Poster 1

Baseline Activity of Telavancin When Tested Against Gram-positive Clinical Isolates Responsible for Documented Infections in USA Hospitals (2011–2012) Applying a Revised Susceptibility Testing Method

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ABSTRACT

Background. Earlier studies reported the telavancin activity tested by a previously established CLSI broth microdilution (BMD) method. This study aimed to test telavancin for susceptibility using the newly revised BMD that utilizes dimethyl sulfoxide (DMSO) as solvent and diluent for panel production, following the CLSI guidelines for water-insoluble agents. Polysorbate-80 (0.002%) was also added in the test medium. This revised method was deemed necessary for greater accuracy and reproducibility of telavancin MIC determinations.

Materials. 10,958 consecutive, non-duplicate isolates were collected from 28 USA sites. Isolates were submitted to a central laboratory and identification was performed by standard algorithms and MALDI-TOF. Susceptibility testing for comparators was performed by CLSI methods (M07-A9). Quality assurance applied revised MIC QC ranges for telavancin and those from CLSI M100-S24 for comparators (11). Interpretation of comparator MIC values was guided by EUCAST (2014) and CLSI (2014) criteria.

Results. Telavancin showed modal MIC, MIC_{50} and MIC_{90} of 0.03, 0.06 and 0.06 µg/mL, respectively, against both methicillin-susceptible (MSSA) and -resistant *S. aureus* (MRSA). Telavancin was 8-fold more active than daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL) and 16- to 32-fold more active than linezolid ($MIC_{50/90}$, 1/1 µg/mL) and vancomycin ($MIC_{50/90}$, 1/1 µg/mL) against MRSA. When tested against coagulase-negative staphylococci (66.6% methicillin-resistant), telavancin showed lowest MIC values ($MIC_{50/90}$, 0.06/0.06 µg/mL), followed by daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL; 100% susceptible), linezolid ($MIC_{50/90}$, 1/1 µg/mL; 99.3% susceptible) and vancomycin ($MIC_{50/90}$, 1/2 µg/mL; 100% susceptible). All *E. faecalis* were inhibited by telavancin ($MIC_{50/90}$, 0.12/0.12 µg/mL) at ≤0.25 µg/mL, except for 21 (3.2% of total) VanA-phenotype vancomycin-resistant isolates, and telavancin had MIC_{50} and MIC_{90} values 8- to 16-fold lower than ampicillin, vancomycin, daptomycin and linezolid ($MIC_{50/90}$, 1/2 µg/mL for all; ≥96.3% susceptible). Overall, streptococci showed telavancin modal MIC results of ≤0.015 µg/mL, except for *S. agalactiae*.

Conclusion. Telavancin exhibited potent activity when tested against this contemporary collection of Gram-positive clinical isolates from the USA using the revised method. These results re-establish the baseline activity for telavancin.

INTRODUCTION

- Telavancin is a once-daily parenteral semi-synthetic lipoglycopeptide agent approved in the United States and Canada for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive pathogens.[1]
- Telavancin was also approved in the United States and Europe for the treatment of adult patients with hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia (HABP/VABP) due to susceptible isolates of *Staphylococcus aureus* (methicillin-resistant strains [MRSA] only in Europe), when alternative medicines are unsuitable.[1]
- The broth microdilution (BMD) susceptibility testing for telavancin was initially established according to the Clinical and Laboratory Standards Institute (CLSI) recommendations described in the M100-S23 (2013) and previous documents.[2]
- These recommendations consisted of the use of dimethyl sulfoxide (DMSO) as solvent for stock solution preparation and water as stock solution diluent for manufacturing 96-well frozen-form panels.[2]
- However, this BMD method was revised and updated recommendations were published in the current M100-S24 (2014) document, which consist of the use of DMSO as solvent for stock solution preparation and diluent, following the current CLSI guidelines for stock solution and dilution preparations of water-insoluble agents.[3]
- Moreover, this revised method encompasses the addition of polysorbate-80 (P-80; 0.002%) to the test medium (see Posters #2566 and #2567 for additional information).[3]
- This revised method for telavancin is consistent with those utilized for other lipoglycopeptide agents, such as dalbavancin and oritavancin.[4,5]
- The susceptibility testing methods for these agents also incorporate P-80, which was shown to be essential for accurate MIC determinations and improved test performance reliability via minimizing the drug-binding to plastic 96-well panels.[4,5]
- However, the use of P-80 (to minimize plastic binding) and DMSO (to increase drug solubility) provided lower telavancin minimum inhibitory concentration (MIC) results when compared with those obtained by the previously established BMD method (see Poster #2567 for additional information).
- Therefore, the objective of this investigation was to reassess the activity of telavancin when tested against a contemporary collection of isolates recovered from hospitalized patients in the USA (2011–2012) using the revised BMD MIC testing method.

MATERIALS AND METHODS

Bacterial strain collection

- A total of 10,958 consecutive, non-duplicate isolates were collected from 28 USA sites.
- These isolates were recovered mostly from SSSI (36%), bacteremia (26%), and respiratory tract infections (24%) and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), as part of the SENTRY Antimicrobial Surveillance Program during 2011–2012.
- Isolates were primarily identified by the participating laboratory and identification confirmed by the reference monitoring laboratory (JMI Laboratories) by standard algorithms and supported by Vitek® 2 (bioMérieux, Hazelwood, MI, USA), and more recently MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility by BMD following the CLSI M07-A9 document.[6]
- Testing was performed using dry-form panels manufactured by ThermoFisher Scientific (formerly TREK Diagnostics Systems/Sensititre™; Cleveland, OH, USA).
  - These panels were previously validated and shown to provide MIC results equivalent to the revised method (supplemented with 0.002% P-80) as described above, and as published in the CLSI M100-S24 (see Poster #2567 for additional information).
- Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event.
- Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* American Type Culture Collection [ATCC] 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619).[3]
- Telavancin MIC ranges when tested against ATCC strains were those established during a QC study conducted according to the CLSI M23-A3 (2008) guideline document using the revised BMD method (see Poster #2566 for additional information).
- The MIC QC ranges for telavancin for the revised BMD method are available in the current M100-S24 document, as follows: *S. aureus* ATCC 29213, 0.03–0.12 µg/mL; *E. faecalis* ATCC 29212, 0.03–0.12 µg/mL; and *S. pneumoniae* ATCC 49619, 0.004–0.015 µg/mL.[3]
- All QC results were within published acceptable ranges.
- MIC interpretations for telavancin when tested against clinical isolates were based on updated breakpoint criteria for the revised BMD method, which were recently approved by the US Food and Drug Administration as part of a labeling supplement for the product VIBATIV™ (telavancin).[1]
- The CLSI M100-S24 (2014) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2014) breakpoint criteria were applied for comparator agents, as available.[3,7]

RESULTS

- Telavancin ($MIC_{50/90}$, 0.03/0.06 µg/mL) was equally potent when tested against methicillin-susceptible (MSSA) and -resistant *S. aureus* (MRSA) isolates (**Table 1**). These MIC_{50} and MIC_{90} results were eight-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), and 16- to 32-fold lower than linezolid ($MIC_{50/90}$, 1/1 µg/mL), and vancomycin ($MIC_{50/90}$, 1/1 µg/mL) against MRSA (**Table 2**).
- When telavancin was analyzed against a subset of *S. aureus* isolates exhibiting elevated MIC results for vancomycin (ie 2–4 µg/mL), slightly higher (two-fold) telavancin modal MIC and MIC_{50} values (0.06 µg/mL for both) were obtained when compared with the control group (0.03 µg/mL for both) (**Table 1**).
- A total of 66.6% of coagulase-negative staphylococci (CoNS) were methicillin-resistant, and telavancin ($MIC_{50/90}$, 0.06/0.06 µg/mL) showed MIC results 16- to 32-fold lower than vancomycin ($MIC_{50/90}$, 1/2 µg/mL) and four- to eight-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL) (**Table 1** and **Table 2**).
- All *E. faecalis* were inhibited by telavancin at the breakpoint for susceptibility (ie ≤0.25 µg/mL), except for 21 (3.2% of total) vancomycin-resistant (VanA phenotype) clinical isolates (**Table 1**). Telavancin ($MIC_{50/90}$, 0.12/0.12 µg/mL) was at least eight-fold more active than comparators tested against vancomycin-susceptible *E. faecalis*, including ampicillin ($MIC_{50/90}$, 1/2 µg/mL), vancomycin ($MIC_{50/90}$, 1/2 µg/mL), and daptomycin ($MIC_{50/90}$, 1/2 µg/mL) (**Table 2**).
- Telavancin ($MIC_{50/90}$, 0.03/0.06 µg/mL) was very active against vancomycin-susceptible *E. faecium* compared to other agents, while higher MIC values ($MIC_{50/90}$, 1/>1 µg/mL) were obtained for VanA-phenotype strains (**Table 1** and **Table 2**).
- Telavancin ($MIC_{50/90}$, ≤0.015/≤0.015 µg/mL) was very potent against *S. pneumoniae*, inhibiting all isolates at ≤0.06 µg/mL. The telavancin MIC_{90} values were at least 32-fold lower than vancomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), levofloxacin ($MIC_{50/90}$, 1/1 µg/mL), and linezolid ($MIC_{50/90}$, 1/1 µg/mL), and 256-fold lower than penicillin ($MIC_{50/90}$, ≤0.06/4 µg/mL) (**Table 1** and **Table 2**).
- Viridans group streptococci (VGS) had low MIC results for telavancin ($MIC_{50/90}$, ≤0.015/0.03 µg/mL), including when tested against subsets of *S. anginosus* and *S. mitis* groups ($MIC_{50/90}$, ≤0.015/0.03 µg/mL for both) (**Table 1**). Moreover, telavancin demonstrated MIC_{90} values at least 32-fold lower than the comparator agents tested against VGS (**Table 2**).
- When tested against *S. pyogenes* ($MIC_{50/90}$, ≤0.015/0.03 µg/mL), telavancin MIC results were slightly lower (≤two-fold) than those obtained for *S. agalactiae* ($MIC_{50/90}$, 0.03/0.06 µg/mL) (**Table 1**). In addition, telavancin and penicillin were overall the most potent agents tested against ß-hemolytic streptococci (ßHS) (**Table 2**).

Table 1. Antimicrobial activity and MIC distribution for telavancin when tested against contemporary (2011–2012) clinical isolates from USA medical centers using a revised BMD testing method

Organism[a] (no. tested)	MIC (µg/mL)		Number (cumulative %) inhibited at telavancin MIC (µg/mL)[b]						
	50%	90%	≤0.015	0.03	0.06	0.12	0.25	0.5	1	>1
S. aureus (6264)										
MSSA (3245)	0.03	0.06	144 (4.4)	**1979 (65.4)**	1113 (99.7)	8 (>99.9)	1 (100.0)	–	–	–
MRSA (3019)	0.03	0.06	73 (2.4)	**1664 (57.5)**	1267 (99.5)	14 (>99.9)	1 (100.0)	–	–	–
Vancomycin MIC, ≤1 µg/mL (6149)	0.03	0.06	214 (3.5)	**3629 (82.5)**	2290 (99.7)	14 (>99.9)	2 (100.0)	–	–	–
Vancomycin MIC, 2–4 µg/mL (115)[c]	0.06	0.06	3 (2.6)	14 (14.8)	**90 (93.0)**	8 (100.0)	–	–	–	–
CoNS (461)	0.06	0.06	76 (16.5)	126 (43.8)	**248 (97.6)**	11 (100.0)	–	–	–	–
E. faecalis (649)	0.12	0.12	2 (0.3)	13 (2.3)	181 (30.2)	**421 (95.1)**	11 (96.8)	0 (96.8)	4[c] (97.4)	17[c] (100.0)
E. faecium										
Vancomycin-susceptible (81)	0.03	0.06	19 (23.5)	**43 (76.5)**	17 (97.5)	2 (100.0)	–			
VanA (241)	1	>1	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.7)	25 (12.0)	101 (53.9)	**111 (90.5)**
S. pneumoniae (1801)	≤0.015	≤0.015	**1778 (98.7)**	22 (1.2)	1 (100.0)	–	–	–	–	–
VGS (446)	≤0.015	0.03	**246 (55.2)**	176 (94.6)	24 (100.0)	–	–	–	–	–
S. anginosus group (120)	≤0.015	0.03	**75 (62.5)**	38 (94.2)	7 (100.0)	–	–	–	–	–
S. mitis group (172)	≤0.015	0.03	**99 (57.6)**	66 (95.9)	7 (100.0)	–	–	–	–	–
ßHS (971)	0.03	0.06	**434 (44.7)**	307 (76.3)	207 (97.6)	23 (100.0)	–	–	–	–
S. pyogenes (449)	≤0.015	0.03	**326 (72.6)**	95 (93.8)	28 (100.0)	–	–	–	–	–
S. agalactiae (393)	0.03	0.06	28 (7.1)	**171 (50.6)**	**171 (94.1)**	23 (100.0)	–	–	–	–

[a] ßHS = ß-hemolytic streptococci; CoNS = coagulase-negative staphylococci; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; VanA = vancomycin and teicoplanin MIC values of >4 and >8 µg/mL, respectively; VGS = viridans group streptococci.
[b] Modal MIC values are shown in bold.
[c] All *S. aureus* exhibited vancomycin MIC results of 2 µg/mL, except for a single isolate (MIC, 4 µg/mL).
[d] All VanA-phenotype.
BMD = broth microdilution; MIC = minimum inhibitory concentration.

CONCLUSIONS

- Telavancin exhibited *in vitro* potency greater than comparator agents when tested against this contemporary collection of Gram-positive clinical isolates using the revised BMD method. VanA-phenotype enterococci were less susceptible to telavancin, a feature also well documented when utilizing the previously established BMD susceptibility testing method.[8]
- Higher (two-fold) modal MIC and MIC_{50} results were observed for telavancin when tested against *S. aureus* displaying decreased susceptibility to vancomycin (MIC, 2–4 µg/mL). However, telavancin inhibited all isolates at the FDA-approved breakpoint for susceptibility (ie ≤0.12 µg/mL).
- This study documents MIC results for telavancin lower than those reported when using the previously established BMD method, which underestimated the *in vitro* drug potency (due to solubility and plastic binding issues).[8]
- These results redefine the benchmark for telavancin activity when tested against USA isolates using the FDA- and CLSI-approved revised method, which will supersede the previously established testing methodology.

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Table 2. Antimicrobial activity of telavancin and comparator agents tested against Gram-positive clinical isolates from the USA using a revised BMD testing method

Organism[a] (no. tested) / Antimicrobial agent	Range	MIC (µg/mL) 50%	MIC (µg/mL) 90%	%Susceptible/%Intermediate/%Resistant[b] CLSI	%Susceptible/%Intermediate/%Resistant[b] EUCAST
MRSA (3019)					
Telavancin	≤0.015–0.25	0.03	0.06	>99.9 / -[c] / -	
Vancomycin	0.25–4	1	1	>99.9 / <0.1 / 0.0	>99.9 / 0.0 / <0.1
Daptomycin	0.12–2	0.25	0.5	99.9 / - / -	99.9 / 0.0 / 0.1
Linezolid	0.25–8	1	1	99.9 / 0.0 / 0.1	99.9 / 0.0 / 0.1
Levofloxacin	≤0.12–>4	4	>4	30.9 / 2.6 / 66.5	30.9 / 2.6 / 66.5
Erythromycin	≤0.12–>16	>16	>16	10.1 / 1.9 / 88.0	10.1 / 0.3 / 89.4
Clindamycin	≤0.25–>2	≤0.25	>2	70.1 / 0.2 / 29.7	69.9 / 0.2 / 29.9
Gentamicin	≤1–>8	≤1	≤1	96.9 / 0.1 / 3.0	96.4 / 0.0 / 3.6
Tetracycline	≤0.25–>8	≤0.25	1	94.8 / 0.5 / 4.7	92.1 / 2.5 / 5.4
Trimethoprim-sulfamethoxazole	≤0.5–>4	≤0.5	≤0.5	97.9 / 0.0 / 2.1	97.9 / 0.3 / 1.8
CoNS (461)				- / - / -	
Telavancin	≤0.015–0.12	0.06	0.06		
Oxacillin	≤0.25–>2	1	>2	33.4 / 0.0 / 66.6	33.4 / 0.0 / 66.6
Vancomycin	0.5–4	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	≤0.06–1	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25–>8	0.5	1	99.3 / 0.0 / 0.7	99.3 / 0.0 / 0.7
Levofloxacin	≤0.12–>4	0.5	>4	55.1 / 1.9 / 43.0	55.1 / 1.9 / 43.0
Erythromycin	≤0.12–>16	>16	>16	38.4 / 1.9 / 59.7	39.0 / 0.5 / 60.5
Clindamycin	≤0.25–>2	≤0.25	>2	72.5 / 2.6 / 24.9	71.2 / 1.3 / 27.5
Gentamicin	≤1–>8	≤1	>8	80.9 / 4.3 / 14.8	77.4 / 0.0 / 22.6
Tetracycline	≤0.25–>8	≤0.25	>8	86.1 / 0.9 / 13.0	76.8 / 9.1 / 14.1
Trimethoprim-sulfamethoxazole	≤0.5–>4	≤0.5	>4	69.2 / 0.0 / 30.8	69.2 / 12.1 / 18.7
Vancomycin-susceptible *E. faecalis* (625)				100.0 / - / -	
Telavancin	≤0.015–0.25	0.12	0.12		
Ampicillin	≤0.25–>8	1	2	99.8 / 0.0 / 0.2	99.7 / 0.1 / 0.2
Vancomycin	0.5–4	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	≤0.06–4	1	2	100.0 / - / -	- / - / -
Linezolid	0.25–2	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	0.25–>4	1	>4	73.8 / 0.8 / 25.4	74.6 / 25.4 / 0.0
Tetracycline	≤0.25–>8	>8	>8	24.6 / 1.0 / 74.4	- / - / -
Vancomycin-susceptible *E. faecium* (81)				- / - / -	
Telavancin	≤0.015–0.12	0.03	0.06		
Ampicillin	≤0.25–>8	>8	>8	38.3 / 0.0 / 61.7	37.0 / 1.3 / 61.7
Vancomycin	0.25–4	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.5–8	2	4	98.8 / - / -	- / - / -
Linezolid	0.25–2	1	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	0.5–>4	>4	>4	33.3 / 7.4 / 59.3	- / - / -
Tetracycline	≤0.25–>8	>8	>8	27.2 / 2.4 / 70.4	- / - / -
S. pneumoniae (1801)				- / - / -	
Telavancin	≤0.015–0.06	≤0.015	≤0.015		
Penicillin[d]	≤0.06–8	≤0.06	4	89.0 / 9.7 / 1.3	- / - / -
Penicillin[e]	≤0.06–8	≤0.06	4	57.3 / 23.1 / 19.6	57.3 / 31.7 / 11.0
Vancomycin	≤0.12–0.5	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	≤0.12–2	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12–>4	1	1	98.9 / 0.2 / 0.9	98.9 / 0.0 / 1.1
Erythromycin	≤0.12–>16	≤0.12	>16	57.1 / 0.5 / 42.4	57.1 / 0.5 / 42.4
Clindamycin	≤0.25–>2	≤0.25	>2	81.0 / 0.6 / 18.4	81.6 / 0.0 / 18.4
Tetracycline	≤0.25–>8	≤0.25	>8	76.3 / 0.3 / 23.4	76.3 / 0.3 / 23.4
VGS (446)					
Telavancin	≤0.015–0.06	≤0.015	0.03	100.0 / - / -	
Penicillin	≤0.06–>8	≤0.06	1	74.0 / 22.9 / 3.1	82.1 / 14.8 / 3.1
Vancomycin	≤0.12–1	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Daptomycin	≤0.06–4	0.25	1	100.0 / - / -	- / - / -
Linezolid	≤0.12–2	1	1	100.0 / - / -	- / - / -
Levofloxacin	≤0.12–>4	1	2	92.4 / 1.3 / 6.3	- / - / -
Erythromycin	≤0.12–>16	1	>16	47.3 / 2.3 / 50.4	- / - / -
Clindamycin	≤0.25–>2	≤0.25	>2	85.4 / 0.9 / 13.7	86.3 / 0.0 / 13.7
Tetracycline	≤0.25–>8	0.5	>8	61.2 / 5.8 / 33.0	- / - / -
ßHS (971)					
Telavancin	≤0.015–0.12	0.03	0.06	100.0 / - / -	
Penicillin	≤0.06–0.12	≤0.06	≤0.06	100.0 / - / -	100.0 / 0.0 / 0.0
Vancomycin	0.25–1	0.5	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Daptomycin	≤0.06–0.5	≤0.06	0.25	100.0 / - / -	100.0 / 0.0 / 0.0
Linezolid	0.25–2	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12–>4	0.5	1	94.1 / 4.8 / 1.1	94.1 / 4.8 / 1.1
Erythromycin	≤0.12–>16	≤0.12	>16	68.7 / 0.4 / 30.9	68.7 / 0.4 / 30.9
Clindamycin	≤0.25–>2	≤0.25	>2	83.1 / 0.4 / 16.5	83.5 / 0.0 / 16.5
Tetracycline	≤0.25–>8	1	>8	51.4 / 1.6 / 47.0	50.4 / 1.0 / 48.6

[a] MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; VGS = viridans group streptococci; ßHS = ß-hemolytic streptococci.
[b] Breakpoint criteria for telavancin according to the labeling supplement for the product VIBATIV® (telavancin), as available. *S. aureus* at ≤0.12 µg/mL for susceptible; *E. faecalis* (vancomycin-susceptible) at ≤0.25 µg/mL for susceptible. Breakpoint for VGS was that from *S. anginosus* group (≤0.06 µg/mL for susceptible), while the interpretive criterion for *S. pyogenes* and *S. agalactiae* (≤0.12 µg/mL for susceptible) was applied for ßHS. Breakpoint criteria for comparator agents were those from CLSI (M100-S24, 2014) and EUCAST (2014), as available.
[c] Breakpoint not available.
[d] Susceptibility breakpoints for parenteral penicillin (non-meningitis).
[e] Susceptibility breakpoints for oral penicillin.
BMD = broth microdilution; CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = minimum inhibitory concentration.

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