

# TD-1607 Tested against Well Characterized Resistant Subsets of *Staphylococcus* spp.

F-969

ICAAC 2014

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## ABSTRACT

**Background:** TD-1607 is a novel heterodimer antibiotic composed of a glycopeptide covalently linked to a cephalosporin moiety (glycopeptide-cephalosporin heterodimer, GP-Ceph). TD-1607 possesses potent, bactericidal activity against Gram-positive organisms and exerts its antimicrobial activity through inhibition of cell wall biosynthesis. TD-1607 is currently in clinical development for the treatment of serious Gram-positive infections. We evaluated the *in vitro* activity of TD-1607 when tested against clinical isolates of *S. aureus* and coagulase-negative staphylococci (CoNS) with various antimicrobial resistance phenotypes.

**Methods:** 261 isolates from worldwide surveillance networks were tested for susceptibility by the reference (CLSI) broth microdilution method against TD-1607 and numerous comparison agents.

**Results:** TD-1607 was active against *S. aureus* (MIC<sub>50/90</sub>, 0.03/0.06 µg/mL [Table 1]) and CoNS (MIC<sub>50/90</sub>, 0.03/0.03 µg/mL) strains overall. *S. aureus* isolates with decreased susceptibility to vancomycin exhibited low TD-1607 MIC values (MIC<sub>90</sub>, 0.03-0.06 µg/mL). The highest TD-1607 MIC value observed was 0.12 µg/mL and was observed for a single vancomycin-intermediate *S. aureus* (VISA) isolate. *S. aureus* strains non-susceptible to daptomycin or linezolid were also susceptible to TD-1607 (MIC<sub>90</sub>, 0.03-0.06 µg/mL). TD-1607 was equally active against USA300 and USA100 clones (MIC<sub>90</sub>, 0.03 µg/mL for both groups). *S. aureus* with SCCmec types I and III exhibited slightly higher (MIC<sub>90</sub>, 0.06 µg/mL) TD-1607 MICs when compared to those with SCCmec types II, IV and IVE/F (MIC<sub>90</sub>, 0.03 µg/mL). TD-1607 was generally 32- to 64-fold more active than vancomycin and 16- to 32-fold more active than teicoplanin when tested against these resistant subsets.

**Conclusions:** TD-1607 demonstrated potent *in vitro* activity against a diverse collection of well characterized resistance subsets of *Staphylococcus* spp. TD-1607 MIC<sub>90</sub> values ranged from 0.03 to 0.06 µg/mL and no MIC value was >0.12 µg/mL.

## INTRODUCTION

The treatment of *Staphylococcus aureus* infections continues to represent a great concern to clinicians. Furthermore, accumulating evidence indicates that methicillin-resistant *S. aureus* (MRSA) infections may be associated with a poorer prognosis than methicillin-susceptible *S. aureus* (MSSA) infections, and inappropriate initial antimicrobial therapy can have an important impact in the clinical outcome of MRSA infections. Thus, therapeutic options against these organisms need constant investigation.

TD-1607 is currently in clinical development for the treatment of serious Gram-positive infections. TD-1607 is a novel heterodimer antibiotic composed of a glycopeptide covalently linked to a cephalosporin moiety (glycopeptide-cephalosporin heterodimer, GP-Ceph). TD-1607 inhibits cell wall biosynthesis and possesses potent, bactericidal activity against Gram-positive organisms *in vitro*. We evaluated the *in vitro* activity of TD-1607 when tested against clinical isolates of *S. aureus* and coagulase-negative staphylococci (CoNS) with various antimicrobial resistance phenotypes.

## MATERIALS AND METHODS

**Bacterial isolates:** A total of 261 strains were tested and the organisms were from USA (177; 67.8%), Europe (39 [14.9%] from 12 countries), Latin America (32 [12.3%] from 6 countries) and the Asia-Pacific region (13 [5.0%] from 6 countries).

- *S. aureus* strains with vancomycin MIC values at 2 µg/mL: 43 strains.
- Vancomycin-intermediate *S. aureus* (VISA; 13 strains), hetero-VISA (hVISA; 21 strains) and vancomycin tolerant strains (MBC/MIC ratio of ≥8: 15 strains): 49 strains total.
- Daptomycin-non-susceptible staphylococci: 21 strains (12 *S. aureus* and 9 CoNS).
- Linezolid-non-susceptible staphylococci including those with target mutations (23S, L3, L4) and/or acquired *ctr* gene: 48 strains (12 *S. aureus* and 36 CoNS).
- *S. aureus* from dominant USA clonal types: 50 strains, including USA300 (PVL-positive; 20 strains), USA100 (20 strains), USA200 (2 strains), USA500 (3 strains), USA600 (2 strains), USA700 (1 strain), USA800 (1 strain) and USA1000 (1 strain).
- *S. aureus* harboring different SCCmecA types: 50 strains, including type I (10 strains), type II (10 strains), type III (10 strains), type IV (10 strains) and type IVE/F (10 strains).

**Susceptibility testing:** Susceptibility testing was performed by reference broth microdilution methods (CLSI M07-A9; 2012) using frozen-form MIC panels prepared by JMI Laboratories with cation-adjusted Mueller-Hinton broth. For TD-1607 (lot # AS000261), a stock solution was prepared at 1600 µg/mL by adding powder to sterile phosphate buffer at pH 6.0 (0.01 mol/L). CLSI (M100-S24; 2014) and EUCAST (version 4.0; 2014) interpretive criteria were applied for comparators agents. Quality control was performed per CLSI M07-A9 (2012) and M100-S24 (2014) protocols using *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212.

## RESULTS

- Among *S. aureus* strains with vancomycin MIC values at 2 µg/mL (43 strains), TD-1607 MIC values ranged from 0.015 to 0.06 µg/mL with MIC<sub>50</sub> and MIC<sub>90</sub> of 0.03 and 0.06 µg/mL, respectively (Table 1).
- When tested against VISA strains (13), TD-1607 MIC values ranged from 0.008 to 0.12 µg/mL, with MIC<sub>50</sub> and MIC<sub>90</sub> of 0.06 µg/mL; whereas hVISA strains (21) exhibited TD-1607 MIC values of 0.015 (2 strains [9.5%]), 0.03 (16 strains [76.2%]) and 0.06 µg/mL (3 strains [14.3%]), with MIC<sub>50</sub> and MIC<sub>90</sub> of 0.03 and 0.06 µg/mL, respectively (Table 1).
- The majority of vancomycin tolerant *S. aureus* strains (14/15 or 93.3%) showed a TD-1607 MIC value of 0.03 µg/mL, and the highest MIC value was only 0.06 µg/mL (one strain; Table 1).
- Daptomycin-non-susceptible and linezolid-non-susceptible *S. aureus* strains were very susceptible to TD-1607, with MIC<sub>50/90</sub> values of 0.03/0.03 µg/mL and 0.03/0.06 µg/mL, respectively (Table 1).
- TD-1607 was very active when tested against a collection of *S. aureus* from dominant USA clonal types; the highest TD-1607 MIC value was only 0.03 µg/mL (MIC<sub>50</sub> and MIC<sub>90</sub>, 0.03 µg/mL; Table 1).
- The highest TD-1607 MIC value among *S. aureus* strains harboring SCCmec types II, IV and IVE/F was only 0.03 µg/mL, whereas among *S. aureus* strains with SCCmec types I and III, TD-1607 MIC values ranged from 0.03 to 0.06 µg/mL (Table 1).
- TD-1607 was also very active against daptomycin-non-susceptible and linezolid-non-susceptible CoNS strains, with MIC<sub>50</sub> values of 0.015 and 0.03 µg/mL, respectively (highest MIC, 0.06 µg/mL; Table 1).
- Against the entire *S. aureus* collection (216 strains), TD-1607 (MIC<sub>50</sub>, 0.03 µg/mL and MIC<sub>90</sub>, 0.06 µg/mL) was 32-fold more potent than vancomycin (MIC<sub>50</sub>, 1 µg/mL and MIC<sub>90</sub>, 2 µg/mL) and 16- to 32-fold more active than teicoplanin (MIC<sub>50</sub>, 0.5 µg/mL and MIC<sub>90</sub>, 2 µg/mL; Table 2).
- Overall, 94.0% of *S. aureus* strains were susceptible (CLSI and EUCAST breakpoint criteria) to vancomycin (MIC<sub>50</sub>, 1 µg/mL and MIC<sub>90</sub>, 2 µg/mL), 90.7% to daptomycin (MIC<sub>50</sub>, 0.5 µg/mL and MIC<sub>90</sub>, 1 µg/mL) and 95.8% to linezolid (MIC<sub>50</sub>, 1 µg/mL and MIC<sub>90</sub>, 2 µg/mL). For teicoplanin (MIC<sub>50</sub>, 0.5 µg/mL and MIC<sub>90</sub>, 1 µg/mL), susceptibility rates were 100.0 and 92.1% by CLSI and EUCAST criteria, respectively (Table 2).
- When tested against CoNS (n= 45; including daptomycin-non-susceptible [9] and linezolid-non-susceptible [36]), TD-1607 (MIC<sub>50</sub> and MIC<sub>90</sub>, 0.03 µg/mL) was 64-fold more active than vancomycin (MIC<sub>50</sub> and MIC<sub>90</sub>, 2 µg/mL) and 64- to 256-fold more active than teicoplanin (MIC<sub>50</sub>, 2 µg/mL and MIC<sub>90</sub>, 8 µg/mL; Table 3).

Table 1. MIC distributions for TD-1607 tested against well characterized resistance subsets of *Staphylococcus* spp.

Organism/ subsets	No. of Isolates	MIC (µg/mL)						MIC <sub>50</sub>	MIC <sub>90</sub>
		0.004	0.008	0.015	0.03	0.06	0.12		
<i>Staphylococcus aureus</i>	216	--	1 (0.5)	14 (6.9)	167 (84.3)	33 (99.5)	1 (100.0)	0.03	0.06
Vancomycin MIC of 2 µg/mL	43	--	--	2 (4.7)	31 (76.7)	10 (100.0)	--	0.03	0.06
VISA	13	--	1 (7.7)	1 (15.4)	3 (38.5)	7 (92.3)	1 (100.0)	0.06	0.06
hVISA	21	--	--	2 (9.5)	16 (85.7)	3 (100.0)	--	0.03	0.06
Vancomycin tolerant	15	--	--	--	14 (93.3)	1 (100.0)	--	0.03	0.03
Daptomycin-non-susceptible	12	--	--	1 (8.3)	9 (83.3)	2 (100.0)	--	0.03	0.06
Linezolid-non-susceptible	12	--	--	3 (25.0)	9 (100.0)	--	--	0.03	0.03
USA300	20	--	--	--	20 (100.0)	--	--	0.03	0.03
USA100	20	--	--	2 (10.0)	18 (100.0)	--	--	0.03	0.03
Other USA clones	10	--	--	1 (10.0)	9 (100.0)	--	--	0.03	0.03
SCCmec type I	10	--	--	--	4 (40.0)	6 (100.0)	--	0.06	0.06
SCCmec type II	10	--	--	1 (10.0)	9 (100.0)	--	--	0.03	0.03
SCCmec type III	10	--	--	--	6 (60.0)	4 (100.0)	--	0.03	0.06
SCCmec type IV	10	--	--	1 (10.0)	9 (100.0)	--	--	0.03	0.03
SCCmec type IVE/F	10	--	--	--	10 (100.0)	--	--	0.03	0.03
Coagulase-negative staphylococci	45	1 (2.2)	3 (8.9)	11 (33.3)	26 (91.1)	4 (100.0)	--	0.03	0.03
Daptomycin-non-susceptible	9	--	--	6 (66.7)	1 (77.8)	2 (100.0)	--	0.015	--
Linezolid-non-susceptible	36	1 (2.8)	3 (11.1)	5 (25.0)	25 (94.4)	2 (100.0)	--	0.03	0.03

Abbreviations: VISA: vancomycin-intermediate *S. aureus*; hVISA: heterogeneous VISA.

Table 2. Activity of TD-1607 and comparator antimicrobial agents when tested against 216 isolates of *Staphylococcus aureus*.

Antimicrobial agent	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	CLSI <sup>a</sup> %S / %I / %R	EUCAST <sup>b</sup> %S / %I / %R
TD-1607	0.03	0.06	0.008 – 0.12	- / - / -	- / - / -
Vancomycin	1	2	0.5 – 8	94.0 / 6.0 / 0.0	94.0 / 0.0 / 6.0
Daptomycin	0.5	1	0.25 – 4	90.7 / - / -	90.7 / 0.0 / 9.3
Teicoplanin	0.5	2	0.25 – 8	100.0 / 0.0 / 0.0	92.1 / 0.0 / 7.9
Linezolid	1	2	0.5 – >16	95.8 / 0.0 / 4.2	95.8 / 0.0 / 4.2
Ceftaroline	1	2	0.25 – 4	74.1 / 22.2 / 3.7	74.1 / 0.0 / 25.9
Oxacillin	>4	>4	0.5 – >4	1.4 / 0.0 / 98.6	1.4 / 0.0 / 98.6
Levofloxacin	>4	>4	≤0.12 – >4	13.4 / 0.5 / 86.1	13.4 / 0.5 / 86.1
Trimethoprim/sulfamethoxazole	≤0.12	0.5	≤0.12 – >4	93.1 / 0.0 / 6.9	93.1 / 0.0 / 6.0
Clindamycin	>4	>4	≤0.12 – >4	44.0 / 0.0 / 56.0	43.5 / 0.5 / 56.0
Tetracycline	≤0.5	>16	≤0.5 – >16	87.0 / 1.0 / 12.0	82.9 / 3.2 / 13.9

a. Criteria as published by the CLSI (2014) and EUCAST (2014).

Table 3. Activity of TD-1607 and comparator antimicrobial agents when tested against 45 isolates of coagulase-negative staphylococci<sup>a</sup>.

Antimicrobial agent	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	CLSI <sup>b</sup> %S / %I / %R	EUCAST <sup>b</sup> %S / %I / %R
TD-1607	0.03	0.03	0.004 – 0.06	- / - / -	- / - / -
Vancomycin	2	2	1 – 4	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Daptomycin	0.5	2	0.25 – 4	77.8 / - / -	77.8 / 0.0 / 22.2
Teicoplanin	2	8	0.25 – >8	95.6 / 0.0 / 4.4	86.7 / 0.0 / 13.3
Linezolid	16	>16	0.5 – >16	22.2 / 0.0 / 77.8	22.2 / 0.0 / 77.8
Ceftaroline	0.5	1	≤0.06 – 4	- / - / -	- / - / -
Oxacillin	>4	>4	≤0.06 – >4	22.2 / 0.0 / 77.8	22.2 / 0.0 / 77.8
Levofloxacin	>4	>4	≤0.12 – >4	13.3 / 2.3 / 84.4	13.3 / 2.3 / 84.4
Trimethoprim/sulfamethoxazole	4	>4	≤0.12 – >4	40.0 / 0.0 / 60.0	40.0 / 28.9 / 31.1
Clindamycin	0.5	>4	≤0.12 – >4	53.3 / 24.5 / 22.2	37.8 / 15.5 / 46.7
Tetracycline	1	2	≤0.5 – >16	91.1 / 2.2 / 6.7	68.9 / 22.2 / 8.9

a. Includes: *S. capitis* (5 strains), *S. cohnii* (2 strains), *S. epidermidis* (26 strains), *S. haemolyticus* (3 strains), *S. hominis* (2 strains), *S. pettenkoferi* (2 strains), *S. sciuri* (2 strains), *S. simulans* (2 strains), and *S. warneri* (1 strain).  
b. Criteria as published by the CLSI (2014) and EUCAST (2014).

## CONCLUSIONS

- TD-1607 exhibited potent *in vitro* activity against a large collection (n = 261) of well characterized resistance subsets of *Staphylococcus* spp. TD-1607 MIC<sub>90</sub> values ranged from 0.03 to 0.06 µg/mL and the highest MIC value was 0.12 µg/mL (one VISA strain only).
- TD-1607 was generally 32- to 64-fold more active than vancomycin and 16-fold more active than daptomycin when tested against resistant subsets of *S. aureus* strains.

## ACKNOWLEDGEMENT

This study was sponsored in part by a research grant from Theravance Biopharma Antibiotics, Inc.

## REFERENCES

1. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition*. Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2014). *M100-S24. Performance standards for antimicrobial susceptibility testing: 24th informational supplement*. Wayne, PA: CLSI.
3. Dantes R, Mu Y, Bellflower R, Aragon D, Dumyat G, Harrison LH, Lessa FC, Lynfield R, Nadle J, Petit S, Ray SM, Schaffner W, Townes J, Fridkin S, Emerging Infections Program-Active Bacterial Core Surveillance MSI (2013). National burden of invasive methicillin-resistant *Staphylococcus aureus* infections, United States, 2011. *JAMA Intern Med* 173: 1970-1978.
4. David MZ, Daum RS, Bayer AS, Chambers HF, Fowler VG, Jr., Miller LG, Ostrowsky B, Baesa A, Boyle-Vavra S, Eells SJ, Garcia-Houchins S, Gialanella P, Macias-Gil R, Rude TH, Ruffin F, Sieth JJ, Volinski J, Spellberg B (2014). *Staphylococcus aureus* bacteremia at 5 US academic medical centers, 2008-2011: Significant geographic variation in community-onset infections. *Clin Infect Dis in press*.
5. EUCAST (2014). Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, January 2014. Available at: [http://www.eucast.org/clinical\\_breakpoints/](http://www.eucast.org/clinical_breakpoints/). Accessed January 2014.
6. Gould IM, David MZ, Esposito S, Garau J, Lina G, Mazzei T, Peters G (2012). New insights into methicillin-resistant *Staphylococcus aureus* (MRSA) pathogenesis, treatment and resistance. *Int J Antimicrob Agents* 39: 96-104.
7. Kurosu M, Siricilla S, Mitachi K (2013). Advances in MRSA drug discovery: where are we and where do we need to be? *Expert Opin Drug Discov* 8: 1095-1116.
8. Leuthner KD, Vidailiac C, Cheung CM, Rybak MJ (2010). In vitro activity of the new multivalent glycopeptide-cephalosporin antibiotic TD-1792 against vancomycin-non-susceptible *Staphylococcus* isolates. *Antimicrob Agents Chemother* 54: 3799-3803.