Gepotidacin (GSK2140944) In Vitro Activity Against Neisseria gonorrhoeae (MIC/MBC, Kill Kinetics, Checkerboard, PAE/SME Tests)

**DJ FARRELL, HS SADER, PR RHOMBERG, NE SCANGARELLA-OMAN, RK FLAMM**

**JMI Laboratories, North Liberty, IA, USA; 2GSK, Collegeville, PA, USA**

**Abstract**

Gepotidacin (GSK2140944) is a new class of antibacterial agents with a unique mechanism of action involving inhibition of bacterial DNA replication and has demonstrated activity against multiresistant, drug-resistant, and drug-nonsusceptible pathogenic organisms.

**Introduction**

Gepotidacin (GSK2140944) is a new class of antibacterial agents with a unique mechanism of action involving inhibition of bacterial DNA replication and has demonstrated activity against multiresistant, drug-resistant, and drug-nonsusceptible pathogenic organisms. A recently completed single center observational study of 250 patients with uncomplicated gonococcal urethritis showed that gepotidacin was well tolerated, with a clinical cure rate of 94.1% and a microbiologic cure rate of 98.4% (Wohlkonig, 2016; Cuny, 2015). In this study, reference in vitro methods were used to evaluate the MIC/MBC and postantibiotic effect (PAE) of gepotidacin against Neisseria gonorrhoeae (N. gonorrhoeae). The PAE for gepotidacin in vitro was also evaluated against N. gonorrhoeae using broth microdilution methods for synergy testing and for post-antibiotic effects.

**Methods**

- **For all in vitro assays described in this study, testing was performed using Fastidious Broth Microdilution (FBM).**
- **Reference in vitro broth microdilution methods were used to evaluate the MIC and MBC for both a susceptible strain (ATCC 49226) and resistant isolate (Rut2820).**
- **MICs were determined by a twofold serial broth dilution method using the Clinical and Laboratory Standards Institute (CLSI) guidelines.**
- **MBCs were evaluated using a time-kill method and comparing the Log10 CFU/mL.**
- **For all isolate testing, gepotidacin and comparator agents were tested at concentrations of 5x MIC, 5x + ½ MIC, 5x + ¼ MIC, 1x MIC, and 0.125 µg/mL.**
- **For the time-kill kinetic and checkerboard methods, the following concentrations were used: gepotidacin 0.125/0.25 µg/mL and comparator agents 0.25/0.5 µg/mL.**
- **Checkerboard synergy testing was performed by broth microdilution.**
- **Gepotidacin was tested against and in combination with moxifloxacin, levofloxacin, and tetracycline.**
- **Checkerboard methods were used to evaluate the synergistic and antagonistic interactions between gepotidacin and comparator agents.**
- **The checkerboard method was used to determine the FIC index (FICi) for the combinational exposure and interpretative criteria for synergy, indifference, and antagonism were used.**

**Results**

- **All in vitro assays described in this study, testing was performed using Fastidious Broth Microdilution (FBM).**
- **Reference in vitro broth microdilution methods were used to evaluate the MIC and MBC for both a susceptible strain (ATCC 49226) and resistant isolate (Rut2820).**
- **MICs were determined by a twofold serial broth dilution method using the Clinical and Laboratory Standards Institute (CLSI) guidelines.**
- **MBCs were evaluated using a time-kill method and comparing the Log10 CFU/mL.**
- **For all isolate testing, gepotidacin and comparator agents were tested at concentrations of 5x MIC, 5x + ½ MIC, 5x + ¼ MIC, 1x MIC, and 0.125 µg/mL.**
- **For the time-kill kinetic and checkerboard methods, the following concentrations were used: gepotidacin 0.125/0.25 µg/mL and comparator agents 0.25/0.5 µg/mL.**
- **Checkerboard synergy testing was performed by broth microdilution.**
- **Gepotidacin was tested against and in combination with moxifloxacin, levofloxacin, and tetracycline.**
- **Checkerboard methods were used to evaluate the synergistic and antagonistic interactions between gepotidacin and comparator agents.**
- **The checkerboard method was used to determine the FIC index (FICi) for the combinational exposure and interpretative criteria for synergy, indifference, and antagonism were used.**

**Conclusions**

- **Gepotidacin demonstrated activity against N. gonorrhoeae isolates tested, exhibiting MIC/MBC values of 0.25/0.5 µg/mL and 0.125/0.25 µg/mL, respectively.**
- **Gepotidacin demonstrated MIC/MBC ratios of 0.5 and 2.0, indicating lack of drug resistance.**
- **Gepotidacin demonstrated bactericidal activity in time-kill studies against N. gonorrhoeae isolates using the comparator agents tetracycline and levofloxacin.**

A summary of PAE results observed from time-kill studies is presented in Table 2. The PAE for gepotidacin was generally of short to modest duration, with an extended PAE of up to 90 hours observed for 5x MIC GEP (0.125 µg/mL) against an isolate of N. gonorrhoeae (strain Rut2820). The PAE for gepotidacin was bactericidal against an isolate of N. gonorrhoeae (strain Rut2820) that was non-susceptible to sulfa drugs and displayed extended PAE for gepotidacin of 12 hours or more. The PAE for gepotidacin was bactericidal against an isolate of N. gonorrhoeae (strain Rut2820) that was non-susceptible to sulfa drugs and displayed extended PAE for gepotidacin of 12 hours or more.

**Acknowledgments**

This study was begun by GSK (GSK) Collaborator and funds were provided by GSK. All study design, data collection, and analysis were funded by GSK. The study was independently monitored and co-supervised by the JMI Laboratories, North Liberty, IA, USA. Robert K. Flamm, PhD, JMI Laboratories, North Liberty, IA, USA; Tel: (319) 665-3576; Email: robert.flamm@jimalabs.com.