

# Assessment of Minimum Inhibitory Concentrations of Telavancin by Revised Broth Microdilution Method in Phase 3 Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia Clinical Isolates

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## ABSTRACT

**Introduction:** The broth microdilution method (BMD) for testing telavancin minimum inhibitory concentrations (MICs) was revised (rBMD) in 2014 to improve the accuracy, precision, and reproducibility of the testing method. The aim of this study was to determine the effect of the revised method on telavancin MIC values for *Staphylococcus aureus* (*S. aureus*) clinical isolates obtained from hospital-acquired pneumonia (HAP) patients.

**Methods:** Isolates from patients who participated in the phase 3 Assessment of

Telavancin for Treatment of HAP Studies were retested using the rBMD method.

**Results:** Retesting of 647 isolates produced a range of telavancin MIC values from 0.015 µg/mL to 0.12 µg/mL with MIC<sub>50/90</sub> values of 0.06/0.06 µg/mL for the total pool of samples. For methicillin-resistant *S. aureus* (MRSA), MIC<sub>50/90</sub> values were 0.06/0.12 µg/mL. These values are up to 4-fold lower than MIC<sub>50/90</sub> values obtained using the original method. These results were used in part to justify lowering the telavancin breakpoints. All tested isolates remained susceptible to telavancin at the revised susceptibility breakpoint of ≤0.12 µg/mL. Overall, the clinical cure rate for microbiologically evaluable telavancin-treated patients was 78% for *S. aureus*, 76% for patients with MRSA, and 79% for patients with isolates with reduced susceptibility to vancomycin (MIC ≥1 µg/mL).

**Conclusion:** Results from the rBMD method support the in vitro potency of telavancin against *S. aureus*.

**Trial registration:** ATTAIN (NCT00107952 and NCT00124020).

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**Keywords:** Hospital-acquired pneumonia; Lipoglycopeptide; *Staphylococcus aureus*; Telavancin; Ventilator-associated pneumonia

## INTRODUCTION

*Staphylococcus aureus* (*S. aureus*) infections are a major cause of pneumonia and are especially implicated in hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia [1]. The recent Infectious Diseases Society of America guidelines recommend treating HAP/VAP patients with either vancomycin or linezolid [2]. Higher vancomycin minimum inhibitory concentrations (MICs) have been associated with more frequent treatment failure and higher mortality rates [3–6]. Telavancin (Theravance Biopharma Antibiotics, Inc., George Town, Grand Cayman, Cayman Islands) is a parenteral bactericidal lipoglycopeptide antibiotic that has a dual mechanism of action [7–10]. Telavancin is approved in the US, Canada, Russia, and Europe for treatment of HAP, including VAP that is caused by susceptible isolates of *S. aureus* (methicillin-resistant *S. aureus* [MRSA] only in Europe). In the US, Russia, and Europe, the indication is limited to infections in which alternative medicines are unsuitable [8, 11, 12]. In the Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia [ATTAIN (ClinicalTrials.gov identifiers NCT00107952 and NCT00124020)] studies, a total of 1503 patients with HAP were treated with telavancin or vancomycin for up to 21 days. Telavancin demonstrated noninferiority to vancomycin, achieving similar cure rates [13].

Drug loss due to binding to plastics in the MIC assay has been found with other

lipoglycopeptides and is resolved with the addition of polysorbate 80 (P-80) [14, 15]. To improve the accuracy and precision of telavancin susceptibility testing, a revised broth microdilution method (rBMD) MIC testing method for telavancin was approved by the US Food and Drug Administration (FDA) and published by Clinical and Laboratory Standards Institute (CLSI) in 2014 to include dimethyl sulfoxide (DMSO) in the diluent to improve solubility and P-80 in the broth microdilution assay cation-adjusted Mueller–Hinton broth (CAMHB) to reduce drug loss due to binding to plastic [8, 16, 17]. This revised method has produced up to 8-fold lower telavancin MIC results compared with the previous method [17] and has been used to establish new values for telavancin activity against a variety of clinical isolates [18, 19]. The FDA and CLSI previously have approved  $\leq 0.12$   $\mu\text{g}/\text{mL}$  as the telavancin MIC susceptibility breakpoint for *S. aureus* [both methicillin-susceptible *S. aureus* (MSSA) and MRSA] isolates; intermediate or resistant breakpoints for telavancin have not been established as of 2016, due to the rarity of telavancin-resistant *S. aureus* isolates [8, 20]. The objective of this study was to determine the effect of the revised method on telavancin MIC values for *S. aureus* clinical isolates obtained from the ATTAIN HAP/VAP patients and evaluate the clinical outcome by the revised telavancin MICs. These results were part of the data package presented to breakpoint setting committees, including FDA, CLSI, and the European Committee on Antimicrobial Susceptibility Testing for the evaluation of the revised telavancin breakpoints.

## METHODS

### Patient Population and Study Procedures

The protocol for the ATTAIN studies has been presented elsewhere [13]. Briefly, these were identical, randomized, double-blind, comparator-controlled phase 3 trials (ClinicalTrials.gov identifiers NCT00107952 and NCT00124020) in which inpatients who developed pneumonia caused by Gram-positive infections were randomized to receive telavancin (10 mg/kg every 24 h) or vancomycin (1 g every 12 h) for 7 to 21 days [13]. The primary endpoint of the study was the investigator-assessed clinical response at a follow-up/test-of-cure visit between 7 and 14 days after the last dose of study medication. Respiratory and blood culture specimens were collected at baseline, and isolates underwent susceptibility testing and confirmation at a central laboratory (Covance Laboratories, Indianapolis, IN, USA; Duke Clinical Research Institute, Durham, NC, USA).

Clinical cure rates by MIC reported in the ATTAIN trials were reassessed using the MICs obtained using the rBMD method. In the ATTAIN studies, the clinically evaluable study population consisted of patients who met study inclusion criteria and adhered to study protocol such that their clinical outcome could be considered to accurately reflect the effects of study medication. The microbiologically evaluable population in the ATTAIN studies included all clinically evaluable patients who had a Gram-positive (*S. aureus* in this analysis) respiratory pathogen at baseline. Presumed microbiological eradication was defined as failing to identify the baseline pathogen in the last postbaseline culture or if the patient was clinically cured and there were no follow-up cultures available.

### rBMD

The analysis of the effects of telavancin on clinical isolates from the ATTAIN studies was performed using the rBMD method at JMI Laboratories (North Liberty, IA, USA). Telavancin stock solutions of 1600 µg/mL were prepared by dissolving dry powder in DMSO in a glass vial; stock solutions were further diluted in DMSO to achieve intermediate concentrations ranging from 0.004 to 8 µg/mL, per CLSI recommendations [16]. The telavancin/DMSO solutions were further diluted 100× in CAMHB containing 0.002% (volume/volume) P-80 (Tween 80; Croda International, Snaith, UK) to minimize adhesion to plastic surfaces. Following dilution, 100-µL aliquots of telavancin solutions ranging in concentration from 0.004 to 8 µg/mL were dispensed into 96-well plates. Comparator agents tested against the same *S. aureus* isolates included linezolid (MIC range 0.25–4 µg/mL), ampicillin (MIC range 0.25–32 µg/mL), and vancomycin (MIC range 0.25–16 µg/mL).

### Clinical Isolates

Isolates were sent from the ATTAIN study central laboratories (Covance Laboratories) to JMI Laboratories for retesting using the rBMD method. The isolates were stored at –80 °C at Covance, then were shipped to JMI laboratories on dry ice, where they were stored at –80 °C. Minimum inhibitory concentration values were assessed for *S. aureus* isolates from the ATTAIN studies. Sample quality was assured via concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* American Type Culture Collection [ATCC®] 29213, *Enterococcus faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619, Manassas, VA,

USA). All QC MIC results for control strains were within acceptable ranges defined by CLSI [16].

### Statistical Analyses

All the analyses were descriptive and performed using SAS<sup>®</sup> 9.4 software (Cary, NC, USA).

### Compliance with Ethics Guidelines

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

## RESULTS

A total of 647 *S. aureus* isolates from patients with HAP in the ATTAIN studies were analyzed for telavancin MICs using the rBMD method (644 samples were tested using the original method). Three isolates that did not have an initial central laboratory MIC result and were not included in the original susceptibility analysis were included in this set of retested isolates. Overall, 240 isolates were MSSA isolates, and 407 were MRSA isolates.

The MIC values obtained using the rBMD method for telavancin and control agents tested against ATTAIN *S. aureus* isolates were within the CLSI-approved and accepted QC ranges determined using *S. aureus* ATCC 29213 (telavancin 0.03–0.12 µg/mL, ampicillin 0.5–2.0 µg/mL, linezolid 1.0–4.0 µg/mL, vancomycin 0.5–2.0 µg/mL) [16].

Telavancin MICs for all *S. aureus* isolates ranged from 0.015 to 0.12 µg/mL, with a range of 0.015 to 0.12 µg/mL for MSSA isolates and 0.015 to 0.12 µg/mL for MRSA isolates (Table 1). For the overall set of *S. aureus* isolates and for

MSSA isolates, telavancin MIC<sub>50/90</sub> values were 0.06/0.06 µg/mL; for MRSA, the telavancin MIC<sub>50/90</sub> values were 0.06/0.12 µg/mL. These results represent a substantial downward shift in telavancin MIC values for *S. aureus* compared with the MICs obtained using the original method (Fig. 1), which produced higher values of MICs for telavancin (MIC<sub>50/90</sub> of 0.25/0.50 µg/mL for the total pool of *S. aureus* isolates).

Among the 528 isolates with reduced susceptibility to vancomycin (MIC ≥ 1 µg/mL), telavancin MIC<sub>50/90</sub> values obtained using the rBMD method were 0.06/0.12 µg/mL. Among these samples, 166 were MSSA and 362 were MRSA, with MIC<sub>50/90</sub> values of 0.06/0.06 µg/mL for MSSA and 0.06/0.12 µg/mL for MRSA, respectively (Table 1). These values were lower than the telavancin MIC<sub>50/90</sub> values for isolates with reduced vancomycin susceptibility generated by the original method, which were 0.25/0.5 µg/mL and 0.5/0.5 µg/mL for MSSA and MRSA, respectively. The isolates with reduced susceptibility to vancomycin remained susceptible to telavancin (rBMD MIC<sub>50/90</sub>) when using the revised FDA-approved breakpoint of <0.12 µg/mL [8].

A total of 183 isolates exhibited a ±1 dilution change in the vancomycin MIC ≥ 1 µg/mL upon retesting. Of those, 1 increased from 0.25 to 0.5 µg/mL, 110 increased from 0.5 to ≥ 1 µg/mL, 11 increased from 1 to 2 µg/mL, 50 decreased from 1 to 0.5 µg/mL, and 11 decreased from 2 to 1 µg/mL. A total of 2 isolates exhibited a 2-dilution change in the vancomycin MIC upon retesting with 1 increasing from 0.5 to 2.0 µg/mL and 1 decreasing from 2.0 to 0.5 µg/mL. These changes can be attributed to random testing differences between two laboratories (Table 1).

The clinical cure rate by revised MIC was assessed in the microbiologically evaluable

**Table 1** Distribution of telavancin MIC values obtained using rBMD on HAP isolates from ATTAIN trials

Organism	Method	MIC ( $\mu\text{g/mL}$ )									
		<i>N</i>	0.015	0.03	0.06	0.12	0.25	0.5	1.0	Range ( $\mu\text{g/mL}$ )	MIC <sub>50/90</sub> ( $\mu\text{g/mL}$ )
<i>S. aureus</i> (all)	Revised	647	3	167	413	64 <sup>a</sup>	–	–	–	0.015–0.12	0.06/0.06
	Original	644	–	–	2	13	346	258	25	0.06–1	0.25/0.50
MSSA	Revised	240	1	94	144	1	–	–	–	0.015–0.12	0.06/0.06
	Original	239	–	–	–	10	178	50	1	0.12–1	0.25/0.5
MRSA	Revised	407	2	73	269	63	–	–	–	0.015–0.12	0.06/0.12
	Original	405	–	–	2	3	168	208	24	0.06–1	0.5/0.5
<i>S. aureus</i> vancomycin MIC $\geq 1 \mu\text{g/mL}$	Revised	528	–	94	370	61	3 <sup>a</sup>	–	–	0.03–0.25	0.06/0.12
	Original	466	–	–	–	7	229	209	21	0.12–1	0.25/0.5
MSSA vancomycin MIC $\geq 1 \mu\text{g/mL}$	Revised	166	–	48	117	1	–	–	–	0.03–0.12	0.06/0.06
	Original	137	–	–	–	5	103	29	–	0.12–0.5	0.25/0.5
MRSA vancomycin MIC $\geq 1 \mu\text{g/mL}$	Revised	362	–	46	253	60	3	–	–	0.03–0.25	0.06/0.12
	Original	329	–	–	–	2	126	180	21	0.12–1	0.5/0.5

Data presented as number of isolates except where indicated

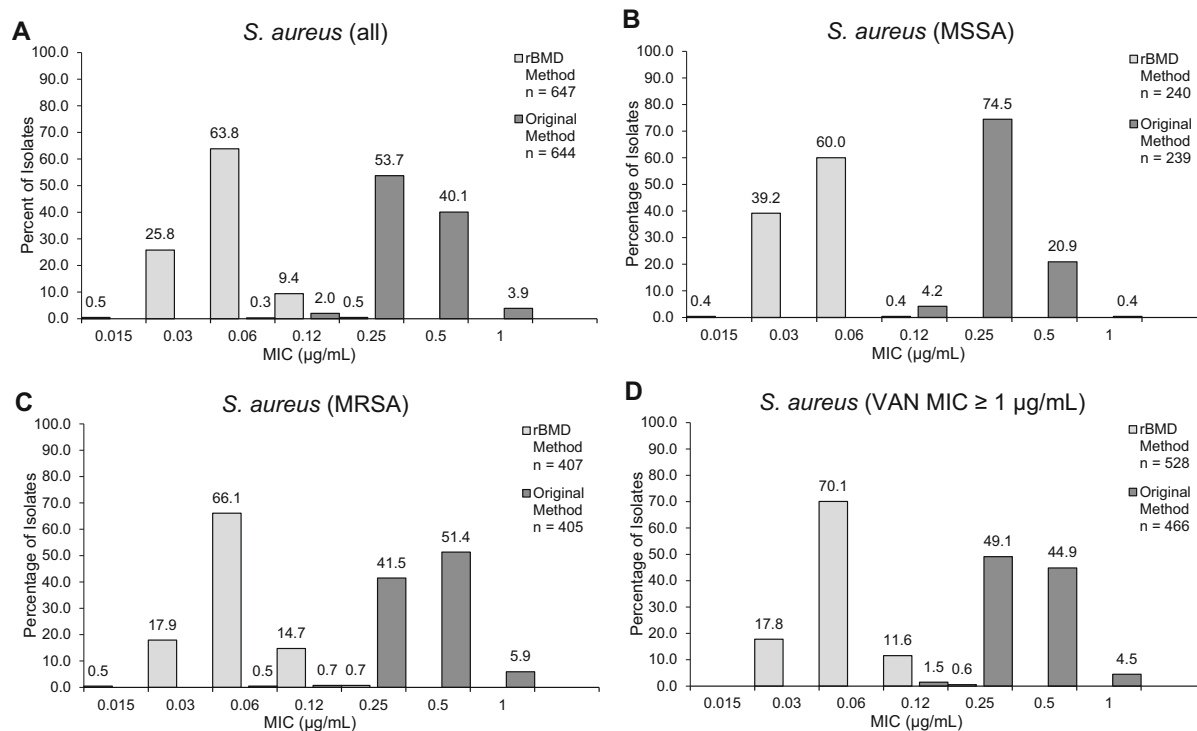
ATTAIN Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia; HAP hospital-acquired pneumonia; MIC minimum inhibitory concentration; MRSA methicillin-resistant *S. aureus*; MSSA methicillin-susceptible *S. aureus*; rBMD revised broth microdilution; *S. aureus* *Staphylococcus aureus*

population of telavancin-treated patients (195 patients). The overall telavancin clinical cure rate for *S. aureus* was 78% (153/195 patients), with clinical cure rates of 83% (62/75 patients) and 76% (91/120 patients) for MSSA- and MRSA-infected patients, respectively (Table 2). The clinical cure rate did not decrease with increasing telavancin MIC values for *S. aureus* obtained using the rBMD method, which ranged from 0.03 to 0.12  $\mu\text{g/mL}$ , as clinical cure rates remained  $\geq 81\%$  and  $\geq 70\%$  for MSSA- and MRSA-infected patients, respectively, for all MIC values (Table 2). Among the 166 microbiologically evaluable telavancin-treated patients with *S. aureus* isolates that demonstrated reduced susceptibility to vancomycin (MIC  $\geq 1 \mu\text{g/mL}$ ), the clinical cure rate was 79% (131/166 patients) for telavancin.

The microbiological eradication rates for the overall *S. aureus*, individual MSSA and MRSA isolates, and isolates with reduced vancomycin susceptibility (MICs  $\geq 1 \mu\text{g/mL}$ ) were comparable (Table 2) [13].

## DISCUSSION

Lipoglycopeptide drug loss due to its binding to plastics is known to affect the MIC determination. The addition of P-80 to the MIC assay has resolved this issue and the FDA-approved rBMD method includes DMSO and P-80 to improve drug solubility and reduce drug loss, respectively [8, 14–17]. Telavancin is a lipoglycopeptide active against a wide range of susceptible Gram-positive pathogens, including *S. aureus* [13]. The objective of this study was to



**Fig. 1** Distribution of telavancin MICs obtained using the rBMD or original BMD method in **a** all *S. aureus* isolates, **b** MSSA isolates, **c** MRSA isolates, and **d** *S. aureus* isolates with vancomycin MICs  $\geq 1$  µg/mL. MIC minimum

inhibitory concentration; *MRSA* methicillin-resistant *S. aureus*; *MSSA* methicillin-susceptible *S. aureus*; *rBMD* revised broth microdilution; *S. aureus* *Staphylococcus aureus*; *VAN* vancomycin

re-evaluate the ATTAIN clinical isolates with the rBMD method that has previously demonstrated lower telavancin MIC values [8, 16, 17].

Telavancin MIC values for MSSA and MRSA obtained using the rBMD method were lower than those that have been published elsewhere using the original method [21, 22], indicating that telavancin is more active in vitro against *S. aureus* isolates than previously considered. In this study, the rBMD method produced an overall 4-fold decrease in the telavancin MIC<sub>50/90</sub> for *S. aureus* compared with the original method. All isolates were susceptible to telavancin, consistent with other studies reporting telavancin susceptibility of *S. aureus* using the rBMD method [18, 19]. Telavancin

also retained its in vitro potency against isolates with reduced susceptibility to vancomycin (MIC  $\geq 1$  µg/mL). Furthermore, the reassessment of ATTAIN study clinical isolates using the rBMD method demonstrated robust clinical cure and microbiological eradication even at the highest telavancin MIC (0.12 µg/mL) observed in the study.

This study is limited by its retrospective nature. The patients were not prospectively stratified by MIC and the reduced sample size prevented extensive statistical analyses of the clinical cure rates. However, the Clopper–Pearson (Exact) confidence interval method [22] was applied to demonstrate that the clinical cure rates were comparable across all *S. aureus* isolates and telavancin MICs.

**Table 2** Clinical cure and microbiological eradication rates in the microbiologically evaluable population of the ATTAIn studies using telavancin MIC values obtained using the rBMD method

	Total	MIC (µg/mL)			
		0.015	0.03	0.06	0.12
Clinical cure, n/N (%; 95% CI <sup>c</sup> )					
<i>S. aureus</i> (all)	153/195 (78; 72, 84)	-	36/46 (78; 64, 89)	103/134 (77; 69, 84)	14/15 (93; 68, 100)
<i>S. aureus</i> (MSSA)	62/75 (83; 72, 90)	-	22/26 (85; 65, 96)	39/48 (81; 67, 91)	1/1 (100; 3, 100)
<i>S. aureus</i> (MRSA)	91/120 (76; 67, 83)	-	14/20 (70; 46, 88)	64/86 (74; 64, 83)	13/14 (93; 66, 100)
<i>S. aureus</i> vancomycin MIC ≥ 1 µg/mL <sup>a</sup>	131/166 (79; 72, 85)	-	26/31 (84; 66, 95)	91/120 (76; 67, 83)	14/15 (93; 68, 100)
Microbiological eradication, n/N (%; 95% CI <sup>c</sup> )					
<i>S. aureus</i> (all)	152/195 (78; 71, 84)	-	34/46 (74; 59, 86)	104/134 (78; 70, 84)	14/15 (93; 68, 100)
<i>S. aureus</i> (MSSA)	62/75 (83; 72, 90)	-	22/26 (85; 65, 96)	39/48 (81; 67, 91)	1/1 (100; 3, 100)
<i>S. aureus</i> (MRSA)	90/120 (75; 66, 82)	-	12/20 (60; 36, 81)	65/86 (76; 65, 84)	13/14 (93; 66, 100)
<i>S. aureus</i> vancomycin MIC ≥ 1 µg/mL <sup>b</sup>	130/166 (78; 71, 84)	-	24/31 (77; 59, 90)	92/120 (77; 68, 84)	14/15 (93; 68, 100)

ATTAIn Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia; CI confidence interval; MIC minimum inhibitory concentration; MRSA methicillin-resistant *S. aureus*; MSSA methicillin-susceptible *S. aureus*; rBMD revised broth microdilution; *S. aureus* *Staphylococcus aureus*

<sup>a</sup> These values included 48/56 patients with MSSA and 83/110 patients with MRSA

<sup>b</sup> These values included 48/56 patients with MSSA and 82/110 patients with MRSA

<sup>c</sup> Clopper–Pearson (Exact) confidence interval [22]

## CONCLUSION

Reassessment of the ATTAIN isolates using the rBMD method demonstrated increased in vitro potency of telavancin against *S. aureus*. These data support lowering the telavancin susceptibility breakpoint to 0.12 µg/mL for *S. aureus*. Moreover, these results suggest that published studies using the previous BMD underestimated the in vitro potency of telavancin [23, 24].

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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