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In vitro Activity of Zosurabalpin and Comparator Agents Tested Against *Acinetobacter baumannii-calcoaceticus* Complex Isolates From China

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Background

- Zosurabalpin (RG6006) is a first-in-class, novel tethered macrocyclic peptide that prevents intracellular transport of lipopolysaccharide by inhibition of the $LptB_2FGC$ complex.
- Currently zosurabalpin is under clinical development for the treatment of difficult-to-treat *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections including those caused by carbapenem-resistant ABC (CRABC) isolates.
- This study evaluated the *in vitro* antimicrobial activity of zosurabalpin against 100 ABC bacterial isolates collected from two (2) Chinese hospitals, using Clinical and Laboratory Standards Institute (CLSI) reference susceptibility testing methods.

Methods

- Bacterial isolates were collected from patients with documented infections from two (2) Chinese hospitals during 2024; bacterial species were identified as ABC complex using DNA sequencing.
- Susceptibility testing was performed by the CLSI reference broth microdilution method and CLSI, FDA, and EUCAST breakpoint criteria were applied for comparator agents (*n*=6; cefiderocol, amikacin, colistin, imipenem, meropenem, and piperacillin-tazobactam).
- Zosurabalpin was tested in cation-adjusted Mueller-Hinton broth (CAMHB) and CAMHB supplemented with 10% or 20% heat-inactivated horse serum (HoS).
  - Zosurabalpin CAMHB MIC endpoints were determined at substantial reduction (SR) and complete inhibition of growth (100%).
  - Zosurabalpin CAMHB with HoS MIC endpoints were determined at complete inhibition of growth (100%).
- Cefiderocol testing was performed in iron-depleted CAMHB while remaining comparator agents were tested in standard CAMHB.

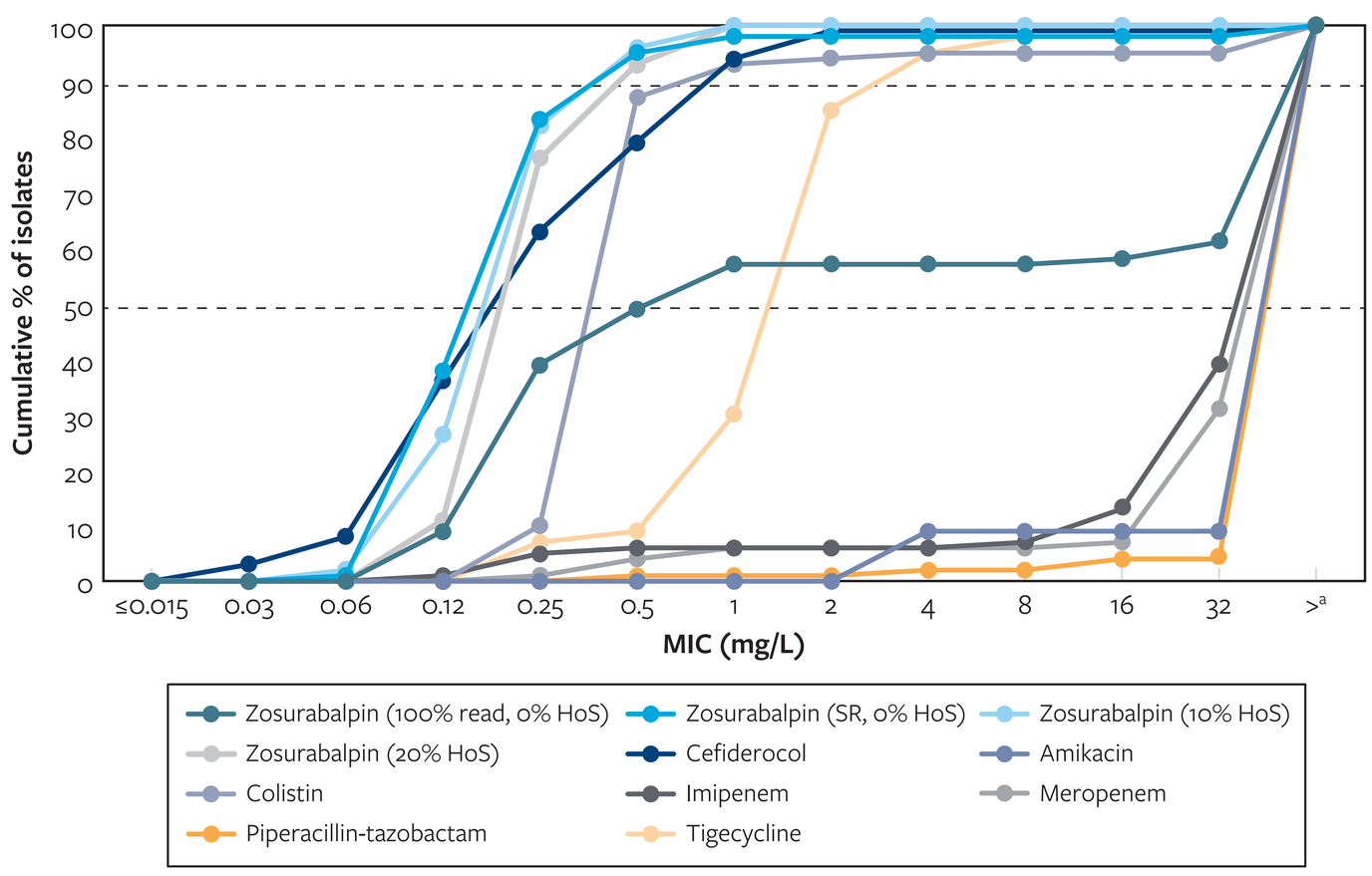
Results

- Zosurabalpin displayed potent activity against this set of ABC isolates from China, with $MIC_{50/90}$ values of 0.25/0.5 mg/L when tested in CAMHB supplemented with 10% or 20% HoS and when tested in CAMHB without serum and read at SR (Table 1).
- All ABC isolates (100%; 100/100) were inhibited at 1 mg/L when tested in CAMHB with HoS and 98% of isolates (98/100) tested in CAMHB and read at SR (Figure 1).
- The zosurabalpin $MIC_{50/90}$ values obtained in CAMHB were 1/>32 mg/L when read at 100%.
- Isolates were resistant to comparator antimicrobial agents including amikacin, imipenem, meropenem, and piperacillin-tazobactam (4%–9% susceptible) when CLSI, EUCAST, and FDA breakpoint criteria were applied (Table 1).
- Most isolates (94%; 94/100) demonstrated resistance to both meropenem and imipenem, indicative of a CRABC phenotype.
- Among comparators, colistin (94% susceptible per EUCAST; $MIC_{50/90}$ values of 0.5/1 mg/L) and cefiderocol (94%/99% susceptible per CLSI/FDA; $MIC_{50/90}$ values of 0.25/1 mg/L) comparator agents displayed activity against the majority of this 100-isolate set.

Conclusions

- Zosurabalpin demonstrated potent *in vitro* activity against recent ABC isolates—including CRABC—collected from patients in two Chinese hospitals during 2024.
- Zosurabalpin MIC values read under SR criteria in CAMHB were similar to those read in CAMHB media supplemented with 10% or 20% HoS ($MIC_{50/90}$ 0.25/0.5 mg/L).
- Zosurabalpin may represent a potential option for treatment of infections caused by CRABC and further studies are needed to demonstrate its clinical effectiveness.

Figure 1. Cumulative MIC distribution of zosurabalpin and comparator agents tested against 100 *Acinetobacter baumannii-calcoaceticus* complex (ABC) isolates from two Chinese hospitals



[a] Greater than the highest concentration tested

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Table 1. Activity of zosurabalpin and comparator agents tested against 100 *Acinetobacter baumannii-calcoaceticus* complex (ABC) isolates from two Chinese hospitals

Antimicrobial Agent	Concentration (mg/L)													% Susceptible[a]		
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>	MIC_{50}	MIC_{90}	CLSI	EUCAST	FDA
Zosurabalpin (100% read, 0% HoS)	0	9	30	10	8	0	0	0	1	3	39	1	>32			
	0.0%	9.0%	39.0%	49.0%	57.0%	57.0%	57.0%	57.0%	58.0%	61.0%	100.0%					
Zosurabalpin (SR, 0% HoS)	1	37	45	12	3	0	0	0	0	0	2	0.25	0.5			
	1.0%	38.0%	83.0%	95.0%	98.0%	98.0%	98.0%	98.0%	98.0%	98.0%	100.0%					
Zosurabalpin (10% HoS)	2	24	56	14	4							0.25	0.5			
	2.0%	26.0%	82.0%	96.0%	100.0%											
Zosurabalpin (20% HoS)	0	11	65	17	7							0.25	0.5			
	0.0%	11.0%	76.0%	93.0%	100.0%											
Cefiderocol	8	28	27	16	15	5	0	0	0	0	1	0.25	1	99.0		94.0
	8.0%	36.0%	63.0%	79.0%	94.0%	99.0%	99.0%	99.0%	99.0%	99.0%	100.0%					
Amikacin[c]						0	9	0			91	>8	>8		9[b]	
						0.0%	9.0%	9.0%			100.0%					
Colistin		0	10	77	6	1	1	0			5	0.5	1		94.0	
		0.0%	10.0%	87.0%	93.0%	94.0%	95.0%	95.0%			100.0%					
Imipenem	0	1	4	1	0	0	0	1	6	26	61	>32	>32	6.0	6.0	6.0
	0.0%	1.0%	5.0%	6.0%	6.0%	6.0%	6.0%	7.0%	13.0%	39.0%	100.0%					
Meropenem		0	1	3	2	0	0	0	1	24	69	>32	>32	6.0	6.0[d]	6.0
		0.0%	1.0%	4.0%	6.0%	6.0%	6.0%	6.0%	7.0%	31.0%	100.0%					
Piperacillin-tazobactam			0	1	0	0	1	0	2	0	96	>128	>128	4.0		4.0
			0.0%	1.0%	1.0%	1.0%	2.0%	2.0%	4.0%	4.0%	100.0%					
Tigecycline		0	7	2	21	55	10	3			2	2	4			
		0.0%	7.0%	9.0%	30.0%	85.0%	95.0%	98.0%			100.0%					

[a] Criteria as published by CLSI (2024), EUCAST (2024), and US FDA (2024).
[b] For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy.
[c] Amikacin was tested below CLSI and FDA breakpoint criteria.
[d] Using meningitis and non-meningitis breakpoints.
Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, Food and Drug Administration; HoS, heat-inactivated horse serum; MIC, minimum inhibitory concentration (mg/L); SR, substantial reduction; US, United States.