**ABSTRACT FOR UEG 2020**

**Prevention of Recurrent *Clostridioides difficile* Infection at Two Years After Treatment with Investigational Microbiota-Based Drug RBX2660: Efficacy, Durability, Microbiome Changes, and Participant Demographics of a Phase 2 Open-Label Clinical Trial**

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**Objective**

*Clostridioides difficile* infection (CDI) is a global disease associated with mortality, morbidity, compromised quality of life, and substantial medical cost. Disruption of the intestinal microbiome contributes to recurrent CDI (rCDI), motivating development of microbiota therapies to prevent rCDI in multi-recurrent individuals. We present the 24-month analysis of safety, efficacy, and microbiome restoration from a Phase 2 open-label trial of the investigational microbiota-based drug RBX2660 for prevention of CDI recurrence. To address potential demographic differences on treatment outcome and durability, we also report a subpopulation analysis.

**Methods**

This multicenter, open-label Phase 2 trial included participants with multi-recurrent CDI who received <2 doses of RBX2660 delivered via enema 7 days apart. Efficacy was defined as absence of CDI recurrence through 8 weeks after the last dose. Durability was defined as continued CDI absence beyond 8 weeks. Safety and durability assessments occurred at 3, 6, 12, and 24 months. A general linear model was performed to assess the influence of sex(female, male), age(>65 years, <65 years), and their interaction on clinical outcome. Participant stool samples were collected prior to and for up to 24 months after treatment, and microbiome changes were assessed by shallow shotgun sequencing.

**Results**

As previously reported, the 8-week efficacy to prevent rCDI (79%;112/142) was higher than the CDI-free rate in the historical control group (31%, 23/75; *p*<.0001). Ninety-seven participants who achieved treatment success at 8 weeks were evaluable for long-term durability of whom 8 experienced a new CDI episode between 8 weeks and 24-months (92% overall durability). Age and sex did not have a statistically significant impact on primary efficacy or durability. The safety profile of RBX2660 was acceptable up to 24 months and consistent with prior reports of microbiota-directed treatments; gastrointestinal disorders were the most common TEAE organ class. Microbiome analysis (503 samples from 110 primary treatment responders) showed that the relative abundance of Bacteroidia and Clostridia increased significantly within 7 days of treatment relative to baseline, concomitant with a decrease of Gammaproteobacteria and Bacilli, with maintenance of these changes throughout 24 months.

**Conclusion**

The microbiota-based drug RBX2660 demonstrated clinical durability in preventing rCDI at 24 months. This maintained efficacy was associated with sustained shifts in microbiome composition following treatment. Importantly, neither efficacy nor durability was dependent on age or sex.

Keywords: recurrent *Clostridioides difficile* infection, microbiome restoration, microbiota-based drug, RBX2660, Phase 2 clinical trial

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