Ridinilazole Reduces Recurrence of *Clostridium difficile* Infection with Minimal Impact on the Gut Microbiota

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Introduction

- *C. difficile* infection (CDI) is one of 3 urgent antibiotic-resistant bacterial threats in the U. S., according to the CDC, and is the leading cause of hospital-acquired diarrhoea.
- A major clinical challenge is the high risk of recurrence (up to 35% following initial infection), with dysbiosis of the gut microbiome.
- Ridinilazole (RDZ) is a novel, oral, peripherally restricted antibacterial that is highly selective for *C. difficile*
- RDZ has shown superior efficacy on Sustained Clinical Response (SCR) compared to vancomycin (VAN) in a Phase 2 clinical trial and preservation of the gut microbiota.

Methods

- ***In vitro* Susceptibility:** MICs were determined by agar dilution on Wilkins-Chalgren plates, or, following the CLSI M11-A7/A8 for *C. difficile,* and, the CLSI M11-A8 and M7-A9 for the panel of bacteria.
- **Multi-center, Double-blind Phase 2 Clinical Trial:** 100 subjects were randomized 1:1 to RDZ (200 mg BID) or VAN (125 mg QID) treatment for 10 days. Primary endpoint was SCR, defined as clinical response at end of therapy (EOT) with no recurrence for 30 days.
- **Microbiome:** Stool samples from 22 patients in each treatment arm were collected at baseline and EOT. Amplicons of the 16S rRNA V4 region were analysed to identify the differences in microbiota composition at the 2 time-points using QIIME and LEfSe.

Results: In vitro *susceptibility*

Table 1: Susceptibility of C. difficile Clinical Isolates to Ridinilazole and Comparators

		MIC range (μg/ml)	MIC_{90} (μg/ml)			
Study (Source of isolates)	N	RDZ	RDZ	VAN	MTZ	FDX
Corbett et al. 2015 (UK)[1]	82	0.06-0.25	0.125	2	8	0.06
Freeman et al. 2015 (EU)[2]	107	0.015-0.5	0.125	2	2	0.125
Goldstein et al. 2013 (US)[3]	50	0.125-0.5	0.25	4	2	0.5
Snydman et al. 2017 (US)[4]	200	0.125-0.5	0.25	2	1	0.5

RDZ: ridinilazole; VAN: vancomycin; MTZ: metronidazole; FDX: fidaxomicin

- Ridinilazole demonstrated potent activity against 439 *C. difficile* isolates with an overall MIC_{90} markedly lower than metronidazole and vancomycin, and, similar to fidaxomicin.
- There was no variation in activity by region, antibiotic resistance profile or ribotype.

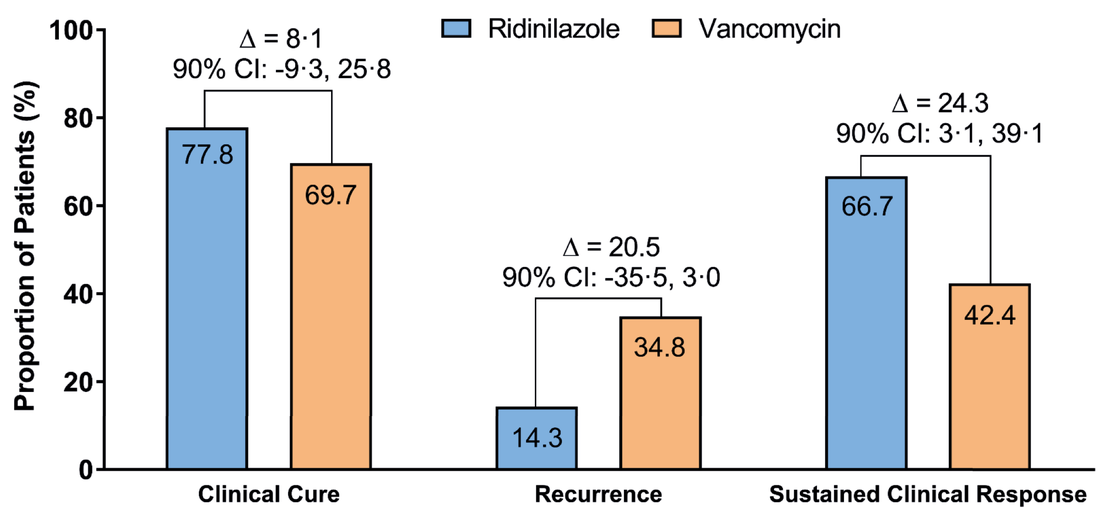
Table 2: Spectrum of Activity

Bacteria (number of isolates)	RDZ MIC range (μg/ml)	MIC_{90} (μg/mL)			
		RDZ	FDX	VAN	MTZ
Bifidobacterium spp. (20)	16->512	>512	0.125	1	128
Lactobacillus spp. (20)	0.06->512	>512	>512	>512	>512
Eggerthella lenta (20)	>512	>512	≤0.03	4	0.5
Finegoldia magna (20)	0.03-512	64	2	0.5	1
Peptostreptococcus anaerobius (20)	0.125–128	64	≤0.03	0.5	1
Enterococcus faecalis (10)	128->512	>512	8	4	>512
Enterococcus faecium (10)	64->512	128	8	256	>512
Streptococcus spp. (10)	0.5->512	>512	128	1	>512
Bacteroides spp. (50)	128->512	>512	>512	128	2
Fusobacterium spp. (20)	4->512	>512	>512	>512	0.5

- Ridinilazole showed limited activity against Gram-positive and Gram-negative anaerobes, especially against the Bacteroidetes, a dominant phylum of the gut microbiome.

Results: Clinical efficacy

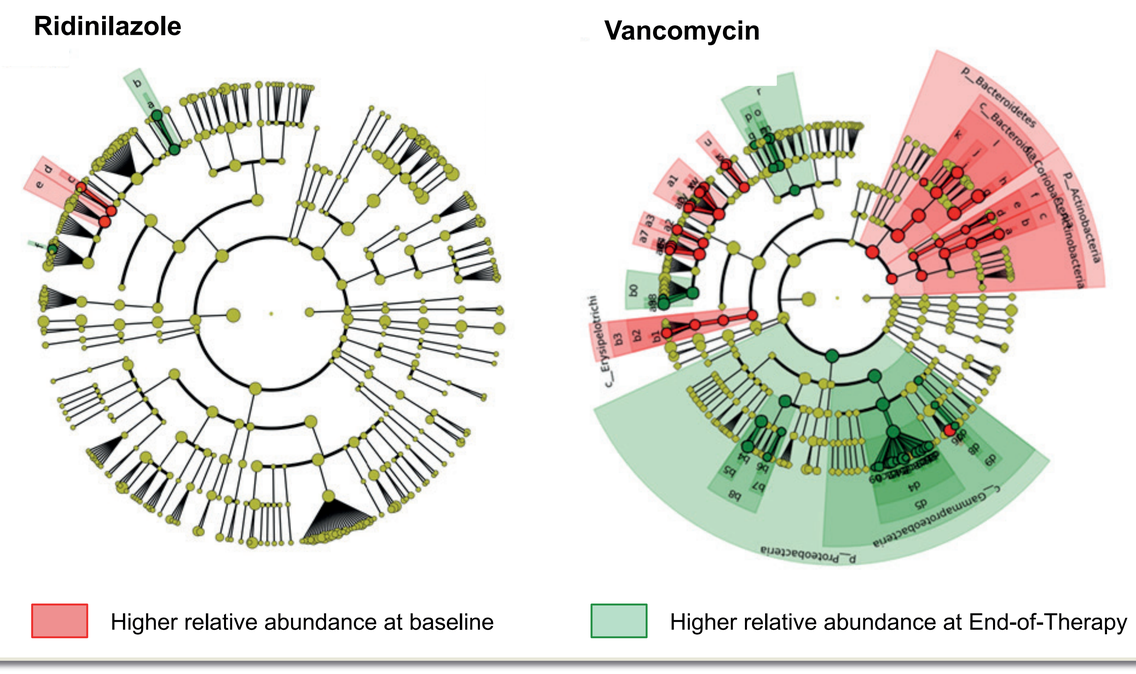
Figure 1: Clinical Cure and Sustained Clinical Response



- Ridinilazole demonstrated superiority for SCR compared to vancomycin.
- The improved SCR rate was driven by a marked reduction in recurrent CDI.

Results: Gut Microbiome

Figure 2: Effects of Vancomycin and Ridinilazole on the Microbiota at Baseline vs EOT



- Vancomycin treatment resulted in dramatic losses in Bacteroidetes (>3log), in 4 families of the Firmicutes, including the Lachnospiraceae and Ruminococcaceae (>2 log), and in Actinobacteria (70% reduction). Simultaneously, an increase in Proteobacteria was observed, primarily in Enterobacteriaceae (> 2 log).
- In contrast, ridinilazole's effect was confined to the Firmicutes, with loss of *C. difficile* and modest decreases in the Clostridiaceae and Ruminococcaceae.

Conclusions

- **Ridinilazole demonstrated potent activity against *C. difficile* clinical isolates with no major variation by geographic region, ribotype or antibiotic resistance phenotype.**
- **Ridinilazole effectively targets *C. difficile* in CDI patients with minimal impact on the gut microbiota.**
- **Preservation of the microbiome likely contributed to the low rate of recurrence, and superior efficacy on SCR, compared to vancomycin.**
- **These data provide evidence of ridinilazole being a microbiome sparing agent to both treat CDI and reduce the recurrence of CDI. Further clinical development is warranted.**

References: 1. Corbett D., et al. (2015) J. A.C; 2. Goldtein E.J. et al. (2013) A.A.C.; 3. Freeman J. et al. (2015) A.A.C; 4. Snydman D.R. et al. (2017) ASM poster # 235. 5; Vickers, R. J., et al. (2017). Lancet Infect Dis.; 6. Thorpe C. M. et al. (2017) ECCMID poster # 1177. ***Acknowledgments:*** We are grateful to all the investigators who participated in the CoDIFy study (NCT02092935) and to the Wellcome Trust for financial support (grant number 099444).