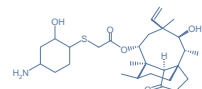


Antimicrobial Activity of BC-3781, an Investigational Pleuromutilin, Tested Against Organisms Isolated From Patients with Community-Acquired Respiratory Tract Infections (CARTI) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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Activity against isolates from ABSSSI (Tables 1 and 3):

- BC-3781 exhibited potent activity against *S. aureus* (MIC_{50/90} 0.12/0.12 µg/mL) with similar MIC distributions among MSSA and MRSA. Only 2 MRSA and 5 MSSA isolates had elevated BC-3781 MIC values (>16 µg/mL) compared to the wild-type population (MIC range, 0.03–0.5 µg/mL). Particularly against MRSA, displaying high resistance rates against macrolides, fluoroquinolones or lincosamides, BC-3781 was the most active compound among those tested.
- Coagulase negative staphylococci were also highly susceptible to BC-3781 (MIC_{50/90} 0.03/0.12 µg/mL), with only 2 isolates having a MIC of ≥16 µg/mL.
- β-hemolytic streptococci including *S. pyogenes* and *S. agalactiae* were highly susceptible to BC-3781 with MIC_{50/90} values of 0.03/0.03 µg/mL and with 99.8% and 100% of isolates being inhibited at ≤0.5 µg/mL, respectively. Among the tested antibiotics BC-3781 was the most active compound being 16- to 32-fold more active than vancomycin (MIC₅₀ 0.5 µg/mL) and linezolid (MIC₉₀ 1 µg/mL).
- BC-3781 displayed also good activity against viridans group streptococci (MIC_{50/90} 0.12/0.05 µg/mL) and *E. faecium* (MIC_{50/90} 0.12/>16 µg/mL) including vancomycin-resistant isolates (MIC_{50/90} 0.12/0.5 µg/mL, data not shown in Tables).

CONCLUSIONS

- BC-3781 demonstrated excellent activity against contemporary pathogens collected worldwide in the course of 2010 SENTRY study from patients with CARTI and ABSSSI including those caused by multidrug-resistant Gram-positive cocci.
- BC-3781 was shown to be one of the most active compounds against the most prevalent respiratory and skin pathogens and its activity was not negatively influenced by resistance to other antimicrobial classes.
- No major difference was noted for the BC-3781 activity by geographic regions.
- There is good evidence (see results of the recently completed clinical Phase II trial; talk L-966, ICAAC 2011) that this potent *in vitro* activity is translated into potent clinical efficacy comparable to that of vancomycin. Further clinical Phase III trials will define the role of BC-3781 for treatment of CARTI and ABSSSI as well as other types of infection.

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Table 1. Frequency of occurrence of BC-3781 MIC values for all CARTI and ABSSSI pathogens tested

Organism (no. isolates)	Cumulative % of isolates inhibited at BC-3781 MIC [µg/mL]						
	0.03	0.06	0.12	0.25	0.5	2	4
CARTI							
<i>H. influenzae</i> (360)	0.3	0.3	0.3	3.3	38.3	86.1	98.3
<i>M. catarrhalis</i> (253)	4.3	6.7	69.2	98.8	100.0	-	-
<i>S. pneumoniae</i> (1473)	4.3	18.0	62.3	95.0	99.8	100.0	-
<i>S. aureus</i> (341)	0.3	41.9	93.0	99.4	100.0	-	-
ABSSSI							
<i>S. aureus</i> (2320)	1.1	42.5	94.0	99.2	99.0	99.7	99.8
CoNS (151)	56.3	88.7	94.0	94.7	95.4	97.4	98.0
β-hemolytic streptococci (401)	93.9	99.0	99.3	99.9	99.9	99.9	99.9
<i>S. pyogenes</i> (159)	98.1	100.0	-	-	-	-	-
<i>S. agalactiae</i> (153)	95.4	99.4	99.35	99.4	99.4	99.4	99.4
Viridans group streptococci (481)	25.0	45.8	2.5	85.4	100.0	-	-
<i>E. faecium</i> (94)	1.19	30.9	63.8	67.0	72.3	76.6	78.7

a. No isolate with this MIC value.

Table 2. Activity of BC-3781 and comparators when tested against organisms isolated from CARTI (n = 2,427)

Antimicrobial agent	MIC ₅₀	MIC ₉₀	Range	CLSI		EUCASAT	
				% S	% R	% S	% R
<i>Streptococcus pneumoniae</i> (1,473) ^a							
BC-3781	0.12	0.25	<0.008–1	-/-	-/-	-/-	-/-
Azithromycin	<0.25	>4	<0.25–>4	62.6/36.6	61.7/37.4	-	-
Ceftriaxone	<0.06	1	<0.06–8	91.3/12	78.0/1.2	-	-
Doxycycline	0.25	8	<0.06–>8	-/-	73.9/25.2	-	-
Erythromycin	<0.06	>8	<0.06–>8	62.8/36.2	62.8/36.2	-	-
Impenem	<0.12	0.5	<0.12–1	79.6/4.4	100.0/0.0	-	-
Levofloxacin	1	1	<0.5–>4	98.9/1.0	98.9/1.1	-	-
Vancomycin	0.25	0.5	<0.12–1	100.0/0	100.0/0.0	-	-
<i>Haemophilus influenzae</i> (360) ^b							
BC-3781	1	2	0.015–8	-/-	-/-	-/-	-/-
Ampicillin	<1	>8	<1–>8	74.4/23.3	74.4/25.6	-	-
Azithromycin	1	2	<0.25–>4	98.3/0	100.0/0.1	-	-
Ceftriaxone	<0.06	>0.06	<0.06–0.5	100.0/0	99.2/0.8	-	-
Doxycycline	0.5	0.5	0.12–2	-/-	98.9/0.0	-	-
Erythromycin	4	8	0.25–>8	-/-	0.3/2.8	-	-
Impenem	0.5	1	<0.12–>4	100.0/0	99.7/0.3	-	-
Levofloxacin	<0.5	>0.5	<0.5–1	100.0/0	100.0/0.0	-	-
<i>Moraxella catarrhalis</i> (253)							
BC-3781	0.12	0.25	<0.008–0.5	-/-	-/-	-/-	-/-
Azithromycin	<0.25	>0.25	<0.25–2	99.6/1	99.6/0.4	-	-
Ceftriaxone	0.25	0.5	<0.06–1	100.0/0	100.0/0.0	-	-
Doxycycline	0.12	0.25	<0.06–4	-/-	99.6/0.4	-	-
Erythromycin	0.25	0.25	<0.06–4	99.6/4	93.5/0.4	-	-
Impenem	<0.12	>0.12	<0.12–0.25	-/-	100.0/0.0	-	-
Levofloxacin	<0.5	>0.5	<0.5–1	100.0/0	100.0/0.0	-	-
<i>Staphylococcus aureus</i> (341) ^b							
BC-3781	0.12	0.12	0.03–0.5	-/-	-/-	-/-	-/-
Daptomycin	<0.25	>2	<0.25–>2	76.5/22.8	75.4/23.5	-	-
Doxycycline	0.12	0.25	<0.06–8	97.9/10.0	95.6/3.9	-	-
Erythromycin	>4	>4	<0.25–>4	43.7/54.4	43.7/55.1	-	-
Levofloxacin	<0.5	>4	<0.5–>4	61.0/38.4	61.0/38.4	-	-
Linezolid	1	1	0.5–2	100.0/0.0	100.0/0.0	-	-
Oxacillin	0.5	>2	<0.25–>2	63.0/37.0	63.0/37.0	-	-
Vancomycin	1	1	0.5–2	100.0/0.0	100.0/0.0	-	-

a. 38.7% non-susceptible to penicillin; b. 23.6% β-lactamase positive; c. 37% MRSA.

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Table 3. Activity of BC-3781 and comparators when tested against organisms isolated from ABSSSI (n = 3,014)

Antimicrobial agent	MIC ₅₀	MIC ₉₀	Range	CLSI		EUCASAT	
				% S	% R	% S	% R
<i>Staphylococcus aureus</i> (2,320) ^a							
BC-3781	0.12	0.12	0.015–>16	-/-	-/-	-/-	-/-
Clinidamycin	<0.25	>2	<0.25–>2	85.6/14.3	85.3/14.4	-	-
Doxycycline	0.12	0.25	<0.06–>8	98.0/0.3	95.0/3.1	-	-
Erythromycin	4	>4	<0.25–>4	49.2/49.4	49.2/50.1	-	-
Levofloxacin	<0.5	>4	<0.5–>4	66.4/31.9	66.4/31.9	-	-
Linezolid	1	1	<0.12–>4	100.0/0.0	100.0/0.0	-	-
Oxacillin	0.5	>2	<0.25–>2	55.0/45.0	55.0/45.0	-	-
Vancomycin	1	1	0.25–2	100.0/0.0	100.0/0.0	-	-
<i>Coagulase-negative staphylococci</i> (151)							
BC-3781	0.03	0.12	<0.008–>16	-/-	-/-	-/-	-/-
Clinidamycin	<0.25	>2	<0.25–>2	70.2/28.5	69.5/29.8	-	-
Doxycycline	0.12	1	<0.06–8	95.4/0.0	90.1/6.0	-	-
Erythromycin	>4	>4	<0.25–>4	43.3/56.0	43.3/56.7	-	-
Levofloxacin	<0.5	>4	<0.5–>4	57.6/38.4	57.6/38.4	-	-
Linezolid	0.5	1	<0.12–1	100.0/0.0	100.0/0.0	-	-
Oxacillin	2	>2	<0.25–>2	33.8/66.2	33.8/66.2	-	-
Vancomycin	1	1	0.25–4	100.0/0.0	98.7/1.3	-	-
<i>β-hemolytic streptococci</i> (401)							
BC-3781	0.03	0.03	<0.008–16	-/-	-/-	-/-	-/-
Clinidamycin	<0.25	>2	<0.25–>2	88.3/11.5	88.5/11.5	-	-
Doxycycline	0.25	8	<0.06–>8	-/-	53.6/45.1	-	-
Erythromycin	<0.25	>4	<0.25–>4	78.6/20.9	78.6/20.9	-	-
Levofloxacin	<0.1	>1	<0.25–>4	99.0/0.2	95.3/1.0	-	-
Linezolid	1	1	0.5–1	100.0/0	100.0/0.0	-	-
Vancomycin	0.25	0.5	0.25–0.5	100.0/0	100.0/0.0	-	-
<i>S. pyogenes</i> (159)							
BC-3781	0.03	0.03	0.015–0.06	-/-	-/-	-/-	-/-
Clinidamycin	<0.25	>2	<0.25–>2	95.6/4.4	95.6/4.4	-	-
Doxycycline	0.12	8	<0.06–>8	-/-	93.8/15.1	-	-
Erythromycin	<0.25	>2	<0.25–>4	91.8/8.2	91.8/8.2	-	-
Levofloxacin	<0.5	1	<0.5–>4	98.1/0.6	90.6/1.9	-	-
Linezolid	1	1	0.5–1	100.0/0	100.0/0.0	-	-
Vancomycin	0.25	0.5	0.25–0.5	100.0/0	100.0/0.0	-	-
<i>S. agalactiae</i> (153)							
BC-3781	0.03	0.03	0.015–16	-/-	-/-	-/-	-/-
Clinidamycin	<0.25	>2	<0.25–>2	77.8/21.6	78.4/21.6	-	-
Doxycycline	8	>8	<0.06–>8	-/-	13.7/85.0	-	-
Erythromycin	<0.25	>4	<0.25–>4	64.1/34.6	64.1/34.6	-	-
Levofloxacin	<0.5	1	<0.5–2	100.0/0.0	98.7/0.0	-	-
Linezolid	1	1	0.5–1	100.0/0	100.0/0.0	-	-
Vancomycin	0.5	0.5	0.25–0.5	100.0/0	100.0/0.0	-	-
<i>Viridans group streptococci</i> (48)							
BC-3781	0.12	0.5	<0.008–0.5	-/-	-/-	-/-	-/-
Clinidamycin	<0.25	>2	<0.25–>2	89.6/10.4	89.6/10.4	-	-
Erythromycin	<0.25	>4	<0.25–>4	58.3/39.6	-/-	-	-
Levofloxacin	<0.5	2	<0.5–>4	95.8/4.2	-/-	-	-
Linezolid	1	1	0.5–2	100.0/0	-/-	-	-
Penicillin	0.06	1	<0.03–>4	83.3/4.2	89.6/4.2	-	-
Vancomycin	0.5	0.5	<0.12–1	100.0/0	100.0/0.0	-	-
<i>Enterococcus faecium</i> (94)							
BC-3781	0.12	>16	0.03–>16	-/-	-/-	-/-	-/-
Daptomycin	2	2	<0.06–>4	100.0/0	-/-	-	-
Doxycycline	0.25	>8	<0.06–>8	60.5/30.9	-/-	-	-
Erythromycin	>4	>4	<0.25–>4	1–34	6.4/92.6	-	-
Linezolid	1	2	0.5–8	98.9/1.1	98.9/1.1	-	-
Penicillin	>4	>4	<0.25–>4	100.0/0.0	-/-	-	-
Quinupristin/dalfopristin	<0.5	4	<0.5–>4	77.7/10.6	77.7/10.6	-	-
Tigecycline	0.12	0.25	<0.03–0.25	100.0/0	100.0/0.0	-	-
Vancomycin	1	>16	0.25–>16	64.9/35.1	64.9/35.1	-	-

a. 45% MRSA.

The objective of this study was to assess the *in vitro* activity of BC-3781 tested against a worldwide contemporary collection of isolates from CARTI and ABSSSI within the SENTRY Antimicrobial Surveillance Platform in 2010.

MATERIALS & METHODS

Organism collection: The activity of BC-3781 was determined against bacterial pathogens causing ABSSSI and CARTI including *S. aureus*, Group A and B streptococci, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* among others. Unique patient isolates were collected within the SENTRY Surveillance