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Quality of Life Changes in Patients with *Clostridium difficile* Infection (CDI): A Randomized, Double-Blind Trial of Ridinilazole (RDZ) Compared to Vancomycin (VAN)

Sumita Paul[1], MD, MPH, Richard J. Vickers[2], PhD, Kevin W. Garey[3], PharmD, MS
[1]Summit Therapeutics, Cambridge, US; [2] Summit Therapeutics, Abingdon, UK; [3]University of Houston, Texas, US

Presenting Author
Sumita Paul, MD, MPH
Sumita.Paul@summitplc.com
201-492-7282

C. difficile is the most frequent hospital-acquired bacteria in the US. CDI is associated with significant morbidity and mortality, and a significantly lower mean EQ-5D index of Health Related Quality of Life (HRQoL) compared to the general population. However, data on the impact that treatment of CDI with antibiotics has on HRQoL are lacking.

Public Health Threat

C. difficile infection (CDI) is one of 3 urgent bacterial threats in the U. S., according to the CDC, and is a leading cause of hospital-acquired diarrhea. It is an immediate public health threat requiring urgent and aggressive action.

- ❑ Current CDI therapy with vancomycin is associated with collateral damage to the gut microbiota priming patients for recurrent CDI.
- ❑ CDI survivors have 46% lower mean EQ-5D index of Health Related Quality of Life (HRQoL) compared to the general population.

Novel Investigational Antibiotic Ridinilazole

- ❑ Ridinilazole (RDZ) is a novel, oral, peripherally restricted antibacterial that is highly selective for *C. difficile*
- ❑ It is being developed to treat CDI **and** reduce the recurrence of CDI

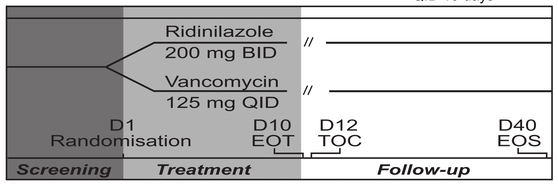
Methods

Randomized double-blind phase 2 study to compare 10 days ridinilazole 200mg BID to vancomycin 125mg QID.

- ❑ We evaluated HRQoL prospectively with the EQ-5D-3L obtained at five time points (baseline, Days 5, 10, 12, and 40) with:
  - ❑ Summary index values calculated using US weights
  - ❑ Evaluation of raw scores for:
    - ❑ Mobility
    - ❑ Self-care
    - ❑ Usual activities
    - ❑ Pain/discomfort
    - ❑ Anxiety/depression
  - ❑ Visual analog scale (VAS) scores.

Group Design

Group	N	Agent	Regimen
1	50	Ridinilazole	200mg BID 10 days
2	50	Vancomycin	125mg QID 10 days



EOT – End of Treatment; TOC – Test of Cure; EOS – End of Study

- ❑ The primary endpoint was sustained clinical response (SCR), defined as cure with no recurrence to 30 days post end of treatment.
- ❑ The primary analysis population consisted of patients with a diagnosis confirmed by a positive free toxin test.

Results

In the primary efficacy analysis of 69 patients:

- ❑ Sustained clinical cure was achieved in 24 of 36 (66.7%) on ridinilazole vs 14 of 33 (42.4%) on vancomycin (treatment difference 21.1%, 90% CI 3.1–39.1) achieving statistical superiority of ridinilazole over vancomycin at the prespecified 10% level.
- ❑ Improved sustained clinical response on ridinilazole was associated with negligible gut microbiota impact vs substantial gut microbiota perturbation on vancomycin; both reduced *C. difficile* to below the limit of detection.
- ❑ Overall, fewer patients on ridinilazole reported any problems over time at Day 5, EOT, TOC, and Day 40 for all 4 out of the 5 domains tested: mobility, self-care, usual activities, and pain/discomfort.
- ❑ Mean changes from baseline in index scores in the vancomycin group took longer to improve and became significantly higher than baseline on Day 12.

Figure 1: EQ-5D-3L – Pain/Discomfort in the Primary Analysis Population

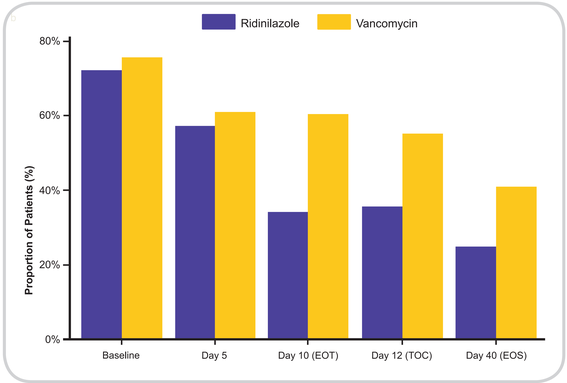


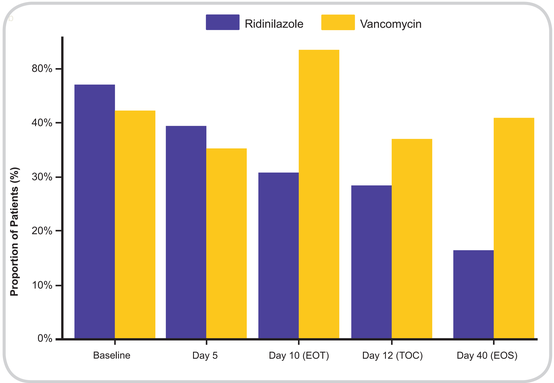
Table 1. Mean Change from Baseline in VAS

Time period	Ridinilazole				Vancomycin			
	N	Mean Change[1]	SD	p value	N	Mean Change[1]	SD	p value
Day 5	33	8.55	18.21	0.0111	31	5.26	19.72	0.1480
Day 10	28	15.75	19.04	0.0002	28	7.14	24.37	0.1325

[1]Positive values on the VAS indicate better quality of life in comparison with baseline.
Abbreviations: N=number of patients in the primary analysis, SD=standard deviation

- ❑ As early as Day 5, only CDI patients on ridinilazole had significant improvements in mean change from baseline in index scores (p=0.008) and VAS scores (p=0.01, Table 1, within-groups)
- ❑ The mean change from baseline in EQ-5D-3L domains showed the highest (significant) improvements in the pain/discomfort domain for both treatment groups across all time points. By Day 40, anxiety/depression improved significantly more with ridinilazole than with vancomycin (p=0.039).

Figure 2: EQ-5D-3L – Anxiety/Depression in the Primary Analysis Population



Conclusions

- ❑ This is the first study to document improvements in HRQoL after antimicrobial treatment for CDI.
- ❑ Ridinilazole improved early and 40-day HRQoL relative to vancomycin.
  - ❑ Early significant improvements occurred by day 5 on ridinilazole but not vancomycin.
  - ❑ Anxiety/depression and pain/discomfort improved significantly with CDI treatment.
  - ❑ By day 40, ridinilazole improved anxiety/depression significantly more than vancomycin.
- ❑ HRQoL should be evaluated in Phase 3 interventional studies for CDI.
- ❑ These results will need to be further studied in the ongoing phase 3 randomized, double-blind, global trials comparing ridinilazole to vancomycin for the treatment of CDI.

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