In vitro Activity of Dalbavancin when Tested Against *Streptococcus pneumoniae* Responsible for Documented Infections in Medical Centres in Five Continents Worldwide (2011-2013)

P0704

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ECCMID 2015
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ABSTRACT

Objectives: To assess the dalbavancin *in vitro* activity tested against *S. pneumoniae* clinical isolates collected from hospitalized patients in five continents worldwide. Dalbavancin was approved (May, 2014) by the Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections. The safety and efficacy of dalbavancin will be assessed in a Phase 3 clinical trial for the treatment of community-acquired bacterial pneumonia (CABP).

Methods: A total of 14,097 isolates collected from 90 centres in North America (two countries, 172 centres), Latin America (11 countries, 21 centres), Europe and adjacent areas (22 countries, 57 centres), and Asia-Pacific (APAC) region (13 countries, 39 centres) and South Africa (1 site) were included. Isolates were submitted to a monitoring laboratory as part of the SENTRY Antimicrobial Surveillance Program for 2011-2013. Bacteria were identified by standard algorithms and MALDI-TOF. Susceptibility testing was performed using CLSI approved methods; interpretation of MIC results used CLSI (2014) and EUCAST (2014) criteria for comparators. Isolates were segregated based on penicillin and ceftriaxone MIC values (EUCAST criteria). *S. pneumoniae* displaying a resistance phenotype (MIC, ≥4 mg/L for penicillin) to at least three drug classes were considered as multidrug-resistant (MDR).

Results: Overall, rate of penicillin-non-susceptible isolates (≥0.12 mg/L) was 40.7%, with highest rates in the APAC region (51.1%), followed by Latin America (47.5%), North America (41.4%) and Europe (32.6%). Similar geographic distributions for ceftriaxone-non-susceptibility rates (≥1 mg/L) were observed, with the highest rate in the APAC region (38.4%), while Latin America (25.8%), North America (20.2%) and Europe (18.9%) had lower percentages. While MDR rates were also highest in the APAC region (54.4%), similar rates were noted between the Americas (19.4 – 19.8%) and European region (21.7%). Dalbavancin ($MIC_{50/90}$, ≤0.03/≤0.03 mg/L), vancomycin ($MIC_{50/90}$, ≤0.25/0.5 mg/L) and linezolid ($MIC_{50/90}$, ≤0.5-1/1 mg/L) demonstrated consistent MIC results across different resistance subsets, including MDR. However, dalbavancin MIC values were at least 8-fold lower than vancomycin and linezolid. Ceftriaxone showed lower MIC values against MDR ($MIC_{50/90}$, 1/2 mg/L) compared to non-MDR isolates ($MIC_{50/90}$, ≤0.06/1 mg/L) with susceptibility rates of 39.2 – 62.1% and 90.1 – 98.8% (CLSI and EUCAST criteria), respectively. Vancomycin (100.0% susceptible), linezolid (100.0% susceptible) and levofloxacin ($MIC_{50/90}$, 1/1 mg/L; 96.4% susceptible) were active against the MDR population.

Conclusion: Dalbavancin had potent and consistent *in vitro* activity against this contemporary and worldwide collection of *S. pneumoniae* clinical isolates, including those exhibiting a MDR phenotype. In addition, dalbavancin had potency greater than comparator agents against these populations. These *in vitro* data support the development of dalbavancin for CABP.

INTRODUCTION

Dalbavancin is a novel lipoglycopeptide with documented potency against Gram-positive clinical isolates. Similar to other glycopeptides, dalbavancin binds to the C-terminal position of D-alanyl D-alanine during peptidoglycan formation, which inhibits transglycosylation during cell division and cell wall formation. In addition, dalbavancin contains a lipophilic side chain that assists its anchoring to the cell membrane and increases its activity against Gram-positive cocci overall. This lipophilic side chain is also responsible for prolonging dalbavancin terminal serum half-life to approximately 14 days, and allowing for a convenient two-dose regimen (1000 mg followed by 500 mg one week later).

Dalbavancin was approved in the United States (USA; 2014) and Europe (2015) for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI). Beyond the pathogens associated with ABSSSI, dalbavancin has demonstrated *in vitro* activity against selected anaerobes, cutaneous Gram-positive flora and *Bacillus anthracis*, *Corynebacterium* spp., *Micrococcus* spp., *Listeria monocytogenes* and species of streptococci, including *Streptococcus pneumoniae*. Therefore, due to the dalbavancin spectrum of activity and advantageous pharmacokinetic (PK), dalbavancin is under consideration for other indications, including community-acquired bacterial pneumonia (CABP). This study assessed the dalbavancin *in vitro* activity tested against *S. pneumoniae* clinical isolates collected from hospitalized patients in five continents worldwide.

MATERIALS AND METHODS

Bacterial isolates. A total of 14,097 isolates collected from 90 centres in North America (two countries, 172 centres), Latin America (11 countries, 21 centres), Europe and adjacent areas (22 countries, 57 centres), and Asia-Pacific (APAC) region (13 countries, 39 centres) and South Africa (1 site) were included. Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), as part of the SENTRY Antimicrobial Surveillance Programme (2011–2013). Isolates were initially identified by the participating laboratory and bacterial identifications confirmed by the reference monitoring laboratory by standard algorithms and supported by MALDI–TOF–MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility testing. Isolates were tested for susceptibility by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07–A10 document. Testing was performed using dry–form panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). Quality assurance was performed by concurrent testing of CLSI–recommended quality control reference strain (*S. pneumoniae* ATCC 49619; M100-S25, 2015). All QC results for dalbavancin and comparators were within published acceptable ranges.

Breakpoint criteria for comparator agents were those from CLSI (M100-S25, 2015) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2015). Data analysis was performed against all isolates in aggregate, and also according to the penicillin and ceftriaxone MIC values (EUCAST breakpoint criteria). *S. pneumoniae* displaying a resistance phenotype (MIC, ≥4 mg/L for penicillin used) to at least three drug classes were considered as multidrug-resistant (MDR).

RESULTS

- Overall, the rate of penicillin-non-susceptible isolates (≥0.12 mg/L) was 40.7%, with highest rates in the APAC region (51.1%), followed by Latin America (47.5%), North America (41.4%) and Europe (32.6%; **Figure 1**).
- Similar geographic distributions for ceftriaxone-non-susceptibility rates (EUCAST breakpoint; ≥1 mg/L) were observed, with the highest rate in the APAC region (38.4%), while Latin America (25.8%), North America (20.2%) and Europe (18.9%) had lower percentages.
- When *S. pneumoniae* isolates were stratified according to a MDR phenotype, MDR rates were considerably elevated in the APAC region (54.4%), while similar rates were noted between the Americas (19.4 – 19.8%) and European countries and adjacent region (21.7%).
- Overall, dalbavancin ($MIC_{50/90/100}$, ≤0.03/≤0.03/0.12 mg/L) had low MIC results when tested against the entire collection of isolates, regardless of resistance phenotype to penicillin ($MIC_{50/90/100}$, ≤0.03/≤0.03/0.06 mg/L) or ceftriaxone ($MIC_{50/90/100}$, ≤0.03/≤0.03/0.06 mg/L; **Table 1**).
- Vancomycin ($MIC_{50/90}$, ≤0.25/0.5 mg/L; 100.0% susceptible), linezolid ($MIC_{50/90}$, ≤0.5-1/1 mg/L; 100.0% susceptible), levofloxacin ($MIC_{50/90}$, 1/1 mg/L; 96.4 – 99.3% susceptible) and teicoplanin (≥99.9% susceptible) demonstrated consistent and acceptable (>90% susceptible) coverage across analysed resistance subsets, including MDR (**Table 2**).
- Other comparator drugs, such as erythromycin and clindamycin demonstrated limited *in vitro* antimicrobial coverage, except for clindamycin ($MIC_{50/90}$, ≤0.25/≤0.25 mg/L; 92.4 – 92.8% susceptible) against penicillin-susceptible isolates (**Table 2**).
- Dalbavancin ($MIC_{50/90/100}$, ≤0.03/≤0.03/0.12 mg/L) and vancomycin ($MIC_{50/90/100}$, 0.25/0.5/1 mg/L) were the most active agents tested against this collection of *S. pneumoniae* and resistant subsets. However, dalbavancin MIC values were at least eight-fold lower than vancomycin and linezolid (**Table 2**).
- Ceftriaxone ($MIC_{50/90}$, 1/2 mg/L) showed higher MIC results against MDR *S. pneumoniae* ($MIC_{50/90}$, 1/2 mg/L) compared to non-MDR isolates ($MIC_{50/90}$, ≤0.06/1 mg/L) with susceptibility rates of 39.2 – 62.1% and 90.1 – 98.8% (CLSI and EUCAST criteria), respectively (**Table 2**).

Table 1. Activity and spectrum of dalbavancin against a worldwide collection of *S. pneumoniae* clinical isolates (2011 – 2013).

Phenotype[a] (no. tested)	MIC (mg/L)		Number (cumulative %) inhibited at MIC (mg/L)[b]		
	50%	90%	≤0.03	0.06	0.12
All (14,097)	≤0.03	≤0.03	**13649 (96.8)**	442 (>99.9)	6 (100.0)
PEN-S (MIC, ≤0.06 mg/L; 8364)	≤0.03	≤0.03	**8024 (95.9)**	334 (>99.9)	6 (100.0)
PEN-NS (MIC, ≥0.12 mg/L; 5733)	≤0.03	≤0.03	**5625 (98.1)**	108 (100.0)	
CRO-S (MIC, ≤0.5 mg/L; 10920)	≤0.03	≤0.03	**10525 (96.4)**	389 (>99.9)	6 (100.0)
CRO-NS (MIC, ≥1 mg/L; 3177)	≤0.03	≤0.03	**3124 (98.3)**	53 (100.0)	
MDR (3447)	≤0.03	≤0.03	**3366 (97.7)**	79 (>99.9)	2 (100.0)
Non-MDR (10650)	≤0.03	≤0.03	**10283 (96.6)**	363 (>99.9)	4 (100.0)

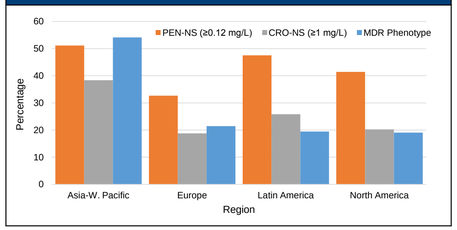
a. Data analysis was performed against all isolates in aggregate and also according to the penicillin and ceftriaxone MIC values (EUCAST breakpoint criteria). PEN-S = penicillin-susceptible; PEN-NS = penicillin-nonsuscceptible; CRO-S = ceftriaxone-susceptible; CRO-NS = ceftriaxone-nonsusceptible. *S. pneumoniae* displaying a resistance phenotype (MIC, ≥4 mg/L for penicillin used) to at least three drug classes were considered as multidrug-resistant (MDR).
b. Modal MIC results are in bold.

Table 2. Antimicrobial activity of dalbavancin and comparator agents against a worldwide collection of *S. pneumoniae* clinical isolates (2011 – 2013).

Phenotype[a] (no. tested)	MIC (mg/L)			% Susceptible/Intermediate/Resistant[b]	
Antimicrobial agent	Range	50%	90%	CLSI	EUCAST
PEN-S (8364)					
Dalbavancin	≤0.03 – 0.12	≤0.03	≤0.03	- / - / -	- / - / -
Penicillin[c]	≤0.06 – 0.06	0.06	0.06	100.0 / 0.0 / 0.0	- / - / -
Penicillin[d]	≤0.06 – 0.06	0.06	0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Erythromycin[e]	≤0.12 – >16	≤0.12	16	79.9 / 0.5 / 19.6	79.9 / 0.5 / 19.6
Clindamycin	≤0.25 – >2	≤0.25	≤0.25	92.4 / 0.4 / 7.2	92.8 / 0.0 / 7.2
Levofloxacin	≤0.12 – >4	1	1	99.3 / 0.1 / 0.6	99.3 / 0.0 / 0.7
Ceftriaxone	≤0.06 – 4	≤0.06	≤0.06	99.9 / 0.1 / <0.1	99.7 / 0.3 / <0.1
Linezolid	≤0.12 – 2	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Tetracycline	≤0.25 – >8	≤0.25	>8	87.6 / 0.4 / 12.0	87.6 / 0.4 / 12.0
Vancomycin	≤0.12 – 1	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – 16	≤2	≤2	- / - / -	>99.9 / 0.0 / <0.1
PEN-NS (5733)					
Dalbavancin	≤0.03 – 0.06	≤0.03	≤0.03	- / - / -	- / - / -
Penicillin[c]	0.12 – >8	1	4	73.4 / 23.5 / 3.1	- / - / -
Penicillin[d]	0.12 – >8	1	4	0.0 / 50.5 / 49.5	0.0 / 73.4 / 26.6
Erythromycin[e]	≤0.12 – >16	16	>16	24.2 / 0.5 / 75.3	24.2 / 0.5 / 75.3
Clindamycin	≤0.25 – >2	≤0.25	>2	52.8 / 0.6 / 46.6	53.4 / 0.0 / 46.6
Levofloxacin	≤0.12 – >4	1	1	98.0 / 0.2 / 1.8	98.0 / 0.0 / 2.0
Ceftriaxone	≤0.06 – >8	1	2	74.8 / 20.5 / 4.7	45.0 / 50.3 / 4.7
Linezolid	≤0.12 – 2	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Tetracycline	≤0.25 – >8	>8	>8	43.2 / 0.3 / 56.5	43.2 / 0.3 / 56.5
Vancomycin	≤0.12 – 1	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – >16	≤2	≤2	- / - / -	99.9 / 0.0 / 0.1
CRO-S (10920)					
Dalbavancin	≤0.03 – 0.12	≤0.03	≤0.03	- / - / -	- / - / -
Penicillin[c]	≤0.06 – 4	≤0.06	0.25	99.9 / 0.1 / 0.0	- / - / -
Penicillin[d]	≤0.06 – 4	≤0.06	0.25	76.4 / 22.7 / 0.9	76.4 / 23.5 / 0.1
Erythromycin[e]	≤0.12 – >16	≤0.12	>16	69.9 / 0.6 / 29.5	69.9 / 0.6 / 29.5
Clindamycin	≤0.25 – >2	≤0.25	>2	86.8 / 0.5 / 12.7	87.3 / 0.0 / 12.7
Levofloxacin	≤0.12 – >4	1	1	99.0 / 0.1 / 0.9	99.0 / 0.0 / 1.0
Ceftriaxone	≤0.06 – 0.5	≤0.06	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Linezolid	≤0.12 – 2	1	1	100.0 / - / -	100.0 / 0.0 / 0.0
Tetracycline	≤0.25 – >8	≤0.25	>8	80.4 / 0.4 / 19.2	80.4 / 0.4 / 19.2
Vancomycin	≤0.12 – 1	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – >16	≤2	≤2	- / - / -	>99.9 / 0.0 / <0.1
CRO-NS (3177)					
Dalbavancin	≤0.03 – 0.06	≤0.03	≤0.03	- / - / -	- / - / -
Penicillin[c]	≤0.06 – >8	4	8	19.5 / 68.4 / 12.1	- / - / -
Penicillin[d]	≤0.06 – >8	4	8	0.6 / 1.8 / 97.6	0.6 / 18.9 / 80.5
Erythromycin[e]	≤0.12 – >16	>16	>16	5.9 / 0.1 / 94.0	5.9 / 0.1 / 94.0
Clindamycin	≤0.25 – >2	>2	>2	19.5 / 0.3 / 80.2	19.8 / 0.0 / 80.2
Levofloxacin	0.5 – >4	1	1	97.5 / 0.2 / 2.3	97.5 / 0.0 / 2.5
Ceftriaxone	1 – >8	2	8	0.0 / 81.1 / 18.9	0.0 / 81.1 / 18.9
Linezolid	≤0.12 – 2	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Tetracycline	≤0.25 – >8	>8	>8	11.9 / 0.3 / 87.8	11.9 / 0.3 / 87.8
Vancomycin	≤0.12 – 1	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – >16	≤2	≤2	- / - / -	99.9 / 0.0 / 0.1
MDR (3447)					
Dalbavancin	≤0.03 – 0.12	≤0.03	≤0.03	- / - / -	- / - / -
Penicillin[c]	≤0.06 – >8	2	4	58.8 / 36.1 / 5.1	- / - / -
Penicillin[d]	≤0.06 – >8	2	4	17.2 / 25.2 / 57.6	17.2 / 41.6 / 41.2
Erythromycin[e]	≤0.12 – >16	>16	>16	0.2 / 0.0 / 99.8	0.2 / 0.0 / 99.8
Clindamycin	≤0.25 – >2	>2	>2	8.7 / 0.3 / 91.0	9.0 / 0.0 / 91.0
Levofloxacin	≤0.12 – >4	1	1	96.4 / 0.3 / 3.3	96.4 / 0.0 / 3.6
Ceftriaxone	≤0.06 – >8	1	2	62.5 / 29.8 / 7.7	39.7 / 52.6 / 7.7
Linezolid	≤0.12 – 2	0.5	1	100.0 / - / -	100.0 / 0.0 / 0.0
Tetracycline	≤0.25 – >8	>8	>8	3.7 / 0.1 / 96.2	3.7 / 0.1 / 96.2
Vancomycin	≤0.12 – 1	0.25	0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Teicoplanin	≤2 – >16	≤2	≤2	- / - / -	99.9 / 0.0 / 0.1

a. Data analysis was performed against all isolates in aggregate and also according to the penicillin and ceftriaxone MIC values (EUCAST breakpoint criteria). *S. pneumoniae* displaying a resistance phenotype (MIC, ≥4 mg/L for penicillin used) to at least three drug classes were considered as multidrug-resistant (MDR).
b. Breakpoint criteria for comparator agents were those from CLSI (M100-S25; 2015) and EUCAST (2015). "-" = breakpoint not available.
c. Susceptibility breakpoints for parenteral penicillin (nonmeningitis).
d. Susceptibility breakpoints for oral penicillin.
e. Predicts susceptibility rates for azithromycin and clarithromycin.

Figure 1. Proportion of penicillin-non-susceptible, ceftriaxone-nonsusceptible and MDR isolates among a worldwide collection of *S. pneumoniae* clinical isolates (2011 – 2013).



CONCLUSIONS

- Dalbavancin had potent and consistent *in vitro* activity against this contemporary and worldwide collection of *S. pneumoniae* clinical isolates, including those exhibiting a MDR phenotype. Dalbavancin inhibited all isolates at ≤0.12 mg/L.
- Dalbavancin and vancomycin were most active agent against resistant strains; albeit, dalbavancin had *in vitro* potency greater than comparator agents against these *S. pneumoniae* populations. These *in vitro* data support the development of dalbavancin for CABP.

ACKNOWLEDGEMENTS

This study was sponsored by an educational/research grant from Durata Therapeutics, a subsidiary of Actavis plc (Branford, Connecticut, United States) via the SENTRY Antimicrobial Surveillance Programme platform.

REFERENCES

1. Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW (2014). Once-weekly dalbavancin versus daily conventional therapy for skin infection. *N Engl J Med* 370: 2169-2179.
2. 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, USA.
3. Clinical and Laboratory Standards Institute (2015). *M100-S25. Performance standards for antimicrobial susceptibility testing: 25th Informational Supplement.* Wayne, PA, USA
4. Dalvance™ Package Insert (2014). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021883s000lbl.pdf. Accessed July 2014.
5. EUCAST (2015). Breakpoint tables for interpretation of MICs and zone diameters. Version 5.0, January 2015. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2015.
6. Jones RN, Flamm RK, Sader HS (2013). Surveillance of dalbavancin potency and spectrum in the United States (2012). *Diagn Microbiol Infect Dis* 76: 122-123.
7. Jones RN, Stilwell MG (2013). Comprehensive update of dalbavancin activity when tested against uncommonly isolated streptococci, *Corynebacterium* spp., *Listeria monocytogenes*, and *Micrococcus* spp. (1357 strains). *Diagn Microbiol Infect Dis* 75: 304-307.
8. Karlowsky JA, Adam HJ, Poutanen SM, Hoban DJ, Zhanel GG; Canadian Antimicrobial Resistance Alliance (CARA) (2011). *In vitro* activity of dalbavancin and telavancin against staphylococci and streptococci isolated from patients in Canadian hospitals: results of the CANWARD 2007-2009 study. *Diagn Microbiol Infect Dis* 69: 342-347.
9. Malabarba A, Goldstein BP (2005). Origin, structure, and activity *in vitro* and *in vivo* of dalbavancin. *J Antimicrob Chemother* 55: ii15-20.