Results of the Phase 2 PUNCH™ CD Safety Study of RBX2660 (microbiota suspension) for Recurrent *C. difficile* Infection

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Presenter Disclosure Information

- Research: Rebiotix, Sanofi-Pasteur, Merck, Microdermis
- Consulting: Rebiotix, Sanofi-Pasteur, Merck, Pfizer, Astellas

Background

- *Clostridium difficile* infection (CDI) places an increasingly large burden on healthcare systems worldwide in terms of morbidity, mortality and costs.[1,2]
- Approximately 25% of patients suffer from recurrence of disease, and recurrent CDI is especially challenging to treat.[3]
- There is increasing recognition that fecal microbiota transplantation (FMT) is an effective treatment for recurrent CDI.[4-6]
- A systematic evaluation of the safety of FMT has not been been done; concerns remain.

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3. Kelly CP. Can we identify patients at high risk of recurrent Clostridium difficile infection? *Clin Microbiol Infect*. 2012;18 (Suppl 6):21-7.
4. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013;368:407-15.
5. Lee CH, Belanger JE, Kassam Z.. The outcome and long-term follow-up of 94 patients with recurrent and refractory *Clostridium difficile* infection using single to multiple fecal microbiota transplantation via retention enema. *Eur J Clin Microbiol Infect Dis*. 2014;33(8):1425-8.
6. Patel NC1, Griesbach CL, DiBaise JK, Orenstein R. Fecal microbiota transplant for recurrent *Clostridium difficile i*nfection: Mayo Clinic in Arizona experience. *Mayo Clin Proc*. 2013 Aug;88(8):799-805.

PUNCH CD Study

- PUNCH CD is a multicenter study of an FMT product for recurrent CDI.
  - 11 sites in US between Aug. 15 and Dec. 13, 2013
- RBX2660: fecal microbiota suspension, a next-generation FMT
  - Enhanced donor screening
  - Standardized microbial load
  - Cryopreserved
  - Administered by enema: 150 ml
- Primary objective: Assess the safety of RBX2660 in terms of product-related adverse events (AE) at 6 months.
- Secondary objective: Efficacy
  - Free from CDI recurrence 8 weeks after last infusion

PUNCH CD Inclusion Criteria

Major inclusion criteria:

- Age ≥ 18 years old
- At least two recurrences of CDI after a primary episode; completed at least two rounds of standard-of-care oral antibiotic therapy

Or,

- At least two episodes of severe CDI resulting in hospitalization
- Could already be taking/or will start a course of oral antibiotics for CDI symptoms
  - But the last 7 days of the regimen must be oral vancomycin (125 mg 4 x/day (500 mg))

PUNCH CD Exclusion Criteria

Major exclusion criteria:

- History of inflammatory bowel disease (ulcerative colitis, Crohn's disease or microscopic colitis); irritable bowel syndrome; chronic diarrhea; celiac disease
- Colostomy
- Evidence of active, severe colitis
- Known exposure to antibiotics within 6 months of study enrollment
- Compromised immune system
- Neutropenia (white blood cell count <1000 cells/µL)

RBX2660 Administration

- First dose
  - Administered within 24-48 hours of completion of a standardized 7 day course of oral vancomycin
  - No bowel prep
- Second dose
  - Permitted if CDI reoccurred ≤ 8 weeks
  - Administered to patients with active CDI symptoms
  - No antibiotics given before treatment

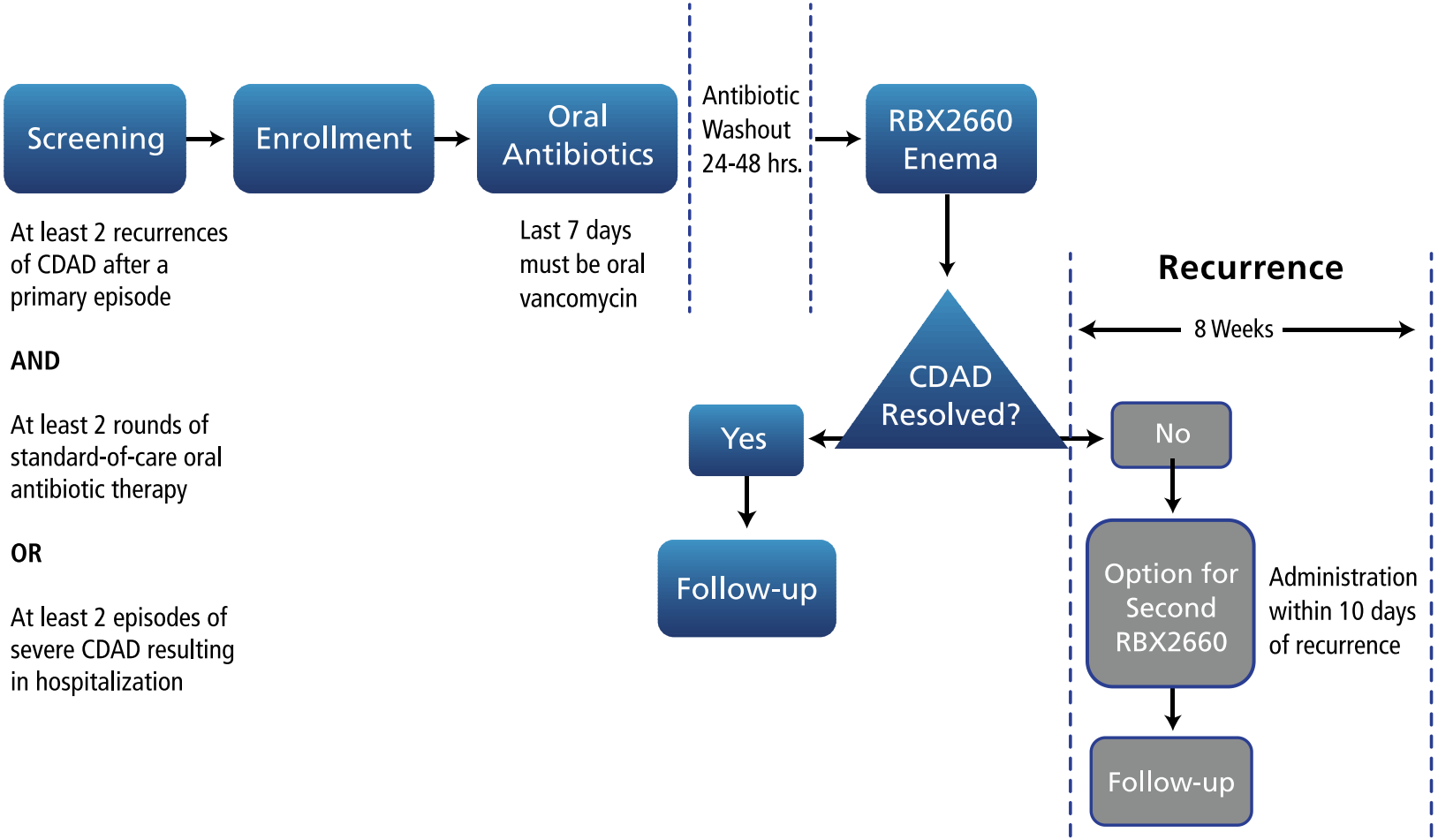
Safety Assessment Methods

- AEs solicited during 6-month follow-up after each dose of RBX2660
  - Patients completed a study diary documenting 11 pre-specified types of AEs through the first 7 days including severity
    - Gas, abdominal bloating, rectal pain, chills/rigors, abdominal pain/cramping, diarrhea, constipation, rectal bleeding, nausea, vomiting, fever
  - Weekly diary through the first 8 weeks
  - Patients asked about AEs during all encounters:
    - Office visits: 7,30 and 60 days
    - Calls: weekly through 8 weeks; at 3 and 6 months

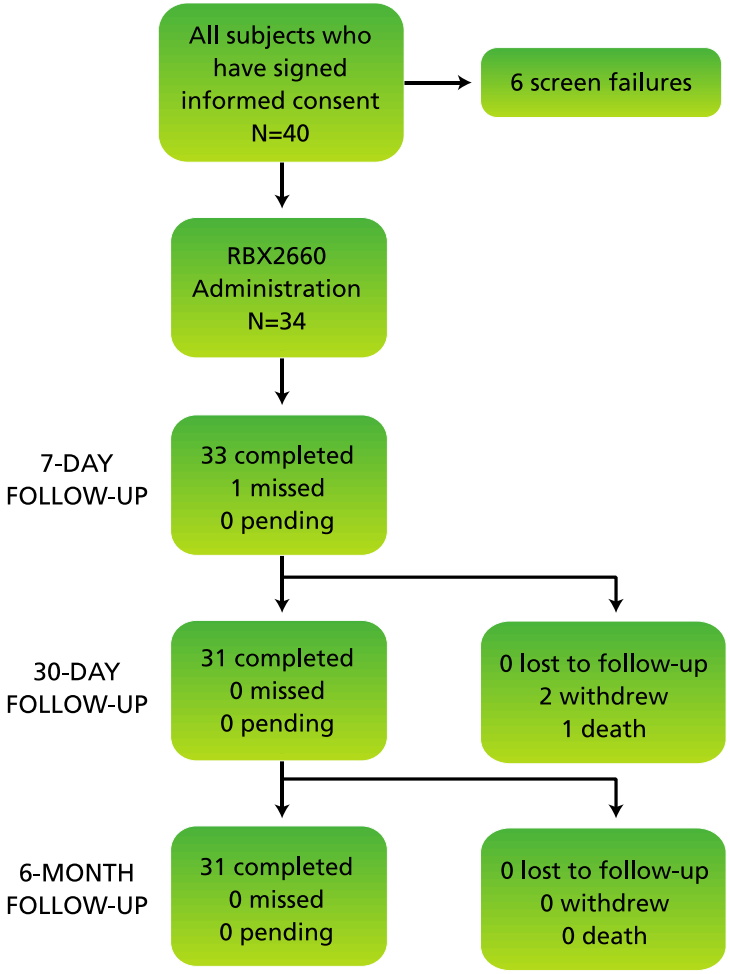
AE Assessment

- Investigator and study medical monitor evaluated AEs for:
  - Seriousness
  - Severity
  - Causality/relatedness to:
    - RBX2660
    - Enema procedure
    - CDI
    - Pre-existing condition

PUNCH CD Study Design



Patient Flow



Demographics

- Mean age 66.8 (range: 26.7-89.6) years
- Female: 67.6%, n=23
- Male: 32.4%, n=11
- Comorbidities
  - GI (n=21)
  - Cardiovascular (n=19)
  - Genitourinary (n=18)
  - HEENT (n=15)
  - Musculoskeletal (n=13)

Safety

- 20 Serious AEs (SAE) reported in 7 patients through 6-month follow-up
  - None adjudicated related to RBX2660 or administration
  - Included 3 cases of recurrent CDI ≤ 8 weeks post-treatment, all of which required hospitalization
  - 12 SAEs in 2 patients with multiple co-morbidities
  - 1 patient death due to respiratory failure
- 188 AEs reported in 28 patients through 6-month follow-up
  - Most common AEs were: flatulence, abdominal pain/cramping, constipation, diarrhea – all self-limiting
  - No difference in the incidence of adverse events with or without antibiotic pretreatment (dose 1 vs. dose 2)

Serious Adverse Events

Patient 12-RBX01-002	Patient 13-RBX01-003	Others
Pneumonia	Pulmonary adenocarcinoma	Severe right abdominal pain, fever, dehydration, vomiting, diarrhea resulting in hospital admission 7 days post dose 2.
Pulmonary edema secondary to dialysis non-compliance	Chest pain following endobronchial biopsy	Broken pelvis due to fall at home
CDI symptoms	Nausea, fatigue and other symptoms following chemotherapy	Viral syndrome/exacerbation of COPD
Diarrhea	Loose bowel movements, cold-like symptoms following small pneumothorax	Respiratory distress and failure
CDI symptoms	Hypoxia	Self-inflicted knife wound while intoxicated
CDI hospitalization		CDI symptoms
Gram-negative bacteremia		CDI symptoms
		UTI during previous hospitalization

Adverse Events: Type

Type	n (%)
GI disorders	107 (56.9)
Infections and infestations	19 (10.1)
General disorders	14 (7.4)
Respiratory, thoracic and mediastinal disorders	9 (4.8)
Nervous system disorders	7 (3.7)
Musculoskeletal and connective tissue disorders	6 (3.2)
Injury, poisoning, procedural complications	5 (2.7)
Psychiatric disorders	4 (2.1)
Metabolism and nutrition disorders	3 (1.6)
Skin and subcutaneous tissue disorders	3 (1.6)
Cardiac disorders	3 (1.6)
Surgical and medical procedures	3 (1.6)
Renal and urinary disorders	2 (1.1)
Investigations	1 (.5)
Ear and labyrinth disorders	1 (.5)
Neoplasms benign, malignant and unspecified	1 (.5)
TOTAL	**188**

Type	n (%)
Diarrhea	26 (24.3)
Flatulence	15 (14.0)
Abdominal pain	14 (13.1)
Constipation	14 (13.1)
Abdominal distension	9 (8.4)
Anorectal discomfort	6 (5.6)
Nausea	5 (4.7)
Vomiting	5 (4.7)
Proctalgia	3 (2.8)
Abdominal discomfort	1 (0.9)
Abdominal pain lower	1 (0.9)
Abdominal pain upper	1 (0.9)
Dyspepsia	1 (0.9)
Food poisoning	1 (0.9)
Gastrointestinal sounds abnormal	1 (0.9)
Gastrooesophageal reflux disease	1 (0.9)
Haematochezia	1 (0.9)
Rectal hemorrhage	1 (0.9)
Toothache	1 (0.9)
TOTAL	**107**

- GI disorders were most commonly reported.
- Of the most common GI AEs - diarrhea, flatulence, abdominal pain, and constipation – all cases were self-limiting

Adverse Events: Frequency

- The incidence of AEs declined over time

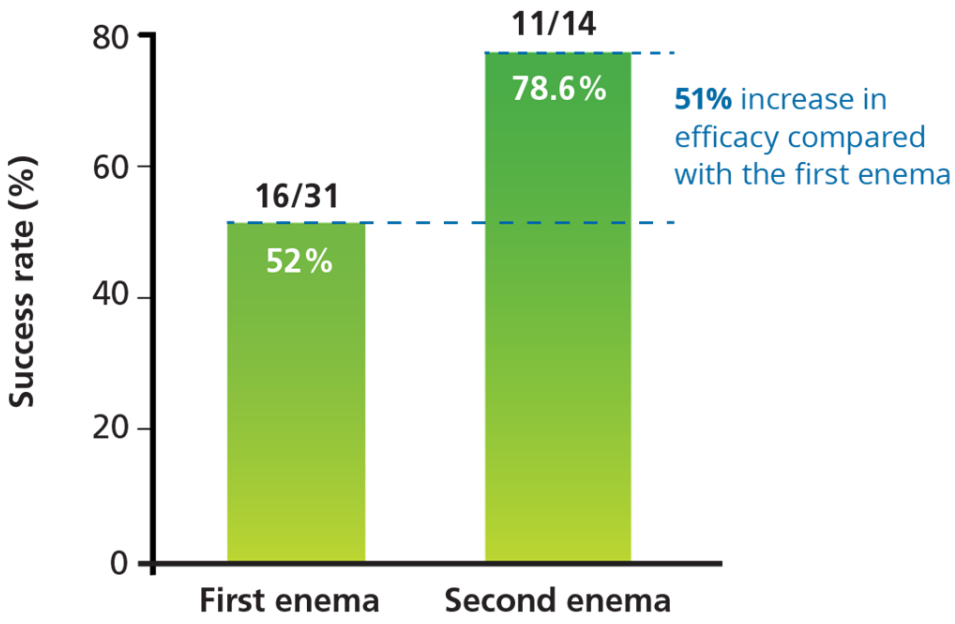
Time	n (%)
Baseline through 7 days	107 (56.9)
Days 8-30	30 (16.0)
Days 31-60	22 (11.7)
Days 61-90	8 (4.3)
Days 91-180	21 (11.2)
Total	188 (100)

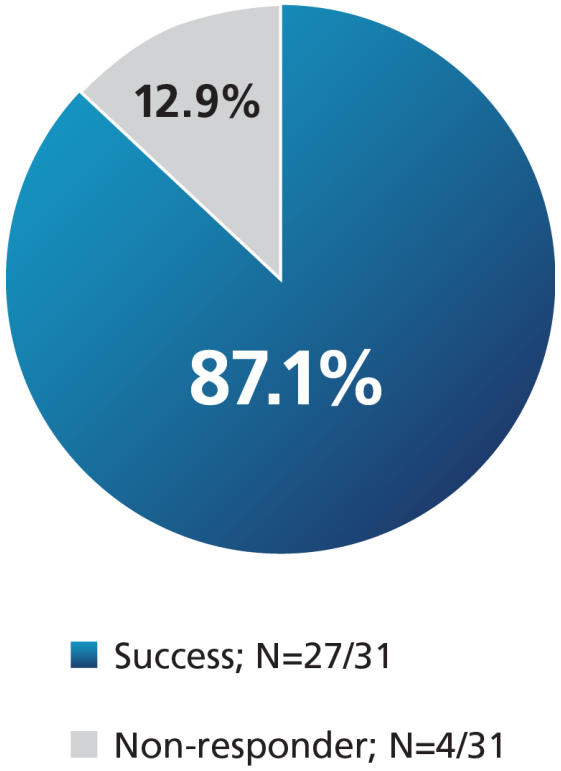
Adverse Events: Dose 1 vs Dose 2

Follow-up Day	AEs Dose 1 Only, n=17	Matched Pairs – Patients who Received 2 Doses of RBX2660 (N=14) AEs (Dose 1 of 2)	AEs (Dose 2 of 2)
0	26	39	0
1	2	3	0
2	0	4	0
3	3	3	0
4	0	2	0
5	0	1	0
6	1	4	0
7	1	1	3

- Fewer AEs after dose 2 than after dose 1
- Dose 2 administered to patients with active CDI; no antibiotic pre-treatment

Efficacy


Success rate (%)
80
60
40
20
0
16/31
52%
11/14
78.6%
51% increase in efficacy compared with the first enema
First enema
Second enema


12.9%
87.1%
Success; N=27/31
Non-responder; N=4/31

Conclusions

- Rigorous assessment of AEs
- Overall satisfactory safety profile
  - No serious AEs attributed to RBX2660 or its administration
- GI-related AEs common within 7 days of first dose
  - Declined over time
  - Less common with second dose
- Overall efficacy (87.1%) is in line with results previously reported in the literature.
  - Efficacy of second dose higher than first