E0348

Health-Related Quality of Life of Week 8 Responders and Non-Responders: Results from the RBX2660 Phase 3 Randomized, Placebo-Controlled Trial in Recurrent *Clostridioides Difficile* Infection (PUNCH CD3)

Paul Feuerstadt, MD, FACG, AGAF[1,2]; Erik R. Dubberke, MD, MSPH[3]; Amy Guo, PhD[4]; Adam Harvey, PhD[5]; Min Yang, MD, PhD[6]; Viviana García-Horton, PhD[7]; Mirko Fillbrunn, PhD[6]; Jonathan Salcedo, PhD[6]; Glenn S. Tillotson, PhD, FIDSA, FCCP[8]; Lindy L. Bancke, PharmD[5]; Kevin W. Garey, PharmD, MS, FASHP[9]

[1]Yale University School of Medicine, New Haven, CT, United States; [2]PACT-Gastroenterology Center, New Haven, CT, United States; [3]Washington University, St Louis, MO, United States; [4]Ferring Pharmaceuticals, Inc., Parsippany, NJ, United States; [5]Rebiotix, a Ferring Company, Roseville, MN, United States; [6]Analysis Group, Inc., Boston, MA, United States; [7]Analysis Group, Inc., New York, NY, United States; [8]GST Micro LLC, North, VA, United States; [9]University of Houston, Houston, TX, United States.

INTRODUCTION

- In 2011 there were an estimated 500,000 incident cases of *Clostridioides difficile* infection (CDI) in the United States. It is the most frequent healthcare associated infection (HAI)[1,2]
- CDI occurs through ingestion of spores followed by colonization of the colon and production of toxins, causing a range of severe symptoms and outcomes including diarrhea, colonic perforation, and death[3-4]
- Over a third of patients experience recurrent *Clostridioides difficile* infection (rCDI), which substantially compromises patients' health-related quality of life (HRQL)[5], in addition to the severe symptoms and outcomes of CDI
- RBX2660, a live biotherapeutic product, was found to consistently reduce rCDI across 6 studies in the clinical development program with over 900 RBX2660 treated patients[6]
- Here we report post-hoc HRQL results as measured using the *Clostridioides difficile* Health-related Quality-of-Life Questionnaire (Cdiff32) of responders (with no recurrence) and non-responders (with a recurrence) within an 8-week blinded period of the RBX2660 phase 3 randomized placebo-controlled trial PUNCH CD3 (NCT03244644)

OBJECTIVE

- Among responders and non-responders, as determined by week 8, to summarize Cdiff32 total and domain-specific (physical, mental, social) scores at baseline and week 8 for patients randomized to RBX2660 or placebo (PBO)
- To summarize changes from baseline (CFB) in Cdiff32 scores from baseline to week 8 by treatment (RBX2660 or PBO) and response status

METHODS

- This analysis included adult patients with rCDI from the phase 3 PUNCH CD3 trial's modified intention-to-treat (mITT) population. The mITT population was defined as all randomized subjects who successfully received blinded treatment but excluding: 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 for the primary endpoint if the reason for exit was not related to CDI symptoms. Patients were required to have a Cdiff32 assessment at both baseline and week 8 to be included in the analysis
- We analyzed results from the *Clostridioides difficile* Health-related Quality-of-Life Questionnaire (Cdiff32), a validated, disease-specific instrument with three domains (physical, mental, and social) and a total score (all ranging from 0–100, with 100 best possible)
- The following analyses were conducted separately for both responders and non-responders (as determined by recurrence by week 8), for the RBX2660 and PBO arms:
  - Absolute scores for the Cdiff32 total and domain scores were summarized at baseline and week 8 via mean and standard deviation
  - Changes from baseline to week 8 were summarized via mean and standard deviation
  - Comparisons of week 8 to baseline within treatment arm were conducted using one-sample Wilcoxon rank-sum tests
- Among responders, adjusted analyses were used to analyze Cdiff32 scores at week 8 with the following covariates: baseline Cdiff32 score, treatment (RBX2660 or PBO), sex, age (years), prior fidaxomicin use, prior proton pump inhibitor use, number of CDI episodes before treatment, and common comorbidities (metabolism and nutrition disorders, surgical and medical procedures, infections and infestations, gastrointestinal disorders, psychiatric disorders). Adjusted regressions were not conducted among non-responders due to low sample size
- Per trial protocol, some patients experiencing recurrence within the blinded 8-week study period received open-label RBX2660 per physician discretion and were therefore excluded. As-observed (no imputation) data were used

KEY TAKEAWAYS

1 In the phase 3 trial PUNCH CD3, HRQL of rCDI patients treated with RBX2660 and with standard antibiotic treatment (i.e., PBO) improved significantly among the responders, with a greater magnitude for RBX2660, particularly for mental health

2 Among the few non-responders, an average improvement of more than 10 points on Cdiff32 was observed for RBX2660-treated patients though not among PBO-treated patients

3 These findings suggest that future research is warranted to further validate the potential benefit of RBX2660 on HRQL of patients with rCDI

RESULTS

Table 1. Baseline characteristics by week 8 response status

	Responders (N=178) Mean ± SD / N (%)	Non-Responders (N=7) Mean ± SD / N (%)
Demographics		
Age (years)	59.3 ± 16.7	66.4 ± 16.4
Sex		
Female	122 (68.5)	6 (85.7)
Male	56 (31.5)	1 (14.3)
Race		
American Indian or Alaska Native	2 (1.1)	0 (0.0)
Asian	1 (0.6)	0 (0.0)
Black or African American	9 (5.1)	1 (14.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
Multiple	1 (0.6)	0 (0.0)
White	163 (91.6)	6 (85.7)
Other	2 (1.1)	0 (0.0)
Disease characteristics		
Number of CDI episodes before treatment	3.1 ± 1.1	2.9 ± 1.5
Duration of prior CDI episode (days)	25.7 ± 14.9	32.6 ± 7.4
Antibiotics used at screening		
Other	6 (3.4)	0 (0.0)
Vancomycin	158 (88.8)	7 (100.0)
Fidaxomicin	14 (7.9)	0 (0.0)
Vancomycin duration on recent CDI (days)	17.4 ± 10.8	27.6 ± 7.0
Prior hospitalization due to CDI	21 (11.8)	4 (57.1)
Proton pump inhibitor use	35 (19.7)	2 (28.6)
Surgical and medical procedures	108 (60.7)	4 (57.1)
Infections and infestations	107 (60.1)	4 (57.1)
Gastrointestinal disorders	97 (54.5)	3 (42.9)
Psychiatric disorders	94 (52.8)	3 (42.9)
Metabolism and nutrition disorders	90 (50.6)	4 (57.1)

[a] Includes patients from the mITT population with both baseline and week 8 Cdiff32 assessments.

Table 2. Cdiff32 component scores at baseline and week 8 by treatment arm and response status

	RBX2660				Placebo			
Component (Mean ± SD)	**Baseline**	**Week 8**	**Change from baseline**	**Unadjusted P-value**	**Baseline**	**Week 8**	**Change from baseline**	**Unadjusted P-value**
Responders								
Total	43.7 ± 17.4	75.8 ± 18.3	32.1 ± 21.4	< 0.001 *	42.4 ± 20.3	70.1 ± 23.2	27.7 ± 19.8	< 0.001 *
Physical	52.6 ± 21.1	84.2 ± 16.9	31.7 ± 22.8	< 0.001 *	49.9 ± 22.7	79.2 ± 21.6	29.3 ± 23.2	< 0.001 *
Mental	32.7 ± 16.8	66.4 ± 22.0	33.7 ± 24.1	< 0.001 *	33.0 ± 20.5	60.1 ± 27.0	27.0 ± 21.4	< 0.001 *
Social	53.5 ± 23.6	80.2 ± 21.3	26.6 ± 27.9	< 0.001 *	49.3 ± 26.5	73.6 ± 27.8	24.3 ± 27.3	< 0.001 *
Non-responders								
Total	61.5 ± 16.7	76.3 ± 5.9	14.8 ± 16.4	0.423	59.0 ± 31.0	57.2 ± 35.0	-1.8 ± 25.6	0.854
Physical	78.0 ± 14.9	91.1 ± 4.7	13.1 ± 19.3	0.423	62.5 ± 35.3	62.1 ± 37.8	-0.5 ± 30.8	0.855
Mental	47.0 ± 19.6	60.7 ± 15.6	13.7 ± 16.2	0.181	54.9 ± 27.7	50.0 ± 33.2	-4.9 ± 23.3	0.854
Social	54.2 ± 15.7	79.2 ± 3.6	25.0 ± 16.5	0.181	60.9 ± 33.2	65.6 ± 34.8	4.7 ± 22.5	1.000

[a] Statistical comparisons of differences between Cdiff32 values at week 8 vs baseline were performed using one-sample Wilcoxon rank-sum tests.

- Among patients with reported Cdiff32 at baseline and week 8, 178 patients (125 RBX2660, 53 PBO) were responders and 7 (3 RBX2660, 4 PBO) were non-responders
- Responders were aged (mean ± SD) 59.3 years ± 16.7 and 68.5% were female while non-responders were aged 66.4 years ± 16.4 and were 85.7% female

Table 3. Multivariable adjusted analyses of Cdiff32 total and domain scores at week 8, among responders[a,b]

Component	RBX2660 treatment coefficient (95% CI)[c]	P-value
Total score	5.9 (-0.1 – 11.9)	0.06
Physical domain	4.9 (-0.85 – 10.6)	0.10
Mental domain	7.4 (0.3 – 14.4)	<0.05 *
Social domain	5.5 (-1.9 – 12.8)	0.15

CI = confidence interval.

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

[b] Adjusted linear regressions were conducted among responders only due to low sample size of non-responders.

[c] The RBX2660 treatment coefficient reflected the adjusted difference-in-difference between change from baseline to week 8 in RBX2660-treated patients and placebo patients.

Adjusted analyses among responders found a statistically significant improvement favoring RBX2660 vs PBO at week 8 for the mental domain (7.4, P<0.05)

- Among responders, improvements from baseline to week 8 were statistically significant (all p<0.001) for the Cdiff32 total score and all three domain scores, for both the RBX2660 and PBO arms
- Among non-responders, numerical but not statistically significant improvements from baseline to week 8 in the total score and all domain scores were observed for RBX2660, while scores remained similar or worsened from baseline to week 8 for PBO

References

1. Guh AY, et al. *Ann Intern Med.* 2018;169(7):ltc49-ltc64.
2. Centers for Disease Control and Prevention. 2021; https://www.cdc.gov/cdiff/what-is.html.
3. Zhu, et al. *Front Cell Infect Microbiol.* 2018
4. Rineh et al. *Expert Rev Anti Infect Ther.* 2014
5. Garey KW, et al. *J Clin Gastroenterol.* 2016 Sep; 50(8): 631–637.
6. Bancke L, et al. *Open Forum Infect. Dis.* 2021;8(Supplement_1): S100–S101

Acknowledgments

This study was funded by Ferring Pharmaceuticals.

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: an employee of Washington University School of Medicine, consultant for and received research grant from Ferring and Pfizer, consultant for Abbott, Merck, Seres, and Summit, received research grant from Synthetic Biologics, and advisory board for Rebiotix; AG: an employee of Ferring Pharmaceuticals; AH and LB: employees of Rebiotix Inc., a Ferring Company; MY, VGH, MF, and JS: 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.

Presented at ACG 2022, October 21 – 26, 2022, Charlotte, NC