Treatment of Recurrent *Clostridioides difficile* Infection With RBX2660 in Patients ≥65 Years Old With Underlying Comorbidities

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FERRING PHARMACEUTICALS — Microbiome Therapeutics Development

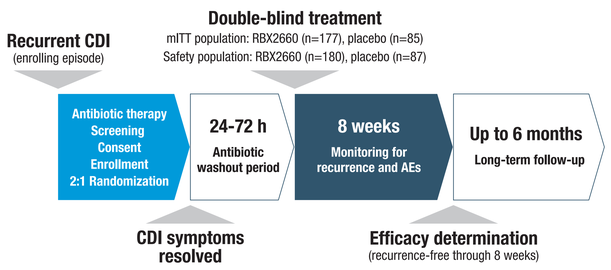
BACKGROUND

- Advanced age and certain underlying comorbidities, including cardiac, renal, and gastrointestinal (GI) disorders, are associated with greater rates of recurrence and increased risk of mortality and morbidity in patients with *Clostridioides difficile* infection (CDI)[1-5]
- Recurrent CDI (rCDI) is a serious and potentially fatal illness that places a profound burden on patients and the health care system, with an estimated 30-day mortality rate of 9% and an annual cost of $2.8 billion in the United States[6,7]
- Microbiota-restoring approaches are being widely evaluated for the treatment of rCDI in controlled clinical studies[8]
- RBX2660 is a standardized, microbiota-based live biotherapeutic product being investigated as a treatment option for rCDI[9-11]
- RBX2660 is administered as a single dose via rectal administration, without the need for sedation, colonoscopy, or bowel preparation
- In this subgroup analysis of PUNCH CD3 (NCT03244644), a prospective, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial, we report outcomes in older patients with rCDI with underlying cardiac, renal, and GI comorbidities

METHODS

- Participants enrolled in PUNCH CD3 were ≥18 years old with ≥1 documented episode of rCDI who completed standard-of-care antibiotic therapy before treatment with RBX2660 or placebo (**Figure 1**)
- Treatment success was defined as remaining free of CDI recurrence 8 weeks after treatment
- Open-label RBX2660 treatment was optional for participants who experienced a CDI recurrence after blinded treatment
- In this subgroup analysis, we assessed the 8-week outcomes of participants ≥65 years old with underlying cardiac disorders, chronic kidney disease (CKD), and GI disorders (**Table 1 and Figure 2**)
- The difference in treatment success rates between RBX2660 and placebo in each subgroup is presented in a forest plot with the 95% CI calculated by an exact method[12]
- Treatment-emergent adverse events (TEAEs) were defined as any adverse event occurring on or after blinded treatment
- TEAEs were summarized for the double-blind treatment period within 8 weeks and censored if a patient received open-label RBX2660 after CDI recurrence

Figure 1. PUNCH CD3 Study Design



AE, adverse event; CDI, *Clostridioides difficile* infection; mITT, modified intent-to-treat.

KEY TAKEAWAYS

1. **RBX2660 reduced rCDI more frequently in older participants with underlying cardiac and GI comorbidities than standard-of-care antimicrobials alone**
2. **Additional assessments are needed to understand the impact of RBX2660 in participants with CKD because of limited numbers in the current study**
3. **Similar to the total RBX2660-treated participant population, most TEAEs experienced by older participants with comorbidities were mild to moderate in severity**
4. **These data highlight the consistent efficacy and safety of RBX2660 across a range of patients, including those with medical complexities**

Table 1. Top 3 Medical Conditions in Participants ≥65 Years Old With Cardiac, Renal, or GI Disorders

Cardiac Disorder Preferred Terms	Placebo, n	RBX2660, n	Renal Disorder Preferred Terms	Placebo, n	RBX2660, n	GI Disorder Preferred Terms	Placebo, n	RBX2660, n
Atrial fibrillation	5	12	CKD	4	17	Gastroesophageal reflux disease	11	37
Congestive heart failure	4	11	Renal failure	0	2	Diverticulum[a]	5	13
Coronary artery disease	4	10	Hemodialysis	1	1	Hemorrhoids[b]	5	8

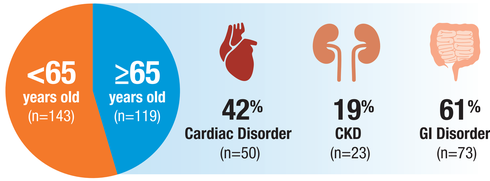
CKD, chronic kidney disease; GI, gastrointestinal.

Participants with cardiac, renal, or GI disorders were identified by searching preferred terms in the medical history at screening based on Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Medical terms are not mutually exclusive. [a]MedDRA preferred term representing diverticulosis. [b]Either internal or external.

RESULTS

Figure 2. Older Participants With Cardiac Disorders, CKD, or GI Disorders

45% (119 of 262) of participants in the mITT population were ≥65 years old

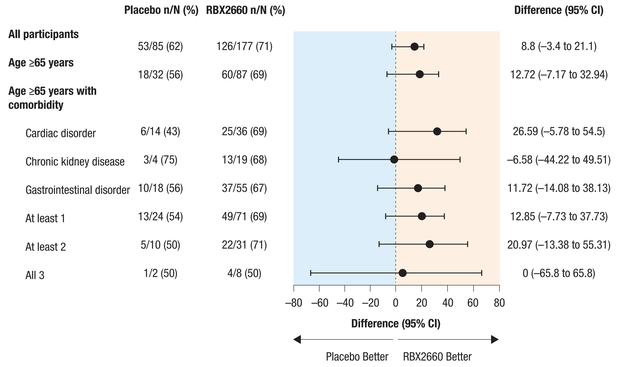


CKD, chronic kidney disease; GI, gastrointestinal; mITT, modified intent-to-treat.

- **RBX2660 treatment success rates in older participants with comorbid conditions were remarkably consistent:**
  - **69% in participants with cardiac disorders**
  - **68% in participants with chronic kidney disease**
  - **67% in participants with gastrointestinal disorders**

Treatment Success

Figure 3. Summary of RBX2660 Treatment Success Across Older Participants With Comorbidities (mITT Population)



mITT, modified intent-to-treat.

At least 1, participants with ≥1 comorbidity among cardiac disorder, CKD, and GI disorder; At least 2, participants with ≥2 comorbidities among cardiac disorder, CKD, and GI disorder.

The low number of participants in some subgroups (CKD [placebo], At least 2 [placebo], All 3) may limit data interpretation.

Safety

- In the total safety population, the overall incidence of TEAEs was 52% with RBX2660 treatment, compared with 44% with placebo treatment (**Table 2**)
- Mild events accounted for most of the difference (40% vs 30%)

Table 2. Summary of TEAEs Within 8 Weeks of Follow-Up of Blinded Treatment (Safety Population)

	Total Safety Population		RBX2660 Safety Population ≥65 Years of Age			
Participants with event, n (%)	Placebo	RBX2660	All	Cardiac Disorder	CKD	GI Disorder
	n=87	n=180	n=89	n=38	n=19	n=57
All TEAEs	38 (43.7)	94 (52.2)	45 (50.6)	23 (60.5)	13 (68.4)	29 (50.9)
Mild	26 (29.9)	72 (40.0)	32 (36.0)	16 (42.1)	9 (47.4)	21 (36.8)
Moderate	23 (26.4)	50 (27.8)	27 (30.3)	15 (39.5)	7 (36.8)	20 (35.1)
Severe	5 (5.7)	13 (7.2)	7 (7.9)	3 (7.9)	2 (10.5)	7 (12.3)
Potentially life-threatening	0	1 (0.6)	1 (1.1)	1 (2.6)	0	1 (1.8)
Serious AEs[a]	4 (4.6)	9 (5.0)	6 (6.7)	4 (10.5)	2 (10.5)	6 (10.5)
TEAEs leading to death	0	1 (0.6)[b]	1 (1.1)[b]	1 (2.6)[b]	0	1 (1.8)[b]

AE, adverse event; CDI, *Clostridioides difficile* infection; CKD, chronic kidney disease; GI, gastrointestinal; TEAE, treatment-emergent adverse event.

Percentage was calculated using the number of participants in the column heading as the denominator.

[a]The serious AEs reported were cardiorespiratory arrest (n=1), abdominal pain (n=1), diarrhea (n=1), ileus (n=1), asthenia (n=1), cellulitis (n=2), *C. difficile* colitis (n=2), CDI (n=2), abdominal abscess (n=1), hand fracture (n=1), postoperative ileus (n=1), dehydration (n=1), failure to thrive (n=1), and alcohol withdrawal syndrome (n=2). *C. difficile* colitis and CDI events were classified as serious AEs because of hospitalization.

[b]1 death during the 8 weeks of safety follow-up after blinded treatment was because of cardiorespiratory arrest in a patient ≥65 years old with a history of cardiac and GI disorders; this event was deemed related to a preexisting condition and unrelated to RBX2660 or the administration procedure.

- **Overall incidence of TEAEs in RBX2660-treated participants:**
  - **51% in participants ≥65 years old**
  - **61%, 68%, and 51% in participants with a cardiac disorder, CKD, or GI disorder, respectively**
- **Most TEAEs were mild or moderate in severity and related to a preexisting condition**
- **Serious AEs were infrequent, and none were considered related to RBX2660 or its administration**

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