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Activity of Zosurabalpin and Comparator Antimicrobial Agents Tested Against *Acinetobacter baumannii-calcoaceticus* Complex (ABC) Isolates Collected Worldwide in 2024

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Background

- Zosurabalpin (ZAB, RG6006) is a first-in-class tethered macrocyclic peptide antibiotic that targets intracellular transport of lipopolysaccharide inhibiting the $LptB_2FGC$ complex.
- Currently zosurabalpin is being developed for the treatment of carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections, a top priority pathogen on the Centers for Disease Control and Prevention (CDC) urgent threat list.
- This agent demonstrates *in vitro* activity against *Acinetobacter baumannii-calcoaceticus* complex clinical isolates, including carbapenem-resistant (CRABC) and multidrug-resistant (MDR) strains.
- The *in vitro* antimicrobial activity of zosurabalpin was monitored as part of the 2024 global SENTRY Antimicrobial Surveillance Program platform against 1,575 ABC bacterial isolates using Clinical and Laboratory Standards Institute (CLSI) reference susceptibility testing methods.

Results

- Zosurabalpin ($MIC_{50/90}$, 0.12/0.5 mg/L) inhibited all ABC isolates at ≤2 mg/L and 99.7% (1,571/1,575) at ≤1 mg/L.
- Resistance rates to standard-of-care agents varied by region, with 81.0%/75.0% MDR/CRABC seen in Latin American isolates (*n*=100), 69.9%/69.9% in Asia-Pacific isolates (*n*=166), 51.7%/50.1% in European isolates (*n*=747), and 31.5%/28.1% in United States isolates (*n*=562).
- Zosurabalpin activity was not impacted by differences in regional resistance rates and retained activity against resistant phenotypes (Figure 1) including CRABC (*n*=723 [45.9% overall]; $MIC_{50/90}$, 0.25/0.5 mg/L) and MDR (*n*=760 [48.3%]; $MIC_{50/90}$, 0.25/0.5 mg/L) isolates, inhibiting 99.7% at ≤1 mg/L and 100% at ≤2 mg/L.
- Among comparators, cefiderocol and sulbactam-durlobactam were the most active agents inhibiting 93.0% and 95.2% of the isolates, respectively.
 - Cefiderocol and sulbactam-durlobactam inhibited 86.3% and 89.6% of the CRABC isolates and 86.6% and 90.1% of the MDR isolates, respectively (Figure 2).
- Susceptibility rates for the remaining agents ranged from 51.4% for ampicillin-sulbactam to 96.4% for colistin (Figure 2).
 - The activity of amikacin, ampicillin-sulbactam, and minocycline comparators was markedly reduced against CRABC and MDR isolates, with susceptibility rates of 3.5–28.3%; colistin susceptibility rates were 93.6–93.7% against these resistant phenotypes (Figure 2).
- Cefiderocol-resistant (*n*=74), sulbactam-durlobactam-resistant (*n*=62), and 24 isolates resistant to both agents were all inhibited by zosurabalpin at ≤1 mg/L.

Methods

- A total of 1575 bacterial isolates were collected in 109 medical centers located in 30 countries in Europe (747 isolates; 47.4% overall; 19 countries), Latin America (100 isolates; 6.3% overall; 4 countries), the Asia-Pacific region (166 isolates; 10.5% overall; 7 countries) and in the United States (562 isolates; 35.7% overall; 9 US census divisions).
- Isolates originated from patients hospitalized with pneumonia (*n*=592), skin and skin structure infections (*n*=317), bloodstream infections (*n*=208), urinary tract infections (*n*=183), and other infections (*n*=275).
- Zosurabalpin was tested in cation-adjusted Mueller-Hinton broth (CAMHB) supplemented with 20% heat-inactivated horse serum (HoS), as approved by the CLSI.
- Comparator agents were tested using CLSI reference methods and CLSI and FDA interpretive breakpoint criteria were applied.
- CRABC were resistant to imipenem and/or meropenem and MDR were resistant to ≥3 antimicrobial classes applying CLSI breakpoints.

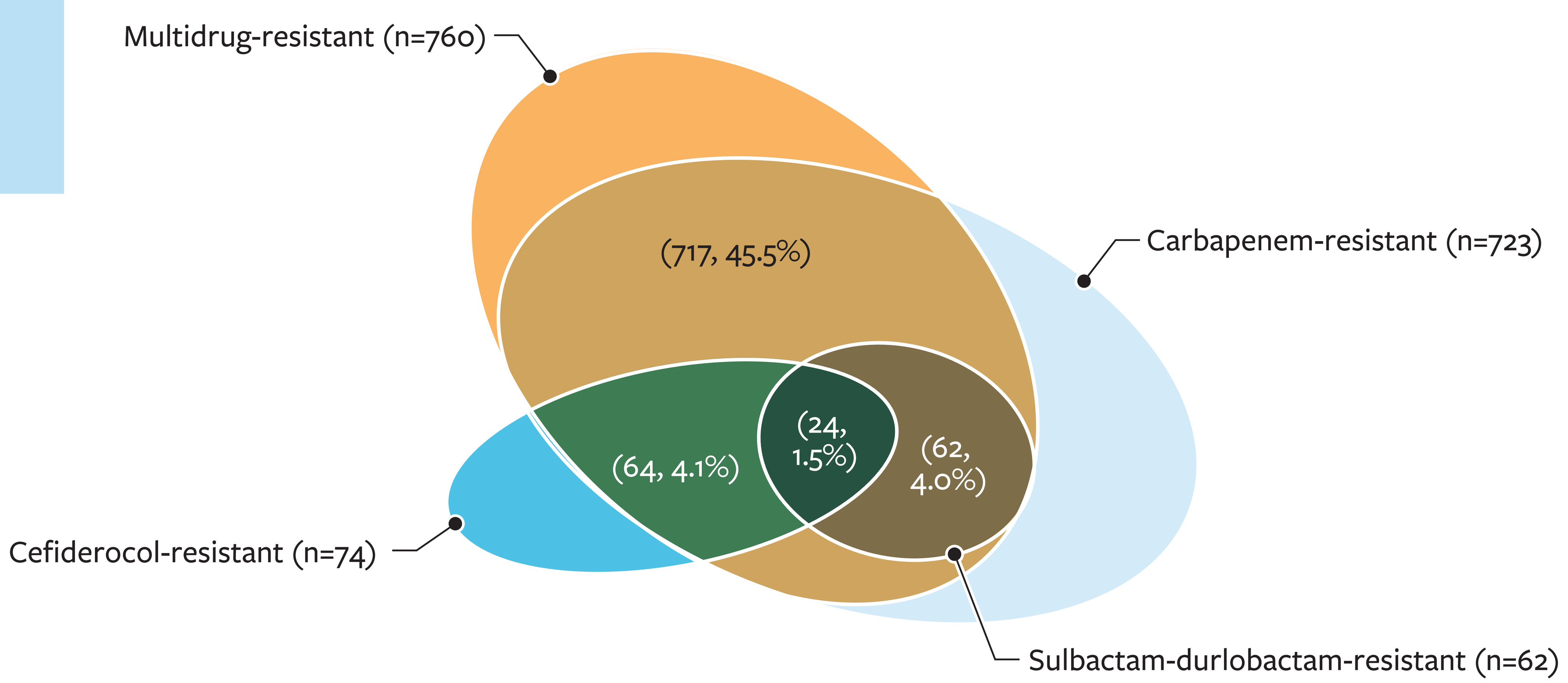
Conclusions

- ABC isolates are often CRABC and/or MDR and therapeutic options to treat infections caused by these isolates remain limited.
- Zosurabalpin sustained potent activity against antimicrobial-resistant and MDR phenotypes, including isolates resistant to new agents including cefiderocol and sulbactam-durlobactam.
- The potent *in vitro* activity of zosurabalpin observed against a large collection of clinical ABC isolates establishes this agent as a potential option to combat the growing threat of antimicrobial resistance and further development is warranted.

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Figure 1. Distribution of 1,575 *A. baumannii-calcoaceticus* complex isolate resistant phenotypes

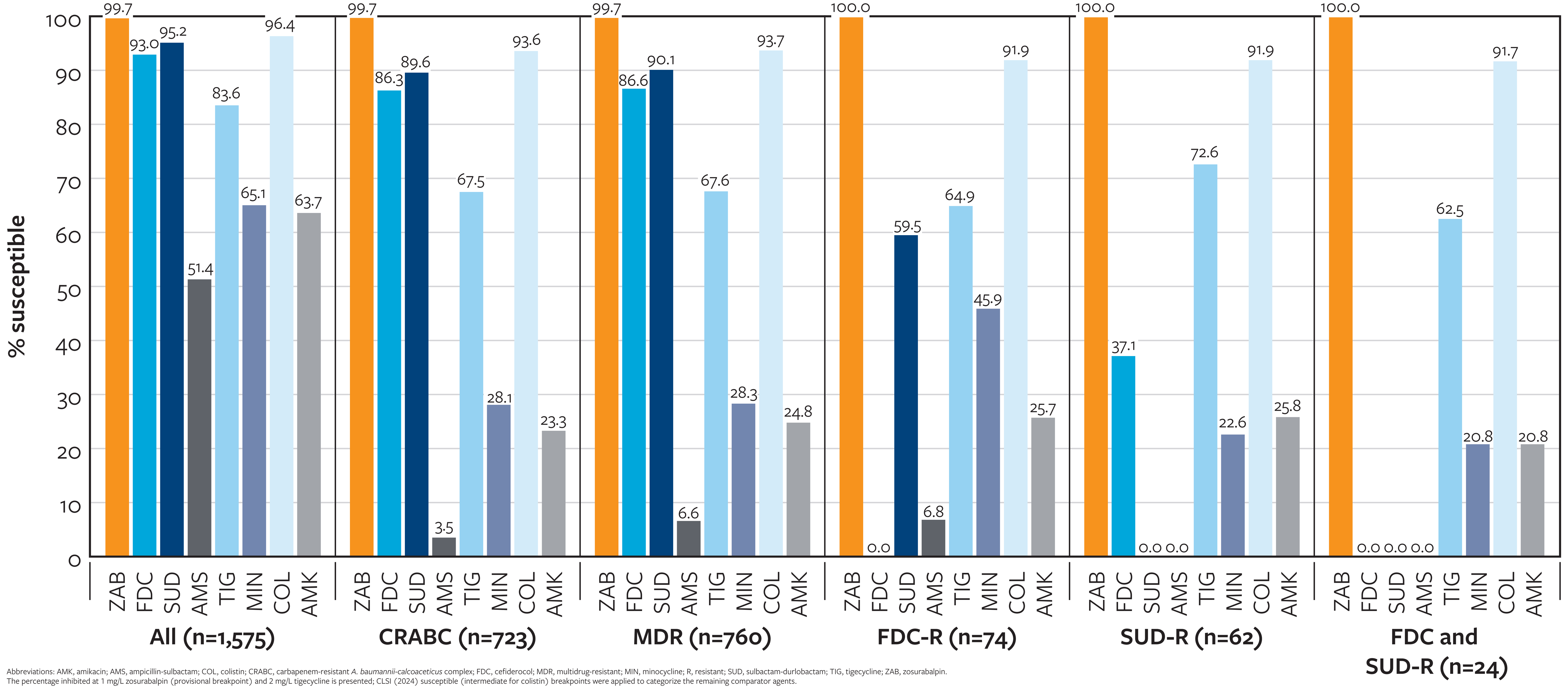


Multidrug-resistant (n=760)
Carbapenem-resistant (n=723)
Cefiderocol-resistant (n=74)
Sulbactam-durlobactam-resistant (n=62)
(717, 45.5%)
(64, 4.1%)
(24, 1.5%)
(62, 4.0%)

	MDR	CRABC	FDC-R	SUD-R
MDR	760	717	67	62
CRABC	717	723	64	62
FDC-R	67	64	74	24
SUD-R	62	62	24	62

Abbreviations: CRABC, carbapenem-resistant *A. baumannii-calcoaceticus* complex; FDC, cefiderocol; MDR, multidrug-resistant; R, resistant; SUD, sulbactam-durlobactam.

Figure 2. Activity of zosurabalpin and comparator agents against 1,575 *A. baumannii-calcoaceticus* complex isolates and resistant phenotypes



% susceptible
0 10 20 30 40 50 60 70 80 90 100
ZAB FDC SUD AMS TIG MIN COL AMK
All (n=1,575)
99.7 93.0 95.2 51.4 83.6 65.1 96.4 63.7
CRABC (n=723)
99.7 86.3 89.6 3.5 67.5 28.1 93.6 23.3
MDR (n=760)
99.7 86.6 90.1 6.6 67.6 28.3 93.7 24.8
FDC-R (n=74)
100.0 0.0 59.5 6.8 64.9 45.9 91.9 25.7
SUD-R (n=62)
100.0 37.1 0.0 0.0 72.6 22.6 91.9 25.8
FDC and SUD-R (n=24)
100.0 0.0 0.0 0.0 62.5 20.8 91.7 20.8

Abbreviations: AMK, amikacin; AMS, ampicillin-sulbactam; COL, colistin; CRABC, carbapenem-resistant *A. baumannii-calcoaceticus* complex; FDC, cefiderocol; MDR, multidrug-resistant; MIN, minocycline; R, resistant; SUD, sulbactam-durlobactam; TIG, tigecycline; ZAB, zosurabalpin.
The percentage inhibited at 1 mg/L zosurabalpin (provisional breakpoint) and 2 mg/L tigecycline is presented; CLSI (2024) susceptible (intermediate for colistin) breakpoints were applied to categorize the remaining comparator agents.

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