# Longitudinal and Spatial Variation in the Human Microbiome in a Phase 2a Clinical Study of Gepotidacin in Adult Females with Uncomplicated Urinary Tract Infection (uUTI)

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## Introduction

- Gepotidacin is a novel, first in class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action[1,2] which confers activity against most strains of *E. coli* and *S. saprophyticus*, including those resistant to current antibiotics[3–5]
- We evaluated the impact of gepotidacin on the human microbiome as an exploratory endpoint in a Phase 2a clinical trial for the treatment of uUTI (NCT03568942)

## Methods

- Gepotidacin 1500 mg BID was administered orally for 5 days
- Samples were collected with consent from 22 study participants from the pharyngeal cavity (saliva swabs), gastrointestinal tract (GIT; stool) and vagina (vaginal swabs) (141/156 samples were used for microbiome analyses after quality control)
- Samples were taken at 3 time points: pre-dosing (Day 1), end of dosing (Day 5), and follow-up visit (Day 28±3 days)
- Relative abundances of microbial species were determined by next-generation DNA sequencing of 16S rRNA variable region 4 (V4) amplicons[6]

**References**

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**Disclosures**

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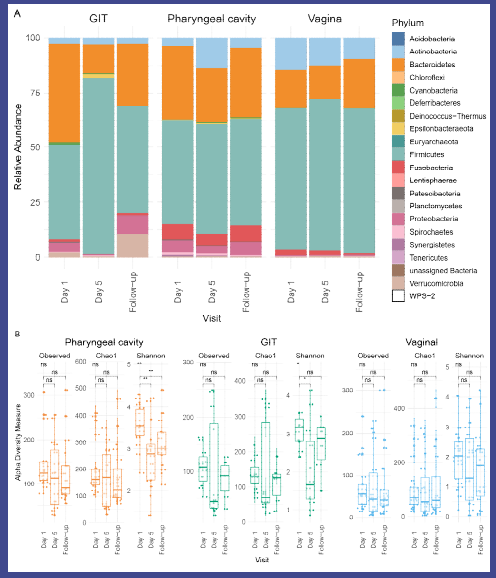
- We evaluated microbiome rebound in gepotidacin-treated patients with uUTI
- Gut, pharyngeal, and vaginal microbiome diversity **significantly declined by end of gepotidacin dosing** (Day 5) but **rebounded to near pre-dose status by follow-up** visit (~Day 28)

**Figure 1.** Microbiome Dynamics
A) Phylum level changes across different body sites and time points;
B) changes in microbiome composition as measured by three indices of alpha diversity:
*$p$≤0.05,
**$p$≤0.005,
*ns*=not significant

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## Results

**Figure 2.** Microbiome Recovery at Follow-up
Changes in beta diversity of microbial communities using constrained correspondence analysis (CCA) on Bray-Curtis distances showing recovery at follow-up. All three microbial communities showed significant recovery in diversity at follow-up

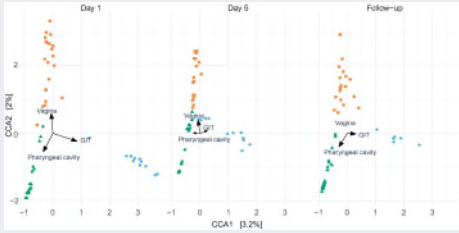


**Figure 3.** Overall Trends for Specific Pathogenic Genera
Depending upon body site, the most impacted genera at Day 5 were *Haemophilus, Neisseria, Staphylococcus,* and *Streptococcus*. Overall trends suggested that gepotidacin in vitro $MIC_{90}$ results measured previously[1,7] are generally predictive of relative abundances of these bacteria in the microbiome (*p≤0.05, ** p≤0.005, ***p≤0.0001)

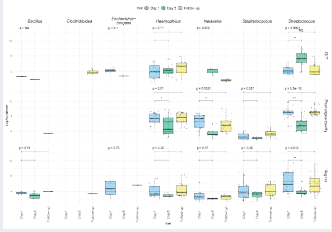

**Figure 4.** Relative Abundance Changes for *E. coli*-related Species
*Escherichia-Shigella* genus was initially found at Day 1 in stool and vaginal samples but greatly reduced or undetectable at Day 5 and follow-up. The *Escherichia-Shigella* genus of the *Enterobacteriaceae* family was not detected at any time points in saliva samples; though a minor *Serratia* occurrence was detected at Day 5