

GSK2251052, a Novel Boron-containing Protein Synthesis Inhibitor, with Comparative *in vitro* Activity against *Pseudomonas aeruginosa* from a Global Population

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Abstract

Background: GSK2251052 (formerly AN3365), a novel boron-containing leucyl-tRNA synthetase inhibitor with *in vitro* activity against *Pseudomonas aeruginosa* and multidrug-resistant *Enterobacteriaceae*, is currently being developed for the treatment of serious Gram-negative bacterial infections. The *in vitro* activity of GSK2251052 was assessed against a large global collection of recent *P. aeruginosa* isolates. **Methods:** The *in vitro* activity of GSK2251052 and 9 comparators was assessed by broth microdilution (CLSI M7-A8) against 2,008 isolates of *P. aeruginosa*. All study isolates were previously collected and frozen at -70 °C in the years 2009-2010 and were hospital-associated clinical isolates from 270 sites in 55 countries. Each isolate was unique, consecutively collected and with only one isolate per patient represented. **Results:** The *in vitro* activity (MIC, µg/mL) of GSK2251052 and comparators for this collection of isolates (n=2,008) is presented below:

Drug	MIC Range	MIC ₅₀	MIC ₉₀	% Sus*
GSK2251052	0.06 - 64	2	4	na
Amikacin	≤0.5 - >64	4	16	90.2
Cefepime	≤0.5 - >32	4	32	75.3
Ceftazidime	≤0.5 - >32	8	>32	66.4
Colistin	≤0.25 - >8	2	8	62.3
Imipenem	≤0.5 - >16	2	16	72.9
Levofloxacin	≤0.25 - >8	1	>8	63.7
Meropenem	≤0.12 - >16	0.5	16	79.3
Pip-Tazo	≤0.5 - >128	8	>128	81.3
Ticar-Clav	≤4 - >128	32	>128	67.5

* %Susceptibility defined by CLSI M100-S21; na= not available/breakpoint not defined.

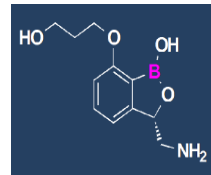
Conclusions: GSK2251052 demonstrated *in vitro* activity against this large global collection of *P. aeruginosa* isolates with an MIC₉₀ of 4 µg/mL. These *in vitro* data suggest that further development of GSK2251052 is warranted as a possible alternative treatment against *P. aeruginosa*.

Introduction

Pseudomonas aeruginosa is a Gram-negative non-fermenting bacterial pathogen implicated in many serious infections. This species has hyper-producing efflux pump mechanisms and metallo-β-lactamases (MBL) that confer resistance to many antimicrobial agents, thereby limiting the availability of therapeutic options.

GSK2251052 (formerly AN3365) is a novel boron-containing leucyl-tRNA synthetase inhibitor with *in vitro* activity against *P. aeruginosa* and multidrug-resistant *Enterobacteriaceae*. Recently, GSK2251052 has shown activity *in vitro* against a limited number of wild-type *P. aeruginosa* as well as against those with selected MBL resistance [1]. This study demonstrates the *in vitro* activity of GSK2251052 against a broad selection of over 2000 clinical isolates of *P. aeruginosa* from a global surveillance study.

Figure 1. Chemical structure of GSK2251052.



Methods

Organisms

All study organisms were clinical isolates previously collected from a diverse global population and frozen at -70 °C in the years 2009 through 2010. All *P. aeruginosa* were hospital-associated, clinical isolates from a multi-national geographic population. Each isolate was a unique, non-replicate isolate, with no more than one isolate per patient represented. There were 2,008 *P. aeruginosa* isolates collected from 270 sites in 55 countries: North America (n=801); Europe (n=593); and other International regions (n=614).

Antimicrobial Susceptibility Testing

Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines in document M7-A8 [2]. Interpretive criteria were applied as defined in CLSI document M100-S21, where available [3]. Mueller Hinton broth was used as the test medium for all *P. aeruginosa*. Testing was performed using custom panels prepared freshly on the same day of testing.

Quality control (QC) testing was performed each day of testing as specified by CLSI using *P. aeruginosa* ATCC 27853 [3].

References

- Biedenbach DJ, Mendes RE, Alley MRK, et al. 2010. Potency and Spectrum of Activity of AN3365, a Novel Boron-containing Protein Synthesis Inhibitor, Tested against Non-fermentative Gram-negative Bacilli. Poster presentation F1-1639; 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 12-15, 2010, Boston, MA USA.
- CLSI. 2009. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard; in CLSI document M7-A8. Eighth edition. Wayne, PA 19087-1898 USA.
- CLSI. 2011. Performance Standards for Antimicrobial Susceptibility Testing; in CLSI document M100-S21. Twenty-first edition. Wayne, PA 19087-1898 USA.

Acknowledgements

This study was funded by GlaxoSmithKline.

Figure 2. Percentage of Isolates by Region for 2008 *P. aeruginosa* from a Global Population of 55 Countries and 270 Sites.

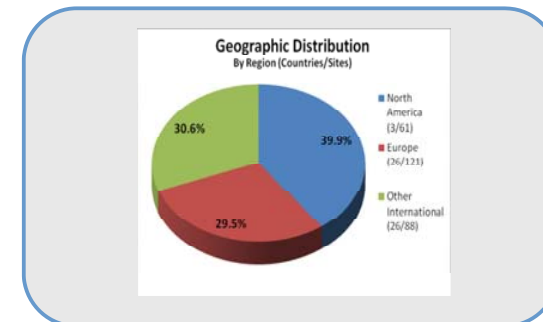


Table 1. Minimum Inhibitory Concentrations (MIC, µg/mL) Summary Table for GSK2251052 and Comparators against 2008 Isolates of *P. aeruginosa* from a Global Population.

Drug	Range	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res
GSK2251052	0.06 - 64	2	4	na	na	na
Amikacin	≤0.5 - >64	4	16	90.2	2.2	7.6
Cefepime	≤0.5 - >32	4	32	75.3	12.2	12.5
Ceftazidime	≤0.5 - >32	8	>32	66.4	10.2	23.4
Colistin	≤0.25 - >8	2	8	62.3	19.7	18.0
Imipenem	≤0.5 - >16	2	16	72.9	5.5	21.6**
Levofloxacin	≤0.25 - >8	1	>8	63.7	5.9	30.4
Meropenem	≤0.12 - >16	0.5	16	79.3	6.7	14.0**
Piperacillin Tazobactam	≤0.5 - >128	8	>128	81.3	na	18.7
Ticarillin Clavulanic Acid	≤4 - >128	32	>128	67.5	na	32.5

* Susceptibilities are defined by CLSI document M100-S21 (Jan 2011), where available; na= not available; ** Using the newly approved CLSI resistant breakpoint (June 2011) of ≥ 8 mg/mL, resistance rates for imipenem and meropenem would be 27.1% and 20.7%, respectively.

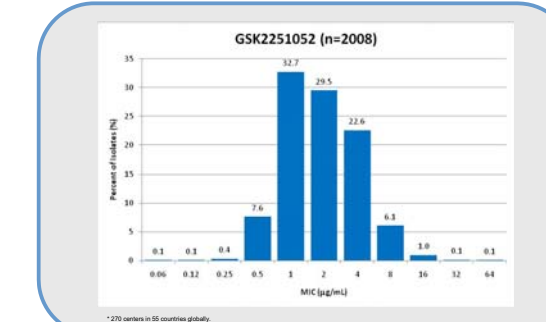
Table 3. Minimum Inhibitory Concentrations (MIC, µg/mL) Summary Table for GSK2251052 and Comparators against 593 Isolates of *P. aeruginosa* from Europe.

Drug	Range	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res
GSK2251052	0.25 - 16	2	4	na	na	na
Amikacin	≤0.5 - >64	4	64	86.2	3.7	10.1
Cefepime	≤0.5 - >32	4	32	74.4	13.2	12.5
Ceftazidime	≤0.5 - >32	8	>32	61.4	12.3	26.3
Colistin	0.5 - >8	2	4	81.1	16.7	2.2
Imipenem	≤0.5 - >16	2	>16	70.2	4.7	25.1**
Levofloxacin	≤0.25 - >8	1	>8	63.4	6.2	30.4
Meropenem	≤0.12 - >16	0.5	16	78.9	6.9	14.2**
Piperacillin Tazobactam	≤0.5 - >128	8	>128	80.3	na	19.7
Ticarillin Clavulanic Acid	≤4 - >128	64	>128	65.1	na	34.9

* Susceptibilities are defined by CLSI document M100-S21 (Jan 2011), where available; na= not available; ** Using the newly approved CLSI resistant breakpoint (June 2011) of ≥ 8 mg/mL, resistance rates for imipenem and meropenem would be 29.8% and 21.7%, respectively.

Results

Figure 3. Percentage of isolates inhibited by GSK2251052 at each MIC for 2008 *P. aeruginosa* from a global population.



* 270 centers in 55 countries globally

Table 2. Minimum Inhibitory Concentrations (MIC, µg/mL) Summary Table for GSK2251052 and Comparators against 801 Isolates of *P. aeruginosa* from North America.

Drug	Range	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res
GSK2251052	0.25 - 64	2	4	na	na	na
Amikacin	≤0.5 - >64	4	8	97.5	1.3	1.3
Cefepime	≤0.5 - >32	4	16	80.2	10.9	9.0
Ceftazidime	≤0.5 - >32	4	>32	71.3	10.4	18.4
Colistin	≤0.25 - >8	4	8	49.7	18.6	31.7
Imipenem	≤0.5 - >16	2	16	78.4	6.6	17.0**
Levofloxacin	≤0.25 - >8	1	>8	62.2	6.1	31.7
Meropenem	≤0.12 - >16	0.5	16	83.3	6.1	10.6**
Piperacillin Tazobactam	≤0.5 - >128	8	>128	84.6	na	15.4
Ticarillin Clavulanic Acid	≤4 - >128	32	>128	72.3	na	27.7

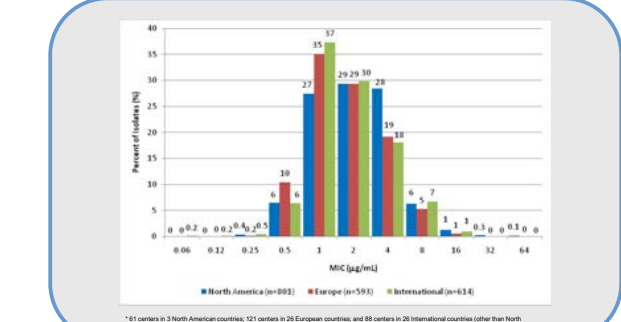
* Susceptibilities are defined by CLSI document M100-S21 (Jan 2011), where available; na= not available; ** Using the newly approved CLSI resistant breakpoint (June 2011) of ≥ 8 mg/mL, resistance rates for imipenem and meropenem would be 23.8% and 16.7%, respectively.

Table 4. Minimum Inhibitory Concentrations (MIC, µg/mL) Summary Table for GSK2251052 and Comparators against 614 Isolates of *P. aeruginosa* from an International Population other than North America and Europe.

Drug	Range	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res
GSK2251052	0.06 - 16	2	4	na	na	na
Amikacin	≤0.5 - >64	4	64	84.5	2.0	13.5
Cefepime	≤0.5 - >32	4	32	69.7	13.0	17.3
Ceftazidime	≤0.5 - >32	8	>32	64.8	7.8	27.4
Colistin	0.5 - >8	2	8	60.8	23.9	15.5
Imipenem	≤0.5 - >16	2	16	71.0	4.7	24.3**
Levofloxacin	≤0.25 - >8	1	>8	65.8	5.2	29.0
Meropenem	≤0.12 - >16	0.5	>16	74.4	7.2	18.4**
Piperacillin Tazobactam	≤0.5 - >128	8	>128	77.9	na	22.2
Ticarillin Clavulanic Acid	≤4 - >128	32	>128	63.7	na	36.3

* Susceptibilities are defined by CLSI document M100-S21 (Jan 2011), where available; na= not available; ** Using the newly approved CLSI resistant breakpoint (June 2011) of ≥ 8 mg/mL, resistance rates for imipenem and meropenem would be 29.0% and 25.6%, respectively.

Figure 4. Frequency distribution of GSK2251052 MICs for 2008 *P. aeruginosa* comparing North American, European and International populations.



* 81 centers in 3 North American countries; 121 centers in 26 European countries; and 88 centers in 26 International countries (other than North America and Europe)

Conclusions

- GSK2251052 demonstrated *in vitro* activity when tested against a large global population of recent clinical *P. aeruginosa* isolates. Greater than 92% of all isolates tested had GSK2251052 MICs of ≤4 µg/mL.
- GSK2251052 maintained MIC₉₀ values of 4 µg/mL in all regional populations of *P. aeruginosa* that were 2- to >32-fold lower than all other antibiotics tested against the global isolates including colistin (MIC₉₀ 8 µg/mL), amikacin (MIC₉₀ 16 µg/mL), levofloxacin (MIC₉₀ >8 µg/mL) and meropenem (MIC₉₀ 16 µg/mL).
- These *in vitro* data suggest that further development of GSK2251052 as a possible alternative treatment against infections caused by *P. aeruginosa* is warranted.