INTRODUCTION

- Clostridioides difficile is among the top 5 pathogens identified in urgent public health threats by the US Centers for Disease Control and Prevention.¹
- Key risk factors for CDI are low diversity of the gut microbiota and low levels of microbial-derived protective secondary bile acids, which have direct inhibitory activity against C. difficile (Figure 1).²
- Current antibiotic therapies for CDI may cause more damage to the gut microbiota and increase the risk of recurrence of CDI, which is ~25% after treatment of a first infection.³

Ridinilazole is an investigational, oral antibiotic with a microbiota-sparing profile that is highly specific and bactericidal against C. difficile.⁴,⁵

METHODS

- This analysis evaluated clinical samples from a Phase 2, randomized, double-blind, clinical study that compared the efficacy of oral ridinilazole (300 mg BID) or vancomycin (1200 mg QD) as CDI treatment (NCT02092935).²
- DNA was extracted from stool samples collected from 43 patients at baseline (BSL) and end of treatment (EOT) was analyzed by metagenomic shotgun sequencing on an Illumina platform.
- For microbiome profiling, shotgun metagenomics was now considered the method of choice over 16S sequencing (Figure 2).⁶,⁷
- α-Diversity was measured with the Shannon index, which considers both the number of bacterial species (richness) and their relative abundance (evenness).
- Statistical analysis was performed on paired samples at BSL and EOT (ridinilazole, n=23; vancomycin, n=20) using Wilcoxon signed rank tests. P-values were corrected for multiple testing to control the false discovery rate (FDR) at a level of 10%, as indicated.

RESULTS

Microbiome Composition: α-Diversity and Relative Abundance of Bacterial Phyla

- At BSL, ridinilazole treatment was associated with 3-5 times lower impact on microbiota diversity (-10% in BSL, P=0.43) than vancomycin (-5% to BSL, P=0.0003) (Figure 4).
- At the genus level, at ridinilazole BSL and EOT, a 1.5-fold increase in Bacteriodes(±0.16) was observed. In contrast, at vancomycin EOT, >16,000 fold reductions in Bacteriodes (P=0.003) and Accumulibacter (FDR P=0.005) were observed, respectively, concurrently with a 5-fold expansion of Proteobacteria (FDR P=0.005).
- At the genus level, at ridinilazole EOT, only a significant reduction of Clostridium was observed (20 fold change [FC]; FDR P=0.05). This corresponded to a reduction in C. difficile species, targeted by ridinilazole. In contrast, vancomycin therapy resulted in significant 3-4-fold decreases in 23 different bacterial genera, including Enterobacteriaceae (46,733±6,327; FDR P=0.002), Bacteroidales (47,103±5,762; FDR P=0.002), and Delftiaatramaticum (45.4±0.06; FDR P=0.002), all consensually good commensals (Figure 5).

Microbiota Metabolic Potential to Produce Protective Secondary Bile Acids

- Based on the literature, numerous bacterial taxa in the gut can perform the reaction of deconjugation and hydrolysis (via Vancomycin 5.) genes (Figure 1).
- A core depression in diversity and relative abundance of both but and Bartonella species was revealed (P=0.005) and a 100% reduction of ta genes (P=0.002) were reported (Table 1).

CONCLUSIONS

- In this metagenomic analysis of fecal samples from a Phase 2 clinical trial, ridinilazole treatment for CDI had minimal impact on gut microbiota diversity compared to vancomycin.
- Ridinilazole treatment preserved the potential of the microbiota to produce protective secondary bile acids.
- In contrast, vancomycin treatment was associated with dramatic changes in the microbiota composition and potential to produce protective secondary bile acids.

These results are consistent with previous bile acid analysis in fecal samples (Figure 2) and provide a mechanistic rationale of the lower rate of recurrence of CDI observed with ridinilazole compared to vancomycin in this Phase 2 study.²

Ridinilazole is currently being evaluated in two Phase 3 studies for the treatment of CDI.

References

6. Clinical Microbiomics, København, Denmark
7. Ridinilazole is an investigational compound that is not approved by any regulatory body.