Potential Role for Telavancin in Bacteremic Infections Due to Gram-Positive Pathogens: Focus on *Staphylococcus aureus*

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*Staphylococcus aureus* bacteremia (SAB) is one of the most common serious bacterial infections and the most frequent invasive infection due to methicillin-resistant *S. aureus* (MRSA). Treatment is challenging, particularly for MRSA, because of limited treatment options.

Telavancin is a bactericidal lipoglycopeptide antibiotic that is active against a range of clinically relevant gram-positive pathogens including MRSA. In experimental animal models of sepsis telavancin was shown to be more effective than vancomycin.

In clinically evaluable patients enrolled in a pilot study of uncomplicated SAB, cure rates were 88% for telavancin and 89% for standard therapy. Among patients with infection due to only gram-positive pathogens enrolled in the 2 phase 3 studies of telavancin for treatment of hospital-acquired pneumonia, cure rates for those with bacteremic *S. aureus* pneumonia were 41% (9/22, telavancin) and 40% (10/25, vancomycin) with identical mortality rates. These data support further evaluation of telavancin in larger, prospective studies of SAB.

**Keywords.** *Staphylococcus aureus*; MRSA; bacteremia; telavancin; experimental.
or antistaphylococcal penicillin, depending on isolate susceptibility) [12] and is an alternative to vancomycin. Resistance to daptomycin has begun to emerge [6] in the following 2 clinical scenarios: in daptomycin-treated patients with undrained infections [12] and in daptomycin-naive patients infected with MRSA strains that display high MIC to vancomycin [7]. Thus, a critical need exists for additional agents that are effective in the treatment of bacteremia and infective endocarditis.

Telavancin is a semisynthetic derivative of vancomycin (Figure 1) that exhibits concentration-dependent bactericidal effects in vitro via a dual mechanism of action of inhibition of bacterial cell wall synthesis and disruption of bacterial cell membrane barrier functions [13]. Telavancin is approved in the United States and Canada for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) due to susceptible gram-positive pathogens. Also, telavancin is approved in the United States and Europe for the treatment of hospital-acquired bacterial pneumonia (HABP), including ventilator-associated bacterial pneumonia (VABP) due to susceptible isolates of}\textit{S. aureus} (MRSA strains only in Europe), when alternative medicines are unsuitable.

IN VITRO ANTIMICROBIAL ACTIVITY OF TELAVANCIN

Since 2007, telavancin’s microbiological activity against clinical isolates has been monitored as part of the SENTRY Antimicrobial Surveillance Program and by numerous other investigators [14–26]. Telavancin MICs were tested according to the Clinical and Laboratory Standards Institute (CLSI) guidelines, which were in place at the time these studies were performed, and susceptibility was interpreted with the corresponding US Food and Drug Administration (FDA) breakpoints, which were approved in 2009 (susceptibility breakpoint ≤1 µg/mL). The MIC testing methodology and corresponding FDA-approved breakpoints have recently been revised (≤0.12 µg/mL for \textit{S. aureus}) and are published in the CLSI M100-S24 guidelines and the telavancin product insert [27], respectively.

In the most recent published surveillance data (2010) on the activity of telavancin against 15 480 nonduplicated gram-positive pathogens (39% of isolates from patients with bacteremia), telavancin (MIC\textsubscript{50/90}, 0.12/0.25 µg/mL) was 2-fold more active than daptomycin (MIC\textsubscript{50/90}, 0.25/0.5 µg/mL)

![Figure 1. Chemical structure of telavancin.](https://academic.oup.com/cid/article-abstract/60/5/787/292124)
and 4- to 8-fold more active than vancomycin and linezolid (MIC$_{50/90}$ for both, 1/1 µg/mL) against MRSA [17] (Table 1).

The in vitro activity of telavancin and its comparators was also tested against 67 vancomycin-susceptible and vancomycin-non-susceptible MRSA isolates collected between 2007 and 2008 in a resistance selection study [28]. All 26 VISA strains were susceptible to telavancin (MIC, ≤1 µg/mL), whereas 12 of 26 (46%) were nonsusceptible to daptomycin at the same concentration. In another analysis, the in vitro activity of telavancin and its comparators against 33 VISA and 13 vancomycin-resistant S. aureus (VRSA) isolates was evaluated. This study similarly found that 100% of the VISA isolates were susceptible to telavancin (MIC, ≤1 µg/mL) and linezolid, while only 30% were daptomycin susceptible. However, telavancin MICs vs 13 VRSA isolates (MIC range, 2–8 µg/mL) were above the susceptibility cutoff, while these isolates remained susceptible against linezolid and daptomycin [29]. In multistep-resistance selection studies, telavancin yielded only a single stable resistant clone out of 10 MRSA strains tested after 43 days of passages, and single-step mutation frequencies for telavancin were lower than the spontaneous mutation frequencies from comparators [28].

All gram-positive isolates obtained during phase 3 studies of telavancin for the treatment of cSSSIs and nosocomial pneumonia (NP) were inhibited by ≤1 µg/mL telavancin [30, 31]. The MIC$_{90}$ for S. aureus was 0.5 µg/mL in both studies, including 39 hVISA isolates recovered during the NP trials.
ANIMAL MODELS OF STAPHYLOCOCCUS AUREUS BACTEREMIA OR INFECTIVE ENDOCARDITIS

The efficacy of telavancin has been studied in animal infection models of bacteremia [32–34] and infective endocarditis [35–37] caused by clinically relevant gram-positive organisms. In these studies, telavancin efficacy was compared with that of agents such as vancomycin or daptomycin at doses that mimicked human-equivalent exposures. The following are a few illustrative examples.

In several murine bacteremic infection models, telavancin treatment resulted in the successful resolution of a MRSA infection, whereas vancomycin treatment did not [32–34]. Telavancin also produced significantly greater reductions in blood and spleen bacterial titers ($P < .05$) vs vancomycin (Figure 2). The mortality rate (day 14) was lower with telavancin than with vancomycin or controls (1/15 [7%], 15/15 [100%], and 15/15

Figure 2. Effects of telavancin and vancomycin on spleen (A) and blood (B) bacterial titers in a murine methicillin-resistant Staphylococcus aureus bacteremia model [32]. For controls at all time points except at $t = 10$ hours ($n = 9$) and $t = 16$ hours ($n = 4$), $n = 10$. For the vancomycin group at all time points except at $t = 40$ hours ($n = 4$), $n = 5$. For the telavancin group at all time points except at $t = 28$ hours ($n = 4$), $n = 5$. Data represent mean ±1 standard error of the mean. Arrow denotes time of dosing. Abbreviations: CFU, colony forming units; LOQ, limit of quantification; SC, subcutaneous. Reproduced from Reyes N, Skinner R, Benton BM, et al Efficacy of telavancin in a murine model of bacteremia induced by methicillin-resistant Staphylococcus aureus. Journal of Antimicrobial Chemotherapy 2006;58(2):462–5 by permission of Oxford University Press.
[100%], respectively). In an immunocompromised murine model of bacteremia caused by glycopeptide intermediate \textit{Staphylococcus aureus} (GISA HIP-5836 (A), GISA Mu50 (B), and heterogeneous vancomycin-intermediate \textit{S. aureus} Mu3 (C)) \cite{33}. For all treatment groups, \( n = 5 \). Data represent mean ± standard error of the mean. Arrows denote time of dosing. \( *P < .05 \) vs pretreatment titer. \( **P < .05 \) vs vancomycin. Abbreviations: CFU, colony forming units; LOQ, limit of quantification; SC, subcutaneous. Reproduced from Hegde SS, Difuntorum S, Skinner R, Trumbull J, Krause KM. Efficacy of telavancin against glycopeptide-intermediate \textit{Staphylococcus aureus} in the neutropenic mouse bacteremia model. Journal of Antimicrobial Chemotherapy 2009;63(4):763–6 by permission of Oxford University Press.

In another study, the efficacy of telavancin and vancomycin in an immunocompromised murine subchronic model of bacteremia caused by hVISA strain Mu3 was compared \cite{34}. Treatment began 4 hours post-inoculation and continued for 4 (telavancin) or 8 days (vancomycin). The shorter course of telavancin was more effective than vancomycin in clearing the infection; none of the telavancin-treated animals had positive blood cultures after the first treatment day, whereas more than 40% of vancomycin-treated animals were bacteremic through days 5–7.

In several rabbit models of infective endocarditis, telavancin was more effective than vancomycin against most of the...
vancomycin-susceptible and VISA strains that were tested [35, 36]. In one study, telavancin was at least as active as vancomycin against the MRSA strain and significantly better than vancomycin against the VISA strain. In the other study, both telavancin and vancomycin demonstrated efficacy in the rabbit model of VISA infective endocarditis. Telavancin was also effective against daptomycin-nonsusceptible strains [37]. In a rabbit model of aortic valve endocarditis in which efficacy of telavancin against daptomycin-resistant MRSA was evaluated (daptomycin MIC range, 2–4 µg/mL; telavancin MIC, ≤0.38 µg/mL), telavancin produced a mean reduction of >4.5 log_{10} colony-forming units per gram in vegetations, kidneys, and spleen compared with untreated or daptomycin-treated rabbits [37]. Telavancin sterilized a significantly higher proportion of tissue cultures (87% in vegetations; 100% in kidney and spleen) compared with low- and high-dose daptomycin (0% in vegetations, kidneys, and spleen; \( P < .0001 \)).

**CLINICAL EXPERIENCE IN TREATMENT OF STAPHYLOCOCCUS AUREUS BACTEREMIA OR INFECTIVE ENDOCARDITIS**

**ASSURE Study**

A phase 2, multinational, randomized, double-blind, active-controlled trial was conducted to evaluate the safety and efficacy of telavancin for the treatment of adult patients with uncomplicated SAB [38]. Patients were randomized to receive either telavancin (10 mg/kg IV q24h) or standard therapy (vancomycin 1 g IV q12h or antistaphylococcal penicillin [nafcillin 2 g IV q6h, oxacillin 2 g IV q6h, or cloxacillin 2 g IV q6h]) for 14 days (blinded dose adjustment of vancomycin was permitted per site-specific guidelines). The primary efficacy endpoint was clinical cure at day 84, defined as resolution of clinical symptoms/signs associated with bacteremia, no evidence of metastatic complications, all cultures negative for *S. aureus* after qualifying blood cultures, and no nonstudy systemic antistaphylococcal medication to which the baseline pathogen was susceptible.

Of 60 patients randomized to telavancin or standard therapy, 58 received 1 or more doses of study medication (n = 29 in each group). The key analysis populations included the all-treated target population (ATT; patients who received 1 or more doses of study medication and fulfilled inclusion/exclusion and continuation criteria [telavancin, n = 15; standard therapy, n = 16]) and the clinically evaluable population (patients in the ATT population who received 12–16 days of study medication and whose study participation did not deviate from the protocol by more than prespecified limits [telavancin, 8; standard therapy, 9]). Baseline characteristics were similar in the 2 ATT treatment groups. All baseline isolates of *S. aureus* (MRSA and MSSA) available for testing were vancomycin susceptible (≤1 µg/mL). Sixteen patients in the telavancin group and 12 patients in the standard therapy group discontinued study medication early. The most common reason for failing to meet continuation criteria was identification of complicated bacteremia (positive follow-up blood cultures).

Cure rates in ATT patients were numerically lower with telavancin (8/15; 53%) vs vancomycin (11/16; 69%; 95% confidence interval (CI) for the difference, −45.9 to 18.5). The response rate in the ATT population was lower because more patients in the telavancin group had missing outcomes at the test-of-cure visit and thus could not be considered cured. Only those patients with complete data and receiving predefined lengths of treatment (for cure or failure) were included in the clinically evaluable population. Similar proportions of clinically evaluable patients were cured in the telavancin and standard treatment arms (88% vs 89%; 95% CI for the difference, −35.5 to 31.9; Table 2) [38, 39]. All clinically evaluable patients with MRSA were cured. Only 1 patient in each group actually failed study treatment. The patient who failed in the telavancin group had...
positive blood cultures for MSSA and was subsequently found to have osteomyelitis. The patient who failed in the standard therapy group died after being readmitted on study day 48 with intestinal ischemia and positive blood cultures for MSSA. Another patient who was considered cured in the standard therapy group had positive blood cultures for S. aureus during follow-up.

Adverse events (AEs) were more common in the telavancin group compared with the standard therapy group; AEs that led to drug discontinuation were similar in both groups (Table 3) [38, 39]. Potential clinically significant increases in serum creatinine (serum creatinine ≥1.5 mg/dL and at least 50% greater than baseline at any time point through the end-of-therapy visit) were more common in telavancin-treated patients (5/25 vs 2/28).

Five (17%) died in the telavancin group and 3 patients (10%) died in the standard therapy group. In the telavancin group, 1 patient who died from endocarditis had withdrawn consent after the first dose, 2 other patients had discontinued early because of failure to meet continuation criteria (1 with endocarditis and 1 with metastatic soft tissue abscess), and 2 patients died after completing study medication (1 with prostate cancer and cardiorespiratory failure and 1 with probable sepsis from the urinary tract). In the standard therapy group, 1 patient died with MSSA bacteremia and intestinal ischemia, 1 patient died from endocarditis, and 1 patient died from a neuroleptic malignant syndrome.

ATTAIN Studies

The ATTAIN studies were 2 methodologically identical, randomized, double-blind, phase 3 trials that compared telavancin with vancomycin for the treatment of hospital-acquired pneumonia (HAP) due to gram-positive pathogens including MRSA [40]. Overall, the pooled studies showed that telavancin was noninferior to vancomycin and indicated improved clinical outcomes compared with vancomycin in the subgroups of patients with monomicrobial S. aureus infections and with S. aureus strains displaying a vancomycin MIC ≥1 µg/mL [40]. As bacteremic HAP is associated with higher mortality than nonbacteremic HAP, particularly when MRSA is the causative pathogen [41], a post hoc analysis of patients with bacteremic HAP enrolled in the ATTAIN studies was conducted [39]. Bacteremic HAP was defined by the identification of a pneumonia-causing pathogen in the blood or of the same pathogen in the lung and blood with identical susceptibility profiles.

The bacteremic HAP subgroup comprised 73 of 1089 patients (7% of pooled ATTAIN modified all-treated population); S. aureus was the most common blood pathogen (Table 4). Based on study definitions, 51 patients (70%) had gram-positive bacteremic HAP (exclusively gram-positive pathogens in blood and respiratory cultures). The vast majority (92% [47/51]) had S. aureus bacteremic HAP, primarily due to MRSA (64% [30/47]).

Cure rates at test of cure were similar in the overall group of patients with S. aureus bacteremic HAP (which included patients with mixed infections) but numerically higher among those treated with telavancin in the subgroups of patients with MRSA and monomicrobial S. aureus bacteremic HAP (Table 2) [38, 39]. Eight patients had blood cultures positive for S. aureus at baseline and in follow-up cultures: 2 in the telavancin group (both MRSA) and 6 in the vancomycin group (2 MSSA, 4 MRSA). However, none of the patients were categorized as cured. None of the S. aureus strains associated with baseline and positive follow-up blood cultures had vancomycin MIC values >1 mg/L, and no increases in vancomycin MICs were detected in any strains.

Rates of serious AEs were comparable between the 2 groups (Table 3) [38, 39]. The rate of renal AEs was similar with telavancin (5/34; 15%) and vancomycin (4/39; 10%); 4 cases of acute renal failure were reported, 3 of which were in the vancomycin group. The proportions of patients who discontinued the study medication due to AEs were similar. The mortality rate in these bacteremic HAP/VABP patients was similar in the 2 treatment groups (both 41%) and was higher than the approximately 20% overall rate observed in the ATTAIN studies [40]. This is consistent with other studies of HABP and VABP, where

### Table 3. Overall Safety and Tolerability in Patients With Bacteremia in Clinical Studies of Telavancin

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>ASSURE [38]</th>
<th>ATTAIN [39]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Telavancin (n = 29)</td>
<td>Standard Therapy (n = 29)</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>26 (90)</td>
<td>21 (72)</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>11 (38)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Discontinuations due to AEs, n (%)</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>5 (17)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; ASSURE, Telavancin for Treatment of Uncomplicated Staphylococcus aureus Bacteremia; ATTAIN, Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia.

a All-treated population.
b All patients with bacteremic hospital-acquired pneumonia.
c Data on file, Theravance Biopharma, Inc.
the presence of bacteremia at least doubled the mortality rate [41–44]. A higher overall 28-day mortality rate was observed among patients with a baseline creatinine clearance (CrCl) <50 mL/min compared with patients with better renal function. The mortality rate among telavancin-treated patients with poor renal function was higher than in vancomycin-treated patients. Hence, the approved product label warns against the use of telavancin in NP patients with preexisting moderate to severe renal insufficiency unless the anticipated benefit outweighs the potential risk.

**Case Series and Case Reports**

The efficacy of telavancin was examined in a retrospective case series of 14 patients with refractory MRSA bacteremia (defined as persistent MRSA bacteremia for longer than 72 hours while on appropriate therapy [vancomycin with a trough ≥10 µg/mL, daptomycin, or both]) either with or without infective endocarditis (modified Duke criteria; n = 10 and n = 4, respectively) [45, 46]. The primary outcome was inpatient mortality; secondary outcomes included 30-day mortality and time to clearance of that for MRSA bacteremia.

Overall inpatient mortality was 43%, and all patients who died were from the subgroup with infective endocarditis (6/10). The time to clearance of MRSA bacteremia for survivors ranged from 0 to 3 days. This rate of clearance compared favorably with prior treatment as these patients had persistent MRSA bacteremia ranging from 3 to 26 days (median, 12 days). It should be noted that this rapid clearance may have been partially due to effects of the prior treatments. Thus, the overall clinical cure rate in these patients with refractory bacteremia, with or without infective endocarditis, was comparable to other frontline agents [12].

The efficacy and safety of telavancin has also been assessed in a separate clinical study in which the treatment of uncomplicated gram-positive bloodstream infections in patients with cancer was described [47]. A total of 38 patients received telavancin (CrCl > 50 mL/min, 10 mg/kg/day; CrCl 30–49 mL/min, 7.5 mg/kg/day) for 14 days or longer (S. aureus infections) or for 7 days or longer (other gram-positive cocci). Twenty-three patients (61%) had hematologic malignancies and 17 (45%) had solid tumors. Eighteen patients (45%) were neutropenic and 7 patients (18%) had received a bone marrow transplant within 1 year of their bacteremia. The most common pathogens were S. aureus (20 patients, 10 MRSA; 10 MSSA), alpha-hemolytic Streptococcus (7 patients), and Enterococcus (5 patients).

Telavancin was effective and generally well tolerated. The overall clinical response rate was 89% (34/38), and the microbiological eradication rate within 96 hours of starting treatment was 95% (36/38). Treatment-related AEs were observed in 32% (12/38) of patients, and these led to treatment discontinuation in 7 patients (18%), primarily as a result of renal toxicity. During follow-up, 5 patients (13%) had serum creatinine at least 2-fold of baseline levels that declined to baseline by the end of the follow-up period [47]. Of note, no other antibiotics were given to the patients during their treatment course.

There are 3 published case reports of patients with bacteremia (2 MRSA, 1 VISA) and/or infective endocarditis treated with telavancin [48–50]. In each of these complicated cases, the patients had organisms resistant to or that had failed to respond to vancomycin and/or daptomycin, with underdosing of daptomycin in 1 case. Telavancin therapy, ranging from 3 to 8 weeks, resulted in prompt clearance of the bacteremia; with additional surgery, all 3 patients responded well.

**Cautions in the Use of Telavancin**

In addition to the aforementioned renal toxicity and higher mortality seen in HAP/VAP patients with moderate to severe renal impairment, other cautions include interference with coagulation testing (eg, prothrombin time/international normalized ratio, activated partial thromboplastin time), unless blood

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**Table 4. Gram-Positive Baseline Bloodstream Pathogens From Patients With Bacteremia in Clinical Studies of Telavancin**

<table>
<thead>
<tr>
<th>Gram-Positive Pathogens, n (%)</th>
<th>Telavancin (n = 8)</th>
<th>Standard Therapy (n = 9)</th>
<th>Total (n = 17)</th>
<th>Telavancin (n = 34)</th>
<th>Vancomycin (n = 39)</th>
<th>Total (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em>, n (%)</td>
<td>8 (100)</td>
<td>9 (100)</td>
<td>17 (100)</td>
<td>26 (76)</td>
<td>27 (69)</td>
<td>53 (73)</td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em>, n (%)</td>
<td>5 (63)</td>
<td>4 (44)</td>
<td>9 (53)</td>
<td>14 (41)</td>
<td>19 (49)</td>
<td>33 (62)</td>
</tr>
<tr>
<td>Methicillin-susceptible <em>Staphylococcus aureus</em>, n (%)</td>
<td>3 (38)</td>
<td>5 (56)</td>
<td>8 (47)</td>
<td>12 (35)</td>
<td>8 (21)</td>
<td>20 (38)</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em>, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>3 (4)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

Abbreviations: ASSURE, Telavancin for Treatment of Uncomplicated *Staphylococcus aureus* Bacteremia; ATTAIN, Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia.

a Clinically evaluable population.

b All patients with bacteremic hospital-acquired pneumonia.
is sampled just prior to a telavancin dose or test kits that are not affected by telavancin are used [51]. Because of potential adverse effects on the developing fetus, women of child-bearing potential should have a pregnancy test prior to therapy. Pregnant women should only receive the drug if the anticipated benefit outweighs the potential risk [27].

CONCLUSIONS

Telavancin is a bactericidal antibiotic with a dual mechanism of action. In vitro data and experimental models of infection support a potential role for telavancin in the treatment of SAB. In murine models of bacteremia and in vitro and rabbit models of infective endocarditis, telavancin demonstrated greater efficacy than vancomycin and similar or greater efficacy than daptomycin. Clinical experience includes bacteremic patients with catheter-associated infections, HAP, osteomyelitis, and endocarditis, which showed comparable clinical cure rates between telavancin and vancomycin, although the findings were based on very small sample sizes. While the drug has been generally well tolerated, nephrotoxicity warrants caution in its use, especially among patients at high risk for development of renal dysfunction. Additional clinical experience is needed to fully assess the effectiveness and safety of telavancin in patients with SAB. These studies will need to include larger numbers of patients than were enrolled in the ASSURE study, as well as patients with complicated bacteremia.

Notes

Acknowledgments. Manuscript editing and formatting assistance was provided by Paul Littlebury, PhD, and Marissa Buttaro, RPh, MPH, of Envision Scientific Solutions.

Author contributions. As study investigators, G. R. C., E. R., M. E. S., M. B., and S. L. B. were involved with the design, data interpretation, and drafting of the ASSURE and/or ATTAIN studies discussed in this review. For this review, all authors contributed substantially to interpretation of the literature, participated in the drafting of the article, and approved the final version before submission.

Financial support. This work was supported by Theravance Biopharma Antimitics, Inc.

Potential conflicts of interest. G. R. C. has served on scientific advisory boards for Theravance, Inc. and Theravance Biopharma Antibiotics, Inc., and received financial support for primary investigator duties from Cerexa and Forest. E. R. has served on advisory boards for Astellas, Atox Bio, Bayer, BiondVax, Pfizer, Theravance, Inc., and Theravance Biopharma Antibiotics, Inc.; has served as a consultant for Roche, Theravance, Inc., and Theravance Biopharma Antibiotics, Inc.; and has received payment for lectures/speaker bureaus from Astellas, Bayer, and Pfizer. M. E. S. has served as a consultant for Achaogen, Astellas, Cempra, Cerexa, Furiex, Nabriva, PRA, The Medicines Company; Theravance, Inc., Theravance Biopharma Antibiotics, Inc., and Trius; has received grants from Duke University (National Institutes of Health); and has received other financial support (including reimbursement for travel expenses and/or manuscript preparation) from Cempra, JMI Laboratories, Theravance, Inc., and Theravance Biopharma Antibiotics, Inc. M. B. has served on scientific advisory boards for Astellas, AstraZeneca, Bayer, Cubist, Gilead, Merck Serono, Novartis, Pfizer, Theravance, Inc., The Medicines Company, and Trius; has received funding for travel or speaker honoraria from Astellas, AstraZeneca, Gilead, Pfizer, Merck Serono, Novartis, Sumimoto, and Teva; and has received research grants from MSD and Pfizer. S. L. B. is an employee of Theravance Biopharma US, Inc. and holds equity securities of Theravance Biopharma, Inc.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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