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isolated from CARTI (n = 2,427)

ABSTRACT

Background: BC-3781 is an investigational semi-synthetic pleuromutilin derivative that inhibits ribosomal protein synthesis. BC-3781 is being developed for both IV and oral treatment by Nabriya Therapeutics AG. We tested BC-3781 against contemporary (2010) bacterial isolates causing community-acquired respiratory tract (CARTI) and acute bacterial skin and skin structure (ABSSSI) infections collected within the SENTRY Antimicrobial Surveillance Program platform.

Infections (ABSSSI)

Methods: Unique patient strains were collected in 84 medical centers worldwide (29 countries), including 2427 organisms from CARTI and 3014 from ABSSSI, BC-3781 and 14 comparators were susceptibility (S) tested by CLSI broth microdilution methods

Results: When tested against ABSSSI strains, BC-3781 exhibited potent activity against S. aureus (MIC₉₀, 0.12 µg/mL) and had similar MIC values among oxacillin-S (MSSA) and -R (MRSA) strains. Only 2 MRSA isolates among oxacillin-s (MSSA) and - R (MRSA) strains. Unity 2 MRSA Isolates (0.2%) had elevated BC-3781 MICs (2 and 4 µg/mL) compared to the wild-type population (MIC range, 0.03-0.5 µg/mL). MIC_{\$2009} values for coagulase-negative staphylococci were 0.03/0.12 µg/mL with only 2 isolates having a MIC of ≥16 µg/mL BC-3781 showed greater activity against vancomycin (VAN)-R (MICg., 0.5 µg/mL) than VAN-S (MIC90, >16 µg/mL). E. faecium. \$\beta\$-immorphytic, and viridans group streptococci were highly susceptible to BC-3781 with 99.8 and 100% of isolates inhibited at ≤0.5 µg/mL, respectively. BC-3781 activity tested against isolates from CARTI is summarized in the Table.

Conclusions: BC-3781 showed potent activity against contemporary organisms isolated worldwide from patients with CARTI and ABSSSI, and its activity was not negatively influenced by R to other antimicrobial classes. Results from ongoing clinical trials will define the role of BC-3781 for treatment CARTI and ABSSSI as well as other types of

Organism BC-37		3781	781 Ceftriaxon		Erythrom	Levofloxacin		
(no. tested)	MIC ₅₀₅₀ a	Range*	MIC _{50/90} *	%S⁵	MIC _{50/90} a	%S ^b	MIC _{50/90} a	%S⁵
SPN (1473)	0.12 / 0.25	≤0.008-1	≤0.06 / 1	91.3	≤0.06 / >8	62.8	1/1	98.9
S. aureus (341)	0.12 / 0.12	0.03-0.5	-	63.0°	>4/>4	43.7	≤0.5/>4	61.0
HI (360)	1/2	0.015-8	≤0.06 / ≤0.06	100.0	4/8	-	≤0.5 / ≤0.5	100.0
MCAT (253)	0.12 / 0.25	≤0.008-0.5	0.25 / 0.5	100.0	0.25 / 0.25	99.6	≤0.5 / ≤0.5	100.0

INTRODUCTION

Pleuromutilin antibiotics are a new class of antibiotics for human use selectively inhibiting bacterial protein synthesis by specific interaction with the 50S ribosomal subunit, BC-3781 is a novel semi-synthetic pleuromutilin derivative developed by Nabriva Therapeutics AG with excellent antibacterial spectrum targeting the most important Gram-positive skin pathogens as well as Grampositive and -negative respiratory pathogens. It is the first-in-class pleuromutilin derivative being developed for systemic treatment of infections in human including acute bacterial skin and skin structure infections (ABSSSI) and respiratory tract infections (RTI). BC-3781 is at an advanced stage of clinical development (completed clinical Phase II: talk L-966, ICAAC 2011) and has the potential for oral and IV treatment of CARTI, including communityacquired bacterial pneumonia and atypical pneumonia, and ABSSSI including those caused by multidrug-resistant Gram-positive cocci

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 Program during 2010 in 84 medical centers worldwide (29 countries), including 2.427 organisms from CARTI and 3.014 from ABSSSI

Susceptibility test methods: MIC values of ABSSSI and CARTI pathogens were determined according to CLSI guidelines (M07-A8, 2009) using validated microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth (with 2.5-5% lysed horse blood added for testing of streptococci or Haemophilus Test Medium for testing H. influenzae), Interpretive criteria for comparator agents were used as published by CLSI (2011) and EUCAST (2011). Quality control was performed as recommended by the CLSI using the following strains: S. aureus ATCC 29213. S. pneumoniae ATCC 49619, H. influenzae ATTC 49247 and E. faecalis ATCC 29212.

RESULTS

Activity against isolates from CARTI (Tables 1 and 2):

- Against S. pneumoniae. BC-3781 was the most active compound with MIC_{50/90} values of 0.12/0.25 µg/mL. BC-3781 was four- to eight-fold more active than levofloxacin (MICso/oo. 1/1 µg/mL) and inhibited strains resistant to the other tested antibiotics independent of susceptibility to penicillin. macrolides or fluoroquinolones. High rates of resistance were observed for azithromycin (35.8%), trimethoprim/ sulfamethoxazole (23.2%) and doxycycline (25.2%).
- BC-3781 also displayed potent activity against the Gramnegative organisms *H. influenzae* (MIC_{50/90} 1/2 µg/mL), independent of β -lactamase production (23.6% of H. influenzae isolates were β -lactamase positive) and M. catarrhalis (MIC_{50/90} 0.12/0.25 µg/mL)
- Against S. aureus (including 37.0% MRSA) BC 3781 was the most active compound with MIC_{50/90} values of 0.12/0.12 µg/ml (range ≤0.03-0.5 µg/mL). BC-3781 was fourto eight-fold more active than linezolid and vancomycin (MIC_{50/90} 1/1 μg/mL). High rates of resistance were observed among MRSA for macrolides (88.9%), fluoroguinolones (86.5%) and lincosamides (48.4%), all being inhibited by BC-3781 (data not shown in Tables)

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

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Organism	Cumulative % of isolates inhibited at BC-3781 MIC [µg/mL									
(no. isolates)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>8	
CARTI										
H. influenzae (360)	0.3	0.3	0.3	3.3	38.3	86.1	98.3	99.4	100.	
M. catarrhalis (253)	4.3	6.7	69.2	98.8	100.0	-	-	-	-	
S. pneumoniae (1473)	4.3	18.0	62.3	95.0	99.8	100.0	-			
S. aureus (341)	0.3	41.9	93.0	99.4	100.0		-			
ABSSSI										
S. aureus (2320)	1.1	42.5	94.7	99.2	99.70	99.7	99.8	99.8	100.	
CoNS (151)	56.3	88.7	94.0	94.7	95.4	97.4	98.0	98.7	100.	
β-hemolytic streptococci (401)	93.8	99.00	99.3	99.8	99.8	99.8	99.8	99.8	100.	
S. pyogenes (159)	98.1	100.0	-	-	-	-			-	
S. agalactiae (153)	95.4	99.4	99.35	99.4	99.4	99.4	99.4	99.4	100.	
Viridans group streptococci (481)		45.8	2.5	85.4	100.0	-			-	
E. faecium (94)	1.19	30.9	63.8	67.0	72.3	76.6	78.7	78.7	100.	
a No isolate with this MIC value.										

Table 2. Activity of BC-3781 and comparators when tested against organisms

MIC., MIC., Range CLSI EUCAST

Antimicrobiai agent	WIIC ₅₀	mic ₉₀	Range	%S / %R	%S / %R
Streptococcus pneumoniae (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.
Ceftriaxone	≤0.06	1	≤0.06 - 8	91.3 / 1.2	78.0 / 1.2
Doxycycline	0.25	8	≤0.06 ->8	-/-	73.9 / 25.
Erythromycin	≤0.06	>8	≤0.06 ->8	62.8 / 36.2	62.8 / 36.
Imipenem	≤0.12	0.5	≤0.12 – 1	79.6 / 4.4	100.0 / 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 / -	100.0 / 0.
Haemophilus influenzae (360) ^b					
BC-3781	1	2	0.015 - 8	-/-	-/-
Ampicillin	≤1	>8	≤1 - >8	74.4 / 23.3	74.4 / 25.
Azithromycin	1	2	≤0.25 - >4	98.3 / -	0.0 / 1.7
Ceftriaxone	≤0.06	≤0.06	≤0.06 - 0.5	100.0 / -	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
Imipenem	0.5	1	≤0.12 – 4	100.0 / -	99.7 / 0.3
Levofloxacin	≤0.5	≤0.5	⊴0.5 – 1	100.0 / -	100.0 / 0.
Moraxella catarrhalis (253)					
BC-3781	0.12	0.25	≤0.008 - 0.5	-/-	-/-
Azithromycin	≤0.25	≤0.25	≤0.25 – 2	99.6 / -	99.6 / 0.4
Ceftriaxone	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.
Doxycycline	0.12	0.25	≤0.06 – 4	-/-	99.6 / 0.4
Erythromycin	0.25	0.25	≤0.06 – 4	99.6 / -	93.5 / 0.4
Imipenem	⊴0.12	≤0.12	≤0.12 - 0.25	-/-	100.0 / 0.
Levofloxacin	≤0.5	≤0.5	⊴0.5 – 1	100.0 / -	100.0 / 0.
Staphylococcus aureus (341) ^c					
BC-3781	0.12	0.12	0.03 - 0.5	-/-	-/-
Clindamycin	≤0.25	>2	≤0.25 ->2	76.5 / 22.6	75.4 / 23.
Doxycycline	0.12	0.25	≤0.06 – 8	97.9 / 0.0	95.6 / 3.8
Erythromycin	>4	>4	≤0.25 ->4	43.7 / 54.3	43.7 / 55.
Levofloxacin	≤0.5	>4	≤0.5 ->4	61.0 / 38.4	61.0 / 38.
Linezolid	1	1	0.5 - 2	100.0 / 0.0	100.0 / 0.
Oxacillin	0.5	>2	≤0.25 ->2	63.0 / 37.0	63.0 / 37.
Vancomycin a. 38.7% non-susceptible to penicillin: b. 23.6	1	1	0.5 - 2	100.0 / 0.0	100.0 / 0.

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	%S / %R	%S / %R
Staphylococcus aureus (2,320) ^a					
BC-3781	0.12	0.12	0.015 - >16	-/-	-/-
Clindamycin	⊴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
Coagulase-negative staphylococci (BC-3781	0.03	0.12	≤0.008 - >16	-/-	-/-
Clindamycin	<0.25	>2	≤0.006 ->16	70.2 / 28.5	69.5 / 29.8
Doxycycline	0.12	1	≤0.25 - >2	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	2	0.25 - 4	100.0 / 0.0	98.7 / 1.3
β-hemolytic streptococci (401) BC-3781	0.03	0.03	<0.008 – 16	-/-	-/-
Clindamycin	<0.25	>2	<0.25 - >2	88.3 / 11.5	88.5 / 11.5
Doxycycline	0.25	8	≤0.25 - >2	-/-	53.6 / 45.1
Erythromycin	<0.25	>4	<0.25 - >4	78.6 / 20.9	78.6 / 20.9
Levofloxacin	<0.5	1	≤0.5 - >4	99.0 / 0.2	95.3 / 1.0
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	0.5 - 0.5	100.0 / -	100.0 / 0.0
S. pyogenes (159)	0.20	0.0	0.20 0.0	100.07	100.07 0.0
BC-3781	0.03	0.03	0.015 - 0.06	-/-	-/-
Clindamycin	≤0.25	≤0.25	≤0.25 - >2	95.6 / 4.4	95.6 / 4.4
Doxycycline	0.12	- 8	<0.06 ->8	-/-	83.6 / 15.1
Erythromycin	< 0.25	< 0.25	≤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 / -	100.0 / 0.0
Vancomycin	0.25	0.5	0.25 - 0.5	100.0 / -	100.0 / 0.0
S. agalactiae (153)					
BC-3781	0.03	0.03	0.015 - 16	-/-	-/-
Clindamycin	≤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 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 - 0.5	100.0 / -	100.0 / 0.0
Viridans group streptococci (48)					
BC-3781	0.12	0.5	≤0.008 – 0.5	-/-	-/-
Clindamycin Erythromycin	≤0.25 <0.25	>2 >4	≤0.25 - >2 <0.25 - >4	89.6 / 10.4 58.3 / 39.6	89.6 / 10.4
Levofloxacin		2		95.8 / 4.2	-/-
Linezolid	≤0.5 1	1	≤0.5 - >4 0.5 - 2	100.0 / -	-/-
Penicillin	0.06	1	0.5 - 2 ≤0.03 - 4	83.3 / 4.2	89.6 / 4.2
Vancomycin	0.06	0.5	≤0.03 = 4	100.0 / -	100.0 / 0.0
Enterococcus faecium (94)	0.5	0.5	50.12 − 1	100.07 -	100.07 0.0
BC-3781	0.12	>16	0.03 ->16	-/-	-/-
Daptomycin	2	2	<0.06 - 4	100.0 / -	-/-
Doxycycline	0.25	>8	≤0.06 - >8	60.6 / 30.9	-/-
Levofloxacin	>4	>4	1->4	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 / 0.0
Tigecycline	0.12	0.25	<0.03 - 0.25	100.0 / -	100.0 / 0.0
Vancomycin	1	>16	0.25 - >16	64.9 / 35.1	64.9 / 35.1
a. 45% MRSA:					

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

- BC-3781 exhibited potent activity against S. aureus (MIC_{sox} 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 (2->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 solor 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 (MIC₀₀ 0.5 µg/mL) and linezolid (MIC₀₀ 1 µg/mL)
- BC-3781 displayed also good activity against viridans group streptococci (MIC_{50/90} 0.12/0.5 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 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
- . 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

trials will define the role of BC-3781 for treatment of CARTI

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 II

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and ABSSSI as well as other types of infection.

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