Background

- Recurrent *Clostridium difficile* infections (rCDI) has been recognized as an urgent health threat.
- Numerous therapeutics are being developed to reduce recurrence and have been evaluated in clinical trials.
- RBX2660 is a standardized microbiota-based drug manufactured from live human-derived microbes and was evaluated in PUNCH CD 2, a randomized, placebo-controlled Phase 2b trial for rCDI.
- Twenty (20) PUNCH CD 2 patients in the placebo arm met response criteria of no CDI recurrence within 8 weeks.
- To contextualize this placebo response observation, we conducted a meta-analysis of response rates among placebo-treated patients in additional rCDI trials.

Methods

- Five (5) blinded, randomized, and placebo-controlled trials were included in this meta-analysis 1-5.
- Studies required patients to have ≥1 or >2 prior CDI recurrences.
- All patients completed standard-of-care antibiotic course prior to experimental treatment.
- Four (4) studies tested a vehicle placebo administered by the same route as the active treatment (oral, intravenous, or enema) 1-4, and 1 study tested an autologous fecal transplant administered via enema.
- Response to treatment was defined as no CDI recurrence within 8-12 weeks.
- The proportional response rates with 95% confidence interval were calculated and compared in aggregate and among studies.

Results

- A total of 154 of 292 placebo-treated patients (53%) met study-specific response criteria.
- Placebo response rates ranged from 43%-58%.
- No study group presented a significantly different outcome from the aggregate cohort.
- No correlation of response with placebo administration route was observed.

Table 1: Randomized, controlled, double-blind studies included in this meta-analysis.

<table>
<thead>
<tr>
<th>REF</th>
<th>LEAD AUTHOR (YEAR)</th>
<th>EXPERIMENTAL TREATMENT</th>
<th>PLACEBO (n)</th>
<th>DELIVERY</th>
<th>PLACEBO RESPONDERS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dubberke (2016)</td>
<td>RBX2660</td>
<td>Saline (44)</td>
<td>Enema</td>
<td>20 (45.5%)</td>
</tr>
<tr>
<td>2</td>
<td>Seres (2016)</td>
<td>SER-109</td>
<td>Glycerol/Saline (30)</td>
<td>Oral</td>
<td>14 (46.7%)</td>
</tr>
<tr>
<td>3</td>
<td>Kelly (2016)</td>
<td>Heterogenous FMT</td>
<td>Autologous FMT (14)</td>
<td>Enema</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td>4</td>
<td>Wilcox (2017)</td>
<td>Bezlotoxumab, B. thetaiotaomicron + FMT</td>
<td>Saline (126)</td>
<td>Intravenous</td>
<td>73 (57.9%)</td>
</tr>
<tr>
<td>5</td>
<td>Surawicz (2000)</td>
<td>Autologous FMT</td>
<td>Vehicle (78)</td>
<td>Oral</td>
<td>41 (52.6%)</td>
</tr>
</tbody>
</table>

The Forest plot shows the placebo success rate for each study included in the meta-analysis with the addition of the aggregate result. Placebo group size (N) is represented by circle diameter.

References

1. Dubberke et al. Presented at Infectious Diseases Week 2016, New Orleans, LA.

Conclusion

- This meta-analysis demonstrates that response rates for blinded placebo-treated patients are consistent among 5 trials of experimental rCDI therapeutics, including a phase 2B trial of RBX2660.
- This analysis provides a useful framework for interpreting published rCDI trials, and for designing and interpreting future rCDI therapeutics trials.
- Further evaluation of placebo response in rCDI patients is warranted.