Safety of Investigational Microbiota-Based Live Biotherapeutic RBX2660 in Individuals with Recurrent *Clostridioides difficile* Infection: Data From Five Prospective Clinical Studies

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BACKGROUND

- *Clostridioides difficile* infection (CDI) is a global issue directly responsible for thousands of deaths, quality-of-life impairment for millions of people living with CDI, and billions of dollars in healthcare costs each year[1]
- While antibiotic therapy is the standard guideline-based treatment for CDI,[2] antibiotic-associated dysbiosis increases risk for C. diff colonization and results in recurrence in 1 out of 6 patients, which requires further antibiotic therapy[3]
- Microbiota restoring approaches are being widely evaluated for treatment of recurrent CDI in controlled clinical studies
- RBX2660, a standardized, microbiota-based investigational live biotherapeutic product, has been evaluated for the reduction of recurrent CDI in 5 prospective clinical studies (3 Phase 2 and 2 Phase 3)
- Herein we report the safety of RBX2660 across 5 clinical studies

METHODS

- Safety data from 5 prospective studies (three Phase 2 and two Phase 3; Table 1) were pooled
- The safety population was defined as any participant exposed to study treatment (RBX2660 or Placebo)
- Studies enrolled adult (≥18 years of age) participants with recurrent CDI who received standard of care antibiotics prior to study treatment
- Studies evaluated a single dose or two doses administered 1 week apart as 1 treatment course
- All studies included 6 months follow-up after last treatment; two studies included 24 months follow-up
- Safety analyses are presented from baseline through 6 months
- Four studies allowed a second, open-label (OL) treatment for CDI recurrence within 8 weeks

TABLE 1: Study Design

STUDY	DESIGN	TREATMENT	Treatment for CDI recurrence? (Y/N)	PARTICIPANTS TREATED
PUNCH CD NCT01925417	Prospective, Open label	RBX2660 - 1 dose	Yes	**34**
PUNCH CD2 NCT02299570	Prospective, Randomized, Double blind, Placebo-controlled	RBX2660 or placebo - 2 doses 1 week apart	Yes	**128**
PUNCH Open Label NCT02589847	Prospective, Open label, Historical control	RBX2660 - 2 doses 1 week apart	No	**149**
PUNCH CD3 NCT03244644	Prospective, Multicenter, Randomized, Double blind, Placebo-controlled	RBX2660 or placebo - 1 dose	Yes	**267**
PUNCH CD3-OLS NCT03931941 (ongoing)	Prospective, Multicenter, Open label	RBX2660 - 1 dose	Yes	**293**

DEMOGRAPHICS AND DISPOSITION

- Table 2 details the demographics and disposition of 832 participants in the safety population
- 749 participants received at least 1 dose RBX2660
  - 177 received a second, OL treatment with RBX2660 for CDI recurrence
- 131 participants were assigned to receive placebo
  - 48 were treatment failures who received a second, open-label treatment with RBX2660 and are presented in the Placebo Followed by RBX2660 group
  - 83 did not receive a second, open-label treatment and are presented in the Placebo Only group
- Participants receiving RBX2660 tended to be older and had more previous episodes of CDI

TABLE 2: Participant Demographics And Disposition of Safety Population

	NUMBER OF PARTICIPANTS n (%)				
		RBX2660			
	Placebo Only (N = 83)	Placebo Followed by OL RBX2660 (N = 48)	RBX2660 Only (N = 572)	RBX2660 Followed by OL RBX2660 (N = 129)	All RBX2660 (N = 749)
Age - Mean (SD)	58.1(16.5)	58.0 (18.2)	61.1 (18.0)	63.5 (18.0)	61.3 (18.0)
Age Group <65 years – n (%)	52 (62.7)	27 (56.3)	302 (52.8)	61 (47.3)	390 (52.1)
Age Group ≥65 years – n (%)	31 (37.3)	21 (43.8)	270 (47.2)	68 (52.7)	359 (47.9)
Female – n (%)	60 (72.3)	30 (62.5)	377 (65.9)	83 (64.3)	490 (65.4)
Race – n (%)					
American Indian or Alaska native	0	0	3 (0.5)	0	3 (0.4)
Asian	0	0	6 (1.0)	0	6 (0.8)
Black or African American	6 (7.2)	1 (2.1)	19 (3.3)	7 (5.4)	27 (3.6)
White	75 (90.4)	46 (95.8)	533 (93.2)	122 (94.6)	701 (93.6)
Number of previous episodes of CDI before study entry, n (%)*					
≤ 3	60 (72.3)	23 (47.9)	321 (56.1)	76 (58.9)	420 (56.1)
> 3	23 (27.7)	25 (52.0)	246 (43.0)	52 (40.3)	323 (43.1)
Participant Disposition					
Received treatment	83 (100.0)	48 (100.0)	572 (100.0)	129 (100.0)	749 (100.0)
Completed 8-wk follow-up	78 (94.0)	42 (87.5)	494 (86.4)	111 (86.0)	647 (86.4)
Completed 6-m follow-up	75 (90.4)	42 (87.5)	422 (73.8)	93 (72.1)	557 (74.4)

** Study 2019-01 is ongoing, 6 participants had incomplete data at the time of this data cut*

SAFETY RESULTS

Of all 832 participants who received ≥1 treatment with RBX2660 or placebo, 571 (68.6%) experienced ≥1 Treatment Emergent Adverse Event (TEAE; Table 3)

- In all treatment groups, most treatment-emergent adverse events (TEAEs) were mild or moderate in severity and were related to preexisting conditions, CDI, or enema
- Potentially life-threatening TEAEs were reported infrequently and in a similar percentage of participants in the Placebo Only (1.2%) and RBX2660 Only group (2.4%)
- Abdominal pain, nausea, and flatulence were reported in ≥ 5% of participants in the RBX2660 Only group compared with the Placebo Only group

TABLE 3: Treatment-Emergent Adverse Events in ≥ 10 % of Participants in Any Treatment Group

	NUMBER OF PARTICIPANTS n (%)				
		RBX2660			
MedDRA System Organ Class and Preferred Term	Placebo Only (N = 83)	Placebo Followed by OL RBX2660 (N = 48)	RBX2660 Only (N = 572)	RBX2660 Followed by OL RBX2660 (N = 129)	All RBX2660 (N = 749)
Participants with ≥1 TEAE	50 (60.2)	37 (77.1)	378 (66.1)	106 (82.2)	521 (69.6)
Gastrointestinal disorders					
Diarrhoea	15 (18.1)	16 (33.3)	119 (20.8)	38 (29.5)	173 (23.1)
Abdominal pain	7 (8.4)	14 (29.2)	83 (14.5)	26 (20.2)	123 (16.4)
Nausea	3 (3.6)	8 (16.7)	50 (8.7)	12 (9.3)	70 (9.3)
Flatulence	1 (1.2)	5 (10.4)	43 (7.5)	12 (9.3)	60 (8.0)
Constipation	5 (6.0)	4 (8.3)	33 (5.8)	17 (13.2)	54 (7.2)
Abdominal distension	3 (3.6)	6 (12.5)	34 (5.9)	11 (8.5)	51 (6.8)
General disorders and administration site conditions					
Chills	4 (4.8)	4 (8.3)	17 (3.0)	13 (10.1)	34 (4.5)
Infections and infestations					
Urinary tract infection	4 (4.8)	1 (2.1)	33 (5.8)	16 (12.4)	50 (6.7)

TOLERABILITY

The tolerability of RBX2660 was exemplified in the low incidence of discontinuations due to adverse events (7 of 749 participants [0.9%] in the All RBX2660 group; Table 4).

TABLE 4: Overall Summary of Tolerability by Treatment Groups

	NUMBER OF PARTICIPANTS n (%)				
		RBX2660			
Characteristic	Placebo Only (N = 83)	Placebo Followed by OL RBX2660 (N = 48)	RBX2660 Only (N = 572)	RBX2660 Followed by OL RBX2660 (N = 129)	All RBX2660 (N = 749)
With TEAEs	50 (60.2)	37 (77.1)	378 (66.1)	106 (82.2)	521 (69.6)
Number of TEAEs	174	203	1529	587	2319
With SAEs	6 (7.2)	5 (10.4)	69 (12.1)	32 (24.8)	106 (14.2)
Discontinued due to AEs	0	0	4 (0.7)	3 (2.3)	7 (0.9)
TEAEs leading to death	0	0	12 (2.1)	6 (4.7)	18 (2.4)
Related to Investigational Product	0	0	1 (0.2)*	0	1 (0.1)*
Related to Enema	0	0	1 (0.2)*	0	1 (0.1)*
Related to *C.diff*	0	0	2 (0.3)	1 (0.7)	3 (0.4)
Related to Pre-Existing Condition	0	0	11 (1.2)	6 (4.7)	17 (2.3)

** One TEAE leading to death occurred within 30 days of treatment and was assessed as possibly related to Investigational Product and enema procedure, and definitely related to C.diff and pre-existing condition*

CONCLUSIONS

- The safety profile of RBX2660 is well characterized, based on the 5 prospective clinical studies included here including 749 participants who received at least 1 dose of RBX2660
- Participants receiving RBX2660 were older and had more previous CDI episodes than those in the Placebo Only group
- Most TEAEs were mild or moderate in severity and unrelated to RBX2660 or placebo. No potentially life-threatening TEAEs were considered related to RBX2660
- RBX2660 was well-tolerated, with low incidence (<1%) of discontinuations due to TEAEs
- Given that CDI is responsible for considerable morbidity, mortality, and healthcare expenditures with mortality particularly high for patients over the age of 65 [4] and that CDI recurrence rate following standard-of-care antibiotics is 25-35%,[3] demonstration of consistent RBX2660 safety supports the potential of RBX2660 as a safe option for reducing CDI recurrence

REFERENCES

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