The carbapenem PZ-601 (SMP-601) has potent *in vitro* Gram-positive, Gram-negative and anaerobic bacterial activity.

Abstract # F1-343

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Revised Abstract

Background: PZ-601 (SMP-601) is a novel broad-spectrum carbapenem. High affinity for penicillin-binding proteins gives this carbapenem enhanced activity against multidrug-resistant Gram-positive (GP) organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), while retaining carbapenem-like spectrum against Gram-negative (GN) pathogens excluding *Pseudomonas spp*. The *in vitro* activity of PZ-601 was compared to 21 other antimicrobials against a wide variety of GP, GN and anaerobic bacteria. **Methods**: This study included 3,294 clinical isolates (1,343 GP; 1,723 GN; 228 anaerobes) collected between 2003 and 2006 from 379 sites in 39 countries encompassing North America, South America, Europe, and Asia. Minimal inhibitory concentrations (MIC) were determined using broth microdilution (aerobes) and agar dilution (anaerobes) according to CLSI guidelines. **Results**: PZ-601 $MIC_{50/90}$ values were 0.03/1 against staphylococci including MRSA; 1/2 against *E. faecalis* including vancomycin-resistant strains; and 0.06/0.5 against *S. pneumoniae*, including pen-resistant strains. PZ-601 $MIC_{50/90}$ values were 0.25/1 against all *E. coli/K. pneumoniae* combined with values of 1/4 against ESBL producing strains. $MIC_{50/90}$ values for *E. cloacae* were 4/8. With $MIC_{50/90}$ values of ≤0.015/0.06, the activity of PZ-601 against peptostreptococci was superior to imipenem and the beta-lactam/beta-lactamase inhibitors. Similar activity of PZ-601 and imipenem were observed against *Bacteroides fragilis*. **Conclusions**: PZ-601 exhibited broad-spectrum *in vitro* activity against a wide range of clinical staphylococci, streptococci, and *E. faecalis*, including resistant phenotypes, and substantial activity against key GN pathogens including ESBL-producing *E. coli* and *K. pneumoniae*.

Introduction

The growing need for new and effective broad-spectrum antibiotics is highlighted by the increasing emergence of multi-resistant gram-positive and gram-negative pathogens, community associated methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae* [3].

The carbapenems are unsurpassed among parenteral beta-lactams in their activity against Gram-negative pathogens, while retaining the stability and safety profiles of other beta-lactams [4]. PZ-601 (SMP-601, SM-216601) is a novel 1beta-methyl carbapenem with enhanced Gram-positive activity while retaining favorable Gram-negative bacterial profiles [5].

This study documents the broad-spectrum antimicrobial profile of PZ-601 against a diverse population of Gram-positive and –negative aerobic and anaerobic pathogens.

Materials and Methods

- Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines [1].
- All study organisms were clinical isolates collected between January 2003 and September 2006 and frozen at –70 °C until subcultured. Testing occurred on second pass subculture. Custom in-house microdilution panels were incubated at 35 °C for 20 to 24 hours before reading the MICs; staphylococci, enterococci and enterobacteriaceae were incubated at 35 °C for 16-20 hrs. All anaerobes were read at 48 hours.
- Quality control testing was performed daily as specified by the CLSI using the following strains: *Staphylococcus aureus* ATCC 29213; *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922 and ATCC 35218; *P. aeruginosa* ATCC 27853; and *Haemophilus influenzae* ATCC 49247 and ATCC 49766 [2].

Results

Table 1. PZ-601 *in vitro* activity ($MIC_{50/90}$; mcg/ml) against Gram-positive aerobic organisms and common resistant phenotypes.

Organism/ Phenotype	PZ-601	Imipenem	Dapto-mycin	Line-zolid	Vanco-mycin
S. aureus MethSus (108)	0.03/0.03	≤0.06/≤0.06	4/8	2/4	1/1
S. aureus MethRes (414)	0.5/1	2/>32	≤0.25/4	2/4	≤0.5/1
Coag-Neg Staph (201)	0.12/0.5	≤0.06/8	0.5/1	1/1	2/2
E. faecalis (102)	1/2	1/2	8/16	2/2	1/2
E. faecium (101)	4/8	>32/>32	2/4	2/4	>32/>32
E. faecium VRE (50)	4/8	>32/>32	2/4	2/4	>32/>32
S. agalactiae (101)	0.015/0.015	≤0.015/≤0.015	1/1	1/2	0.5/0.5
S. pneumoniae (106)	0.06/0.25	0.12/0.5	0.06/0.06	1/1	0.25/0.25
S. pneumoniae PenR (55)	0.25/0.5	0.25/1	0.06/0.06	1/1	0.25/0.25
S. pyogenes (105)	≤0.004/0.008	≤0.015/≤0.015	≤0.03/0.06	1/1	0.5/0.5
S. viridans (105)	0.015/0.06	0.03/0.12	0.25/1	1/2	0.25/0.5

Results

Table 2. PZ-601 *in vitro* activity ($MIC_{50/90}$; mcg/ml) against Gram-negative aerobic organisms.

Organism	PZ-601	Imi-penem	Ceftri-axone	Levo-floxacin	Pip-Tazo
C. freundii (102)	2/16	0.5/1	0.5/>64	≤0.5/2	4/>128
E. cloacae (211)	4/8	0.5/1	0.5>64	≤0.5/1	8/>128
E. coli (260)	0.25/1	≤0.12/0.25	≤0.25/>64	≤0.5/>8	2/16
E. coli ESBL (47)	1/2	≤0.12/0.25	>64/>64	>8/>8	4/16
K. pneumoniae (257)	0.25/4	0.25/0.5	≤0.25/>64	≤0.5/>8	16>128
K. pneumoniae ESBL (47)	1/8	≤0.12/1	>64/>64	8/>8	16/>128
M. morganii (103)	1/4	4/4	≤0.25/8	≤0.5/4	≤0.5/4
P. mirabilis (100)	0.25/0.25	2/4	≤0.25/≤0.25	≤0.5/≤0.5	≤0.5/≤0.5
P. vulgaris (100)	0.25/2	4/4	1/64	≤0.5≤0.5	≤0.5/1
S. marcescens (180)	4/8	0.25/1	0.54	≤0.51	4/16

Table 3. PZ-601 *in vitro* activity ($MIC_{50/90}$; mcg/ml) against other Gram-negative non-enterobacteriaceae, *A. baumannii* and *P. aeruginosa.*

Organism	PZ-601	Imi-penem	Ceftri-axone	Levo-floxacin	Pip-Tazo
A. baumannii (100)	4/64	1/64	64/>64	8/>8	128/>128
P. aeruginosa (101)	16/64	2/16	64/>64	1/>8	8/>128

Table 4. PZ-601 *in vitro* activity ($MIC_{50/90}$; mcg/ml) against anaerobic organisms *B. fragilis* and *Peptostreptococcus* spp.

Organism	PZ-601	Imi-penem	Amox-Clav	Cefox-itin	Metro-nidazole
B. fragilis (108)	0.12/4	.025/1	0.5/4	8/16	1/1
Peptostrep-tococcus spp (120)	≤0.015/0.06	0.12/1	0.25/0.5	0.25/1	0.5/1

Conclusions

- PZ-601 is a broad-spectrum carbapenem with enhanced activity against Gram-positive pathogens that retains significant Gram-negative and anaerobic activity.
- PZ-601 has MIC_{90} values ≤1 mcg/ml against methicillin-resistant *S. aureus*, coagulase-negative staphylococci, and all streptococcal species in this study, including penicillin-resistant *S. pneumoniae*. Significant Gram-positive activity extends to vancomycin-resistant *E. faecalis*.
- PZ-601 demonstrated significant *in vitro* activity against common anaerobic pathogens, *B. fragilis* and *Peptostreptococcus*, and against most enterobacteriaceae including ESBL producing strains.
- Further development of PZ-601 is warranted especially in clinical situations where MRSA, VRE or multiresistant pathogens may be suspected.

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