AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

SUSCEPTIBILITY

In Vitro Activity of KBP-7072, a Novel Third-Generation Tetracycline, against 531 Recent Geographically Diverse and Molecularly Characterized *Acinetobacter baumannii* Species Complex Isolates

Michael D. Huband,[a] Rodrigo E. Mendes,[a] Michael A. Pfaller,[a,b] Jill M. Lindley,[a] Gregory J. Strand,[a] Vincent J. Benn,[c] Jay Zhang,[c] Li Li,[d] Min Zhang,[d] Xiaojuan Tan,[d] Qingmei Liu,[d] Robert K. Flamm[a]

[a]JMI Laboratories, North Liberty, Iowa, USA
[b]University of Iowa, Iowa City, Iowa, USA
[c]KBP Biosciences USA, Inc., Princeton, New Jersey, USA
[d]KBP Biosciences Co., Ltd., Jinan, China

ABSTRACT KBP-7072 is a novel third-generation tetracycline (aminomethylcycline) antibacterial that overcomes common efflux and ribosomal protection resistance mechanisms that cause resistance in older-generation tetracyclines. KBP-7072 completed phase 1 clinical development studies for safety, tolerability, and pharmacokinetics (ClinicalTrials.gov identifier NCT02454361) and multiple ascending doses in healthy subjects (ClinicalTrials.gov identifier NCT02654626) in December 2015. Both oral and intravenous formulations of KBP-7072 are being developed. In this study, we evaluated the *in vitro* activities of KBP-7072 and comparator agents by CLSI document M07 (2018) broth microdilution against 531 recent geographically diverse and/or molecularly characterized *Acinetobacter baumannii-A. calcoaceticus* species complex (*A. baumannii*) isolates from the United States, Europe, Asia-Pacific (excluding China), and Latin America. *A. baumannii* isolates included carbapenem-resistant, colistin-resistant, tetracycline-resistant, and extended-spectrum-β-lactamase (ESBL)- and metallo-β-lactamase (MBL)-producing isolates. Overall, KBP-7072 ($MIC_{50/90}$, 0.25/1 mg/liter) was comparable in activity to colistin (92.8%/92.8% susceptible [S] [CLSI/EUCAST]) against *A. baumannii* isolates, inhibiting 99.2% of isolates at ≤2 mg/liter and 97.6% of isolates at ≤1 mg/liter. KBP-7072 was equally active against *A. baumannii* isolates, including carbapenem-resistant, colistin-resistant, and tetracycline-resistant isolates, regardless of geographic location, and maintained activity against ESBL- and MBL-producing isolates. KBP-7072 outperformed comparator agents, including ceftazidime (40.3% S [CLSI]), gentamicin (48.2%/48.2% S [CLSI/EUCAST]), levofloxacin (39.5%/37.9% S [CLSI/EUCAST]), meropenem (42.0%/42.0% S [CLSI/EUCAST]), piperacillin-tazobactam (33.3% S [CLSI]), and all tetracycline-class comparator agents, which include doxycycline (67.3% S [CLSI]), minocycline (73.8% S [CLSI]), tetracycline (37.2% S [CLSI]), and tigecycline (79.5% inhibited by ≤2 mg/liter). The potent *in vitro* activity of KBP-7072 against recent geographically diverse, molecularly characterized, and drug-resistant *A. baumannii* isolates supports continued clinical development for the treatment of serious infections, including those caused by *A. baumannii*.

KEYWORDS *Acinetobacter*, KBP-7072, aminomethylcycline, susceptibility, tetracycline

Tetracycline antibacterials with broad-spectrum activity became available beginning in the late 1940s (1, 2). Tetracyclines have also been used to treat atypical infections, including those caused by *Chlamydia* spp., *Mycoplasma* spp., *Rickettsia* spp., and some

Citation Huband MD, Mendes RE, Pfaller MA, Lindley JM, Strand GJ, Benn VJ, Zhang J, Li L, Zhang M, Tan X, Liu Q, Flamm RK. 2020. *In vitro* activity of KBP-7072, a novel third-generation tetracycline, against 531 recent geographically diverse and molecularly characterized *Acinetobacter baumannii* species complex isolates. Antimicrob Agents Chemother 64:e02375-19. https://doi.org/10.1128/AAC.02375-19.

Address correspondence to Michael D. Huband, michael-huband@jmilabs.com.

Received 26 November 2019
Returned for modification 23 December 2019
Accepted 7 February 2020
Accepted manuscript posted online 18 February 2020
Published 21 April 2020

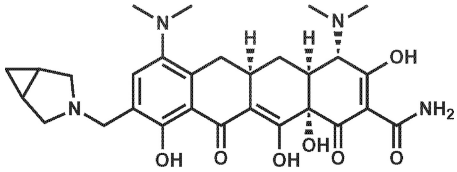

FIG 1 KBP-7072 compound structure.

protozoans (1). Over decades of use, resistance mechanisms, including efflux and ribosomal protection, have developed and substantially reduced how effective tetracyclines are against many important bacterial pathogens (2–4).

KBP-7072 (Fig. 1) is a potent, broad-spectrum, third-generation tetracycline (aminomethylcycline) antibacterial being developed (oral and intravenous formulations) for the treatment of community-acquired pneumonia (CAP) that overcomes many of these common tetracycline resistance mechanisms (5, 6). KBP-7072 has demonstrated potent *in vitro* activity against methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci and has received qualified infectious disease product (QIDP) and fast-track status for CAP (7). In addition, KBP-7072 has completed phase 1 clinical development (December 2015) for safety, tolerability, pharmacokinetics, and multiple ascending doses in healthy subjects (8, 9).

Newer aminomethylcycline tetracyclines, such as KBP-7072 and omadacycline, have shown potent *in vitro* activity against *Enterobacteriaceae* isolates that produce extended-spectrum β-lactamases (ESBLs) and carbapenemases as well as multidrug-resistant (resistant to $\geq$3 classes of agents) and carbapenem-resistant *Acinetobacter baumannii* (CRAB) isolates (10). Carbapenem-resistant *A. baumannii* was recognized by the World Health Organization in 2017 as a critical (priority 1) pathogen to help guide the research, discovery, and development of new antibacterials (11, 12). In this study, the *in vitro* activities of KBP-7072 and comparator agents were evaluated against 531 recent geographically diverse and/or molecularly characterized *A. baumannii* isolates, which included carbapenem-resistant, colistin-resistant, tetracycline-resistant, and ESBL- and metallo-β-lactamase (MBL)-producing *A. baumannii* isolates.

RESULTS

Overall activity of KBP-7072. The *in vitro* activities of KBP-7072 and comparator agents against 531 recent geographically diverse and/or molecularly characterized *A. baumannii* isolates are detailed in Table 1 as MIC range, $MIC_{50/90}$, percent susceptible (S), percent intermediate (I), and percent resistant (R) according to CLSI/EUCAST breakpoint interpretive criteria and in Table 2 according to frequency and cumulative

TABLE 1 Activities of KBP-7072 and comparators against 531 recent geographically diverse *Acinetobacter baumannii* isolates

Antimicrobial agent (no. of isolates tested)	MIC range (mg/liter)	$MIC_{50/90}$ (mg/liter)	CLSI[a]			EUCAST[a]		
			% S	% I	% R	% S	% I	% R
KBP-7072 (531)	≤0.015 to 4	0.25/1	99.2[b]					
Tigecycline (531)	0.06 to 16	1/4	79.5[c]	18.2	2.3			
Doxycycline (453)	≤0.06 to >8	1/>8	67.3	2.0	30.7			
Minocycline (454)	≤0.03 to >8	1/>8	73.8	6.8	19.4			
Tetracycline (457)	0.5 to >8	>8/>8	37.2	7.2	55.6			
Ceftazidime (531)	0.5 to >16	>16/>16	40.3	6.0	53.7			
Colistin (528)	≤0.5 to >8	≤0.5/1	92.8		7.2	92.8		7.2
Gentamicin (531)	≤2 to >8	8/>8	48.2	4.9	46.9	48.2		51.8
Levofloxacin (531)	0.03 to >4	>4/>4	39.5	2.8	57.6	37.9	1.3	60.8
Meropenem (531)	0.12 to >8	>8/>8	42.0	0.8	57.3	42.0	2.3	55.7
Piperacillin-tazobactam (520)	≤0.06 to >128	>64/>64	33.3	5.2	61.5			

[a]Criteria according to CLSI (2019) and EUCAST (2019) guidelines (22, 24).
[b]Percent inhibited at ≤2 mg/liter for comparison purposes only.
[c]Tigecycline FDA breakpoint criteria for *Enterobacteriaceae* applied to *A. baumannii* isolates for comparison purposes only (25).

TABLE 2 Antimicrobial activities of KBP-7072 and tetracycline comparators against *Acinetobacter baumannii* isolates

Antimicrobial (no. of isolates)	No. (cumulative %) of isolates inhibited at MIC (mg/liter) of:															MIC_{50} (mg/liter)	MIC_{90} (mg/liter)
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>[a]		
KBP-7072 (531)	5 (0.9)	62 (12.6)	121 (35.4)	46 (44.1)	49 (53.3)	165 (84.4)	70 (97.6)	9 (99.2)	4 (100.0)							0.25	1
Tigecycline (531)		0 (0.0)	5 (0.9)	53 (10.9)	97 (29.2)	62 (40.9)	58 (51.8)	147 (79.5)	97 (97.7)	9 (99.4)	3 (100.0)					1	4
Doxycycline (453)		0 (0.0)	30 (6.6)	80 (24.3)	66 (38.9)	28 (45.0)	35 (52.8)	30 (59.4)	36 (67.3)	9 (69.3)					139 (100.0)	1	>8
Minocycline (454)	0 (0.0)	8 (1.8)	34 (9.3)	64 (23.3)	74 (39.6)	42 (48.9)	52 (60.4)	40 (69.2)	21 (73.8)	31 (80.6)					88 (100.0)	1	>8
Tetracycline (457)					0 (0.0)	5 (1.1)	37 (9.2)	55 (21.2)	73 (37.2)	33 (44.4)					254 (100.0)	>8	>8

[a]>, greater than the highest concentration tested.

percent inhibition. KBP-7072 ($MIC_{50/90}$, 0.25/1 mg/liter; 97.6% and 99.2% inhibited at ≤1 mg/liter and ≤2 mg/liter, respectively) and colistin ($MIC_{50/90}$, ≤0.5/1 mg/liter; 92.8%/92.8% S [CLSI/EUCAST]) were the most active agents tested against *A. baumannii* (Table 1). *A. baumannii* susceptibilities to tetracycline-class comparators were 67.3% S, 73.8% S, and 37.2% S for doxycycline, minocycline, and tetracycline, respectively (Table 1). In addition, only 79.5% of *A. baumannii* isolates were inhibited by ≤2 mg/liter of tigecycline (FDA susceptibility breakpoint for *Enterobacteriaceae*) (Tables 1 and 2). Based on MIC_{90} values, KBP-7072 (MIC_{90}, 1 mg/liter) was 4-fold more potent than tigecycline (MIC_{90}, 4 mg/liter) and more than 8-fold more potent than doxycycline, minocycline, and tetracycline (MIC_{90} values of >8 mg/liter). Comparator agents were only marginally active against *A. baumannii* isolates. The comparator agents included ceftazidime (40.3% S [CLSI]), gentamicin (48.2%/48.2% S [CLSI/EUCAST]), levofloxacin (39.5%/37.9% S [CLSI/EUCAST]), meropenem (42.0%/42.0% S [CLSI/EUCAST]), and piperacillin-tazobactam (33.3% S [CLSI]) (Table 1).

Activity of KBP-7072 against 38 colistin-resistant isolates. The *in vitro* activities of KBP-7072 and comparator agents against a subset of 38 colistin-resistant *A. baumannii* isolates are detailed in Table 3. KBP-7072 ($MIC_{50/90}$, 0.5/1 mg/liter) was the most active agent tested, inhibiting 92.1% and 100.0% of these isolates at ≤1 mg/liter and ≤2 mg/liter, respectively (Table 3). Tetracycline-class comparators demonstrated limited activity against colistin-resistant *A. baumannii* isolates, and these comparators included doxycycline ($MIC_{50/90}$, >8/>8 mg/liter; 39.4% S [CLSI]), minocycline ($MIC_{50/90}$, 8/32 mg/liter; 45.5% S [CLSI]), tetracycline ($MIC_{50/90}$, >16/>16 mg/liter; 21.2% S [CLSI]), and tigecycline ($MIC_{50/90}$, 2/8 mg/liter; 52.6% inhibited at ≤2 mg/liter) (Table 3). Other comparator agents that were largely inactive against colistin-resistant *A. baumannii* isolates included ceftazidime (28.9% S [CLSI]), gentamicin (28.9%/28.9% S [CLSI/EUCAST]), levofloxacin (23.7%/21.1% S [CLSI/EUCAST]), meropenem (26.3%/26.3% S [CLSI/EUCAST]), and piperacillin-tazobactam (13.9% S [CLSI]) (Table 3).

Activity of KBP-7072 against 304 carbapenem (meropenem)-resistant isolates. The *in vitro* activities of KBP-7072 and comparator agents against a subset of 304 carbapenem (meropenem)-resistant *A. baumannii* isolates are detailed in Table 4.

TABLE 3 Activities of KBP-7072 and comparators against 38 colistin-resistant *Acinetobacter baumannii* isolates

Antimicrobial agent (no. of isolates tested)	MIC range (mg/liter)	$MIC_{50/90}$ (mg/liter)	CLSI[a]			EUCAST[a]		
			% S	% I	% R	% S	% I	% R
KBP-7072 (38)	0.03 to 2	0.5/1	100.0[b]					
Tigecycline (38)	0.12 to 8	2/8	52.6[c]	36.9	10.5			
Doxycycline (33)	≤0.06 to >8	>8/>8	39.4	3.0	57.6			
Minocycline (33)	0.06 to 32	8/32	45.5	15.2	39.4			
Tetracycline (33)	1 to >16	>16/>16	21.2	6.1	72.7			
Ceftazidime (38)	2 to >32	>32/>32	28.9	5.3	65.8			
Colistin (38)	4 to >8	>8/>8	0.0		100.0	0.0		100.0
Gentamicin (38)	0.25 to >16	>16/>16	28.9	2.6	68.4	28.9		71.1
Levofloxacin (38)	0.06 to >32	32/>32	23.7	2.6	73.7	21.1	2.6	76.3
Meropenem (38)	0.25 to >32	>32/>32	26.3	0.0	73.7	26.3	0.0	73.7
Piperacillin-tazobactam (36)	≤0.06 to >128	>128/>128	13.9	8.3	77.8			

[a]Criteria according to CLSI (2019) and EUCAST (2019) guidelines (22, 24).
[b]Percent inhibited at ≤2 mg/liter for comparison purposes only. The highest MIC was 4 mg/liter.
[c]Tigecycline FDA breakpoint criteria for *Enterobacteriaceae* applied to *A. baumannii* isolates for comparison purposes only (25).

TABLE 4 Activities of KBP-7072 and comparators against 304 meropenem-resistant *Acinetobacter baumannii* isolates

Antimicrobial agent (no. of isolates tested)	MIC range (mg/liter)	$MIC_{50/90}$ (mg/liter)	CLSI[a]			EUCAST[a]		
			% S	% I	% R	% S	% I	% R
KBP-7072 (304)	0.03 to 4	0.5/1	98.7[b]					
Tigecycline (304)	0.12 to 16	2/4	65.5[c]	30.9	3.6			
Doxycycline (274)	≤0.06 to >8	8/>8	49.3	2.9	47.8			
Minocycline (275)	≤0.03 to >8	2/>8	57.8	10.9	31.3			
Tetracycline (278)	1 to >8	>8/>8	8.6	7.2	84.2			
Ceftazidime (304)	1 to >16	>16/>16	5.3	6.2	88.5			
Colistin (301)	≤0.5 to >8	≤0.5/2	90.7		9.3	90.7		9.3
Gentamicin (304)	≤2 to >8	>8/>8	16.8	7.2	76.0	16.8		83.2
Levofloxacin (304)	0.12 to >4	>4/>4	1.6	3.3	95.1	1.6	0.0	98.4
Meropenem (304)	8 to >8	>8/>8	0.0	0.0	100.0	0.0	2.6	97.4
Piperacillin-tazobactam (304)	64 to >64	>64/>64	0.0	1.3	98.7			

[a]Criteria according to CLSI (2019) and EUCAST (2019) guidelines (22, 24).
[b]Percent inhibited at ≤2 mg/liter for comparison purposes only. The highest MIC was 4 mg/liter.
[c]Tigecycline FDA breakpoint criteria for *Enterobacteriaceae* applied to *A. baumannii* isolates for comparison purposes only (25).

KBP-7072 ($MIC_{50/90}$, 0.5/1 mg/liter; 95.7% and 98.7% inhibited at ≤1 mg/liter and ≤2 mg/liter, respectively) was the most active agent tested against meropenem-resistant *A. baumannii* isolates (Table 4). Tetracycline-class comparators, which included doxycycline ($MIC_{50/90}$, 8/>8 mg/liter; 49.3% S [CLSI]), minocycline ($MIC_{50/90}$, 2/>8 mg/liter; 57.8% S [CLSI]), tetracycline ($MIC_{50/90}$, >8/>8 mg/liter; 8.6% S [CLSI]), and tigecycline ($MIC_{50/90}$, 2/4 mg/liter; 65.5% inhibited at ≤2 mg/liter), demonstrated limited activity against the meropenem-resistant *A. baumannii* isolates (Table 4). With the exception of colistin (90.7%/90.7% S [CLSI/EUCAST]), comparator agents, including ceftazidime (5.3% S [CLSI]), gentamicin (16.8%/16.8% S [CLSI/EUCAST]), levofloxacin (1.6%/1.6% S [CLSI/EUCAST]), and piperacillin-tazobactam (0.0% S [CLSI]), were inactive against meropenem-resistant *A. baumannii* isolates (Table 4).

Activity of KBP-7072 against 254 tetracycline-resistant isolates. The *in vitro* activities of KBP-7072 and comparator agents were evaluated against a subset of 254 tetracycline-resistant *A. baumannii* isolates (Table 5). KBP-7072 ($MIC_{50/90}$, 0.5/1 mg/liter; 95.3% and 98.4% inhibited at ≤1 mg/liter and ≤2 mg/liter, respectively) was the most active agent tested against tetracycline-resistant *A. baumannii* isolates (Table 5). Tetracycline-class comparators, including doxycycline ($MIC_{50/90}$, >8/>8 mg/liter; 41.3% S [CLSI]), minocycline ($MIC_{50/90}$, 4/>8 mg/liter; 52.8% S [CLSI]), and tigecycline ($MIC_{50/90}$, 2/4 mg/liter; 63.0% inhibited at ≤2 mg/liter), demonstrated limited activity against tetracycline-resistant *A. baumannii* isolates (Table 5). Except for colistin (90.5%/90.5% S [CLSI/EUCAST]), other comparator agents, including ceftazidime (9.1% S [CLSI]), gentamicin (16.9%/16.9% S [CLSI/EUCAST]), levofloxacin (6.3%/4.7% S [CLSI/EUCAST]), mero-

TABLE 5 Activities of KBP-7072 and comparators against 254 tetracycline-resistant *Acinetobacter baumannii* isolates

Antimicrobial agent (no. of isolates tested)	MIC range (mg/liter)	$MIC_{50/90}$ (mg/liter)	CLSI[a]			EUCAST[a]		
			% S	% I	% R	% S	% I	% R
KBP-7072 (254)	0.03 to 4	0.5/1	98.4[b]					
Tigecycline (254)	0.25 to 16	2/4	63.0[c]	32.3	4.7			
Doxycycline (252)	0.25 to >8	>8/>8	41.3	3.6	55.2			
Minocycline (252)	0.25 to >8	4/>8	52.8	12.3	34.9			
Tetracycline (254)	>8 to >8	>8/>8	0.0	0.0	100.0			
Ceftazidime (254)	4 to >16	>16/>16	9.1	5.1	85.8			
Colistin (253)	≤0.5 to >8	≤0.5/2	90.5		9.5	90.5		9.5
Gentamicin (254)	0.25 to >8	>8/>8	16.9	5.9	77.2	16.9		83.1
Levofloxacin (254)	0.12 to >4	>4/>4	6.3	3.1	90.6	4.7	1.2	94.1
Meropenem (254)	0.12 to >8	>8/>8	7.4	0.4	92.1	7.5	1.2	91.3
Piperacillin-tazobactam (254)	≤0.06 to >64	>64/>64	3.9	3.5	92.5			

[a]Criteria according to CLSI (2019) and EUCAST (2019) guidelines (22, 24).
[b]Percent inhibited at ≤2 mg/liter for comparison purposes only. The highest MIC was 4 mg/liter.
[c]Tigecycline FDA breakpoint criteria for *Enterobacteriaceae* applied to *A. baumannii* isolates for comparison purposes only (25).

TABLE 6 Activities of KBP-7072 and comparators against *Acinetobacter baumannii* isolates stratified by geographic region

	North America ($n = 169$)		Europe ($n = 171$)		Latin America ($n = 81$)		Asia-Pacific ($n = 110$)	
Compound	$MIC_{50/90}$ (mg/liter)	% S	$MIC_{50/90}$ (mg/liter)	% S	$MIC_{50/90}$ (mg/liter)	% S	$MIC_{50/90}$ (mg/liter)	% S
KBP-7072[a]	0.06/1	98.8	0.25/1	98.8	0.5/1	100.0	0.25/1	100.0
Tigecycline[b]	0.5/4	85.8	1/4	78.4	2/4	69.1	1/4	79.1
Doxycycline[c]	0.25/>8	85.4	1/>8	58.2	4/>8	51.3	1/>8	77.1
Minocycline[c]	0.25/4	90.6	0.5/>8	66.1	2/32	61.5	1/8	79.8
Tetracycline[c]	4/>16	53.1	>8/>8	37.6	>8/>8	11.1	>8/>8	41.8
Ceftazidime	8/>32	64.5	>32/>32	28.1	>16/>16	17.3	>32/>32	39.1
Colistin	0.25/2	91.7	≤0.5/4	89.5	0.25/0.5	98.7	≤0.5/1	95.5
Gentamicin	1/>16	72.2	>8/>8	40.4	>8/>8	21.0	>8/>8	43.6
Levofloxacin	0.25/>16	60.4	>4/>4	30.4	>4/>4	12.4	>4/>4	41.8
Meropenem	1/>32	62.1	>8/>8	35.1	>8/>8	14.8	>8/>8	41.8
Piperacillin-tazobactam	32/>128	48.8	>64/>64	26.9	>64/>64	10.0	>64/>64	37.4

[a]Percent inhibited at ≤2 mg/liter for comparison purposes only. The highest MIC was 4 mg/liter.
[b]Tigecycline FDA breakpoint criteria for *Enterobacteriaceae* applied to *A. baumannii* isolates for comparison purposes only (25).
[c]Criteria according to CLSI (2019) guidelines (22).

penem (7.4%/7.4% S [CLSI/EUCAST]), and piperacillin-tazobactam (3.9% S [CLSI]), were inactive against these isolates (Table 5).

Activities of KBP-7072 and tetracycline comparators stratified by geographic region. KBP-7072 inhibited 96.5% to 100.0% and 98.8% to 100.0% of all *A. baumannii* isolates at ≤1 mg/liter and ≤2 mg/liter, respectively, regardless of geographic region, whereas tigecycline inhibition at ≤2 mg/liter varied from 69.1% for *A. baumannii* isolates from Latin America to 85.8% for isolates from North America (Table 6). In general, KBP-7072 and tigecycline MIC_{90} values were 1 mg/liter and 4 mg/liter, respectively, regardless of geographic region; however, KBP-7072 and tigecycline MIC_{50} values were lowest in North America (0.06 mg/liter and 0.5 mg/liter, respectively) and highest in Latin America (0.5 mg/liter and 2 mg/liter, respectively) (Table 6). Similarly, susceptibilities of tetracycline-class comparator agents, including doxycycline, minocycline, and tetracycline, were lowest for *A. baumannii* isolates from Latin America (51.3% S, 61.5% S, and 11.1% S, respectively) and highest against *A. baumannii* isolates from North America (85.4% S, 90.6% S, and 53.1% S, respectively) (Table 6). Comparator agents, including ceftazidime, gentamicin, levofloxacin, meropenem, and piperacillin-tazobactam, also demonstrated the lowest susceptibilities against *A. baumannii* isolates from Latin America (10.0% S to 21.0% S) and the highest susceptibilities against *A. baumannii* isolates from North America (48.8% S to 72.2% S) (Table 6).

Activity of KBP-7072 against molecularly characterized isolates. MIC values for KBP-7072 and comparator agents against individual isolates of ESBL-, carbapenemase-, and/or MBL-producing *A. baumannii* isolates are presented in Table 7. KBP-7072 was the most active agent tested against individual *A. baumannii* isolates containing an ESBL (GES or CTX-M-), carbapenemase (KPC-3 or OXA), and/or MBL (IMP or NDM), with

TABLE 7 Activities of KBP-7072 and comparator agents against ESBL- and MBL-producing *Acinetobacter baumannii* isolates[a]

	MIC (mg/liter)						
Collection no.	KBP-7072	TGC	CAZ	GM	LEV	MEM	β-Lactamase profile
674334	0.12	1	>32	≤1	>4	>8	GES-22, OXA-23, OXA-51
689088	0.06	0.5	>32	8	>4	>8	GES-11, OXA-23, OXA-51
764370	0.5	2	>32	>8	>4	>8	CTX-M-15, KPC-3, OXA-23, OXA-66, OXA-9, SHV-11, TEM-1
919444	0.06	0.25	>32	>8	>4	>32	CTX-M-115, CARB-16, OXA-72, OXA-90 TEM-1
1003787	0.06	0.5	>32	>16	>16	>32	CTX-M-115, CARB-16, OXA-72, OXA-90
143038	0.5	2	>16	>8	>4	>8	IMP-1, OXA-51
143675	0.5	2	>16	>8	>4	>8	IMP-1, OXA-51
177190	0.12	0.5	>16	≤2	>4	>8	IMP-1, OXA-51
602690	0.5	2	>32	>8	>4	>8	NDM-1, OXA-51, TEM-1
602847	1	2	>32	>8	>4	>8	NDM-1, OXA-23, OXA-51, TEM-1

[a]TGC, tigecycline; CAZ, ceftazidime; GM gentamicin; LEV, levofloxacin; MEM, meropenem; ESBL, extended-spectrum β-lactamase; MBL, metallo-β-lactamase.

MIC values of 0.06 mg/liter to 0.5 mg/liter, 0.5 mg/liter, and 0.12 to 1 mg/liter, respectively (Table 7).

All ESBL- and MBL-producing *A. baumannii* isolates were resistant to ceftazidime, levofloxacin, and meropenem, with MIC values of >16 mg/liter, >4 mg/liter, and >8 mg/liter, respectively (Table 7).

DISCUSSION

Approximately one-half of the estimated 1,000,000 global *A. baumannii* infections that occur annually are carbapenem resistant; of those 500,000 infections, approximately 22,950 cases occur annually in the United States (13). Few therapeutic options currently exist for treating carbapenem-resistant *A. baumannii* infections, which tend to be extensively drug resistant or pandrug resistant, mostly due to the worldwide expansion of international clones well adapted to the nosocomial environment (14–16).

Previous studies by Lepak et al. (5) in a neutropenic murine pneumonia model against *Staphylococcus aureus* and *Streptococcus pneumoniae* have shown that the area under the concentration-time curve (AUC)/MIC ratio is the pharmacokinetic/pharmacodynamic (PK/PD) parameter that correlates best with KBP-7072 *in vivo* efficacy. In that study, KBP-7072 epithelial lining fluid (ELF) concentrations ranged from 82% to 238% compared to free plasma concentrations. KBP-7072 phase 2 dose selection discussions for CAP are ongoing with the U.S. Food and Drug Administration (FDA). A similar aminomethylcycline (omadacycline) received FDA approval in October 2018, with a susceptibility breakpoint of 4 mg/liter for CAP against *Klebsiella pneumoniae*. Based on this information and available Gram-positive PK/PD data for KBP-7072, conservative estimates of 1 mg/liter and 2 mg/liter were applied for the *in vitro* analysis of KBP-7072 MIC results against *A. baumannii*.

As observed with other newer tetracycline antibacterials, including eravacycline, omadacycline, and tigecycline, KPB-7072 is able to overcome many of the common efflux and ribosomal protection resistance mechanisms that cause resistance in older-generation tetracyclines (6). Combination treatments consisting of carbapenems, colistin, rifampin, and tigecycline have been studied; however, each of these drugs has limitations (14). New antibacterial agents in clinical development with *in vitro* activity against *A. baumannii* include cefiderocol (17), sulbactam-durlobactam (18), and KBP-7072.

Overall, KBP-7072 ($MIC_{50/90}$, 0.25/1 mg/liter) was comparable in activity to colistin (92.8% S) against *A. baumannii* isolates, inhibiting 99.2% of *A. baumannii* isolates at ≤2 mg/liter and 97.6% of isolates at ≤1 mg/liter. Compared to other recent tetracyclines, KBP-7072 ($MIC_{50/90}$, 0.25/1 mg/liter) was comparable in activity to eravacycline ($MIC_{50/90}$, 0.25/1 mg/liter) (19, 20), 4-fold more potent than tigecycline ($MIC_{50/90}$, 1/4 mg/liter), and 8- to 16-fold more potent than omadacycline ($MIC_{50/90}$, 4/8 mg/liter) (10, 21). KBP-7072 was equally active against carbapenem-resistant, colistin-resistant, and tetracycline-resistant isolates of *A. baumannii*; maintained activity against ESBL-phenotype and MBL-producing isolates; and remained active against *A. baumannii* isolates regardless of geographic location. Interestingly, KBP-7072 outperformed, based on MIC_{90} values, all comparator agents, including tigecycline, that are often clinically used against carbapenem-resistant and multidrug-resistant *A baumannii* isolates. In general, KBP-7072 MIC_{50} and MIC_{90} results were similar to those observed for colistin.

In summary, these data document the potent *in vitro* activity of KBP-7072 against a challenge set of recent geographically diverse and molecularly characterized *A. baumannii* isolates and support the agent's continued clinical development for the treatment of serious infections, including those caused by drug-susceptible and -resistant *A. baumannii* isolates.

MATERIALS AND METHODS

Organisms. A collection of 531 recent (98.1% from 2018) geographically diverse *A. baumannii* isolates were recovered from patients with documented infections in 34 countries, including the United States (61 medical centers; 169 isolates [31.8%]) and countries in Europe (29 medical centers; 171 isolates [32.2%]), Latin America (9 medical centers; 81 isolates [15.3%]), and the Asia-Pacific region (17 medical

centers; 110 isolates [20.7%]), as part of the SENTRY Antimicrobial Surveillance Program. *A. baumannii* isolates were collected from patients with bloodstream infections (115 isolates [21.7%]), patients with skin and skin structure infections (113 isolates [21.3%]), hospitalized patients with pneumonia (301 isolates [56.7%]), and patients with urinary tract infections (2 isolates [0.4%]) and included only 1 isolate/patient/infection episode. Bacterial identifications were confirmed by JMI Laboratories using matrix-assisted laser desorption ionization–time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Colistin-resistant *A. baumannii* isolates were defined as having colistin MIC values at ≥4 mg/liter (22). MBL-producing *A. baumannii* isolates were defined as containing an IMP, VIM, or NDM β-lactamase-encoding gene and displaying a meropenem MIC value of ≥8 mg/liter. ESBL-producing *A. baumannii* isolates were defined as containing an ESBL gene, e.g., $bla_{\text{CTX-M}}$ or bla_{GES}, and displaying a ceftazidime MIC value of ≥32 mg/liter, and carbapenemase-producing *A. baumannii* isolates were defined as containing a carbapenemase (KPC-3 or OXA) and having a meropenem MIC value of ≥8 mg/liter. In this study, test organisms consisted of 490 colistin-susceptible *A. baumannii* isolates, 38 colistin-resistant *A. baumannii* isolates, 5 MBL-producing (IMP and NDM) *A. baumannii* isolates, and 5 ESBL (CTX-M and GES)- and/or carbapenemase (KPC and OXA)-producing *A. baumannii* isolates. Colistin susceptibility results were not available for three of the MBL-producing *A. baumannii* isolates. Colistin-resistant and MBL- and ESBL-producing *A. baumannii* isolates were molecularly characterized using next-generation sequencing and high-resolution *in silico* analysis (16).

Antimicrobial susceptibility testing. Reference broth microdilution susceptibility testing was performed at JMI Laboratories according to CLSI document M07 guidelines (23) and interpreted using CLSI document M100 (22), EUCAST (24), and FDA (25) breakpoint interpretive criteria. Freshly prepared cation-adjusted Mueller-Hinton broth (CLSI document M100) (22) was used to inoculate test panels containing KBP-7072 (KBP BioSciences, Princeton, NJ) and tigecycline (lot number R09410; U.S. Pharmacopeia, Rockville, MD). KBP-7072 and tigecycline test ranges were 32 mg/liter to 0.015 mg/liter and 16 mg/liter to 0.015 mg/liter, respectively. Historical susceptibility data from the SENTRY Antimicrobial Surveillance Program were included for ceftazidime, colistin, doxycycline, gentamicin, levofloxacin, meropenem, minocycline, piperacillin-tazobactam, and tetracycline. Tigecycline was included in this study as well as the SENTRY Antimicrobial Surveillance Program and was used as a bridge compound for the comparator agent susceptibility data. Broth microdilution MIC values were validated by concurrently testing CLSI quality control reference strains (22). The bacterial inoculum density was monitored by colony counts.

ACKNOWLEDGMENTS

This study was performed by JMI Laboratories and supported by KBP Biosciences, which included funding for services related to preparing the manuscript. JMI Laboratories contracted to perform services in 2018 for Achaogen, Inc.; the Albany College of Pharmacy and Health Sciences; Allecra Therapeutics; Allergan; AmpliPhi Biosciences Corp.; Amplyx; Antabio; the American Proficiency Institute; Arietis Corp.; Arixa Pharmaceuticals, Inc.; Astellas Pharma, Inc.; Athelas; Basilea Pharmaceutica, Ltd.; Bayer AG; Becton, Dickinson and Company; bioMérieux SA; Boston Pharmaceuticals; Bugworks Research, Inc.; CEM-102 Pharmaceuticals; Cepheid; Cidara Therapeutics, Inc.; CorMedix, Inc.; DePuy Synthes; Destiny Pharma; Discuva Ltd.; Dr. Falk Pharma GmbH; Emery Pharma; Entasis Therapeutics; Eurofarma Laboratorios SA; the U.S. Food and Drug Administration; the Fox Chase Chemical Diversity Center, Inc.; Gateway Pharmaceutical, LLC; GenePOC, Inc.; Geom Therapeutics, Inc.; GlaxoSmithKline plc; Harvard University; Helperby; HiMedia Laboratories; F. Hoffmann-La Roche, Ltd.; Icon plc; Idorsia Pharmaceuticals, Ltd.; Iterum Therapeutics plc; Laboratory Specialists, Inc.; Melinta Therapeutics, Inc.; Merck & Co., Inc.; Microchem Laboratory; Micromyx; MicuRx Pharmaceuticals, Inc.; Mutabilis Co.; Nabriva Therapeutics plc; NAEJA-RGM; Novartis AG; Oxoid, Ltd.; Paratek Pharmaceuticals, Inc.; Pfizer, Inc.; Polyphor, Ltd.; Pharmaceutical Product Development, LLC; Prokaryotics, Inc.; Qpex Biopharma, Inc.; Ra Pharmaceuticals, Inc.; Roivant Sciences, Ltd.; Safeguard Biosystems; Scynexis, Inc.; SeLux Diagnostics, Inc.; Shionogi and Co., Ltd.; SinSa Labs; Spero Therapeutics; Summit Pharmaceuticals International Corp.; Synlogic; T2 Biosystems, Inc.; Taisho Pharmaceutical Co., Ltd.; TenNor Therapeutics, Ltd.; Tetraphase Pharmaceuticals; The Medicines Company; Theravance Biopharma; the University of Colorado; the University of Southern California—San Diego; the University of North Texas Health Science Center; VenatoRx Pharmaceuticals, Inc.; Vyome Therapeutics, Inc.; Wockhardt; Yukon Pharmaceuticals, Inc.; the Zai Lab; and Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare. V.J.B., J.Z., L.L., M.Z., X.T., and Q.L. are employees of and may hold stock options in KBP Biosciences.

REFERENCES

1. Roberts MC. 2003. Tetracycline therapy: update. Clin Infect Dis 36:462–467. https://doi.org/10.1086/367622.
2. Chopra I. 2002. New developments in tetracycline antibiotics: glycylcyclines and tetracycline efflux pump inhibitors. Drug Resist Updat 5:119–125. https://doi.org/10.1016/s1368-7646(02)00051-1.
3. Grossman TH. 2016. Tetracycline antibiotics and resistance. Cold Spring Harb Perspect Med 6:a025387. https://doi.org/10.1101/cshperspect.a025387.
4. Chopra I. 2001. Glycylcyclines: third-generation tetracycline antibiotics. Curr Opin Pharmacol 1:464–469. https://doi.org/10.1016/s1471-4892(01)00081-9.
5. Lepak AJ, Zhao M, Liu Q, Wang P, Wang Y, Bader JC, Ambrose PG, Andes DR. 2019. Pharmacokinetic/pharmacodynamic evaluation of a novel aminomethylcycline antibiotic, KBP-7072, in the neutropenic murine pneumonia model against *Staphylococcus aureus* and *Streptococcus pneumoniae*. Antimicrob Agents Chemother 63:e02404-18. https://doi.org/10.1128/AAC.02404-18.
6. Kaminishi T, Schedlbauer A, Ochoa-Lizarralde B, de Astigarraga E, Çapuni R, Yang F, Benn V, Liu Q, Tan X, Zhang M, Connell SR, Fucini P. 2018. The third-generation tetracycline KBP-7072 exploits and reveals a new potential of the primary tetracycline binding pocket. bioRxiv 508218. https://doi.org/10.1101/508218.
7. Wang Y, Liu Q, Zhang B. 2016. Antibacterial activity of KBP-7072 against clinical isolates of drug-resistant bacteria, abstr Monday-565. Abstr ASM Microbe, 2016, 16 to 20 June 2016, Boston, MA.
8. ClinicalTrials.gov. 2015. Safety, tolerability and pharmacokinetics of KBP-7072. National Library of Medicine, Bethesda, MD. https://clinicaltrials.gov/ct2/show/NCT02454361?cond=kBP-7072&draw=2&rank=1.
9. ClinicalTrials.gov. 2015. A multiple ascending dose study of KBP-7072 in healthy subjects. National Library of Medicine, Bethesda, MD. https://clinicaltrials.gov/ct2/show/NCT02654626?cond=kBP-7072&draw=2&rank=2.
10. Pfaller MA, Huband MD, Shortridge D, Flamm RK. 2018. Surveillance of omadacycline activity tested against clinical isolates from the United States and Europe: report from the SENTRY Antimicrobial Surveillance Program, 2016. Antimicrob Agents Chemother 62:e02327-17. https://doi.org/10.1128/AAC.02327-17.
11. Piperaki ET, Tzouvelekis LS, Miriagou V, Daikos GL. 2019. Carbapenem-resistant *Acinetobacter baumannii*: in pursuit of an effective treatment. Clin Microbiol Infect 25:951–957. https://doi.org/10.1016/j.cmi.2019.03.014.
12. WHO. 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. WHO, Geneva, Switzerland. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf.
13. Spellberg B, Rex JH. 2013. The value of single-pathogen antibacterial agents. Nat Rev Drug Discov 12:963. https://doi.org/10.1038/nrd3957-c1.
14. Viehman JA, Nguyen MH, Doi Y. 2014. Treatment options for carbapenem-resistant and extensively drug-resistant *Acinetobacter baumannii* infections. Drugs 74:1315–1333. https://doi.org/10.1007/s40265-014-0267-8.
15. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18:268–281. https://doi.org/10.1111/j.1469-0691.2011.03570.x.
16. Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. 2019. Antimicrobial susceptibility of *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex and *Stenotrophomonas maltophilia* clinical isolates: results from the SENTRY Antimicrobial Surveillance Program (1997-2016). Open Forum Infect Dis 6:S34–S46. https://doi.org/10.1093/ofid/ofy293.
17. Kazmierczak KM, Tsuji M, Wise MG, Hackel M, Yamano Y, Echols R, Sahm DF. 2019. In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-non-susceptible Gram-negative bacilli, including serine carbapenemase- and metallo-beta-lactamase-producing isolates (SIDERO-WT-2014 Study). Int J Antimicrob Agents 53:177–184. https://doi.org/10.1016/j.ijantimicag.2018.10.007.
18. Barnes MD, Kumar V, Bethel CR, Moussa SH, O'Donnell J, Rutter JD, Good CE, Hujer KM, Hujer AM, Marshall SH, Kreiswirth BN, Richter SS, Rather PN, Jacobs MR, Papp-Wallace KM, van den Akker F, Bonomo RA. 2019. Targeting multidrug-resistant *Acinetobacter* spp.: sulbactam and the diazabicyclooctenone beta-lactamase inhibitor ETX2514 as a novel therapeutic agent. mBio 10:e00159-19. https://doi.org/10.1128/mBio.00159-19.
19. Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Quale J. 2015. Activity of eravacycline against *Enterobacteriaceae* and *Acinetobacter baumannii*, including multidrug-resistant isolates, from New York City. Antimicrob Agents Chemother 59:1802–1805. https://doi.org/10.1128/AAC.04809-14.
20. Hwang S, Efimova E, Fyfe C, Hawser S, Morrissey I. 2019. Global in vitro surveillance of eravacycline against Gram-negative and Gram-positive clinical isolates, including multidrug-resistant pathogens, collected in 2017, abstr Friday-543. ASM Microbe, 20 to 24 June 2019, San Francisco, CA.
21. Huband MD, Pfaller MA, Shortridge D, Flamm RK. 2019. Surveillance of omadacycline activity tested against clinical isolates from the United States and Europe: results from the SENTRY Antimicrobial Surveillance Programme, 2017. J Glob Antimicrob Resist 19:56–63. https://doi.org/10.1016/j.jgar.2019.02.017.
22. CLSI. 2019. Performance standards for antimicrobial susceptibility testing: 29th informational supplement. M100Ed29. CLSI, Wayne, PA.
23. CLSI. 2018. M07Ed11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard, 11th ed. CLSI, Wayne, PA.
24. EUCAST. 2019. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, January 2019. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf.
25. FDA. 2019. US FDA-recognized antimicrobial susceptibility test interpretive criteria. FDA, Silver Spring, MD. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm.