# In Vitro Activity of Sulopenem and Comparator Agents Against Anaerobic Clinical Isolates from the SENTRY Surveillance Program 2018-2020

Steven I. Aronin, MD<sup>1</sup>, Sailaja Puttagunta, MD<sup>1</sup>, Michael W. Dunne, MD<sup>2</sup>, Chris Blankers<sup>3</sup>, Joshua M. Maher<sup>3</sup>, Michael Huband, BS<sup>3</sup>

<sup>1</sup>Iterum Therapeutics, Old Saybrook, CT; <sup>2</sup>Bill and Melinda Gates Medical Research Institute, Cambridge, MA; <sup>3</sup>JMI Labs, North Liberty, IA

#### **ABSTRACT**

**Background:** Sulopenem is a thiopenem antibiotic with an oral and parenteral formulation being developed for the treatment of urinary tract infection (UTI) and complicated intra-abdominal infection. We evaluated the *in vitro* antimicrobial activity of sulopenem against 559 anaerobic isolates from 2018-2020 from the SENTRY surveillance program.

Materials/methods: Anaerobic clinical isolates from bloodstream infections (BSI: 196 isolates; 34.9% overall), skin and skin structure infections (SSSI: 180 isolates; 32.1% overall), intra-abdominal infections (IAI: 28 isolates; 5.0% overall), pneumonia in hospitalized patients (4 isolates; 0.7%), urinary tract infections (UTI: 4 isolates; 0.7% overall), and other infection types (149 isolates; 26.6%) were collected 2018-2020 from patients at 42 medical centers in the United States and Europe and tested for susceptibility to sulopenem by pathogen and infection type using agar dilution methodology according to Clinical and Laboratory Standards Institute (CLSI) M11 (2018) guidelines. Cumulative MIC distribution data for sulopenem and comparators are presented by CLSI, the European Committee on Antimicrobial Susceptibility Testing, and the United States Food and Drug Administration breakpoint interpretive criteria.

**Results:** Sulopenem demonstrated potent *in vitro* antibacterial activity against a collection of 559 recent anaerobic clinical isolates (287 Gram-negative and 272 Gram-positive) from Europe and the United States.

Antimicrobial agent	No. of isolates	MIC <sub>50</sub>	MIC <sub>90</sub>	<b>MIC Range</b>
Sulopenem Agar	559	0.12	1	≤0.015 to >16
Clindamycin Agar	559	0.5	>4	≤0.03 to >4
Meropenem Agar	559	0.12	1	≤0.015 to >8
Metronidazole Agar	559	1	>16	≤0.06 to >16
Moxifloxacin Agar	559	0.5	8	≤0.06 to >8
Piperacillin-tazobactam Agar	559	0.25	16	≤0.06 to >64
Tigecycline Agar	559	0.25	2	≤0.06 to >8

Sulopenem (MIC<sub>50/90</sub>, 0.12/1 mg/L; 98.9% inhibited at  $\leq$ 4 mg/L) and meropenem (MIC<sub>50/90</sub>, 0.12/1 mg/L; 98.4%/96.8%/98.4% susceptible [CLSI/EUCAST/FDA]) were the most active compounds tested, while susceptibility for other commonly used anaerobic agents ranged from 75%/78.9%/75% (CLSI/EUCAST/FDA) for clindamycin to 94.3%/88.7%/94.3% (CLSI/EUCAST/FDA) for piperacillin-tazobactam. In vitro MIC<sub>50/90</sub> (µg/mL) was similar across infection types and geographic region.

**Conclusions:** Sulopenem has potent *in vitro* activity against recent anaerobic clinical isolates from patients with BSI, SSSI, IAI, pneumonia, and UTI.

#### INTRODUCTION

- Sulopenem is a thiopenem antibiotic with an oral and parenteral formulation being developed for the treatment of urinary tract infection (UTI) and complicated intra-abdominal infection.
- We evaluated the *in vitro* antimicrobial activity of sulopenem against 559 anaerobic isolates from patients in the United States and Europe with an inpatient or community-acquired infection.

#### METHODS

- Anaerobic clinical isolates from bloodstream infections (BSI: 196 isolates; 34.9% overall), skin and skin structure infections (SSSI: 180 isolates; 32.1% overall), intra-abdominal infections (IAI: 28 isolates; 5.0% overall), pneumonia in hospitalized patients (4 isolates; 0.7%), urinary tract infections (UTI: 4 isolates; 0.7% overall), and other infection types (149 isolates; 26.6%) were collected 2018-2020 from patients at 42 medical centers in the United States and Europe and tested for susceptibility to sulopenem and comparator agents using agar dilution methodology according to CLSI M11 (2018) guidelines.
- Cumulative MIC distribution data for sulopenem for each infection type and each pathogen are presented by CLSI, the European Committee on Antimicrobial Susceptibility Testing, and the United States Food and Drug Administration breakpoint interpretive criteria.

#### RESULTS

## Table 1: *In vitro* Antibacterial Activity of Sulopenem Against Anaerobic Isolates

Organism/organism group

Organism/organism group	ivo. Of isolates	WIIC <sub>50</sub>	WIIC <sub>90</sub>	wiic Kange
Gram-negative Anaerobes:				
Bacteroides fragilis	109	0.12	1	≤0.015 to >16
Prevotella species	34	0.06	0.12	≤0.015 to 0.12
Other <i>Bacteroides</i> species	27	0.12	0.5	≤0.015 to 2
Bacteroides thetaiotamicron	25	0.25	1	0.06 to 2
Bacteroides vulgatus	18	0.25	1	0.06 to 1
Bacteroides ovatus	15	0.25	1	0.12 to 1
Fusobacterium nucleatum	13	0.12	0.12	≤0.015 to 0.5
Veillonella parvula	12	0.12	2	0.03 to 8
Fusobacterium necrophorum	11	≤0.015	0.06	≤0.015 to 0.25
Gram-positive Anaerobes:				
Cutibacterium acnes	73	0.03	0.06	≤0.015 to 0.06
Clostridium perfringens	65	0.12	0.25	≤0.015 to 1
Parvimonas micra	31	0.03	0.06	0.03 to 0.12
Eggerthella lenta	20	1	1	0.25 to 2
Other <i>Clostridium</i> species	20	0.25	4	0.06 to 4
Actinomyces species	14	0.25	0.5	0.06 to 0.5
Finegoldia magna	14	0.12	0.25	≤0.015 to0.25
Peptoniphilus species	10	≤0.015	0.03	≤0.015 to 0.12
*Includes organisms with results for 10 or more	isolates			

#### RESULTS

### Table 2: Antimicrobial Activity of Sulopenem and Comparator Agents Tested Against 559 Anaerobic Isolates

Antimicrobial Agent	No. of	mg/L				CLSIa		EUCAST			
	Isolates	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC Range	%S	%I	%R	%S	%I	%R	
Sulopenem Agar	559	0.12	1	≤0.015 to >16							
Clindamycin Agar	559	0.5	>4	≤0.03 to >4	75.0	3.9	21.1	78.9		21.1	
Meropenem Agar	559	0.12	1	≤0.015 to >8	98.4	1.1	0.5	96.8	2.7	0.5	
Metronidazole Agar	559	1	>16	≤0.06 to >16	83.2	0.3	16.5	81.9		18.1	
Moxifloxacin Agar	559	0.5	8	≤0.06 to >8	82.6	4.0	13.4				
Piperacillin- tazobactam Agar	559	0.25	16	≤0.06 to >64	94.3	3.9	1.8	88.7	5.6	5.7	
Tigecycline Agar	559	0.25	2	≤0.06 to >8							

a Criteria as published by CLSI (2021), EUCAST (2021), and the US FDA (2021).

Organisms included: Actinobaculum schaalii (3), Actinomyces canis (1), A. europaeus (1), A. naeslundii (1), A. neuii (2), A. odontolyticus (4), A. oris (2), A. radingae (2), Bacteroides caccae (5), B. fragilis (109), B. fragilis group (3), B. ovatus (15), B. ovatus/Bacteroides xylanisolvens (2), B. stercoris (1), B. thetaiotaomicron (25), B. thetaiotaomicron/Bacteroides faecis (8), B. uniformis (7), B. vulgatus (18), Bifidobacterium breve (2), B. longum (1), Clostridium cochlearium (1), C. innocuum (3), C. perfringens (65), C. ramosum (4), C. septicum (8), C. sporogenes (2), C. tertium (2), Collinsella aerofaciens (1), Cutibacterium acnes (73), C. avidum (4), Eggerthella lenta (20), Facklamia hominis (1), Finegoldia magna (14), Fusobacterium necrophorum (11), F. nucleatum (13), F. periodonticum (1), F. varium (1), Paeniclostridium sordellii (2), Parabacteroides distasonis (9), P. gordonii (1), Parvimonas micra (31), Peptoniphilus asaccharolyticus (1), P. harei/ indolicus (7), Peptostreptococcus anaerobius (6), P. stomatis (1), Porphyromonas asaccharolytica (1), P. somerae (2), Prevotella bergensis (1), P. bivia (5), P. buccae (6), P. corporis (1), P. denticola (3), P. disiens (2), P. intermedia (4), P. loescheii (1), P. melaninogenica (4), P. nigrescens (2), P. oris (2), Slackia exigua (2), unspeciated Actinomyces (1), unspeciated Bacteroides (1), unspeciated Prevotella (3), unspeciated Peptoniphilus (2), unspeciated Veillonella (3), Veillonella atypica (2), V. parvula (12), and V. parvula group (1).

#### T 1 1 5 A

Table 5: Activity of Sulopenem Against Anaerobes by Infection Type

Infection		No. and Cumulative Percent of Isolates Inhibited at a Sulopenem MIC (mg/L) of:											mg/L	
type (no. of isolates)	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16	MIC <sub>50</sub>	MIC <sub>9</sub>
All (559)	51 (9.1%)	82 (23.8%)	128 (46.7%)	104 (65.3%)	100 (83.2%)	36 (89.6%)	34 (95.7%)	8 (97.1%)	10 (98.9%)	1 (99.1%)	1 (99.3%)	4 (100%)	0.12	1
BSI (196)	17 (8.7%)	17 (17.3%)	40 (37.8%)	38 (57.1%)	42 (78.6%)	16 (86.7%)	18 (95.9%)	5 (98.5%)	1 (99.0%)	0 (99.0%)	0 (99.0%)	2 (100%)	0.12	1
SSTI (180)	21 (11.7%)	33 (30.0%)	38 (51.1%)	36 (71.1%)	30 (87.8%)	10 (93.3%)	6 (96.7%)	1 (97.2%)	3 (98.9%)	0 (98.9%)	1 (99.4%)	1 (100%)	0.06	0.5
Other (148) <sup>a</sup>	12 (8.1%)	27 (26.4%)	38 (52.0%)	22 (66.9%)	24 (83.1%)	9 (89.2%)	7 (93.9%)	2 (95.3%)	5 (98.6%)	1 (99.3%)	0 (99.3%)	1 (100%)	0.06	1
IAI (28)	1 (3.6%)	3 (14.3%)	10 (50.0%)	7 (75.0%)	3 (85.7%)	1 (89.3%)	2 (96.4%)	0 (96.4%)	1 (100%)				0.06	1
Pneumonia (4)	0 (0.0%)	1 (25.0%)	1 (50.0%)	1 (75.0%)	0 (75.0%)	0 (75.0%)	1 (100%)						0.06	
UTI (3)	0 (0.0%)	1 (33.3%)	1 (66.7%)	0 (66.7%)	1 (100%)								0.06	

## Table 3: Antimicrobial Activity of Sulopenem and Comparator Agents Against Gram-negative Clinical Anaerobic Isolates

Antimicrobial Agent	No. of Isolates			CLSIa		EUCASTa				
		MIC <sub>50</sub>	MIC <sub>90</sub>	MIC Range	%S	%I	%R	%S	%	%R
Sulopenem Agar	287	0.12	1	≤0.015 to >16						
Clindamycin Agar	287	0.5	>4	≤0.03 to >4	64.1	5.2	30.7	69.3		30.7
Meropenem Agar	287	0.12	1	≤0.015 to >8	96.9	2.1	1.0	93.7	5.2	1.0
Metronidazole Agar	287	1	2	≤0.06 to >16	97.9	0.3	1.7	97.6		2.4
Moxifloxacin Agar	287	0.5	>8	≤0.06 to >8	76.0	5.6	18.5			
Piperacillin- tazobactam Agar	286	0.5	16	≤0.06 to >64	92.7	3.8	3.5	85.7	7.0	7.3
Tigecycline Agar	286	0.5	4	≤0.06 to >8						

## Table 4: Antimicrobial Activity of Sulopenem and Comparator Agents Against Gram-positive Clinical Anaerobic Isolates

	No. of			CLSIa		EUCASTa				
	Isolates	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC Range	%S	%I	%R	%S	%I	%R
Sulopenem Agar	272	0.06	0.5	≤0.015 to 4						
Clindamycin Agar	272	0.12	>4	≤0.03 to >4	86.4	2.6	11.0	89.0		11.0
Meropenem Agar	272	0.06	0.5	≤0.015 to 2	100.0	0.0	0.0	100.0	0.0	0.0
Metronidazole Agar	272	1	>16	≤0.06 to >16	67.6	0.4	32.0	65.4		34.6
Moxifloxacin Agar	272	0.25	4	≤0.06 to >8	89.7	2.2	8.1			
Piperacillin- tazobactam Agar	272	0.12	2	≤0.06 to 64	96.0	4.0	0.0	91.9	4.0	4.0
Tigecycline Agar	272	0.12	2	≤0.06 to >8						

#### CONCLUSIONS

- Sulopenem has potent in vitro activity against recent Grampositive and Gram-negative anaerobic clinical isolates from patients with bloodstream infections, skin and skin structure infections, intra-abdominal infections, pneumonia in hospitalized patients, and urinary tract infections
- Sulopenem's potent in vitro activity against anaerobic clinical isolates was similar across infection type and across geographic region
- Sulopenem's in vitro activity against anaerobic clinical isolates compares favorable to other commonly used anaerobic agents
- Sulopenem has potent in vitro activity against anaerobic clinical isolates, offering both an intravenous treatment and a potential oral step-down option for inpatients with bloodstream infection, intra-abdominal infection, and urinary tract infection

