Next Generation Fecal Transplant for Recurrent *C. difficile* Infection with and without Antibiotic Pre-Treatment:

LESSONS LEARNED FROM THE PUNCH CD PHASE 2 SAFETY STUDY

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Presenter Disclosure Information

- No financial relationships to disclose

Background

- Antibiotic-mediated disruption of the intestinal microbiota is a risk factor for *Clostridium difficile* infection (CDI)
- Approximately 25% of patients suffer from recurrence of disease following standard antibiotic therapy[1]
- CDI is one of the first diseases formally linked to perturbation of the intestinal microbiota[2]
- There is increasing recognition that restoration of a healthy gut microbiota is necessary to limit *Clostridium difficile* colonization[3]

1. Kelly CP. Can we identify patients at high risk of recurrent Clostridium difficile infection? *Clin Microbiol Infect*. 2012;18 (Suppl 6):21-7.
2. Young V. The intestinal microbiota in health and disease. *Curr Opin Gastroenterol*. 2012;28:63-9.
3. Seekatz AM, Aas J, Gessert CE, et al. 2014. Recovery of the gut microbiome following fecal microbiota transplantation. *mBio*.5(3):e00893-14.

RBX2660 (microbiota suspension)

- First in a new category of drugs using live human-derived microbes to treat recurrent CDI
- Currently in clinical study under FDA IND
  - PUNCH CD, Phase 2 multicenter non-randomized study completed
  - Prospective randomized double-blind controlled PUNCH CD Phase 2B study is next step (scheduled to start in fall 2014)
  - Both studies are first of their kind; breaking new ground

Open Questions

- Preconceived notions about microbiota restoration therapy at the time that the PUNCH CD study was designed:
  - Antibiotic pretreatment needed to control CDI symptoms prior to treatment in order for the therapy to work
  - Bowel prep was required for success
  - Use of a related donor was preferred; a non-related donor could be used as a last resort
- Based on experiences with FMT – but untested
- Will focus on the question of antibiotic pretreatment in the PUNCH CD Study

PUNCH CD Inclusion Criteria

Major inclusion criteria:

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

Or,

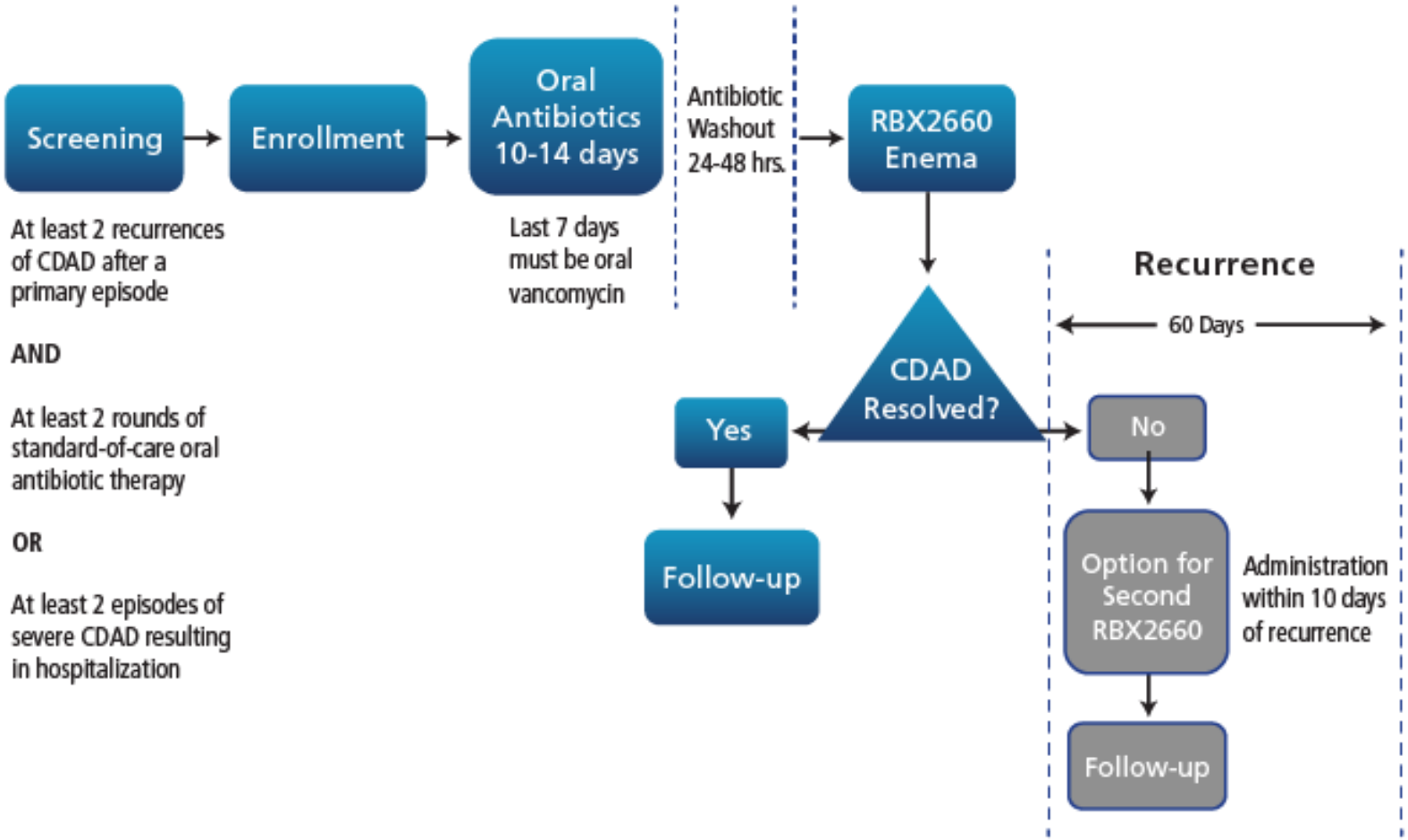
- At least two episodes of severe CDI resulting in hospitalization
- Taking or will start a course of oral antibiotics for CDI symptoms
  - 10-14 days
  - including at least 7 days of oral vancomycin (125 mg 4 x/day (500 mg)) for the last 7 days of the regimen

PUNCH CD Exclusion Criteria

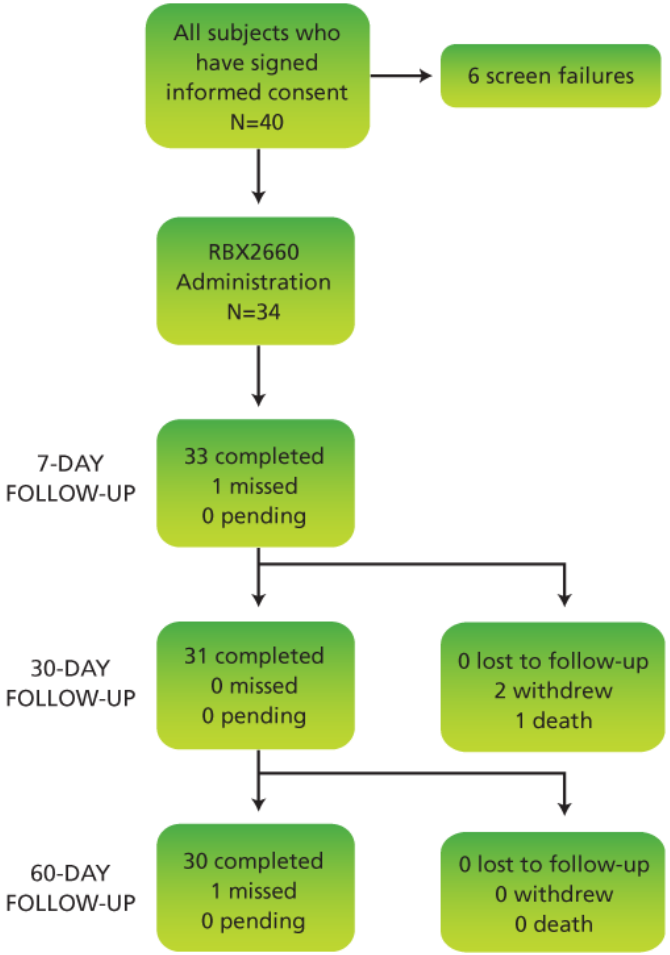
Major exclusion criteria:

- History of IBD, ulcerative colitis, Crohn's disease, or microscopic colitis; IBS; chronic diarrhea; celiac disease
- Colostomy
- Evidence of active, severe colitis
- Planned surgery requiring perioperative antibiotics within 6 months of study enrollment
- Compromised immune system
- Neutropenia (white blood cell count <1000 cells/µL)

PUNCH CD Study Design



Patient Flow



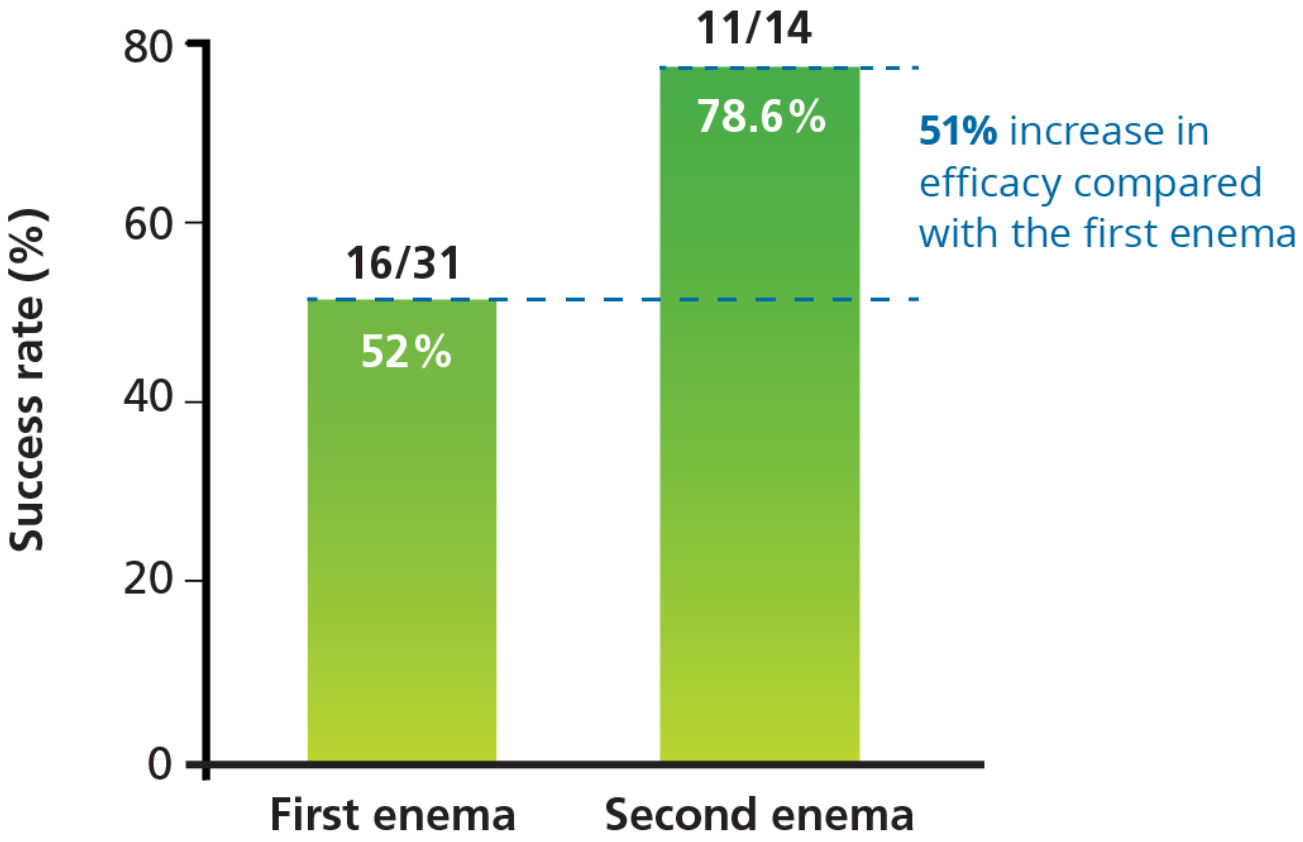
RBX2660 Administration

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

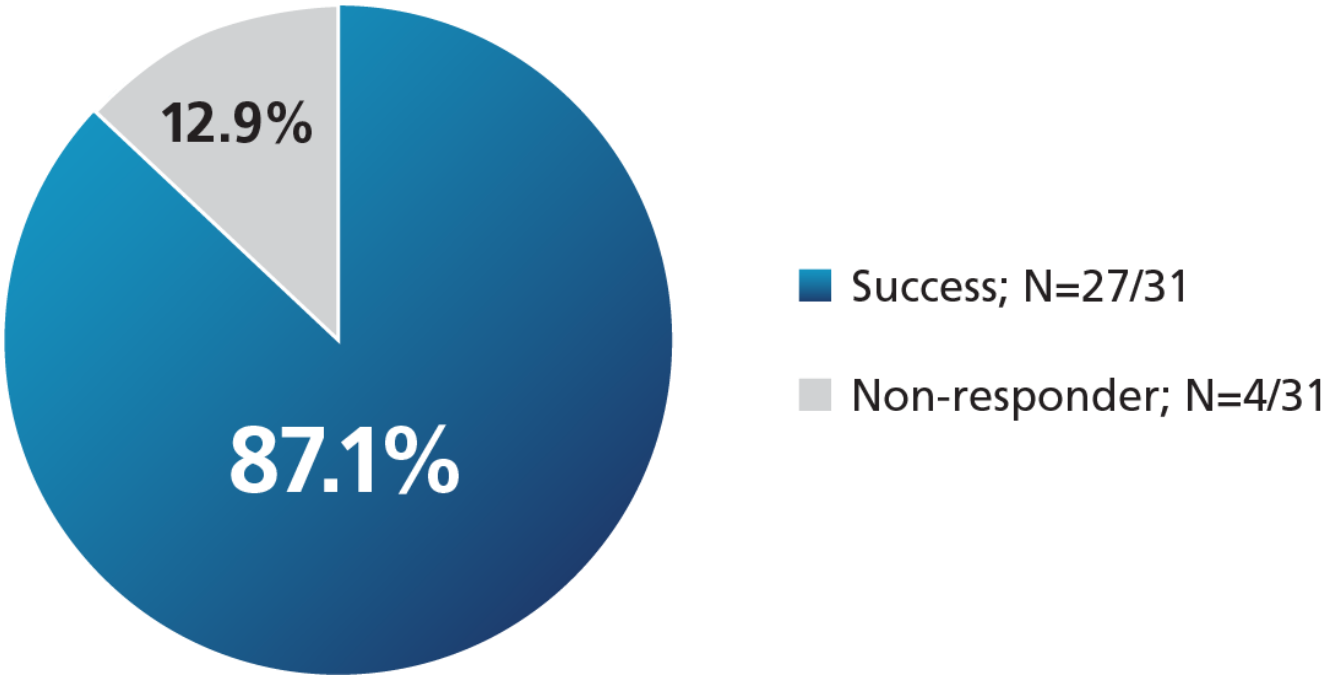
Study Population

- 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)

RBX2660 Treatment Efficacy



Overall Efficacy



Safety

- No product- or procedure-related SAEs
- No difference in the incidence of adverse events with or without antibiotic pretreatment

Safety

Most Common Adverse Events Through 60-Day Follow-up

Type	No. Events	Patients n/N%
Diarrhea	24	10/34 (29.4)
Flatulence	15	13/34 (38.2)
Abdominal pain	14	10/34 (29.4)
Constipation	12	12/34 (35.3)
Abdominal distension	9	7/34 (20.6)

Serious Adverse Events Through 60-Day Follow-up

Type	No. Events	Patients n/N (%)
Clostridium difficile infection	3	3/34 (5.9)
Pneumonia	1	1/34 (2.9)
Pelvic fracture	1	1/34 (2.9)
Stab wound	1	1/34 (2.9)
Chronic obstructive pulmonary disease	1	1/34 (2.9)
Pulmonary edema	1	1/34 (2.9)
Respiratory failure	1	1/34 (2.9)

Lessons Learned

- Enema administration of a biologic drug containing live human-derived microbes demonstrated preliminary safety and efficacy with or without antibiotic pretreatment
- Overall efficacy was comparable with results reported in the literature for fecal transplant

Thank you!