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.

PUNCH CD Study

- PUNCH CD is a multicenter study of an FMT product for recurrent CDI.
- 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
Investigator and study medical monitor evaluated AEs for:

- Seriousness
- Severity
- Causality/relatedness to:
  - RBX2660
  - Enema procedure
  - CDI
  - Pre-existing condition
PUNCH CD Study Design

At least 2 recurrences of CDAD after a primary episode

AND

At least 2 rounds of standard-of-care oral antibiotic therapy

OR

At least 2 episodes of severe CDAD resulting in hospitalization

Recurrence

CDAD Resolved?

Yes → Follow-up

No → Option for Second RBX2660 → Follow-up

RBX2660 Enema

Antibiotic Washout 24-48 hrs.

Oral Antibiotics

Last 7 days must be oral vancomycin

Screening → Enrollment
Patient Flow

All subjects who have signed informed consent N=40

6 screen failures

RBX2660 Administration N=34

33 completed 1 missed 0 pending

7-DAY FOLLOW-UP

31 completed 0 missed 0 pending

0 lost to follow-up 2 withdrew 1 death

30-DAY FOLLOW-UP

6-MONTH FOLLOW-UP

31 completed 0 missed 0 pending

0 lost to follow-up 0 withdrew 0 death
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

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

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

- 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

<table>
<thead>
<tr>
<th>Time</th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>Baseline through 7 days</td>
<td>107 (56.9)</td>
</tr>
<tr>
<td>Days 8-30</td>
<td>30 (16.0)</td>
</tr>
<tr>
<td>Days 31-60</td>
<td>22 (11.7)</td>
</tr>
<tr>
<td>Days 61-90</td>
<td>8 (4.3)</td>
</tr>
<tr>
<td>Days 91-180</td>
<td>21 (11.2)</td>
</tr>
<tr>
<td>Total</td>
<td>188 (100)</td>
</tr>
</tbody>
</table>
Adverse Events: Dose 1 vs Dose 2

<table>
<thead>
<tr>
<th>Follow-up Day</th>
<th>AEs Dose 1 Only, n=17</th>
<th>AEs (Dose 1 of 2)</th>
<th>AEs (Dose 2 of 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>26</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>4</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

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

51% increase in efficacy compared with the first enema

Success rate (%)

First enema: 16/31 = 52%
Second enema: 11/14 = 78.6%

Success: N=27/31
Non-responder: N=4/31

87.1%
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