ABSTRACT

Introduction: Dalbavancin is a long-acting, bactericidal, lipoglycopeptide antibiotic approved by the US Food and Drug Administration and the European Medicines Agency for treatment of acute bacterial skin and skin structure infections in adults, with potent activity against Gram-positive pathogens, including methicillin-susceptible and methicillin-resistant Staphylococcus aureus. Here we describe the clearance and clinical outcomes of patients with S. aureus bacteremia in five clinical trials of skin and skin structure infections or catheter-related bloodstream infections that evaluated the efficacy and safety of dalbavancin.

Methods: Patients with uncomplicated S. aureus bacteremia identified in blood cultures drawn at baseline (before study drug) with at least one follow-up blood culture are described from four phase 3 trials in skin and skin structure infections and one phase 2 catheter-related infection study. Dalbavancin was administered as a single-dose (1500 mg intravenous [IV]) or a two-dose regimen (1000 mg IV on day 1, 500 mg IV on day 8). Comparators included vancomycin IV or linezolid IV/oral for 10–14 days.

Results: All 39 patients (100%) who received dalbavancin, including 8 patients on the single-dose regimen, had clearance of bacteremia versus 19/20 patients (95%) treated with comparators (vancomycin or linezolid). At end of treatment, 33/36 dalbavancin-treated patients (92%) achieved clinical success versus 18/23 patients (78%) treated with comparators.

Conclusions: All 39 patients with uncomplicated S. aureus bacteremia treated with dalbavancin (single- or two-dose regimen) and with follow-up blood cultures had clearance of their bloodstream infection. Clinical response rates...
were similar to daily comparator therapy for 10–14 days.

**Trial Registration**: DISCOVER 1, NCT01339091; DISCOVER 2, NCT01431339; DUR001-303, NCT02127970; VER001-9; VER001-4, NCT00057369.

**Keywords**: Acute bacterial skin and skin structures infections; Bacteremia; Dalbavancin; Gram-positive

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### Key Summary Points

**Why carry out this study?**

Dalbavancin is a long-acting, bactericidal, lipoglycopeptide antibiotic approved by the US Food and Drug Administration and the European Medicines Agency for treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. We wished to explore the clinical outcomes and microbiological clearance in patients with ABSSSI, complicated skin and skin structure infections, or catheter-related bloodstream infections that had *Staphylococcus aureus* bacteremia at baseline in phase 2 and 3 efficacy studies.

**What was learned from this study?**

Dalbavancin, administered as a single-dose or two-dose regimen, can effectively treat uncomplicated *S. aureus* bacteremia in patients with ABSSSI.

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### INTRODUCTION

Dalbavancin is a second-generation, semisynthetic, lipoglycopeptide antibiotic structurally related to teicoplanin [1]. Dalbavancin binds to the terminal d-alanyl-d-alanine of the stem peptide in newly growing cell wall peptidoglycan, preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits, thereby interrupting cell wall synthesis and resulting in bacterial cell death [1–3].

Dalbavancin is a long-acting, bactericidal, lipoglycopeptide antibiotic approved by the US Food and Drug Administration and the European Medicines Agency for treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults [2, 3]. Dalbavancin has shown potent activity against Gram-positive pathogens responsible for ABSSSI, in particular *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), streptococci, and vancomycin-susceptible *Enterococcus faecalis* [4, 5]. In addition, an in vitro susceptibility study showed that dalbavancin was 4- to 8-fold more potent than daptomycin, and 16-fold more potent than vancomycin or linezolid against MRSA in isolates of patients with skin and skin structure infections [6]. Plasma concentrations of dalbavancin exceed bactericidal concentrations for 14 days after administration of 1500 mg as a single dose or 1000 mg followed by 500 mg a week later (two-dose regimen; Fig. 1) [3, 7]. The safety of dalbavancin has been evaluated previously in a pooled analysis of seven phase 2 and phase 3 clinical trials and was found to have overall adverse event rates similar to or lower than those for patients receiving comparator agents [8].

Phase 2 and 3 efficacy studies have been conducted and completed with dalbavancin to explore the clinical outcomes and microbiological clearance in patients with ABSSSI, complicated skin and skin structure infections (cSSSI), or catheter-related bloodstream infections [4, 5, 9, 10]. This analysis focused on the patients with *S. aureus* bacteremia at baseline in these studies.

### METHODS

All studies were conducted in accordance with the Declaration of Helsinki, the study protocol, the International Conference on Harmonisation tripartite guideline for Good Clinical Practice (ICH E6[R1]), and the institutional review board or ethics committee at each study site. All patients provided written informed consent before participation.
Data were analyzed from patients enrolled in the dalbavancin ABSSSI, cSSSI, or catheter-related bloodstream infection studies (Table 1) [4, 5, 9, 10]. Blood cultures were drawn at baseline before study drug treatment from two different anatomical sites (not through an existing intravascular line) and then repeated every 48–72 h until cultures were negative. If clinically indicated, blood cultures were collected at the time of treatment discontinuation or for determination of treatment failure. Patients in whom \textit{S. aureus} was identified (through the baseline blood cultures) were selected for further assessment. The catheter-related bloodstream infection study required removal of the catheter in all patients with \textit{S. aureus} bacteremia [9]. Data regarding clearance of bacteremia were provided for patients with at least one follow-up post-baseline blood culture. Documented clearance of bacteremia was defined by laboratory data showing follow-up blood culture(s) negative for the baseline blood pathogen on or before day 12, no subsequent blood culture(s) (after the negative follow-up blood culture; if obtained) positive for the baseline blood pathogen, and no more than two blood cultures (taken on different dates) positive for the baseline blood pathogen. Clinical success at end of treatment (EOT) in these studies was typically defined as resolution of signs and symptoms of the presenting illness (e.g., a decrease in lesion area, no fever, and local signs of fluctuance/warmth absent [DUR001-301 and DUR001-302] or improved and no worse than mild [DUR001-303]), tenderness/swelling/induration no worse than mild, purulent drainage improved and no worse than mild, and no requirement for new systemic or concurrent antibiotics. Clinical success for the treatment of catheter-related bloodstream infection or cSSSIs was defined as resolution of all signs and symptoms of the presenting illness, with no requirement for new systemic antibiotics [VER001-4 and VER001-9] and no fever [VER001-4] (Table 1).

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Fig. 1 Serum concentration of dalbavancin 1500 mg after intravenous administration as a 30-min infusion in a single-dose or two-dose regimen. Adapted with permission from Dunne M and Puttagunta S. Clearance of \textit{Staphylococcus aureus} bacteremia in patients treated with dalbavancin. Presented at IDWeek, October 2–6, 2013; San Francisco, CA. [http://www.idweek.org](http://www.idweek.org)
| Study number and title | Treatment | Definition of clinical success (end of treatment visit) | Total treated, n | Received dalbavancin, n | Received comparator, n | S. aureus bacteremia in dalbavancin patients<sup>a</sup> | S. aureus bacteremia in comparator patients<sup>a</sup> |
|-----------------------|-----------|--------------------------------------------------------|-----------------|-----------------------|-----------------------|---------------------------------------------------|---------------------------------------------------|
| ABSSSI                |           |                                                        |                 |                       |                       | 568                                              | 3 (MSSA, n = 2; MRSA, n = 1)                       |
| DUR001-301            | IV dalbavancin. 1000 mg on day 1, 500 mg on day 8, IV placebo q12h to match vancomycin, possible switch to oral placebo q12h after 3 days of IV therapy; treatment duration 10–14 days | Decrease in lesion area, no fever, absence of local signs of fluctuance/warmth, local tenderness/swelling/induration no worse than mild, purulent drainage improved and no worse than mild (for wound infection), no concurrent antibiotics, and patient survival | 284              | 284                   | 3 (MSSA, n = 2; MRSA, n = 3) | 3 (MSSA, n = 0)                                    |
|                       | IV comparator. IV vancomycin 1000 mg or 15 mg/kg q12h, IV placebo to match dalbavancin, possible switch to orally administered linezolid 600 mg q12h after 3 days of IV vancomycin therapy; treatment duration 10–14 days | | | | | | |
Table 1 continued

| Study number and title | Treatment | Definition of clinical success (end of treatment visit) | Total treated, n | Received dalbavancin, n | Received comparator, n | S. aureus bacteremia in dalbavancin patientsa | S. aureus bacteremia in comparator patientsa |
|------------------------|-----------|----------------------------------------------------------|------------------|------------------------|------------------------|---------------------------------------------|---------------------------------------------|
| DUR001-302             | IV dalbavancin. 1000 mg on day 1, 500 mg on day 8, IV placebo q12h to match vancomycin, possible switch to oral placebo q12h after 3 days of IV therapy; treatment duration 10–14 days | Decrease in lesion area, no fever, absence of local signs of fluctuance/warmth, local tenderness/swelling/induration no worse than mild, purulent drainage improved and no worse than mild (for wound infection), no concurrent antibiotics, and patient survival | 735               | 368                    | 367                    | 7 (MSSA, n = 7; MRSA, n = 0)                     | 6 (MSSA, n = 5; MRSA, n = 1)                     |

Phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin with possible switch to orally administered linezolid) for the treatment of ABSSSI [5].
| Study number and title | Treatment | Definition of clinical success (end of treatment visit) | Total treated, n | Received dalbavancin, n | Received comparator, n | S. aureus bacteremia in dalbavancin patients | S. aureus bacteremia in comparator patients |
|-----------------------|-----------|--------------------------------------------------------|------------------|-------------------------|------------------------|---------------------------------------------|---------------------------------------------|
| DUR001-303            | *IV dalbavancin 2-dose regimen.* 1000 mg on day 1, 500 mg on day 8 | Decrease in lesion area by ≥ 80%, no fever, local signs of fluctuance/warmth improved and no worse than mild, local tenderness/swelling/induration no worse than mild, purulent drainage improved and no worse than mild (for wound infection), no concurrent antibiotics, and patient survival | 695              | 346 2-dose dalbavancin | N/A                    | 7 (MSSA, n = 4; MRSA, n = 3) | N/A |
|                       | *IV dalbavancin, single-dose regimen.* 1500 mg on day 1 | | | 349 single-dose dalbavancin | | 8 (MSSA, n = 7; MRSA, n = 1) | |

**cSSSI**

| Study number and title | Treatment | Definition of clinical success (end of treatment visit) | Total treated, n | Received dalbavancin, n | Received comparator, n | S. aureus bacteremia in dalbavancin patients | S. aureus bacteremia in comparator patients |
|-----------------------|-----------|--------------------------------------------------------|------------------|-------------------------|------------------------|---------------------------------------------|---------------------------------------------|
| VER001-9              | *IV dalbavancin.* 1000 mg on day 1, 500 mg on day 8, possible switch to oral placebo q12h; treatment duration 14 days | Resolution of signs and symptoms such that patient did not receive new systemic antibiotics | 854              | 571                     | 283                    | 4 (MSSA, n = 1; MRSA, n = 3) | 2 (MSSA, n = 0; MRSA, n = 2) |
|                       | *IV linezolid.* 600 mg q12h; possible switch to orally administered linezolid 600 mg q12h; treatment duration 14 days | | | | | |

Catheter-related bloodstream infections
| Study number and title | Treatment | Definition of clinical success (end of treatment visit) | Total treated, \( n \) | Received dalbavancin, \( n \) | Received comparator, \( n \) | \( S. \) aureus bacteremia in dalbavancin patients* | \( S. \) aureus bacteremia in comparator patients* |
|------------------------|-----------|--------------------------------------------------------|------------------|-----------------|-----------------|----------------------------------|----------------------------------|
| VER001-4               | \( IV \) dalbavancin. Weekly: 1000 mg on day 1, 500 mg on day 8 \((n = 33)\). Daily: 650 mg on day 1, 65 mg on days 2–14 \((n = 7)\). Total dose received: 780 mg \((n = 1)\), 845 mg \((n = 1)\), 1000 mg \((n = 3)\), 1170 mg \((n = 1)\), 1500 mg \((n = 34)\) | No fever, resolution of all signs and symptoms of catheter-site infection, and no additional systemic antibiotics | 74 | 40 | 34 | 10b | 9b |
| Phase 2, randomized, open-label, multicenter study to evaluate the safety and efficacy of dalbavancin vs vancomycin in the treatment of catheter-related bloodstream infections with suspected or confirmed Gram-positive bacterial pathogens [9] | \( IV \) comparator. \( IV \) vancomycin: 1000 mg q12h, or dose-adjusted for renal impairment. Could switch to \( IV \) nafcillin or oxacillin 2 g q4h or q6h after pathogen identification and susceptibility testing | | | | | | |

*ABSSSI acute bacterial skin and skin structure infection, cSSSI complicated skin and skin structure infection, \( IV \) intravenous, MRSA methicillin-resistant \( Staphylococcus \) aureus, MSSA methicillin-susceptible \( Staphylococcus \) aureus, N/A not applicable, q4h every 4 h, q6h every 6 h, q12h every 12 h

*Patients with follow-up blood culture available for assessment (postbaseline)

*MRSA and MSSA breakdown could not be confirmed for this specific analysis
RESULTS

Fifty-nine patients with *S. aureus* bacteremia at baseline had follow-up blood cultures available for assessment. Thirt-nine patients were treated with dalbavancin; eight of these patients received dalbavancin 1500 mg as a single dose. Twenty patients received a comparator drug, vancomycin or linezolid (Table 1).

The clinical studies pooled for analysis included patients with *S. aureus* bacteremia, including MRSA. *S. aureus* cleared in all 39 patients (100%) who were treated with dalbavancin and who had follow-up blood cultures available for assessment. By comparison, *S. aureus* bacteremia cleared in 19/20 patients (95%) treated with comparator (Table 2) and in all eight patients receiving single-dose dalbavancin.

None of the clinical failures in the dalbavancin group resulted from persistent underlying bacteremia. The reasons for clinical failure in patients receiving dalbavancin included local signs of tenderness to palpation and swelling/induration that were worse than mild, local signs of fluctuance and localized heat/warmth that had not resolved, receipt of a concomitant antibiotic, or unplanned surgical intervention for ABSSSI more than 72 h after study drug administration.

### Table 2

| Infection, n/N | Dalbavancin | Comparator |
|---------------|-------------|------------|
|               | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT |
| ABSSSI        |             |            |               |                       |            |               |               |
| DUR001-301    | 3/3         | 3/4        | 2/3           | 2/3                    | 1/3        | 3/3           |
| DUR001-302    | 7/7         | 6/7        | 5/6           | 6/6                    | 5/6        | 5/6           |
| DUR001-303    | 15/15       | 14/15      | 14/14         | N/A                    | 14/14      | N/A           |
| cSSSI         |             |            |               |                       |            |               |               |
| VER001-9      | 4/4         | –          | 3/4           | 2/2                    | –          | 2/2           |
| Catheter-related bloodstream infections | | | | | | |
| VER001-4      | 10/10       | –          | 9/9           | 9/9                    | –          | 8/12          |
| Total, n/N (%) | 39/39 (100) | 23/26 (88) | 33/36 (92) | 19/20 (95) | 6/9 (67) | 18/23 (78) |

*ABSSSI* acute bacterial skin and skin structure infection, *cSSSI* complicated skin and skin structure infection, *EOT* end of treatment, *N/A* not applicable (no comparator drug)

# Patients with a follow-up blood culture available for assessment (postbaseline)

| Infection, n/N | Dalbavancin | Comparator |
|---------------|-------------|------------|
|               | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT |

| Infection, n/N | Dalbavancin | Comparator |
|---------------|-------------|------------|
|               | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT |

| Infection, n/N | Dalbavancin | Comparator |
|---------------|-------------|------------|
|               | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT |

| Infection, n/N | Dalbavancin | Comparator |
|---------------|-------------|------------|
|               | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT | Clearance of bacteremia | ≥ 20% Reduction in lesion size at 48–72 h | Clinical success at EOT |

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In the ABSSSI studies, a greater proportion of patients in the dalbavancin group had at least a 20% reduction in lesion size 48–72 h after the start of treatment in 23/26 patients (88%) compared with 6/9 patients (67%) in the comparator group. Across all five studies, patients in the dalbavancin group had higher rates of clinical success at EOT (33/36 patients [92%]) than those in the comparator group (18/23 patients [78%]).

DISCUSSION

In this analysis of phase 2 and 3 clinical trial data, all 39 patients with uncomplicated S. aureus bacteremia at baseline who were treated with dalbavancin, either as a single dose or a two-dose regimen, and had follow-up blood cultures available for assessment had clearance of their bloodstream infection. Clinical outcomes in patients receiving either a single-dose or two-dose dalbavancin regimen were similar to those of patients receiving daily treatment with comparator drugs for 10–14 days.

The clinical success rate of dalbavancin in this pooled analysis was higher than vancomycin, linezolid, or daptomycin, as reported in other clinical trials of S. aureus bacteremia, although the patient populations and definitions of success differed between the studies. In a pooled meta-analysis of patients with S. aureus bacteremia, the clinical success rates of vancomycin and linezolid were 52% and 55%, respectively, with microbiological success in 73% and 69% of patients [11]. In addition, in an open-label randomized trial, the clinical success rate of daptomycin in the treatment of uncomplicated S. aureus bacteremia was 56% [12]. In an open-label study that investigated catheter-related bloodstream infections in patients with complicated skin and skin structure infections, the clinical success was 82% and 83% in the linezolid and vancomycin groups, respectively, with microbiologic success occurring in 67% of patients in each group [13].

Recent anecdotal reports of the efficacy of dalbavancin in bloodstream infections have been published [14–26]. A retrospective cohort study conducted in the University Hospital of Vienna between January 2015 and December 2016 showed that microbiological and clinical success was achieved in 93% (25/27) of patients who received dalbavancin either as primary or sequential treatment for infective endocarditis. In these patients, the pathogens were predominantly S. aureus (n = 9) and E. faecalis (n = 4) [18]. Another retrospective study described the efficacy and safety of dalbavancin in 69 adult patients (catheter-related bacteremia, n = 8; endocarditis, n = 7) treated between 2016 and 2017 across 29 institutions in Spain. In patients with catheter-related bacteremia, the pathogens were MRSA (n = 3), coagulase-negative staphylococci (CoNS) (n = 3), methicillin-susceptible S. aureus (MSSA; n = 2), and Enterococcus spp. (n = 1); in patients with endocarditis, the pathogens were CoNS (n = 2), Enterococcus spp. (n = 2), MRSA (n = 1), and Streptococcus spp. (n = 1). Clinical success was achieved for 75% of patients with catheter-related bacteremia and 86% of patients with endocarditis [20].

Four case reports described successful treatment with dalbavancin [16, 19, 21, 23]: the first described successful treatment of a 54-year-old man with MSSA bacteremia secondary to septic phlebitis [21], the second showed successful treatment of a 27-year-old woman with MRSA tricuspid-valve endocarditis with septic pulmonary emboli [16], and the fourth showed successful treatment of an 88-year-old woman with MRSA prosthetic vascular graft infection [23]. A phase 2b multicenter randomized clinical trial (NCT04775953) that is currently enrolling patients will compare the safety and efficacy of dalbavancin with standard-of-care antibiotics for the completion of therapy of complicated S. aureus bacteremia or right-sided native valve infective endocarditis in patients who have cleared their bacteremia [27].

Limitations of this study include the fact that clinical success was defined differently across the studies, primarily owing to evolving...
definitions in regulatory guidance for skin infection. The more recent studies used the newer definition of clinical success or the improvement and resolution of clinical signs and symptoms, such as pain or reduction in lesion size. These studies also used an updated definition of ABSSSI [28]. Another limitation is the small sample size of patients with S. aureus bacteremia at baseline, an expected finding given that four of the five trials enrolled patients with skin infection and that, for the 15 patients with S. aureus bacteremia in DUR001-303 randomized to either single- or two-dose dalbavancin, there was no corresponding control group receiving comparator antibiotics.

CONCLUSIONS

Dalbavancin is indicated for treatment of adults with ABSSSI caused by designated susceptible strains of Gram-positive microorganisms and offers an alternative to treat S. aureus bacteremia in these patients. Dalbavancin can be given either as a single dose of 1500 mg or as a 1000-mg dose followed 1 week later by 500 mg. The current subgroup analysis helps lay the groundwork for a randomized controlled trial further evaluating the efficacy of dalbavancin in the treatment of S. aureus bacteremia.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies, which were performed in accordance with the Declaration of Helsinki, the study protocol, the International Conference on Harmonisation
tripartite guideline for Good Clinical Practice (ICH E6(R1)), and the institutional review board or ethics committee at each study site.

**Data Availability.** The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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