Significant Improvement in Health-Related Quality of Life (HRQL) with RBX2660: Results from a Phase 3 Randomized, Placebo-Controlled Trial in Recurrent Clostridioides difficile Infection (PUNCH CD3)

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INTRODUCTION

- *Clostridioides difficile* is an anaerobic gram-positive, spore-forming, toxin-producing bacillus transmissible through the fecal-oral route. *Clostridioides difficile* infection (CDI) is the most frequent healthcare associated infection in the US[1]
- Recurrence of *Clostridioides difficile* infection (rCDI) is common: up to 35% of patients treated for an initial episode of CDI develop a recurrence and of those, up to 65% of patients will recure more than once[2-4]
- Standard treatment for CDI and rCDI typically involves vancomycin or fidaxomicin.[5] However, antimicrobial therapy alone commonly fails to achieve a long-lasting cure and patients often recur with severe clinical and economic consequences. RBX2660 is a first-in-class, investigational, microbiota-based live biotherapeutics[6] currently under investigation for reducing the rate of recurrent CDI
- Here we report 8-week health-related quality of life (HRQL) results measured using the *Clostridioides difficile* Health-related Quality-of-Life Questionnaire (Cdiff32)—a validated, disease-specific instrument— from RBX2660's randomized, double-blinded, placebo-controlled phase 3 trial PUNCH CD3 (NCT03244644)

OBJECTIVE

- To assess Cdiff32 total and domain-specific (i.e., physical, mental, social) scores for rCDI patients treated with RBX2660 or placebo (PBO) at baseline and weeks 1, 4, and 8
- To compare differences in change from baseline to week 8 in Cdiff32 total and domain-specific scores between rCDI patients treated with RBX2660 vs PBO

DATA AND METHODS

- The analysis included adult patients with rCDI from the PUNCH CD3 trial's modified intention-to-treat (mITT) population, which analyzed subjects according to their randomized treatment assignment despite any treatment misallocations and included all randomized subjects who successfully received blinded treatment, but excluded subjects who withdrew prior to treatment, subjects in whom treatment was attempted but not completed and, subjects who discontinued from the study prior to evaluation of treatment failure/success if the reason for exit is not related to CDI symptoms
- The Cdiff32 instrument comprises 32 items related to the physical, mental, and social health of patients with CDI. Total score and three domain scores (i.e., physical, mental, and social relationships) were calculated and rescaled to range from 0 to 100 (100 being best possible). Patients were required to have a baseline CDIFF32 assessment as well as at least one follow-up assessment with CDIFF32 at week 1, 4, or 8 to be included
- Absolute scores were summarized via mean and standard deviation at baseline and follow-up (weeks 1, 4, and 8) by treatment arm, and compared to baseline using Wilcoxon rank-sum tests. Change from baseline to follow-up (weeks 1, 4, and 8) was summarized via mean and standard deviation by treatment arm, and compared at week 8 across treatments using Wilcoxon signed-rank tests
- Changes in Cdiff32 from baseline to week 8 were also compared between RBX2660 and PBO using adjusted analyses controlling for baseline Cdiff32 score, gender (male vs female), age, number of CDI episodes before treatment, metabolism and nutrition disorders, surgical and medical procedures, infections and infestations, gastrointestinal disorders, psychiatric disorders, prior treatment with fidaxomicin, and proton pump inhibitor use
- Per trial protocol, missing data were imputed via last observation carried forward (LOCF). Some patients experiencing recurrence after blinded treatment received open-label RBX2660 per physician discretion; these participants were excluded unless, per LOCF, data were available from the blinded period for week 8. Sensitivity analyses were conducted using as-observed data

KEY TAKEAWAYS

1 This analysis of PUNCH CD3 found that most patients reported improvements in HRQL for both PBO and RBX2660 as early as week 1 and continuing throughout the blinded study period

2 Although improvements in HRQL were observed for both arms, RBX2660-treated patients had more profound and sustained HRQL improvements than patients treated with PBO across all domains and total score at all time points, with statistically significant differences found for the total score and mental domain at week 8

3 This study suggests that microbiota restoration therapy is associated with improved HRQL for rCDI patients. Future research may link these improvements directly with microbiota changes

RESULTS

Table 1. Baseline characteristics by treatment[a]

	Placebo N = 66[b]	RBX2660 N = 140[b]
Demographics		
Age (years), Mean ± SD	57.3 ± 16.4	61.1 ± 16.9
Age group < 65 years, N (%)	44 (66.7)	72 (51.4)
Sex - Female, N (%)	47 (71.2)	95 (67.9)
Height (cm), Mean ± SD	167.9 ± 10.4	167.4 ± 10.2
Weight (kg), Mean ± SD	76.1 ± 18.6	77.9 ± 19.9
Race group - Non White, N (%)	8 (12.1)	9 (6.4)
Ethnicity - Hispanic or Latino, N (%)	4 (6.1)	2 (1.4)
Disease characteristics		
Number of CDI episodes before treatment, Mean ± SD	3.1 ± 1.2	3.2 ± 1.2
Antibiotics used at baseline, N (%) Vancomycin Fidaxomicin Other	 61 (92.4) 4 (6.1) 1 (1.5)	 123 (87.9) 12 (8.6) 5 (3.6)
Proton pump inhibitor use, N (%)	16 (24.2)	31 (22.1)
Surgical and medical procedures, N (%)	34 (51.5)	88 (62.9)
Infections and infestations, N (%)	40 (60.6)	82 (58.6)
Gastrointestinal disorders, N (%)	36 (54.5)	78 (55.7)
Psychiatric disorders, N (%)	34 (51.5)	76 (54.3)
Metabolism and nutrition disorders, N (%)	34 (51.5)	78 (55.7)

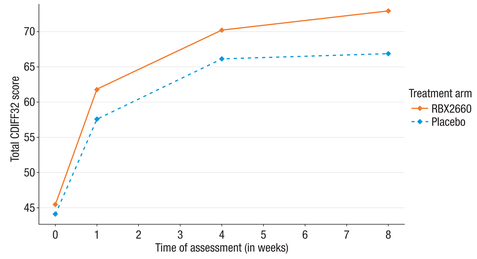
CDI: *Clostridioides difficile* infection, Cdiff32: Clostridioides difficile Health-related Quality-of-Life Questionnaire, LOCF: last observation carried forward, mITT: modified intent-to-treat, SD: standard deviation.

[a] Includes patients from the mITT population with both baseline and week 8 Cdiff32 readings (after LOCF imputation).

[b] The sample size for weeks 1 and 4 may differ from the sample size at baseline and week 8 due to LOCF imputation.

A total of 206 patients (140 RBX2660, 66 PBO) were included, baseline patient characteristics and comorbidities are reported in Table 1

Figure 1. Unadjusted Cdiff32 total scores during blinded treatment period, stratified by treatment



Cdiff32 scores improved significantly from baseline to weeks 1, 4, and 8 for both arms, with numerically greater improvements for RBX2660 through week 8 (Figs. 1 & 2, Table 2)

Figure 2. Unadjusted Cdiff32 domain scores during blinded treatment period, stratified by treatment

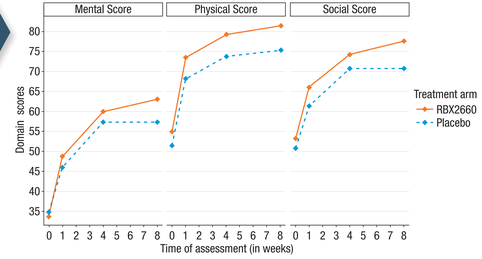


Table 2. Summary of changes from baseline to weeks 1, 4, and 8 by treatment

		Baseline	Week 1	Week 4	Week 8
Total score	RBX2660	44.9 ± 17.4	16.2 ± 19.5	25.2 ± 22.4	27.8 ± 23.6
	PBO	44.7 ± 20.6	14.3 ± 17.3	21.0 ± 23.4	22.2 ± 22.4
Physical domain score	RBX2660	33.4 ± 16.7	18.5 ± 23.2	25.2 ± 24.7	27.3 ± 25.7
	PBO	35.8 ± 20.8	17.3 ± 21.7	21.6 ± 25.3	23.7 ± 25.2
Mental domain score	RBX2660	54.0 ± 21.5	15.0 ± 20.6	26.5 ± 24.1	30.0 ± 25.6
	PBO	51.7 ± 22.6	12.0 ± 17.5	21.2 ± 24.6	21.5 ± 23.8
Social domain score	RBX2660	53.6 ± 23.9	12.3 ± 24.6	20.3 ± 27.6	23.6 ± 29.3
	PBO	51.8 ± 26.5	11.8 ± 19.7	18.6 ± 26.9	19.0 ± 27.7

Baseline Cdiff32 scores across treatment arms are reported in Table 2

- At week 8, statistically significant differences were found for mental domain (unadjusted: 8.01±3.64; adjusted: 7.07, 95% confidence interval: [0.28, 13.86], both P<0.05) and total score (adjusted: 6.11 [0.14, 12.08], P<0.05), all favoring RBX2660 over PBO
- Similar results were found for the as-observed analyses, with additional statistically significant differences found for the physical domain in addition to the mental domain and total score in favor of RBX2660 over placebo (6.57 [0.84, 12.30], P<0.05)

Table 3. Multivariable adjusted analyses for week 8 between RBX2660 and placebo[a]

	LOCF-imputed data N=206			As-observed data N=185[b]		
	Point estimate	95% CI	p-value	Point estimate	95% CI	p-value
Total score	6.11	(0.14, 12.08)	< 0.05	7.19	(1.23, 13.15)	< 0.05
Physical domain score	5.51	(-0.34, 11.36)	0.07	6.57	(0.84, 12.30)	< 0.05
Mental domain score	7.07	(0.28, 13.86)	< 0.05	8.32	(1.38, 15.25)	< 0.05
Social domain score	5.94	(-1.04, 12.91)	0.10	6.48	(-0.64, 13.59)	0.08

mITT: modified intent-to-treat, CI: confidence interval.

[a] The adjusted analysis adjusted for baseline Cdiff32 score, treatment group, sex, age (years), number of CDI episodes before treatment, treated with fidaxomicin, proton pump inhibitor use, metabolism and nutrition disorders, surgical and medical procedures, infections and infestations, gastrointestinal disorders, psychiatric disorders.

[b] The sample size for the as-observed analysis differed based on availability of data across domain scores.

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Disclosures

PF: an employee of PACT-Gastroenterology Center, consultant, speakers bureau, and advisory board for Ferring/Rebiotix, consultant and advisory board for Seres Therapeutics, consultant for Merck and Co. and advisory board for Takeda Pharmaceuticals; ED: research support from Pfizer and Ferring; consultant for Merck, Ferring, Pfizer, and Seres Therapeutics; AG: an employee of Ferring Pharmaceuticals; AH and LB: employees of Rebiotix Inc., a Ferring Company; MY, VGH, and MF: employees of Analysis Group, Inc.; GT: an employee of GST Micro LLC and consultant for Ferring, Spero, Taro Pharmaceuticals; KWG: an employee of University of Houston College of Pharmacy, Consultant for Ferring Pharmaceuticals, received research grant from Acurx, Summit, Paratek Pharmaceuticals and Seres health.

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