P1453

Placebo Responders in a Randomised Controlled Trial of RBX2660 for Recurrent *C. Difficile* Infection: Predictive Value of 16s rRNA Microbiome Analysis

Courtney Jones, BS[a] and Bill Shannon, PhD, MBA[b]

[a]Rebiotix Inc., Roseville, MN; BioRankings, St. Louis, MO, USA

Background

- Disruption of the gut microbiota, primarily by antibiotics, has been demonstrated as a risk factor for *Clostridium difficile* infection (CDI).
- Restoration of a variable intestinal microbiota protects against recurrence of CDI.
- A number of novel non-antibiotic therapies targeted at recurrent CDI are currently under investigation.
- Recently reported results of randomised, double-blinded, placebo controlled studies of non-antibiotic therapies for multiply recurrent CDI have found higher than anticipated placebo response rates (47%-63%).[1-3]

Objective

- To determine whether 16s rRNA analysis can be used as a predictive biomarker in the assessment of the placebo response to a microbiota-based drug targeted at recurrent CDI.

Methods

- PUNCH CD 2 was a randomised, double-blinded, placebo-controlled trial of RBX2660, a microbiota-based drug targeted at recurrent CDI.
- Patients were randomised 1:1:1 to receive either: 2 doses of RBX2660; 2 doses of placebo; or 1 dose of RBX2660 and 1 dose of placebo. RBX2660 was administered via enema with doses 7 days apart.
- Success was defined as the absence of *C. difficile*-associated diarrhoea at 8 weeks following completion of the last treatment. Failure was defined as recurrence of CDI symptoms; a positive stool test; a need for CDI retreatment; and no other cause for CDI symptoms within 8 weeks (all 4 criteria were required).
- In the intention-to-treat population, a total of 44 patients were randomised to the placebo arm of the study.
- Longitudinal 16s rRNA analysis was performed on patient stool after the second dose for the first 28 consecutive patients in the placebo arm using the MiSeq platform. The variable region V4 was targeted to identify the operational taxonomic units (OTUs) in each sample.

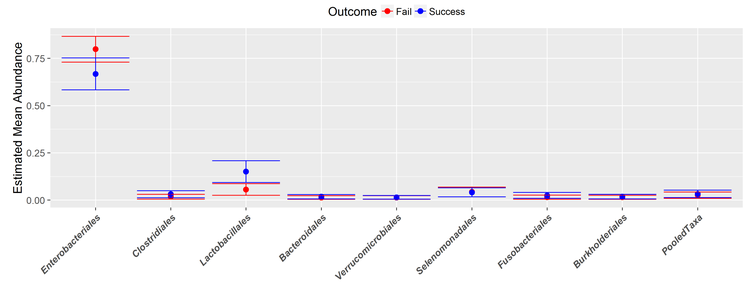
RBX2660

- RBX2660 is a microbiota-based drug containing live human-derived microbes.
- Each dose of RBX2660 consisted of 50 gm of human stool/150 mL of suspension in a single-dose ready-to-use enema bag.
- Manufactured using standardised, quality-controlled processes.

Results

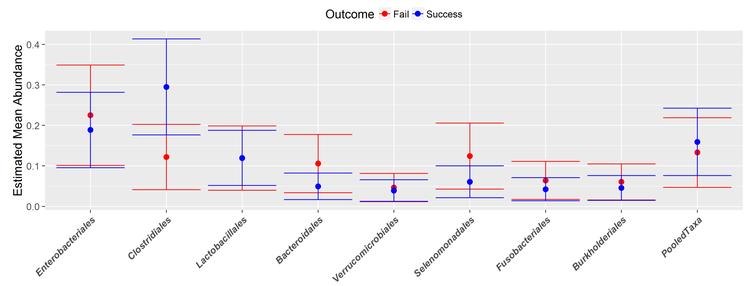
- For the 28 consecutive patients in the placebo arm who were sequenced, 13 (46%) responded and 15 (54%) failed. Considering all 44 patients in the placebo arm, 45.5% (20/44) responded and 54.5% (24/44) failed.
- At baseline, the microbiota profiles of the 28 patients were similar, P = 0.89 (Figure 1).
- There was no significant difference in the estimated mean abundance of bacterial taxa between patients who responded to or failed placebo at 7 days, p = 0.39 and 30 days, P = 0.84 (Figures 2 and 3).
  - *Clostridiales* and *Enterobacteriales* predominated at both the 7- and 30-day follow-up.
- Overall, there was no significant variation in the intestinal microbiota of patients who responded to placebo and those who did not.

Figure 1. Microbiota Profiles at Baseline



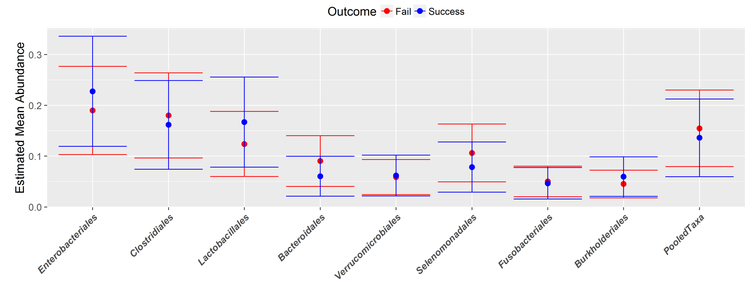
At baseline, the profiles of the success and failed placebo groups appear similar. The "Pooled" group consists of the least abundant taxa which jointly represent <5% of the overall abundance.

Figure 2. Microbiota Profiles at 7 Days Post Dose 2



At 7-day follow-up, there was no significant difference between the patients who responded to placebo and those who failed. The "Pooled" group consists of the least abundant taxa which jointly represent <5% of the overall abundance.

Figure 3. Microbiota Profiles at 30 Days Post Dose 2



At 30-day follow-up, there was no significant difference between the patients who responded to placebo and those who failed. The "Pooled" group consists of the least abundant taxa which jointly represent <5% of the overall abundance.

Conclusions

- In this randomised placebo-controlled study of RBX2660 for recurrent CDI, 16 rRNA analysis was not predictive of which patients receiving placebo went on to further recurrences of CDI and which did not.
- Further studies are needed to explore reasons for the placebo response rate and to explore the possibility of a predictive analytical method.

References

1. Kelly CR, Khoruts A, Staley C, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent *Clostridium difficile* infection: A randomised trial. *Ann Intern Med.* 2016 Aug 23. Epub ahead of print.

2. Seres Therapeutics announces interim results from SER-109 Phase 2 ECOSPOR study in multiply recurrent *Clostridium difficile* infection [news release]. Cambridge, MA: Seres Therapeutics, Inc. communication; July 29, 2016. http://ir.seresthera peutics.com/phoenix.zhtml?c=254006&p=irol-newsArticle&ID=2190006. Accessed August 8, 2016.

3. Wilcox M, Gerding D, Poxton I, et al. Bezlotoxumab (BEX) alone and with actoxubab (ACT) for prevention of recurrent *C. difficile* infection (rCDI) in patients on standard of care (SoC) antibiotics: integrated results of 2 Phase 3 Studies (MODIFY 1 and MODIFY II). Abstract presented at ID Week 2015. October 7-11, 2016, San Diego, CA.

The research was sponsored by Rebiotix Inc., Roseville, MN, USA.

Corresponding Author

Courtney Jones
2660 Patton Road
Roseville, MN 55113
Tel: 651-705-8770
cjones@rebiotix.com