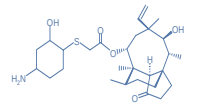
L1-1660

Microbiological Activity and Outcome of the Pleuromutilin BC-3781 in a Clinical Phase 2 Trial in Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

S PAUKNER[1], Z IVEZIC-SCHOENFELD[1], KJ TACK[3], D SAHM[2], WT PRINCE[1]

[1] Nabriva Therapeutics AG, Vienna, Austria; [2] Eurofins Medinet Ltd, VA, USA; [3] Brighton MI, USA

BC-3781



Nabriva Therapeutics AG
Leberstrasse 20
A-1110 Vienna
Austria
www.nabriva.com
+43-1-74093-0
susanne.paukner@nabriva.com

ABSTRACT

Background: The novel pleuromutilin antibiotic BC-3781 has completed the first clinical phase 2 study in patients with severe ABSSSI caused by Gram-positive (G+) pathogens. We present the antibacterial *in vitro* activity of BC-3781 and comparators against the collected isolates and the microbiological responses in patients treated with BC−3781 (100 and 150 mg i.v. q12h) in comparison to vancomycin (VAN, ≥1 g bid).

Methods: Susceptibility testing of BC-3781, VAN and other antibiotics was performed by broth microdilution according to CLSI guidelines. All *S. aureus* were evaluated for the presence of PVL. PFGE typing was performed for all MRSA.

Microbiological evaluation was performed at test-of-cure with eradication defined as absence of the target organism or of evaluable material to culture in a patient with clinical cure.

Results: From 207 patients enrolled, 156 G+ baseline pathogens were isolated from the infection site or blood culture: 87.8% *S. aureus* (76.6% MRSA; 97.1% PVL positive; 68.9% USA300), 4.5% *S. pyogenes*, 3.2% *S. agalactiae*, 2.6% Group C, F, G *Streptococcus* spp. and 1.9% viridans group *Streptococcus* spp. BC-3781 displayed very good antibacterial activity *in vitro* with $MIC_{50/90}$ against *S. aureus* of 0.12/0.25 µg/ml (VAN $MIC_{50/90}$ 1/1 µg/ml; 69.3% macrolide resistant). Against *Streptococcus* spp. BC−3781 showed $MIC_{50/90}$ of ≤0.03/0.06 µg/ml (VAN $MIC_{50/90}$ 0.5/0.5 µg/ml). No resistance development was observed for BC-3781 or VAN during the study.

BC-3781 demonstrated very good activity with overall microbiological eradication rates of 80.0% and 84.3% (modified intent-to-treat population) at doses of 100 mg and 150 mg correlating well with the clinical success rates. For MRSA in particular, eradication rates for BC-3781 were 82.4% and 87.5% (100 and 150 mg). These were comparable to VAN with eradication rates of 82.4% and 82.1%.

Conclusions: BC-3781 demonstrated potent clinical and microbiological efficacy in this clinical trial reflecting its excellent antibacterial activity *in vitro*.

INTRODUCTION

Acute bacterial skin and skin structure infections (ABSSSI) are characterized by a wide range of disease presentations including wound infection, cellulitis/erysipelas, cutaneous abscesses and burn infections. The majority of these infections are caused by Gram-positive bacteria such as *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), and the ß-hemolytic *Streptococcus pyogenes* and *Streptococcus agalactiae*. Resistance development to commonly used antibacterial agents constantly increases the medical need for new agents overcoming this problem.

BC-3781 is a novel semi-synthetic pleuromutilin antibiotic acting, like other pleuromutilin antibacterials, at the peptidyl transferase centre of the large ribosomal subunit thereby inhibiting protein synthesis. *In vitro*, BC-3781 demonstrated potent activity against *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus faecium*, *Haemophilus influenzae* and other atypical respiratory pathogens including multi-resistant strains. It is therefore being developed for treatment of ABSSSI and community-acquired bacterial pneumonia (CABP) as an intravenous/oral switch therapy.

This study presents the microbiological results of the clinical phase 2 trial in patients with severe ABSSSI caused by Gram-positive pathogens treated with 100 or 150 mg i.v. (q12h) BC−3781 for 5-14 days in comparison to vancomycin (VAN, ≥1 g, q12h).

MATERIALS & METHODS

The clinical phase 2 trial was a multi-center, double-blind, parallel-group study involving 210 patients. The microbiological outcome was assessed at test of cure (TOC; 7-14 days post end of treatment) for the modified intent to treat (MITT) and the microbiological evaluable (ME) populations. The MITT population was defined as patients (n = 152) who had a documented Gram-positive pathogen culture at baseline. The ME population was defined as patients (n = 129) with a confirmed diagnosis of ABSSSI who had received at least 80% of the study medication, had a response assessment at TOC and a baseline Gram-positive pathogen recovered from pretreatment cultures. Eradication was defined as a negative culture for the target organism or lack of evaluable material to culture in a patient with clinical cure (presumed eradication).

Bacterial isolates were collected from biopsies or blood cultures by local laboratories. Identification to species level (by classical bacteriological means), MIC testing and further characterization was done by a central laboratory (Eurofins Medinet Ltd, VA, USA).

MIC values of BC-3781 and comparators were determined by broth microdilution according to the CLSI (M7-A8, M100-S20) using Sensititre® panels manufactured by Trek Diagnostics Inc. (Thermo Fisher Scientific). Concurrent MIC testing of QC organisms was performed using *S. aureus* ATCC29213, *S. pneumoniae* ATCC 49619 and preliminary QC limits as approved by the CLSI and published earlier.[3]

All *S. aureus* isolates were evaluated for the presence of Panton-Valentine leukocidin (PVL) and *mecA* using multiplex PCR.[1] All MRSA were evaluated by PFGE to test the relatedness of clinical trial isolates overall and relative to the USA typing strains USA100-1100 using a >80% cutoff for relatedness.[2] Intrapatient relatedness was determined based on variation in pattern essentially as described earlier.[4]

RESULTS

Baseline Infection Characteristics

- The baseline infection characteristics of the clinically evaluable and MITT populations are summarized in Figure 1 and Figure 2.
- The primary infection type was cellulitis followed by abscess with cellulitis and wound infection (Figure 1).
- Overall, 74.9% of patients (ITT) had a bacterial pathogen and 97.4% of these had a Gram-positive pathogen isolated at baseline (pre-treatment). The most common pathogen isolated from the primary infection site and blood was *S. aureus* (90.8% of MITT patients) with 69.1% of patients having a MRSA (Figure 2).
- The majority of *S. aureus* isolates were positive for PVL (97.1% of MRSA and 56.3% if MSSA) and the most prevalent USA subtype among MRSA was USA300 (68.9%). 31.1% of isolates were non-USA type.

Antibacterial Activity of BC-3781 and Comparators

- BC-3781 demonstrated potent antibacterial activity against the isolated bacterial baseline pathogens with $MIC_{50/90}$ values of 0.12/0.25 µg/ml against *S. aureus* (VAN $MIC_{50/90}$, 1/1 µg/ml) and ≤0.03/0.06 µg/ml against *Streptococcus* spp. (VAN $MIC_{50/90}$, 0.5/0.5 µg/ml). (Table 1)
- BC-3781 was fully active against isolates being resistant to macrolides, fluoroquinolones or lincosamides (Table 1).
- No resistance development (≥ 4-fold increase from baseline MIC) was observed for BC-3781 or VAN during the study.
- 100% of the *S. aureus* and *S. pneumoniae* QC results of BC-3781 MIC testing (MITT) were within the specified QC ranges (0.06-0.25 µg/ml and 0.06-0.5 µg/ml, respectively)

Figure 1. Baseline Infection Characteristics for the CE population (n = 165)

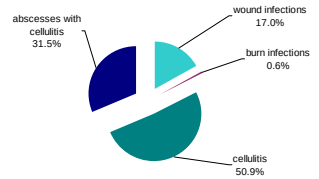
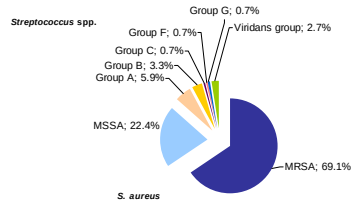


Figure 2. Key Baseline Pathogens in the MITT Population (n = 152)



Microbiological and Clinical Outcome

- BC-3781 100 mg and 150 mg demonstrated consistently high efficacy rates across a wide range of microbiological and clinical outcomes at several time points including TOC (7-14 days post completion of therapy). Microbiological eradication and clinical success rates at TOC for the MITT and ME population for all pathogens, *S. aureus*, and separately MRSA, are summarized in Table 2.
- Overall, the clinical success rates for BC-3781 100 and 150 mg at TOC by baseline pathogen were with 90.0% and 88.9% (CE) similar to those for the vancomycin group (92.2%). Similarly, the clinical success rates for the MITT population were 82.0% and 82.4% for BC-3781 100 mg and 150 mg, respectively being again similar to that of vancomycin (82.4%).
- BC-3781 displayed microbiological eradication rates of 80.0% and 84.3% at doses of 100 mg and 150 mg, respectively (MITT) and 84.8% and 90.7%, respectively (ME) being comparable to those of vancomycin (82.4%, MITT; 95.0% ME), and correlating well with the clinical success rates.
- For MRSA (with the majority of isolates being PVL-positive) in particular, microbiological eradication rates for BC-3781 100 mg and 150 mg were 82.4% (MITT; ME, 84.4%) and 87.5% (MITT; ME, 92.6%) comparable to those of vancomycin (MITT, 82.1%; ME, 93.5%). This correlated well with the clinical success rates of 85.3% and 87.5% for BC-3781 100 and 150 mg (MITT; VAN, 82.1%).
- Against MRSA USA300 BC-3781 100 mg and 150 mg displayed good clinical success rates of 84.0% and 94.7% for the MITT population and 87.0% and 94.1% for the ME population, compared to those for vancomycin (MITT, 77.8%; ME, 90.0%).

Table 1. $MIC_{50/90}$ [µg/ml] of BC-3781 and Comparators Against Key Baseline Pathogens (MITT)

Species/ Antibiotic Agent	MIC_{50}	MIC_{90}	Range	%S[a]	%R[a]
S. aureus (137)					
BC-3781	0.12	0.25	0.12-0.5	-	-
Amoxicillin / Clavulanic acid	>4	>4	0.12 - >4	34.3	57.7
Azithromycin	>8	>8	0.5->8	25.5	69.3
Clindamycin	0.12	0.25	0.12->4	97.8	2.2
Daptomycin	0.5	1	0.25-1	100.0	0.0
Doxycycline	0.25	0.25	≤0.12-4	100.0	0.0
Linezolid	2	2	0.25-4	100.0	0.0
Moxifloxacin	1	2	≤0.03->4	44.5	25.5
Oxacillin	>4	>4	0.25->4	27.0	73.0
Tigecycline	0.12	0.25	0.06-0.5	-	-
Vancomycin	1	1	0.5-1	100.0	0.0
MRSA (105)					
BC-3781	0.12	0.25	0.12-0.5	-	-
Amoxicillin / Clavulanic acid	>4	>4	0.25 - >4	14.3	75.2
Azithromycin	>8	>8	1->8	13.3	82.9
Clindamycin	0.12	0.25	0.12->4	97.1	2.9
Daptomycin	0.5	1	0.25-1	100.0	0.0
Doxycycline	0.25	0.25	≤0.12-4	100.0	0.0
Linezolid	2	2	0.25-4	100.0	0.0
Moxifloxacin	1	2	≤0.03->4	38.1	28.6
Oxacillin	>4	>4	0.25->4	4.8	95.2
Tigecycline	0.12	0.25	0.06-0.5	-	-
Vancomycin	1	1	0.5-1	100.0	0.0
S. agalactiae (5)					
BC-3781	-	-	≤0.03-0.06	-	-
Amoxicillin / Clavulanic acid	-	-	0.06-0.12	-	-
Azithromycin	-	-	0.12-8	80.0	20.0
Clindamycin	-	-	0.06-0.06	100.0	0.0
Daptomycin	-	-	0.25-1	100.0	0.0
Doxycycline	-	-	8-16	-	-
Linezolid	-	-	1-1	-	-
Moxifloxacin	-	-	0.12-0.5	-	-
Oxacillin	-	-	0.25-0.5	-	-
Tigecycline	-	-	0.03-0.06	-	-
Vancomycin	-	-	≤0.25-0.5	100.0	0.0
S. pyogenes (7)					
BC-3781	-	-	≤0.03-0.06	-	-
Amoxicillin / Clavulanic acid	-	-	≤0.03-≤0.03	-	-
Azithromycin	-	-	0.12->8	71.4	14.3
Clindamycin	-	-	0.06-0.06	100.0	0.0
Daptomycin	-	-	0.06-0.5	100.0	0.0
Doxycycline	-	-	≤0.12-8	-	-
Linezolid	-	-	0.5-1	-	-
Moxifloxacin	-	-	0.12-0.25	-	-
Oxacillin	-	-	0.06-0.06	-	-
Tigecycline	-	-	0.03-0.06	-	-
Vancomycin	-	-	0.5-0.5	100.0	0.0
Streptococcus spp.[b] (16)					
BC-3781	≤0.03	0.06	≤0.03-0.12	-	-
Amoxicillin / Clavulanic acid	≤0.03	0.12	≤0.03-0.12	-	-
Azithromycin	0.12	>8	≤0.06->8	75.0	18.8
Clindamycin	0.06	0.12	0.06->4	93.8	6.2
Daptomycin	0.25	0.5	≤0.03-1	100.0	0.0
Doxycycline	4	8	≤0.12-16	-	-
Linezolid	1	1	≤0.12-1	100.0	0.0
Moxifloxacin	0.12	0.25	≤0.03-0.5	-	-
Oxacillin	0.06	0.5	≤0.03-0.5	-	-
Tigecycline	0.03	0.06	≤0.015-0.12	-	-
Vancomycin	0.5	0.5	≤0.25-1	100.0	0.0

[a]*, according to CLSI M100-S20 (2010); [b] *S. pyogenes* (7), *S. agalactiae* (5), Group C, F, G *Streptococcus* spp. (4)

Table 2. Microbiological Eradication and Clinical Success Rates at TOC by Baseline Pathogen

Study Population	Pathogen	Treatment Arm: BC−3781 100 mg q12h	BC−3781 150 mg q12h	Vancomycin ≥ 1 g* q12h
Microbiological Eradication Rate [%] at TOC [1,2]				
MITT	All pathogens	80.0	84.3	82.4
	S. aureus	79.5	87.2	85.1
	MRSA	82.4	87.5	82.1
ME	All pathogens	84.8	90.7	95.0
	S. aureus	82.9	90.2	94.9
	MRSA	84.4	92.6	93.5
Clinical Success Rate [%] at TOC [1]				
CE	All pathogens	90.0	88.9	92.2
MITT	All pathogens	82.0	82.4	82.4
	S. aureus	81.8	87.2	85.1
	MRSA	85.3	87.5	82.1
	MRSA USA300	84.0	94.7	77.8
ME	All pathogens	87.0	88.4	95.0
	S. aureus	85.4	90.2	94.9
	MRSA	87.5	92.6	93.5
	MRSA USA300	87.0	94.1	90.5

* Dose: vancomycin 1 g or vancomycin adjusted individually according to local institutional guidelines
[1] Percentage of clinical and microbiological outcomes at TOC by baseline pathogen is calculated on the basis of the number of patients with a specific pathogen isolated at baseline
[2] Patients with indeterminate or missing clinical responses were included in the denominator, and, thus, are considered as non-eradication
CE clinically evaluable; ITT intent-to-treat; ME microbiologically evaluable; MITT modified intent-to-treat

CONCLUSIONS

- BC-3781 displayed potent *in vitro* activity against the isolated baseline pathogens including *S. aureus* and *Streptococcus* spp.
- Clinical efficacy of BC-3781 was demonstrated in this study with microbiological eradication at doses of 100 mg and 150 mg q12h being comparable to efficacy rates of vancomycin (>1g q12h).
- The results of this clinical phase 2 trial provide the first proof of concept for the systemic use of a pleuromutilin antibiotic for the treatment of ABSSSI and support the continued clinical evaluation of BC-3781 in serious infections.

SELECTED REFERENCES

1. McClure JA et al. 2006. Novel multiplex PCR assay for detection of the staphylococcal virulence marker panton-valentine leukocidin genes and simultaneous discrimination of methicillin-susceptible from –resistant staphylococci. J Clin Microbiol. 44:1141
2. McDougal LK et al. 2000. Pulse-field gel electrophoresis typing of oxacillin-resistant *Staphylococcus aureus* isolates from the United States: establishing a national database. J Clin Microbiol. 41:5113
3. Ross JE et al. 2012. Disk Diffusion and MIC Quality Control Ranges for BC-3205 and BC-3781, Two Novel Pleuromutilin Antibiotics. J Clin Microbiol. (EPub ahead of print)
4. Tenover FC et al. 1995. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. J Clin Microbiol. 33:2233

52nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 9-12, 2012