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In vitro Activity of GSK1322322, a Novel Peptide Deformylase Inhibitor, against 4,836 Pathogens from Skin and Soft Tissue Infections and Respiratory Tract Infections

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Abstract

Background: GSK1322322 is an antibacterial agent currently in development that inhibits peptide deformylase (PDF) function, a clinically unexploited target. GSK1322322 demonstrates targeted antibacterial activity against multi-drug resistant respiratory and skin pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and represents a new antibiotic class with a novel mode of action. In a large surveillance study, the *in vitro* activity of GSK1322322, azithromycin (AZ), clindamycin (CLINDA) and levofloxacin (LEVO), was investigated against community and hospital-associated skin and soft tissue infection (SSTI) pathogens, *S. aureus* (SA) and *Streptococcus pyogenes* (SP), and respiratory tract infection (RTI) pathogens, *Streptococcus pneumoniae* (SPN), *Haemophilus influenzae* (HI), and *Moraxella catarrhalis* (MC).
Methods: 4,836 recently collected (2004-2008) clinical SSTI and RTI pathogens including resistant phenotypes were evaluated. Minimum inhibitory concentrations (MICs) were determined by broth microdilution according to CLSI guidelines.
Results: *In vitro* activities of GSK1322322, AZ, CLINDA and LEVO:

Organism	N	MIC_{50}/MIC_{90} (mg/ml)			
		GSK1322322	AZ	CLINDA	LEVO
S. aureus	809	2/4	>8/>8	0.12/>4	0.25/>8
MRSA	391	2/4	>8/>8	0.12/>4	8/>8
MSSA	418	2/4	1/>8	0.12/0.25	0.25/0.5
AZ_RES	444	2/4	>8/>8	0.12/>4	4/>8
LEVO_RES	255	2/4	>8/>8	0.12/>4	8/>8
D-Test-POS	90	2/4	>8/>8	0.12/0.25	0.25/>8
S. pyogenes	398	0.5/0.5	0.12/0.25	0.03/0.06	0.5/1
AZ_RES	38	0.25/0.5	>8/>8	0.06/>4	0.5/1
S. pneumoniae	961	1/2	0.12/>8	0.06/>4	1/1
PEN-RES	166	0.5/1	>8/>8	>4/>4	1/8
AZ-RES	337	0.5/1	>8/>8	>4/>4	1/8
LEVO-RES	56	0.5/2	4/>8	0.06/>4	>8/>8
H. influenzae	2553	2/4	1/2	>4/>4 [a]	0.015/0.03 [a]
BL-Pos	580	2/8	1/2	4/>4 [b]	0.015/0.03 [b]
M. catarrhalis	115	1/1	≤0.03/0.06	1/2	0.03/0.06
BL-Pos	39	1/2	≤0.03/0.06	1/2	0.03/0.03

[a] n=1048; [b] n=247

Conclusion: GSK1322322 demonstrates excellent *in vitro* activity against common SSTI and RTI pathogens including MRSA, AZ- and LEVO-resistant SA and PEN-, AZ-, and LEVO-resistant SPN, HI and MC.

Introduction

GSK1322322 is an antibacterial agent currently in development that inhibits peptide deformylase (PDF) function, a clinically unexploited target. GSK1322322 demonstrates targeted antibacterial activity against multi-drug resistant respiratory and skin pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and represents a new antibiotic class with a novel mode of action. In a large surveillance study, the *in vitro* activity of GSK1322322, azithromycin, clindamycin and levofloxacin, was investigated against community and hospital-associated skin and soft tissue infection (SSTI) pathogens, *S. aureus* and *S. pyogenes*, and respiratory tract infection (RTI) pathogens, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

Methods

- All study organisms were clinical isolates previously collected and frozen at -70 °C in the years 2004 through 2008 with the exception of *H. influenzae* which were collected from 2001 – 2008. The isolates were collected from 50 countries in 6 global regions (Figure 1). All *S. aureus* and *S. pyogenes* were from skin and soft tissue infections (SSTI), and all *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae* were from community-associated respiratory tract infections (RTI), one isolate per patient, all ages included (Figure 2).
- Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines [1]. Mueller Hinton broth was used for *S. aureus* and *M. catarrhalis* with 3% lysed horse blood added for *S. pneumoniae* and *S. pyogenes*. Haemophilus Test Medium (HTM) broth was used for *H. influenzae*. Testing was performed using panels prepared freshly on the same day of testing. Study drugs included GSK1322322, azithromycin, clindamycin, and levofloxacin.
- Resistant phenotypes were interpreted according to the breakpoints of penicillin, azithromycin, clindamycin, and levofloxacin as defined in CLSI document M100-S20 (2010) [2]. Beta-lactamase production was determined on all *H. influenzae* using the cefinase disk methodology. D-Test for inducible clindamycin resistance (Macrolide-Lincosamide-Streptogramin B [MLSBi] resistance phenotype) was performed against all azithromycin-resistant/clindamycin-susceptible or intermediate *S. aureus* according to the disk approximation test as described by the CLSI [2].
- Quality control testing was performed each day of testing as specified by CLSI using the following isolates: *S. aureus* ATCC 29213; *S. aureus* BAA-977 (D-Test control); *S. pneumoniae* ATCC 49619; and *H. influenzae* ATCC 49247 and ATCC 49766.

Results

Figure 1. Distribution (%) of isolates categorized by geographic region and number of countries per region (n)

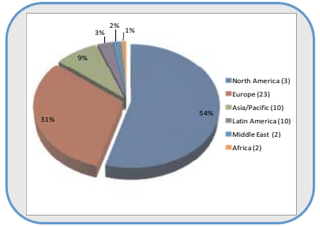

Figure 2 Distribution (%) of SSTI and RTI isolates categorized by Age Groups

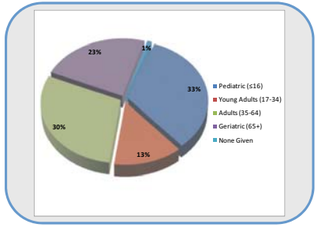

Table 1. Summary of *in vitro* activity for GSK1322322 and comparators against 398 isolates of *S. pyogenes* and macrolide-resistant phenotypes from SSTI sources

Organism/ Phenotype (n)	Drug	MIC (µg/ml) Range	MIC_{50}	MIC_{90}
S. pyogenes (n=398)	GSK1322322	0.06-1	0.5	0.5
	Azithromycin	≤0.03->8	0.12	0.25
	Clindamycin	≤0.015->4	0.03	0.06
	Levofloxacin	0.008->8	0.5	1
Macrolide-Resistant *	GSK1322322	0.06-0.5	0.25	0.5
	Azithromycin	>8->8	>8	>8
S. pyogenes (n=38)	Clindamycin	0.03->4	0.06	>4
	Levofloxacin	0.12-2	0.5	1

*Macrolide phenotypes are determined by the susceptibility of *S. pyogenes* to azithromycin as defined by CLSI breakpoints in document M100-S20, 2010.

Table 2. Summary of *in vitro* activity for GSK1322322 and comparators against 809 isolates of *S. aureus* and resistant phenotypes from SSTI sources

Organism/ Phenotype (n)	Drug	MIC (µg/ml) Range	MIC_{50}	MIC_{90}
S. aureus (n=809)	GSK1322322	0.12-8	2	4
	Azithromycin	0.5->8	>8	>8
	Clindamycin	≤0.015->4	0.12	>4
	Levofloxacin	0.12->8	0.25	>8
Methicillin-Resistant *	GSK1322322	0.12-8	2	4
	Azithromycin	1->8	>8	>8
S. aureus (n=391)	Clindamycin	≤0.015->4	0.12	>4
	Levofloxacin	0.12->8	8	>8
Macrolide-Resistant *S. aureus* (n=444)	GSK1322322	0.12-8	2	4
	Azithromycin	>8 ->8	>8	>8
	Clindamycin	≤0.015->4	0.12	>4
	Levofloxacin	0.12->8	4	>8
Levofloxacin-Resistant *S. aureus* (n=90)	GSK1322322	0.12-8	2	4
	Azithromycin	1->8	>8	>8
	Clindamycin	≤0.015->4	0.12	>4
	Levofloxacin	4->8	8	>8
D-Test [b]	GSK1322322	0.25-8	2	4
Positive	Azithromycin	>8->8	>8	>8
S. aureus (n=90)	Clindamycin	0.06-0.5	0.12	0.25
	Levofloxacin	0.12->8	0.25	>8

*Methicillin phenotypes are determined by the susceptibility of *S. aureus* to cefoxitin as defined in the CLSI document M100-S20, 2010.
[b] D-Test is a test that screens for inducible macrolide-lincosamide-streptogramin B resistance (MLSBi) in azithromycin-resistant and clindamycin-susceptible or intermediate isolates.

Table 3. Summary of *in vitro* activity for GSK1322322 and comparators against 961 isolates of *S. pneumoniae* and resistant phenotypes from RTI sources

Organism/ Phenotype (n) [a]	Drug	MIC (µg/ml) Range	MIC_{50}	MIC_{90}
S. pneumoniae (n=961)	GSK1322322	≤0.03 - 4	1	2
	Azithromycin	≤0.03 - >8	0.12	>8
	Levofloxacin	0.015 - >8	1	1
Penicillin-Resistant	GSK1322322	0.06 - 4	0.5	1
	Azithromycin	≤0.03 - >8	>8	>8
(n=166)	Levofloxacin	0.5 - >8	1	8
Macrolide-Resistant (n=337)	GSK1322322	≤0.03 - 4	0.5	1
	Azithromycin	2 - >8	>8	>8
	Levofloxacin	0.25 - >8	1	8
Levofloxacin-Resistant (n=56)	GSK1322322	0.06 - 4	0.5	2
	Azithromycin	0.06 - >8	4	>8
	Levofloxacin	8 - >8	>8	>8

[a] Drug Resistant Phenotypes of *S. pneumoniae* were determined by the resistant breakpoints of the individual drugs as defined in CLSI document M100-S20, 2010.

Table 4. Summary of *in vitro* activity for GSK1322322 and comparators for 2553 Isolates of *Haemophilus influenzae* from RTI sources

Organism/ Phenotype (n)	Drug *	MIC (µg/ml) Range	MIC_{50}	MIC_{90}
H. influenzae (n=2553)	GSK1322322	≤0.03 - 32	2	4
	Azithromycin	0.06 - >8	1	2
	Levofloxacin [a]	0.008 - 1	0.015	0.03
β-lactamase Negative (n=1973)	GSK1322322	≤0.03 - 32	2	4
	Azithromycin	0.06 - >8	1	2
	Levofloxacin [b]	0.008 - 1	0.015	0.03
β-lactamase Positive (n=580)	GSK1322322	≤0.03 - 32	2	8
	Azithromycin	0.12 - >8	1	2
	Levofloxacin [c]	0.008 - 0.5	0.015	0.03

* Levofloxacin was tested against a subset of isolates yielding lower n's:
* n=1048; [b] n=801; [c] n=247

Table 5. Summary of *in vitro* activity for GSK1322322 and comparators for 115 Isolates of *Moraxella catarrhalis* from RTI sources

Organism/ Phenotype (n)	Drug	MIC (µg/ml) Range	MIC_{50}	MIC_{90}
M. catarrhalis (n=115)	GSK1322322	0.06 - 2	1	1
	Azithromycin	≤0.03 - 0.12	≤0.03	0.06
	Levofloxacin	0.015 - 0.06	0.03	0.06
β-lactamase Negative (n=22)	GSK1322322	0.06 - 2	1	1
	Azithromycin	≤0.03 - 0.06	≤0.03	≤0.03
	Levofloxacin	0.015 - 0.06	0.03	0.06
β-lactamase Positive * (n=39)	GSK1322322	0.06 - 2	1	2
	Azithromycin	≤0.03 - 0.06	≤0.03	0.06
	Levofloxacin	0.03 - 0.06	0.03	0.03

* Not all isolates were tested for beta-lactamase.

Table 6. Summary of *in vitro* activity for GSK1322322 and comparators against 1328 pediatric (≤16 yo) isolates from RTI sources

Organism	Drug [a]	MIC (µg/ml) Range	MIC_{50}	MIC_{90}
S. pneumoniae (n=295)	GSK1322322	0.06-4	0.5	2
	Azithromycin	<0.03->8	0.12	>8
	Levofloxacin	0.5->8	1	1
H. influenzae (n=989)	GSK1322322	0.06-32	1	4
	Azithromycin	0.06->8	1	2
	Levofloxacin [b]	0.008-0.5	0.015	0.03
M. catarrhalis (n=44)	GSK1322322	0.12-2	1	1
	Azithromycin	<0.03-0.06	<0.03	0.06
	Levofloxacin	0.015-0.06	0.03	0.06

[a] Levofloxacin was tested against a subset of *H. influenzae*, n=371.

Conclusions

- GSK1322322 inhibited the *in vitro* growth of *S. aureus* and *S. pyogenes*, the two most common causative bacteria isolated from SSTI, with MIC_{90} values of 4 and 0.5 µg/ml, respectively. For the same *S. aureus* isolates, the MIC_{90} was >4 µg/ml for azithromycin, clindamycin, and levofloxacin. MIC_{90}s for the comparators and *S. pyogenes* were azithromycin 0.25 µg/ml, clindamycin 0.06 µg/ml, and levofloxacin 1 µg/ml.
- GSK1322322 demonstrated a MIC_{90} value of 4 µg/ml against resistant subsets of *S. aureus* including methicillin, macrolide, and levofloxacin resistant isolates, and those indicating a positive MLSBi phenotype. GSK1322322 had a MIC_{90} of 0.5 µg/ml against macrolide-resistant isolates of *S. pyogenes*.
- GSK1322322 inhibited the *in vitro* growth of common RTI pathogens *H. influenzae, S. pneumoniae*, and *M. catarrhalis* with MIC_{90} values of 4, 2, and 1 µg/ml, respectively.
- GSK1322322 demonstrated excellent activity against the resistant phenotypes of *S. pneumoniae* with a MIC_{90} of ≤ 2 µg/ml for the penicillin, macrolide and levofloxacin resistant strains. Although the GSK1322322 MIC_{90} was 8 µg/ml for beta-lactamase producing *H. influenzae* in this study, 89.8% were inhibited at ≤ 4 µg/ml (data not shown).
- GSK1322322 holds promise as a new and more potent compound to combat resistance common in SSTI and RTI pathogens.

Acknowledgements

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References

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