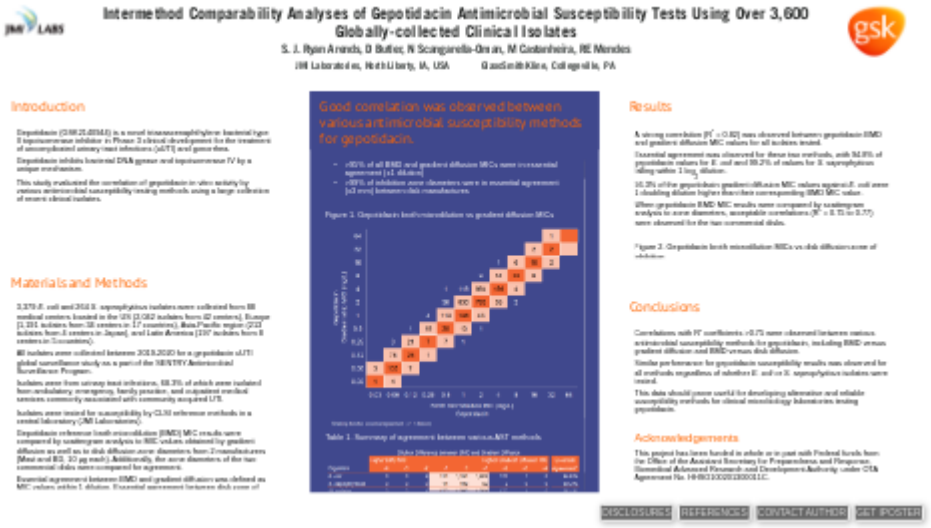
Intermethod Comparability Analyses of Gepotidacin Antimicrobial Susceptibility Tests Using Over 3,600 Globally-collected Clinical Isolates



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INTRODUCTION

Gepotidacin (GSK2140944) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in Phase 3 clinical development for the treatment of uncomplicated urinary tract infections (uUTI) and gonorrhea.

Gepotidacin inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism.

This study evaluated the correlation of gepotidacin in vitro activity by various antimicrobial susceptibility testing methods using a large collection of recent clinical isolates.

MATERIALS AND METHODS

3,379 *E. coli* and 264 *S. saprophyticus* isolates were collected from 88 medical centers located in the US (2,042 isolates from 42 centers), Europe (1,191 isolates from 34 centers in 17 countries), Asia-Pacific region (213 isolates from 4 centers in Japan), and Latin America (197 isolates from 8 centers in 5 countries).

All isolates were collected between 2019-2020 for a gepotidacin uUTI global surveillance study as a part of the SENTRY Antimicrobial Surveillance Program.

Isolates were from urinary tract infections, 68.3% of which were isolated from ambulatory, emergency, family practice, and outpatient medical services commonly associated with community acquired UTI.

Isolates were tested for susceptibility by CLSI reference methods in a central laboratory (JMI Laboratories).

Gepotidacin reference broth microdilution (BMD) MIC results were compared by scattergram analysis to MIC values obtained by gradient diffusion as well as to disk diffusion zone diameters from 2 manufacturers (Mast and BD, 10 µg each). Additionally, the zone diameters of the two commercial disks were compared for agreement.

Essential agreement between BMD and gradient diffusion was defined as MIC values within 1 dilution. Essential agreement between disk zone of inhibition measurements within 3 mm.

GOOD CORRELATION WAS OBSERVED BETWEEN VARIOUS ANTIMICROBIAL SUSCEPTIBILITY METHODS FOR GEPOTIDACIN.

- >95% of all BMD and gradient diffusion MICs for all isolates combined were in essential agreement (±1 dilution)
- >99% of inhibition zone diameters were in essential agreement (±3 mm) between disk manufactures

Figure 1. Gepotidacin broth microdilution vs gradient diffusion MICs for all isolates - *E. coli* (n = 3,379) and *S. saprophyticus* (n = 264)

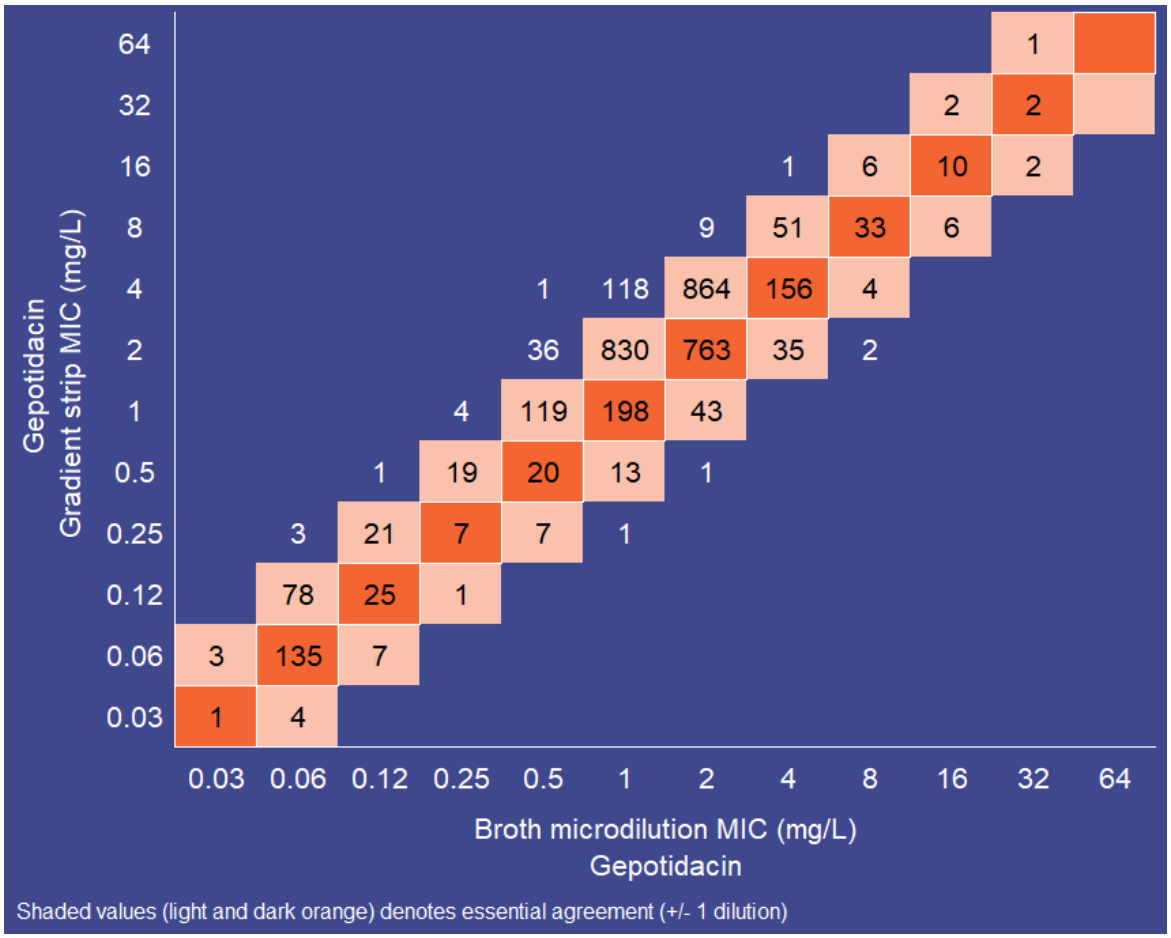


Table 1. Summary of agreement between various Gepotidacin AST methods

Dilution Difference between Gepotidacin BMD and Gradient Diffusion

Organism	Higher BMD MIC -4	-3	-2	-1	0	+1	Higher Gradient Diffusion MIC +2	+3	+4	Essential Agreement[a]
E. coli	0	0	4	111	1,191	1,902	170	1	0	94.8%
S. saprophyticus	0	0	0	11	159	92	2	0	0	99.2%
All isolates	0	0	4	122	1,350	1,994	172	1	0	95.1%

Zone Diameter Difference (mm) between Gepotidacin BD and MAST Disks

Organism	Larger MAST Zone Diameter ≥ -4	-3	-2	-1	0	Larger BD Zone Diameter 1	2	3	≥ 4	Essential Agreement
E. coli	2	0	14	93	615	1,377	1,085	168	25	99.2%
S. saprophyticus	2	0	5	21	77	84	65	9	1	98.9%
All isolates	4	0	19	114	692	1,461	1,150	177	26	99.2%

[a] Essential agreement (shaded values) defined as values within 1 dilution for BMD and gradient diffusion MICs or within 3 mm for disk diffsuion inhibition zones

RESULTS

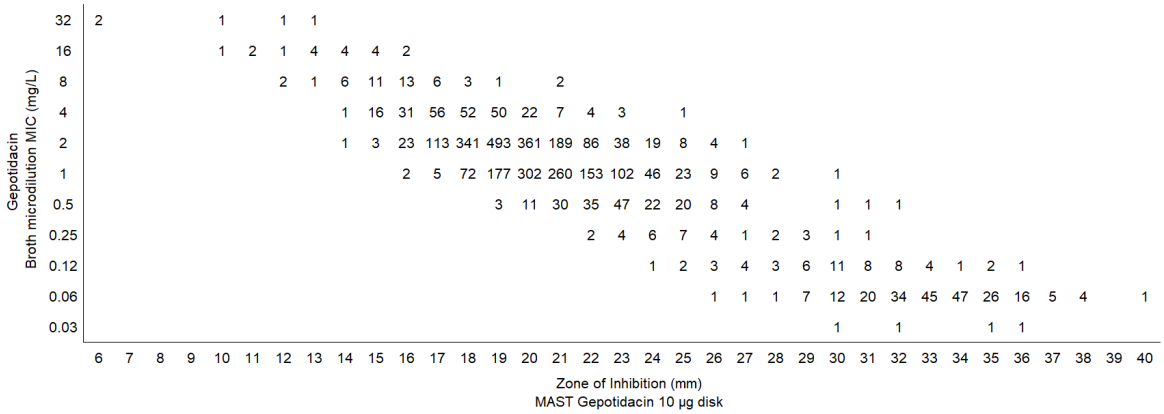
A strong correlation ($R^2 = 0.82$) was observed between gepotidacin BMD and gradient diffusion MIC values for all isolates tested.

Essential agreement was observed for these two methods, with 94.8% of gepotidacin values for *E. coli* and 99.2% of values for *S. saprophyticus* falling within 1 $\log_2$ dilution.

56.3% of the gepotidacin gradient diffusion MIC values against *E. coli* were 1 doubling dilution higher than their corresponding BMD MIC value.

When gepotidacin BMD MIC results were compared by scattergram analysis to zone diameters, acceptable correlations ($R^2 = 0.75$ to 0.77) were observed for the two commercial disks.

Figure 2. Gepotidacin broth microdilution MICs vs MAST disk diffusion zones of inhibition for all isolates - *E. coli* (n = 3,379) and *S. saprophyticus* (n = 264)



Similar scatterplot was observed between gepotidacin BMD values and BD zones of inihibiton ($R^2 = 0.75$)

The two gepotidacin commercial disks performed similarly, with 99.2% agreement (±3 mm) between zone diameter values and an $R^2 = 0.94$.

On average, the gepotidacin BD disk zones diameters measured 1.2 mm larger than the observed gepotidacin Mast disk zones.

CONCLUSIONS

Correlations with R^2 coefficients >0.75 were observed between various antimicrobial susceptibility methods for gepotidacin, including BMD versus gradient diffusion and BMD versus disk diffusion.

Similar performance for gepotidacin susceptibility results was observed for all methods regardless of whether *E. coli* or *S. saprophyticus* isolates were tested.

This data should prove useful for developing alternative and reliable susceptibility methods for clinical microbiology laboratories testing gepotidacin.

Acknowledgements

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DISCLOSURES

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N Scangarella-Oman and D Butler are employees and share holders of GlaxoSmithKline

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