to have measurable concentrations on day 14 [24]. In healthy volunteers and in patients with SSSIs enrolled in clinical trials, dalbavancin showed similar pharmacokinetics (half-life ~8 days, volume of distribution at steady state 15.7 l) [25,26]. In clinical trials, patients with SSSIs were able to sustain mean plasma concentrations of 30 μg/ml for approximately a week. Patients who also received a second dose on day 8 were able to sustain plasma concentrations of 20 μg/ml for 20 days [28]. In a study of healthy volunteers, the mean peak concentration of dalbavancin in blister fluid was 67.3 μg/ml. The mean penetration of dalbavancin into blister fluid was 59.6%. By day 7, the mean concentration of dalbavancin in blister fluid was 30.3 μg/ml. These

values are well above the MIC_{90} values for pathogens commonly implicated in complicated SSSIs [29].

Dalbavancin is excreted by both the kidneys and liver. In total, 40% is excreted unchanged in the urine and up to 50% is excreted into feces via the bile [23,30]. In patients with mild renal impairment, the mean area under the concentration–time curve values did not change in comparison with controls, and therefore dose adjustment is not required. The mean area under the concentration–time curve values were approximately 50% higher in patients with moderate renal impairment or end-stage renal disease receiving hemodialysis and 100% higher in patients with severe renal impairment not on hemodialysis (creatinine clearance <30 ml/min). Therefore, dose adjustment is not considered necessary in patients with mild or moderate renal impairment or for patients with end-stage renal disease receiving hemodialysis. A lower dose of dalbavancin (750 mg initially followed by 375 mg, 1 week later) may be considered for patients with severe renal impairment [31]. However, during continuous renal replacement therapy with high dialysate and ultrafiltration rates, dalbavancin's transmembrane clearance matched and often exceeded literature-derived dalbavancin renal clearances. Therefore, dalbavancin dosage may need to be adjusted depending on renal replacement therapy parameters [32]. The mean area under the concentration–time curve values were similar in patients with mild hepatic impairment and were approximately 27–36% lower in patients with moderate to severe hepatic impairment compared with controls. Therefore, no dosage adjustment is recommended in patients with any degree of hepatic impairment [31].

Clinical studies

Table 1 briefly shows the characteristics of the RCTs conducted thus far, comparing dalbavancin with other antibiotics for the treatment of patients with SSSIs. One Phase II and five Phase III trials have been completed, and outcomes have been presented in various forms. Table 2 shows the outcomes of these trials.

■ Seltzer *et al.* (2003)

The first open label RCT comparing dalbavancin with various antibiotics for the treatment of adult, nonpregnant patients with (mainly) complicated SSSIs that were suspected or known to be caused by Gram-positive bacteria was published in 2003 [28]. The trial had three arms and enrolled 62 patients. Patients in the first arm received one dose of iv. dalbavancin 1100 mg, patients in the second arm received one dose of iv. dalbavancin 1000 mg followed by 500 mg of iv. dalbavancin 1 week later, and patients in the third arm received iv. antibiotics determined by the investigator before randomization (ceftriaxone, cefazolin, cephalexin, clindamycin, linezolid, vancomycin or piperacillin/tazobactam). Metronidazole, aztreonam or ceftazidime could be added to the antibiotic regimen of any group if Gram-negative coverage was needed according to the opinion of the investigators. The study was conducted in the USA from July 2001 until May 2002.

The primary end point was clinical response (cure, improvement or failure) at the end of treatment (EoT; 10–12 days after the last dalbavancin dose) and at the follow-up (FU) visit, which was conducted approximately 14 days after the evaluation at the EoT. The secondary end point was microbiologic response. For patients who received one dose of dalbavancin, clinical success at the EoT was 75 and 81% for the intent-to-treat (ITT) and the clinically evaluable (CE) populations, respectively. The corresponding rates at the FU assessment were 60 and 62%, respectively. Clinical success rates were better (although not statistically significant) among patients who received two dalbavancin doses at the EoT and FU assessments (ITT: 91% and CE: 94% for both). Finally, clinical success in the comparator antibiotics group was at the EoT, 81% for both ITT and CE populations and at the FU, 76% for both ITT and CE populations. For patients infected with MRSA, clinical success at the FU visit was 50% for one-dose dalbavancin, 80% for two-dose dalbavancin and 50% for the comparator antibiotics.

All isolated pathogens were susceptible to dalbanacin with an MIC_{90} of 0.12–0.25 mg/l (lowest values of all tested antibiotics). At the FU visit, *S. aureus* eradication rates among microbiologically evaluable (ME) patients were higher for patients in the two-dose dalbavancin group (90%) than for patients in the one-dose dalbavancin (50%) and comparator groups (60%). There was no change in dalbavancin MIC for isolates that persisted. For ME populations with infections due to *Streptococcal spp.* the eradication rates were 80% for two-dose dalbavancin, 67% for one-dose dalbavancin and 71% for comparators.

■ Jauregui *et al.* (2005)

The second published trial was a DB RCT comparing dalbavancin with linezolid for the treatment of adult patients with SSSIs that were suspected or known to be caused by Gram-positive bacteria and required initial parenteral therapy according to the evaluation of the investigators [33]. The trial enrolled 854 patients, who were randomized in 2:1 ratio to receive either iv. dalbavancin 1000 mg on day 1 followed by iv. dalbavancin 500 mg on day 8 or iv. linezolid 600 mg twice daily. Patients in both arms could switch to oral treatment with either placebo or linezolid according to the pre-assigned group. Metronidazole or aztreonam could be added in both groups if coverage against Gram-negative bacteria was needed. The study was conducted in Europe and North America from January 2003 until May 2004.

Table 1. Characteristics of randomized-controlled trials comparing dalbavancin with other antibiotics for the treatment of patients with skin and skin structure infections.

Author (year)	Published	Study design	Region/ period	Patients (n)	Compared antibiotics	Additional antibiotics allowed	Inclusion criteria	Exclusion criteria	End points	Ref.
Seltzer (2003)	Yes	Phase II, OL RCT	USA/July 2001–May 2002	62	Variable	Metronidazole, ceftazidime, aztreonam	Adults, non-pregnant, suspected or known Gram-positive complicated SSSIs	Clcr <50 ml/min, compromised vascularity, osteomyelitis, glycopeptide hypersensitivity	EoT, FU	[28]
Jauregui (2005)	Yes	Phase III, DB RCT	International/ January 2003–May 2004	854	Linezolid	Metronidazole, aztreonam	Adults, suspected or known Gram-positive SSSIs requiring initial parenteral therapy	Oteomyelitis, more than two surgical interventions	4d, EoT, FU	[33]
Goldstein (2005)	Abstract	Phase III, DB RCT	International NA	565	Cefazolin	NA	Uncomplicated SSSIs	NA	FU	[35,101]
Goldstein (2005)	Abstract	Phase III, OL RCT	International NA	156	Vancomycin	NA	Suspected or confirmed MRSA SSSIs	NA	FU	[35,101]
DISCOVER 1 (2012)	No	Phase III, DB/DD RCT	International/ April 2011–September 2012	573	Vancomycin (switch to linezolid is possible after 3 days)	NA	Adults, suspected or proven SSSIs due to Gram-positive bacteria, required initial iv. therapy	Contraindications for study drugs, pregnancy, osteomyelitis, gangrene, VRE, catheter- or device-associated infection, DFI, decubitus ulcer, sustained shock, burns, impaired vascularity, more than two surgical interventions, immunosuppression, antibiotics in prior 30 days, participation in other study	2/3 d, EoT, FU	[36,102]
DISCOVER 2 (2013)	No	Phase III, DB/DD RCT	International/ September 2011–November 2012	739	Vancomycin (switch to linezolid is possible after 3 days)	NA	Adults, suspected or proven SSSIs due to Gram-positive bacteria, required initial iv. therapy	Contraindications for study drugs, pregnancy, osteomyelitis, gangrene, VRE, catheter- or device-associated infection, DFI, decubitus ulcer, sustained shock, burns, impaired vascularity, more than two surgical interventions, immunosuppression, antibiotics in prior 30 days or participation in other study	2/3 d, EoT, FU	[37,103]

2/3/4 d: Assessment performed on day 2, 3 or 4; Clcr: Creatinine clearance; DB: Double-blind; DD: Double-dummy; DFI: Diabetic foot infections; EoT: End of treatment; FU: Follow up; iv.: Intravenous; MRSA: Methicillin-resistant *Staphylococcus aureus*; NA: Not available; OL: Open-label; RCT: Randomized-controlled trial; SSSIs: Skin and skin structure infections; VRE: Vancomycin-resistant enterococci.

Table 2. Outcomes of randomized-controlled trials comparing dalbavancin with other antibiotics for the treatment of patients of skin and skin structure infections.

Author (year)	Effectiveness ITT 3/4 d	Effectiveness ITT EoT	Effectiveness ITT FU	Effectiveness CE 3/4 d	Effectiveness CE EoT	Effectiveness CE FU	Adverse events attributed	Serious adverse events	Adverse events withdrawn	Ref.
Seltzer (2003)	NA	19/21 (90.5%) vs 17/21 (80.9%)	19/21 (90.5%) vs 16/21 (76.2%)	NA	16/17 (94.1%) vs 17/21 (80.9%)	16/17 (94.1%) vs 16/21 (76.2%)	10/21 (47.6%) vs 12/21 (57.1%)	NA	0/21 (0%) vs 1/21 (5%)	[28]
Jauregui (2005)	NA	NA	437/571 (76.5%) vs 234/283 (82.7%)	283/340 (83.2%) vs 155/178 (87.1%)	NA (92.3%) vs NA (94.2%)	386/434 (88.9%) vs 206/226 (91.2%)	145/571 (25.4%) vs 91/283 (32.2%)	1/571 (0.2%) vs 2/283 (0.7%)	22/571 (3.9%) vs 9/283 (3.2%)	[33]
Goldstein (2005)	NA	NA	279/367 (76%) vs 141/186 (75.8%)	NA	NA	237/266 (89.1%) vs 131/147 (89.1%)	82/514 (16%) vs 54/269 (20.1%)[†]	1/514 (0.2%) vs 3/269 (1.1%)[†]	17/514 (3.1%) vs 12/269 (4.5%)[†]	[35,101]
Goldstein (2005)	NA	NA	92/107 (86%) vs 32/49 (65.3%)	NA	NA	71/79 (88.9%) vs 26/30 (86.7%)	82/514 (16%) vs 54/269 (20.1%)[†]	1/514 (0.2%) vs 3/269 (1.1%)[†]	17/514 (3.1%) vs 12/269 (4.5%)[†]	[35,101]
DISCOVER 1 (2012)	239/288 (83%) vs 233/285 (81.8%)	236/288 (81.9%) vs 247/285 (86.7%)	241/288 (83.7%) vs 251/285 (88.1%)	NA	214/246 (87%) vs 222/243 (91.4%)	212/226 (93.8%) vs 220/229 (96.1%)	35/284 (12.3%) vs 52/284 (18.3%)	5/284 (1.8%) vs 12/284 (4.2%)	5/284 (1.8%) vs 6/284 (2.1%)	[36,102]
DISCOVER 2 (2013)	285/371 (76.8%) vs 288/368 (78.3%)	329/371 (88.7%) vs 315/368 (85.6%)	327/371 (88.1%) vs 311/368 (84.5%)	NA	303/324 (93.5%) vs 280/302 (92.7%)	283/294 (96.3%) vs 257/272 (94.5%)	45/368 (12.2%) vs 37/367 (10.1%)	2/368 (0.5%) vs 2/367 (0.5%)	9/368 (2.4%) vs 7/367 (1.9%)	[37,103]

[†]Includes data from a third trial on patients with catheter-related bacteremia, which enrolled 75 patients [39]. The data shown refer to both trials by Goldstein *et al.*

3/4 d: Assessment performed on day 3 or 4; CE: Clinically evaluable; EoT: End of treatment; FU: Follow-up; NA: Not available; ITT: Intent-to-treat.

The primary end point was clinical response at the EoT and at the FU visit. Patients were also assessed on day 4 and 8 and following the FDA Draft Guidance for treatment of skin infections – which recommended the implementation of an outcome assessment at 48–72 h postbaseline of the cessation of spread plus resolution of elevated temperatures as the primary point for comparisons in noninferiority studies, rather than the test of cure historically measured post-therapy. A retrospective analysis of this new end point was announced as a conference abstract [34]. The secondary end point was microbiologic response. Data for the ITT population were not provided in the published article. However, an analysis for the ITT population is provided at the Durata Therapeutics website, where two different analyses are presented [101]. In the first, designated as original analysis, dalbavancin was marginally noninferior to linezolid (76.5 vs 82.7%). In the second analysis performed by the FDA, there was no difference between dalbavancin and linezolid (73.2 vs 75.3%). In the CE population, dalbavancin showed similar effectiveness to linezolid for all end points (EoT 92.3 vs 94.2%; FU 88.9 vs 91.2% and day 3 or 4 assessment 83.2 vs 87.1%).

S. aureus was the most commonly isolated pathogen, recovered from samples of 89% of patients with positive cultures. In turn, 57% of *S. aureus* isolates were MRSA. In the ME population, dalbavancin was not inferior to linezolid (89.5 vs 87.5%) at the FU visit. MRSA eradication rates at the FU visit (eradicated or presumed eradicated) were 91 and 89% for the dalbavancin and linezolid arms, respectively. Specific data for eradication rates of other pathogens were not available. Pathogens isolated at baseline persisted at the EOT visit for 8 and 7% of patients in the dalbavancin and linezolid arms, respectively, and for fewer than 2% of patients in both treatment arms at the FU visit. Recurrence of initial pathogen(s) at the FU visit was documented for 1% for the dalbavancin arm and 4% for the linezolid arm). Emergence of new pathogens at the FU visit (superinfections) occurred rarely (<1% of patients in both arms).

■ Conference abstracts

Two additional RCTs have been presented as conference abstracts but have never been published. Therefore, most of the data regarding inclusion and exclusion criteria, as well as more detailed data regarding outcomes, were not available [35,101].

The first one was a Phase III DB RCT that enrolled 565 patients and compared iv. dalbavancin and iv. cefazolin for the treatment of uncomplicated SSSIs [35,101]. Patients received either iv. 1000 mg dalbavancin on day 1 with the option to follow with a 500 mg dose on day 8, with a possible switch to an oral placebo given every 6 h, or iv. cefazolin 500 mg every 8 h, with a possible switch to oral cephalexin 500 mg every 6 h. The trial was conducted in seven countries. Clinical response at the FU visit was the primary end point of the trial. In the ITT population, 76% of dalbavancin-treated patients and 75.8% of the cefazolin/cephalexin-treated patients achieved the primary end point. In the CE population, clinical success was similar for both dalbavancin and cephalosporin treatment groups (both 89.1%).

The second one was a Phase III open-label RCT that enrolled 156 patients with complicated SSSIs where the cause was known or suspected to be MRSA [35,101]. Patients enrolled in the study were randomized to receive either iv. dalbavancin 1000 mg on day 1 and 500 mg on day 8, or iv. vancomycin 1000 mg every 12 h, with a possible switch to 500 mg oral cephalexin every 6 h following parenteral therapy if the pathogen was susceptible. The RCT was conducted in two countries. Efficacy was assessed by determining clinical and microbiological responses at the EoT and at the FU visit. In the ITT population, response rate in the dalbavancin arm was 86%, while that in the vancomycin arm it was 65.3%, a statistically significant finding in favor of dalbavancin. In the CE population, dalbavancin was effective in 89.9% while vancomycin was effective in 86.7% of patients.

■ DISCOVER 1

DISCOVER 1 was a Phase III, DB, double-dummy RCT conducted in North America and Europe from April 2011 until September 2012 following a special protocol agreement between the FDA and Durata Therapeutics [36,102]. The European Medicines Agency also provided scientific advice for this protocol. In this RCT, dalbavancin was compared with vancomycin for the treatment of adult patients with acute SSSIs that were suspected or proven to be caused by Gram-positive bacteria. Patients were enrolled if they required at least 3 days of iv. therapy. Patients were randomized to receive either iv. dalbavancin 1000 mg on day 1 followed by 500 mg on day 8 or iv. vancomycin 1 g (or 15 mg/kg) every 12 h. The protocol allowed for patients whose condition had improved to switch to oral linezolid 600 mg every 12 h after day 3. All patients received a matching placebo.

The primary end point of the study was early clinical response (at 49–72 h) postrandomization according to the FDA criteria. The secondary end points were clinical response at the EoT (day 14, European Medicines Agency primary end point) and FU visit (day 28) in ITT, CE and ME populations, pathogen eradication, as well as safety of the study medications. The study enrolled 573 patients. The basic characteristics of the enrolled patients were not different between the two groups. In addition, site of infection, signs and symptoms, clinical and laboratory findings were not different between the two groups. In the ITT population, early clinical response was seen in

83.3% of patients in the dalbavancin group and 81.8% of patients in the vancomycin/linezolid group. In a sensitivity analysis for the primary end point that included patients with >20% reduction in lesion area, response was also similar between the two groups (89.9 vs 90.9%). At the EoT, there was no difference between the two groups in both the ITT (81.9 vs 86.7%) and CE (87 vs 91.4%) populations. In a separate analysis according to the investigators' assessment, dalbavancin was as effective as vancomycin/linezolid in the ITT (90.3 vs 91.9%) and CE (94.7 vs 97.5%) populations. At the FU visit, dalbavancin was also as effective as vancomycin/linezolid in the ITT (83.7 vs 88.1%) and CE (93.8 vs 96.1%) populations. Time to fever resolution and time to cessation of spread of the infection was similar in the two groups.

The ME population included 251 patients. In this RCT, 83 patients with MRSA infections were enrolled in the microbiological ITT population; the ME population consisted of 66 patients. The primary end point at the microbiological ITT population was achieved in 84% of dalbavancin-treated patients and 82% of the vancomycin/linezolid-treated patients. In the ME population, at the EoT assessment the corresponding figures were 85.7 and 96.8%, respectively. The corresponding figures at the late FU were 93.8 and 100%, respectively. Similar effectiveness was also observed between the two groups for patients with MSSA infections (83.8 vs 88.5% at EoT; 95 vs 100% at FU). Few patients with streptococcal infections were enrolled; effectiveness for both dalbavancin and vancomycin/linezolid was 85.7% at the EoT. Few patients developed bacteremia (eight in the dalbavancin and six in the vancomycin/linezolid groups), which resolved in five and three patients, respectively. Three and two patients of the dalbavancin and vancomycin/linezolid group did not have a FU blood culture. Documented persistence of bacteremia was observed in one patient in the vancomycin/linezolid group.

■ DISCOVER 2

DISCOVER 2 was a Phase III, DB, double-dummy RCT conducted in North America, Europe, Asia and South Africa from September 2011 until November 2012 following a special protocol agreement between the FDA and Durata Therapeutics [37,103]. As in DISCOVER 1, the European Medicines Agency provided scientific advice for the protocol of DISCOVER 2. In this RCT, dalbavancin was compared with vancomycin for the treatment of adult patients with acute SSSIs, which were suspected or proven to be caused by Gram-positive bacteria. Patients were enrolled if they required at least 3 days of iv. therapy and were randomized to receive either iv. dalbavancin 1000 mg on day 1 followed by 500 mg on day 8 or iv. vancomycin 1 g (or 15 mg/kg) every 12 h. The protocol allowed for patients receiving vancomycin initially, whose condition had improved after day 3, to switch to oral linezolid 600 mg every 12 h. All patients received a matching placebo.

The primary end point of the study was early clinical response (at 49–72 h) postrandomization. The secondary end points were clinical response at the EoT (day 14) and FU visit (day 28) in ITT, CE and ME populations, pathogen eradication, as well as safety of the study medications. The study enrolled 739 patients. In the ITT population, early clinical response was seen in 76.8% of patients in the dalbavancin group and 78.3% of patients in the vancomycin/linezolid group. In a sensitivity analysis for the primary end point that included patients with >20% reduction in lesion area, response was also similar between the two groups (87.6 vs 85.9%). At the EoT, there was no difference between the two groups in both the ITT (88.7 vs 85.6%) and CE (93.5 vs 92.7%) populations. In a separate analysis according to the investigators' assessment, dalbavancin was as effective as vancomycin/linezolid in the ITT (92.2 vs 90.2%) and CE (96.9 vs 96%) populations. At the FU visit, dalbavancin was also as effective as vancomycin/linezolid in the ITT (88.1 vs 84.5%) and CE (96.3 vs 94.5%) populations. Time to fever resolution and time to cessation of spread of the infection was similar in the two groups.

Data regarding ME population (287 patients) and isolated bacteria from the DISCOVER 2 program were available for the EoT and FU. In total, 74 patients with MRSA infections were enrolled in this RCT and comprised the microbiological ITT population; the ME population consisted of 67 patients. The primary end point at the microbiological ITT population was achieved in 76% of dalbavancin-treated patients and 86% of the vancomycin/linezolid-treated patients. In the ME population, at the EoT assessment the corresponding figures were 97.7 and 100%, respectively. Similar effectiveness was also observed between the two groups for patients with MSSA infections (93.4 vs 92.7% at EoT; 96.1 vs 93.4% at FU). A total of 81 patients with streptococcal infections were enrolled; effectiveness for dalbavancin was 93.5% and for vancomycin/linezolid was 91.4% at the EoT. In total, 31 patients with bacteremia (20 in the dalbavancin and 11 in the vancomycin/linezolid groups) were recorded, which resolved in 85 and 81.8% of patients, respectively. Three and one patients of the dalbavancin and vancomycin/linezolid group did not have a FU blood culture, respectively. Documented persistence of bacteremia was observed in one patient in the vancomycin/linezolid group.

Safety

Thus far, dalbavancin's safety has been studied in 1758 patients receiving treatment for SSSIs. Additional

evidence comes from animal studies as well as studies in patients with catheter-related bacteremia or healthy volunteers. Overall, dalbavancin was well tolerated without frequent serious adverse events or adverse events that resulted in withdrawal of patients from the studies. As expected, the frequency of adverse events varied in the individual studies (12.2%–47.6%), but in all of them dalbavancin had similar or even fewer adverse events than comparator antibiotics [28,33,35]. Adverse events were described as mild and the majority of them resolved spontaneously in the following days without treatment. In addition, the duration of adverse events exhibited by dalbavancin were similar to the duration of adverse events exhibited by comparator antibiotics in all trials. The most commonly reported adverse events were nausea or vomiting, diarrhea or loose stools, elevated liver enzymes (alanine aminotransferase, and γ-glutamyl transferase), elevated lactate dehydrogenase levels, headache, rash and/or pruritus, and thrombocytopenia. Currently, there is no evidence relating dalbavancin with renal or hepatic toxicity [30], which represents an advantage over vancomycin and telavancin [38].

Figure 1 shows a pooled analysis of the available data from Phase II and III RCTs regarding the safety of dalbavancin for the treatment of patients with SSSIs. Statistical analyses were performed with Review Manager (RevMan), version 5.0 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark, 2008). The heterogeneity among the trials was assessed by using a χ^2 test ($p < 0.10$ was defined to indicate significant heterogeneity) or I^2. Publication bias was assessed using the Egger test by the funnel plot method, with $p < 0.05$ indicating potential bias. Pooled risk ratios and 95% CI were calculated by the Mantel–Haenszel fixed-effect model. In this analysis patients from two Phase II and five Phase III studies were included. One of them, a Phase II study that enrolled 75 patients, was not performed in patients with SSSIs but in patients with catheter-related bacteremia [39]. Dalbavancin was associated with fewer total drug-related adverse events than comparator antibiotics (risk ratio [RR]: 0.83; 95% CI: 0.71–0.96; I^2: 13%) and fewer serious adverse events (Figure 2; RR: 0.40; 95% CI: 0.19–0.88; I^2: 0%). The frequency of serious adverse events was low in all RCTs. On the other hand, there was no difference between dalbavancin and comparator antibiotics regarding patients who were withdrawn from the studies due to adverse events (Figure 3; RR: 0.96; 95% CI: 0.62–1.49; I^2: 0%). In a company review, infusion-related adverse events were documented in 2.2% of patients receiving dalbavancin and 3.1% of patients receiving comparator antibiotics. In the dalbavancin-treated patients, 76% of events did not occur on the day of dalbavancin administration and were mostly associated with indwelling catheters. In the same review it was reported that the median duration of adverse events was 3 and 4 days in the dalbavancin and comparator arms, respectively [40].

Finally, an open-label RCT studied the safety and tolerability of dalbavancin of increasing dosing durations. Pharmacokinetic parameters were also monitored in this study. In total, 18 healthy adult (18–55 years) volunteers were enrolled and divided into three dosing cohorts of six subjects each. All of them received 1000 mg of iv. dalbavancin on day 1. Cohort 1 subsequently received 500 mg iv. doses on days 8, 15 and 22 (4 weeks); cohort 2 received additional 500 mg iv. doses on days 29 and 36 (6 weeks); and cohort 3 received additional 500 mg doses on days 43 and 50 (8 weeks). The systemic exposure of dalbavancin on the last day of dosing was similar after 4–8 weeks of dosing with no observable accumulation after a total of 8 weeks of administration. No serious adverse events were reported during the study. The most commonly reported dalvavancin-related adverse event was mild pain in the extremity, reported by two subjects, without evidence of thrombophlebitis. No subject withdrew or was discontinued from the study. No laboratory abnormality was attributed to dalbavancin [41].

Studies reporting on specific potential adverse events have also been conducted in healthy volunteers. A Phase I trial evaluated the potential ototoxicity of dalbavancin. In this dose escalation study of dalbavancin (up to 1120 mg or cumulative doses of 1600 mg administered over a 1-week period), healthy volunteers underwent medical and audiologic assessments to assess potential adverse events. Audiologic monitoring included air-conduction thresholds in the conventional (0.25–8 kHz) and high-frequency (10–16 kHz) ranges. At baseline, subjects were also tested using word recognition, bone conduction testing if indicated, and tympanometry. None of the volunteers demonstrated vestibular or auditory toxicity after dalbavancin administration [42].

A DB, placebo- and positive-controlled trial studied the potential electrocardiographic changes after dalbavancin administration in 200 healthy volunteers. The study evaluated single iv. doses of dalbavancin 1000 mg and 1500 mg. Oral moxifloxacin 400 mg was the positive-control treatment, which was not blinded. On day 1 ECGs were extracted from a continuous Holter recording. The largest increase in QTc interval after 1000 mg dalbavancin was 1.5 ms at 6 h and after 1500 mg dalbavancin the largest increase in QTc interval was 0.2 ms at 24 h. The peak change after a single-dose of 400 mg moxifloxacin was 12.9 ms at 2 h. The data support that dalbavancin administration did not have a clinically relevant effect on the QTc interval [43].

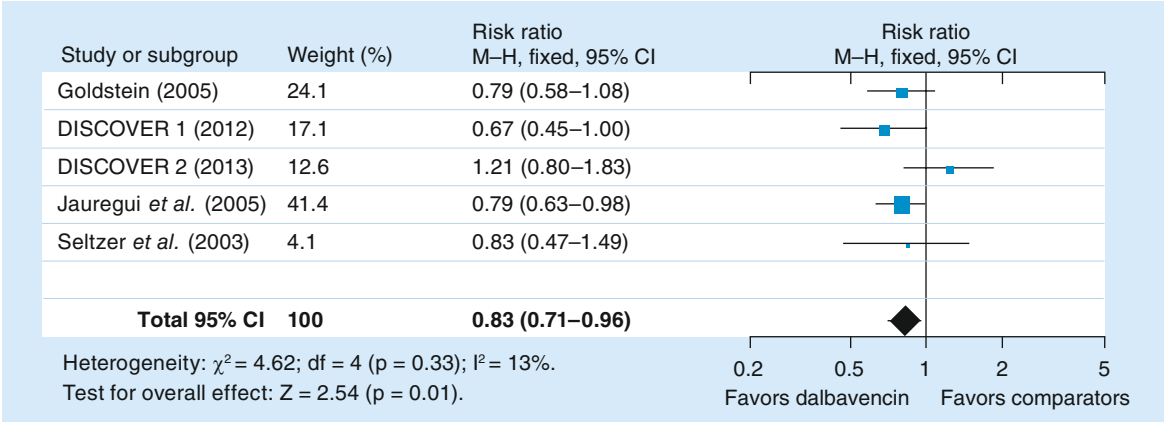

Figure 1. Risk ratios of total adverse events for individual antibiotic comparison with dalbavancin in the intent-to-treat population. Vertical line shows the no-difference point between the two regimens and the horizontal line shows the 95% CI.
df: Degrees of freedom; M–H: Mantel-Haenszel.

The effect of dalbavancin administration on the intestinal flora was studied in 12 healthy volunteers who received iv. dalbavancin 1000 mg. Fecal samples were collected for 60 days. A small increase in the number of colonizing enterococci and *Eschericia coli* was observed. There was no impact on the number of other enterobacteriaceae and yeasts as well as anaerobic intestinal microflora such as lactobacilli, clostridia (including *Clostridium difficile*) and bacteroides. Volunteers were not colonized by dalbavancin resistant (MIC ≥4 µg/ml) aerobic or anaerobic bacteria [44].

The potential for development of resistance has been further studied in an *in vitro* study. Direct selection and serial passage studies for the detection of resistance development were performed with a MSSA isolate, three MRSA isolates, one vancomycin-intermediate *S. aureus* isolate, and one methicillin-resistant *Staphylococcus epidermidis* isolate. The same staphylococcal strains were subjected to serial passage in the presence of sub-MICs of dalbavancin over 20 consecutive days. All studies failed to produce stable mutants with decreased susceptibility to dalbavancin [35].

The potential interaction of dalbavancin with other antibiotics (oxacillin, gentamicin, clindamycin, levofloxacin, rifampicin, vancomycin, quinupristin/dalfopristin, linezolid and daptomycin was studied *in vitro*. Antagonism was not observed between dalbavancin and any of the antimicrobials tested. However, dalbavancin was synergistic or partially synergistic with oxacillin for staphylococci, including methicillin-resistant strains, vancomycin-intermediate *S. aureus* and enterococci [45]. Since dalbavancin is not metabolized by the P450 cytochrome system, the administration of P450 inducers or inhibitors do not appear to affect the metabolism of dalbavancin [23,26,27].

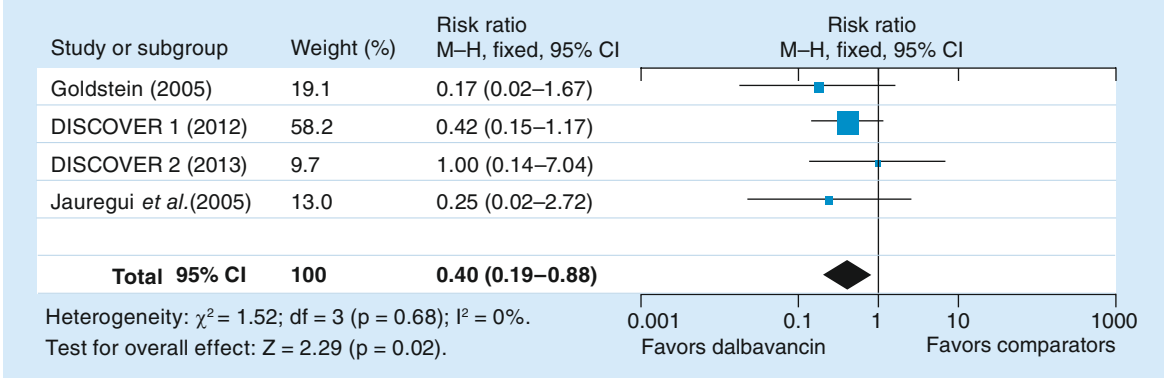

Figure 2. Risk ratios of patients with serious adverse events for individual antibiotic comparison with dalbavancin in the intent-to-treat population. Vertical line shows the no-difference point between the two regimens and the horizontal line shows the 95% CI.
df: Degrees of freedom; M–H: Mantel-Haenszel.

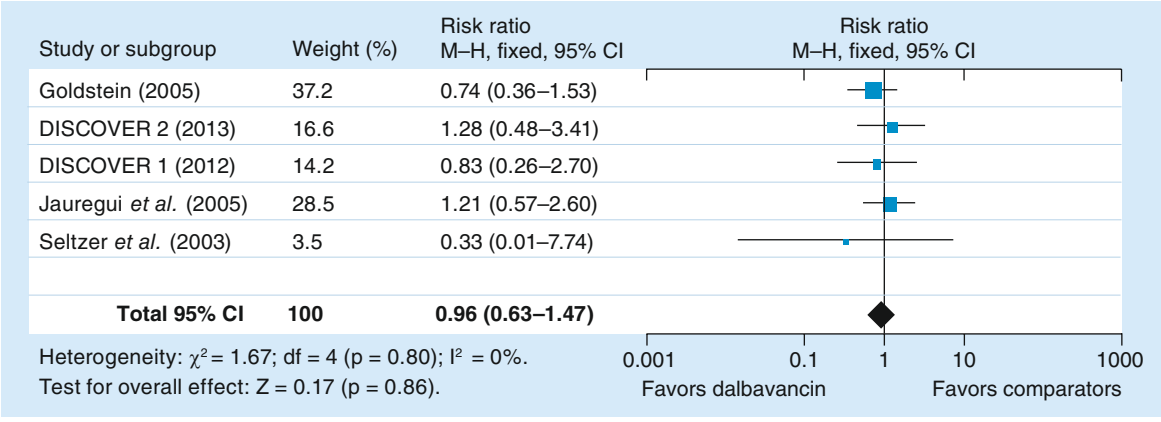

Figure 3. Risk ratios of patients withdrawn from studies due to adverse events for individual antibiotic comparison with dalbavancin in the intent-to-treat population. Vertical line shows the no-difference point between the two regimens and the horizontal line shows the 95% CI.
df: Degrees of freedom; M–H: Mantel-Haenszel.

Future perspective

Dalbavancin has been tested in large RCTs for the treatment of patients with proven or suspected SSSIs due to Gram-positive bacteria. The currently available data suggest that it is at least as effective as comparator antibiotics for the treatment of patients with SSSIs in addition to a favorable safety profile. However, there are several issues that require further study. One of them is its effectiveness against infections due to glycopeptide-intermediate *S. aureus*, heteroresistant glycopeptide-intermediate *S. aureus*, and vancomycin-resistant enterococci (VRE) or even vancomycin-resistant *S. aureus*. Since dalbavancin is not effective against VRE expressing the VanA phenotype, its effectiveness should be studied and verified against other VRE strains. Other antibiotics, such as linezolid or daptomycin, have been proven to be effective for the treatment of patients with VRE infections [46]. The most reliable treatment option for glycopeptide-intermediate *S. aureus*, heteroresistant glycopeptide-intermediate *S. aureus* and vancomycin-resistant *S. aureus* is not known. However, the growing use of linezolid and daptomycin led to the development of resistance to these antibiotics and outbreaks due to linezolid-resistant *S. aureus* isolates have been published [47,48]. Although *in vitro* studies support a low probability for development of dalbavancin-resistant strains, development of resistance to dalbavancin after its introduction in clinical practice is inevitable [44]. The main concern is the long half-life of dalbavancin, which would allow exposure to subtherapeutic levels for an extended period of time, thus enabling development of resistance in clinical settings.

Another issue is the effectiveness of dalbavancin against MRSA with vancomycin MIC >1 μg/ml. Patients with or without bacteremia due to MRSA with vancomycin MIC >1 μg/ml have higher mortality than patients with vancomycin MIC ≤1 μg/ml [49,50]. Although clinical data are not available at the moment, the higher potency of dalbavancin against *S. aureus in vitro* than other antibiotics (including older and newer glycopeptides, linezolid and daptomycin) and the fact that dalbavancin MIC does not depend on vancomycin MIC values, suggest that dalbavancin could be an attractive choice for the treatment of such infections. Thus far, clinical data suggest that daptomycin and telavancin are more effective than vancomycin for the treatment of patients with MRSA isolates with decreased vancomycin susceptibility [38,51].

In addition, data are needed for the effectiveness of dalbavancin for the treatment of patients whose treatment with other agents failed (salvage therapy). Data are also needed for the effectiveness of dalbavancin for the treatment of patients with more severe SSSIs, such as those with gangrene, infected burns, diabetic foot and decubitus ulcer infections, impaired vascularity, immunosuppression, sustained shock and underlying osteomyelitis. The favorable safety profile of dalbavancin following repeated administration suggests that it could be used for the treatment of patients that require longer, sustained treatment (osteomyelitis, endocarditis). Finally, the promising initial data regarding the effectiveness of dalbavancin for the treatment of patients with catheter-related bacteremia should be verified in larger trials [39].

Dalbavancin's long half-life allows for weekly administration, a property that could allow for earlier hospital discharge and subsequently reduced cost. Data supporting cost–effectiveness of dalbavancin is

not available thus far. Data from cost–effectiveness analyses with linezolid (an antibiotic that allows early switch to oral therapy and hospital discharge) as well as data from outpatient antibiotic treatment for patients with SSSIs, which could be easily facilitated with dalbavancin, suggest that cost savings could be substantial [52,53]. In addition, dalbavancin could be associated with even lower cost, since insertion and complications of peripherally inserted catheters account for up to 28–43% of outpatient antibiotic treatment [53].

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Executive summary

Background

- Dalbavancin is a lipoglycopeptide with a long half-life that allows weekly administration with sustained plasma and tissue levels.

Effectiveness & safety

- Dalbavancin has been as effective as comparator antibiotics for the treatment of patients with skin and skin structure infections due to proven or suspected Gram-positive bacteria.
- It has a favorable safety profile. The main adverse events were related to the GI tract and were mild in severity.
- The currently available data do not relate dalbavancin with renal toxicity.

Future challenges

- The effectiveness of dalbavancin for the treatment of patients with more severe infections and bacteria such as vancomycin-resistant enterococci, glycopeptide-intermediate *Staphylococcus aureus*, heteroresistant glycopeptide-intermediate *S. aureus* and methicillin-resistant *S. aureus* with vancomycin minimum inhibitory concentration >1 µg/ml should be further studied.

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