Durable Prevention of Recurrent *C. difficile* Infection with RBX2660: Results of the PUNCH CD 2 Trial

Mayur Ramesh, MD;* Sahil Khanna, MBBS, MS;* Julie Messer, BS;* Matt Adams, MS;* Henry Ford Hospital, Detroit, MI; Division of Gastroenterology & Hepatology, Mayo Clinic, Rochester, MN; *Rebiotix Inc., Roseville, MN

Background

- Antibiotic exposure is a major risk factor for the development of *Clostridium difficile* infection (CDI).
- Antibiotic treatment of CDI with standard of care antibiotics contributes to persistent disruption of the intestinal microbiota and predisposes to recurrent infection. The risk of recurrence increases following a second episode.
- Microbiota-based drugs have shown promise in durable prevention of recurrence.

Methods

- Patients with recurrent CDI enrolled in the three-arm PUNCH CD 2 trial were randomized 1:1:1 to receive either: 2 doses of RBX2660 (Group A); 2 doses of placebo (Group B); or 1 dose of RBX2660 and 1 dose of placebo (Group C) via enema with doses 7 days apart (Figure 1).
- Failures in any study group were eligible to receive open-label treatment with up to 2 doses of RBX2660.
- Success was measured as the absence of CDI symptoms at 8 weeks post treatment.
- Failure was defined as the presence of diarrhea, with or without other CDI symptoms, at less than 8 weeks after last treatment; a positive stool test for *C. difficile*; the need for retreatment for CDI and no other cause for diarrhea was identified (all four criteria were required).
- Safety follow-ups were scheduled in clinic at 1, 4 and 8 weeks and via telephone at 2, 3 and 5-7 weeks and at 3, 6, 12, and 24 months. Durability assessments occurred concurrently and are ongoing until 24 months.

Major Inclusion Criteria

- Age ≥ 18 years old
- At least two episodes of severe CDI resulting in hospitalization
- At least two recurrences of CDI after a primary episode
- White blood cell count >1000 cells/µL
- History of inflammatory bowel disease (ulcerative colitis, Crohn’s disease or microscopic colitis); irritable bowel syndrome; chronic diarrhea; celiac disease
- Colon cancer
- Evidence of active colitis
- Known exposure to antibiotics within 60 days prior to enrollment

Major Exclusion Criteria

- History of inflammatory bowel disease (ulcerative colitis, Crohn’s disease or microscopic colitis); irritable bowel syndrome; chronic diarrhea; celiac disease
- Colon cancer
- Evidence of active colitis
- Known exposure to antibiotics within 60 days prior to enrollment
- Compromised immune system
- White blood cell count <1000 cells/µL
- Known exposure to antibiotics within 6 months after study enrollment
- Evidence of active colitis
- History of inflammatory bowel disease (ulcerative colitis, Crohn’s disease or microscopic colitis); irritable bowel syndrome; chronic diarrhea; celiac disease
- Colon cancer
- Evidence of active colitis
- Compromised immune system
- History of inflammatory bowel disease (ulcerative colitis, Crohn’s disease or microscopic colitis); irritable bowel syndrome; chronic diarrhea; celiac disease

Results

- A total of 107 patients (median age 63, range: 18-92 years; 59.8% female) at 21 centers in the U.S. and Canada received at least 1 dose of RBX2660 (Table 1).
- The overall success rate of patients who received at least one dose of RBX2660 in the blinded and open-label phases of the trial was 95.8% (95/99) (Table 1).
- Of the successful patients, 4.2% (4/95) developed a new episode of CDI confirmed by a positive test > 8 weeks after the last RBX2660 treatment (Table 2).
- The long-term CDI-free rate (median follow-up: 8.3 months; range: 1.6 to 14.9 months) was 95.8% (95/99) (Table 3).

Conclusions

- RBX2660, a microbiota-based drug, provided a durable cure for recurrent CDI in a randomized, double-blinded, placebo-controlled trial with up to 12 months follow-up. Long-term follow-up to 24 months is ongoing.
- Longitudinal assessment of the impact of RBX2660 treatment on the intestinal microbe profiles of patients may provide additional insight into durable prevention of CDI.

### TABLE 1. PATIENTS WHO RECEIVED AT LEAST 1 DOSE OF RBX2660 (N=107)

<table>
<thead>
<tr>
<th>Group</th>
<th>n (N)</th>
<th>Success (%)</th>
<th>Failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>41 (41)</td>
<td>74 (90.2)</td>
<td>9 (19.8)</td>
</tr>
<tr>
<td>B</td>
<td>24 (24)</td>
<td>21 (87.5)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>C</td>
<td>42 (42)</td>
<td>95 (88.8)</td>
<td>12 (11.2)</td>
</tr>
</tbody>
</table>

### TABLE 2. RECURRENCES AFTER SUCCESSFUL TREATMENT WITH RBX2660

1. After antibiotics for a dog bite
2. During a hospital stay for small bowel obstruction
3. Unknown
4. Unknown

### TABLE 3. DURABILITY OF RBX2660 TREATMENT

<table>
<thead>
<tr>
<th>Group</th>
<th>Overall CDI-Free Rate</th>
<th>3 Months CDI-Free Rate</th>
<th>6 Months CDI-Free Rate</th>
<th>12 Months CDI-Free Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>95.8% (95/99)</td>
<td>91.9% (90/98)</td>
<td>90.3% (90/98)</td>
<td>89.4% (87/96)</td>
</tr>
<tr>
<td>B</td>
<td>89.5% (21/24)</td>
<td>87.5% (21/24)</td>
<td>85.7% (19/22)</td>
<td>79.2% (15/19)</td>
</tr>
<tr>
<td>C</td>
<td>95.7% (95/99)</td>
<td>79.9% (77/97)</td>
<td>72.2% (60/84)</td>
<td>72.2% (60/84)</td>
</tr>
</tbody>
</table>

* Corresponding Author

Mayur Ramesh, MD
Transplant Infectious Diseases & Immunotherapy, Henry Ford Hospital
2799 West Grand Blvd, 313 CFP
Transplant Infectious Diseases & Immunotherapy
Corresponding E-mail: mramesh1@hfhs.org

The PUNCH CD 2 trial was sponsored by Rebiotix Inc., Roseville, MN.