Correlations of Broth Microdilution MIC and Disk Diffusion Results for an Investigational Agent, BC-3205 Among Potentially Indicated Species

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Materials and Methods

**Bacterial isolates**
A total of 730 recent (2006-2009) clinical isolates were tested from patients hospitalized in North America (USA 52.2 %), Europe (39.2 %) and smaller numbers in the Asia-Pacific Region and Latin America. Isolates included methicillin-susceptible S. aureus (MRSA; 112 strains, including various SCCamercedin clones). Coagulase-negative staphylococci (456 included eight numbers of methicillin-susceptible (51) and methicillin-resistant (51) strains. The non-vancomycin-susceptible (VSSA) population included 155 strains treated similar to the standard method but was fostered in the study to determine tentative epidemiologic cutoff values (ECV) for MIC and disk diffusion tests with BC-3205. Comparator agents included azithromycin (AZ, isolates 32 and clindamycin (CL). 2 mg/l M100-S20. Performance standards for antimicrobial susceptibility testing: 20th informational supplement. Activities and resistance determinants were not observed.

**Quality control (QC) ranges and interpretive criteria for both MIC and zone diameters for comparator compounds were as published in the CLSI M100-S20.** The MICs for both BC-3205 and the comparator compounds were reported in Table 1. The MIC distributions of the investigational Nabriva agent BC-3205 tested against 730 Gram-positive cocci.

**Figure 1. MIC distribution of BC-3205 comparing epidemiologic and non-epidemiologic results for all 730 Staphylococcus spp. (279 strains)**

**Figure 2. BC-3205 scattergram comparing MIC and zone diameter results for all β-haemolytic streptococci (202 strains)**

**Figure 3. BC-3205 scattergram comparing MIC and zone diameter results for all MRSA (12 strains)**

**Figure 4. BC-3205 scattergram comparing MIC and zone diameter results for all β-haemolytic streptococci (202 strains)**

**Table 1. MIC frequency distributions of the investigational Nabriva agent BC-3205 tested against 730 Staphylococcus spp.**

**Conclusions**
A total of 20-µg BC-3205 zone diameters with the CLSI reference MIC values were excellent and strain intermediately interpreted error (3.0 %) was noted when using a susceptible zone of ≥15 mm and ≥20 mm, respectively (two strains), and CoNS isolates that exhibited a non-wildtype phenotype for BC-3205 harbored staphylococci isolates recovered from human clinical species carrying these resistance determinants are extremely rare. As BC-3205 MIC versus zone diameter scattergrams indicate that the proposed wildtype/ECV and susceptible breakpoints, regardless of species tested, provided a near perfect correlation (99.4 % absolute categorical agreement) between in vitro test results. Only a single strain would produce a potential serious major error using the proposed ECV/breakpoints from this study. Correlations of 20-µg BC-3205 disk zone diameters with the CLSI reference MIC values were excellent with asterically marked (0.4 %) interpretative error when using a susceptible (ECV) breakpoint of ≤1 mg/l (220 mm). These tentative criteria should be considered for early clinical trials. Cross-resistance with other agents (macrolides, oxazolidinones, linezolid) was not demonstrated.

**Selected References**
- Clinical and Laboratory Standards Institute (2004). CLSI guideline for antibiotic susceptibility testing: 18th informational supplement. CLSI, Wayne, PA.
- Clinical and Laboratory Standards Institute (2002). CLSI guideline for antibiotic susceptibility testing: 15th informational supplement. CLSI, Wayne, PA.
- Clinical and Laboratory Standards Institute (1986). CLSI guideline for antibiotic susceptibility testing: 7th informational supplement. CLSI, Wayne, PA.