RBX2660, A Microbiota-Based Drug for the Prevention of Recurrent *Clostridium difficile* Infection, Is Safe and Effective: Results from a Randomised, Double-Blinded, Placebo-Controlled Trial

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Disclosure

- Dr. Orenstein is a member of the Physician Advisory Board of Rebiotix Inc., Roseville, MN USA

Background

- *Clostridium difficile* infection (CDI) is a serious worldwide health threat.
- Recurrence is common and difficult to prevent with standard of care antibiotics.
- Perturbation of the intestinal microbiota, primarily by antibiotics, facilitates symptomatic infection.
- Restoration of a diverse intestinal microbiota has been shown to protect against recurrence.
- Microbiota-based therapies appear highly effective in preventing CDI recurrences.
  - Evidence based on case reports, case series and few randomized controlled trials.
- There are needs for:
  - High-quality evidence on efficacy and safety in the context of randomised double-blinded, placebo-controlled trials.
  - A standardised, off-the-shelf microbiota product.

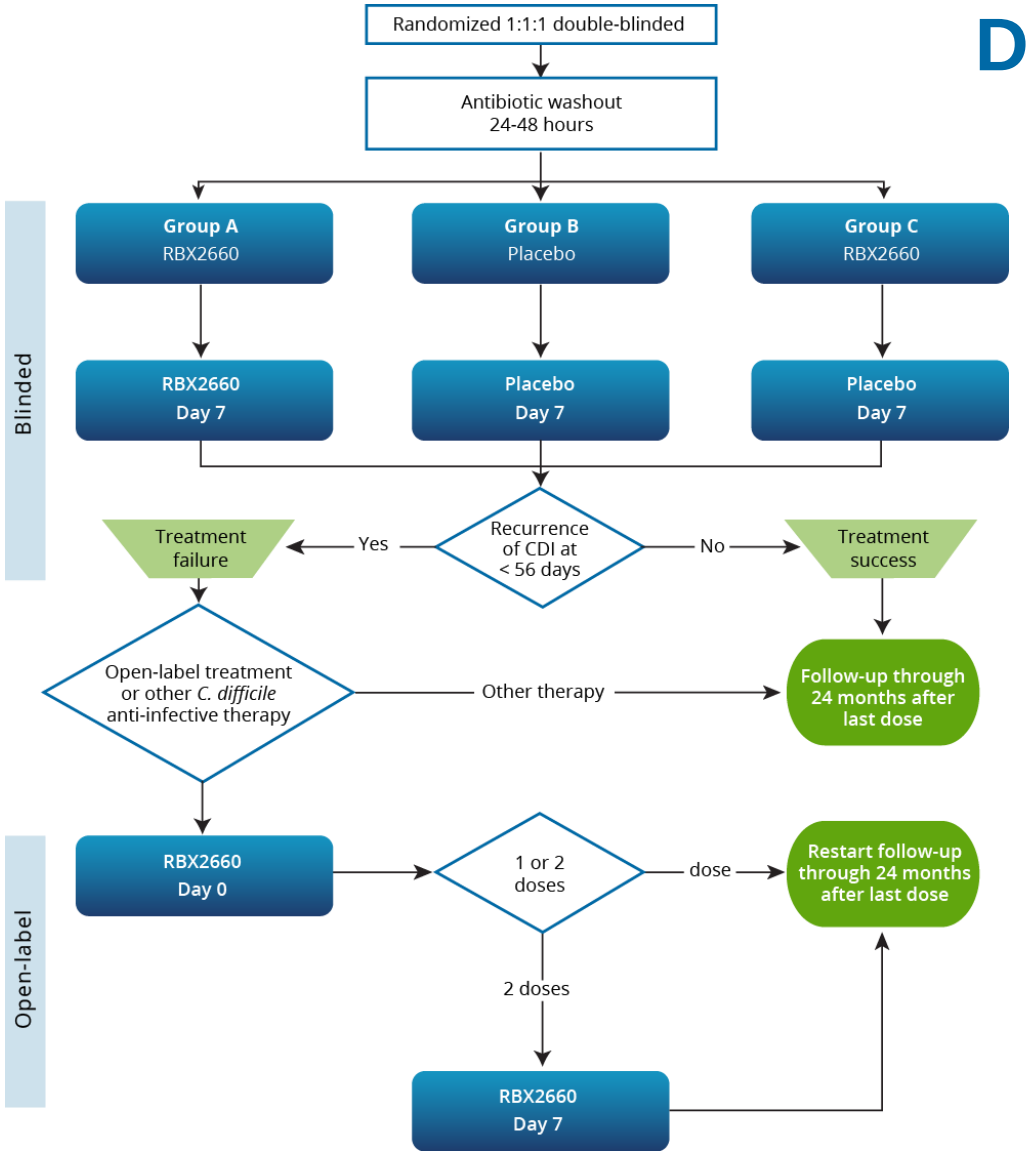
PUNCH CD 2 Trial

- A randomised, double-blinded placebo-controlled trial carried out at 21 centers in the United States and Canada between December 10, 2014 through November 13, 2015.
- Objectives: To assess the dose, safety and efficacy of RBX2660, a microbiota-based drug targeted at recurrent CDI, in a randomised, double-blinded, placebo-controlled trial.
- Participants were randomized: 1:1:1 to the following groups
  - Group A: 2 doses of RBX2660
  - Group B: 2 doses of placebo
  - Group C: 1 dose of RBX2660 and 1 dose of placebo

RBX2660

- Consists of 50 gm of human stool in 150 mL of liquid suspension with ≥10^7 live organisms/mL of suspension. Available in a single-dose ready-to-use enema bag.
- Each unit identified by a unique batch number traceable to a specific donor and recipient.
- Stored frozen at ≤−80°C in a secure location at the manufacturer and then shipped frozen to the site in a temperature-controlled container.
- Thawed in a refrigerator for 24 hours and administered to the patient within 48 hours after thawing.
- Blinding: Investigational product (RBX2660 and placebo) shrouded in an opaque brown sleeve.
  - Enema administrator who was not involved in study follow-up procedures shrouded the tubing set and delivered the enema.
  - Biohazard container used for disposal was opaque to prevent accidental visualisation during administration and disposal.

Design



- Participants entering the study had at least two recurrences of CDI and a positive test for CD≤60days prior to enrollment.
- Antibiotic control of CDI symptoms prior to enrollment
- 24-48 hour washout prior to dosing
- All doses administered via enema, 7 days apart.
- Failures in the blinded phase could receive up to 2 doses of open-label, active treatment.

Major Enrollment Criteria

Inclusion:

- Age ≥ 18 years
- Positive stool test for *C. difficile* with active symptoms ≤ 60 days of enrollment
- At least 2 recurrences of CDI after a primary episode

Or,

- At least 2 episodes of CDI resulting in hospitalisation

Exclusion:

- Ongoing or anticipated antibiotic therapy for a condition other than CDI
- Prior FMT
- Other known or expected causes of diarrhea and/or immunocompromising conditions
- IBD, IBS
- Pregnant, breastfeeding, or intent to become pregnant during study participation

Endpoints

- Primary endpoint:
  - Efficacy at 8 weeks of 2 doses (1 treatment) of RBX2660 compared with 2 doses (1 treatment) of placebo
- Secondary endpoints:
  - 1 dose of RBX2660 and 1 dose of placebo compared with 2 doses of placebo
  - 2 doses of RBX2660 compared with 1 dose of RBX2660 and 1 dose of placebo
  - Efficacy of *C. difficile* therapies administered to confirmed treatment failures
  - Safety

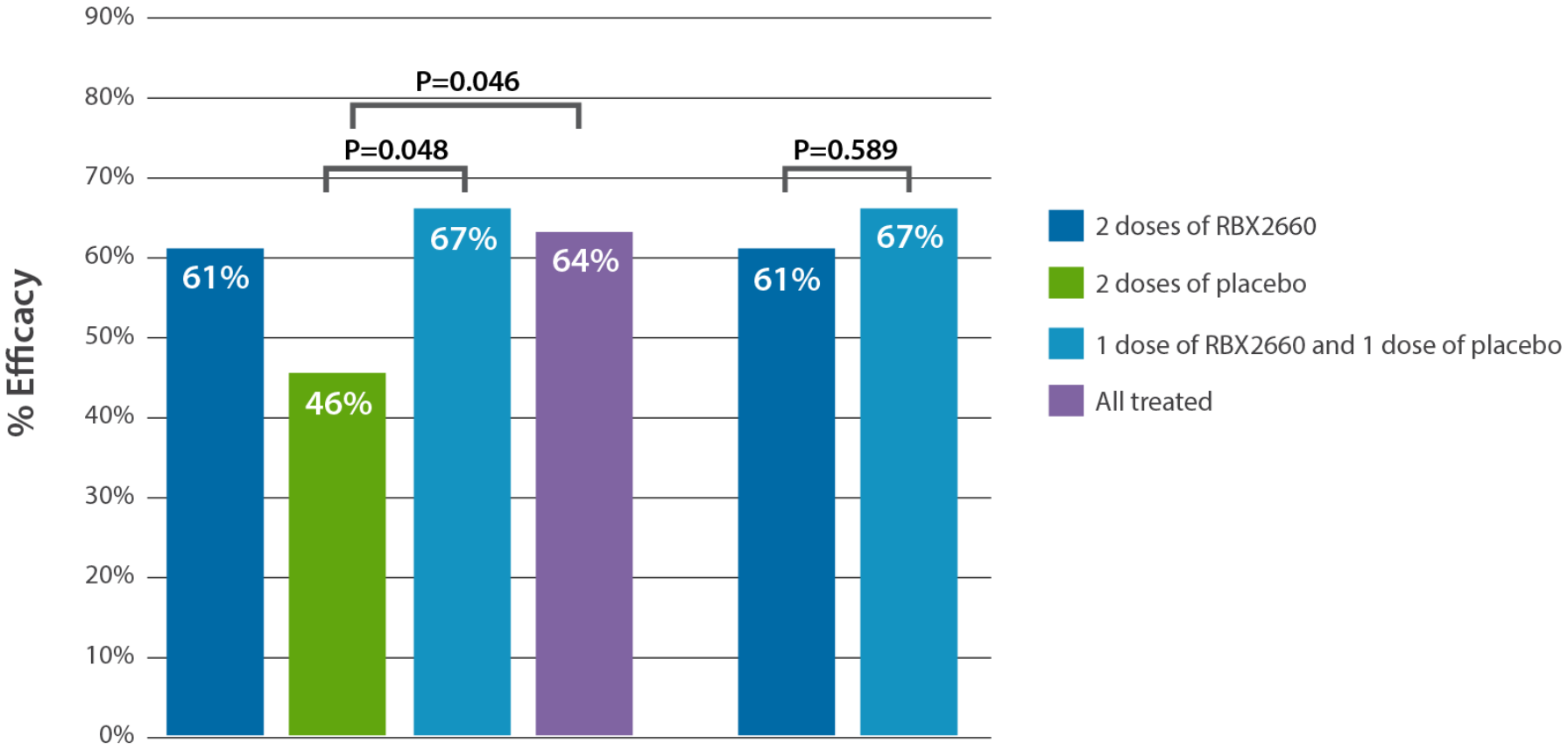
Definitions

- Success:
  - Absence of diarrhoea -without the need for retreatment with a *Clostridium difficile* anti-infective therapy or faecal transplant- through 8 weeks after administration of the second dose of the assigned treatment in the blinded phase
- Failure (All 4 criteria required):
  - Presence of diarrhoea, with or without other CDI symptoms, at <8 weeks after last treatment
  - A positive stool test for *Clostridium difficile*
  - Need for retreatment for CDI
  - No other cause for diarrhoea identified

Baseline Characteristics

Characteristic	2 Doses of RBX2660 (N=41)	2 Doses of Placebo (N=44)	1 Dose of RBX2660 and 1 Dose of Placebo (N=42)
Mean age – years	62.8 ±19	58.8 ± 19	61.5 ± 20
Female sex- no. (%)	25 (61)	30 (68)	24 (57)
Race-White – no. (%)	39 (95)	42 (96)	40 (95)
Antibiotic used at screening – no. (%) Vancomycin Fidaxomicin Other	38 (93) 1 (2) 2 (5)	39 (89) 2 (5) 3 (6)	36 (86) 2 (5) 4 (10)
Median number of CDI episodes – no., (interquartile range)	4.0 (2)	3.0 (1)	4.0 (1)
Mean duration of CDI episode, days	18.8 ± 14	19.5 ± 17	16.4 ± 11
Healthcare-acquired CDI infection – no. (%)	10 (5.7)	10 (6.0)	13 (7.8)

Results: Efficacy- Blinded ITT



- There was no difference between 2 doses of RBX2660 and 1 dose of RBX2660, P > 0.05.
- No escalating dose effect.

Blinded and Open-Label Efficacy by Treatment Group

Group	Blinded treatment success	Open-label treatment success	Overall success
A: 2 doses of RBX2660	61% (25/41)	69% (11/16)	89% (36/41)
B: 2 doses of placebo	45% (20/44)	NA	45% (20/24)
C: 1 dose of RBX2660 and 1 dose of placebo	67% (28/42)	71% (10/14)	90% (38/42)
A and C	64% (53/83)	70% (21/30)	89% (74/83)
Placebo failures	NA	88% (21/24)	88% (21/24)

- Overall treatment success for subjects who received at least 1 dose of RBX2660 (blinded and open-label): 88.6% (95/107).

Phase 2B: Overall Safety Events

Type	Total (Subjects)
Adverse Events	580 (94)
Serious Adverse Events (SAEs)	45 (26)
Unanticipated Adverse Events (UAE's)	0

Adverse Events:

- 42% gastrointestinal, 10% general, 9% infection
- Top 5 were: diarrhea, abdominal pain, flatulence, constipation, nausea

RBX2660: A Safe Treatment

Treatment (Product) Related Adverse Events

P=0.542

Key Safety Events	2 Doses of RBX2660	2 Doses of Placebo	1 Dose of RBX2660
Adverse Event Rate (events, patients, % pts)	57, 14, 34%	33, 13, 30%	17, 10, 23%
Serious Adverse Events (n, % pts)	3, 7%*	0	0

Procedure (Enema) Related Adverse Events

P=0.077

Key Safety Events	2x RBX2660	2x Placebo	1x RBX2660
Adverse event Rate (events, patients, % pts)	39, 9, 22%	30, 17, 39%	15, 8, 19%
Serious Adverse Events (n, % pts)	0	0	0

*All 3 SAE's were listed as 'possibly' related to treatment. SAE's were abdominal cramping, constipation, and recurrent myeloid leukemia (pre-existing).

Durability

Snapshot as of 4-12-16

	8 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Long-term Infection-free rate %, n,N	95 successful subjects**	98.9 91/95	95.7 67/70	87.5 14/16	NA	NA

- The long-term CDI-free rate (median follow-up: 8.3 months; range 1.6 to 14.9 months) was 95.8% (91/95).
- Of all successful patients who received at least one active treatment, 4.2% (4/95) developed a new episode of CDI confirmed by a positive test > 8 weeks after the last RBX2660 treatment:
  - After antibiotics for a dog bite (n=1); during a hospital stay for small bowel obstruction(n=1); unknown (n=2)

* Number of patients who have reached follow-up milestones as of 4-12-16; 24 month follow-up expected Q1 2018

** 95 patients = 74 successful All Treated + 21 placebo failures successfully treated in open label

Conclusions

- RBX2660 administered via enema is a safe and effective treatment for recurrent CDI.
- AEs were primarily gastrointestinal; there were no unanticipated AEs.
- RBX2660 provided a durable cure.
- The results were consistent with those achieved in the open-label PUNCH CD trial.

Thank you!