Altering the Microbiome: Patients with a Successful Outcome Following Microbiota-Based RBX2660 Treatment Trend Toward Human Microbiome Project Healthy Subjects’ Profile

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Background

• Recurrent Clostridium difficile infections (rCDI) are strongly associated with intestinal dysbiosis.
• RBX2660 is a standardized microbiota-based drug designed to prevent rCDI by potentially restoring a healthier intestinal microbiome.
• The effect of RBX2660 on rCDI patient microbiomes was evaluated by comparing pre- and post-treatment samples collected from a Phase 2 controlled open-label study of RBX2660 to a healthy intestinal microbiome, as defined by the Human Microbiome Project (HMP).

Methods

• Prospective, multicenter, controlled open-label Phase 2 study (NCT02589847) consisting of an RBX2660 treatment arm and a historical control group.
• Antibiotics were discontinued 24-48 hours prior to administration of the first enema.
• Participants received up to 2 doses of RBX2660 delivered via enema with doses 2-3 days apart.
• Success was defined as the absence of CDI at 8 weeks following completion of the last treatment.
• Patients were classified as a treatment failure if all four (4) of the following criteria were met: recurrence of diarrhea less than 8 weeks after administration of the last assigned study enema, a positive laboratory diagnosis of C. difficile as conducted by the study investigator, a need for retreatment for CDI, and no assignment of study enema.
• Clinical efficacy results have been previously published (Figure 1).

RBX2660

Standardized, stabilized microbiota product that is ready-to-use in an easy-to-administer format

Disclaimer: This analysis was funded by Rebiotix Inc., Roseville, MN.

Figure 1: RBX2660 efficacy is significantly higher than historical controls and consistent across patient populations (p<0.0001). Data are presented as % (N=total).

Microbiome Analysis

• Patients in the RBX2660 treatment arm were asked to voluntarily submit stool samples at baseline (pre-treatment) and at multiple time points up to 12 months after treatment.
• Longitudinal sample sets (baseline, 7, and 30 days after treatment) were collected from 17 successful patients (n=55 samples) and 17 failed patients (n=54 samples).
• Stool samples were sequenced using BoosterShot (CoreBiome, Minneapolis, MN), an ultra-shallow shotgun sequencing that generates taxonomic profiles with species-level resolution.
• Relative abundance data from successful patient samples were grouped longitudinally and compared using a Bray-Curtis dissimilarity calculation with non-metric multi-dimensional scaling. Additional analyses were performed based on the Dirichlet Multinomial distribution to compare group mean relative taxonomic abundance(s) and within group dispersion (theta).
• Differentiation between sample communities was visualized using a Kulback-Leibler (KL) divergence analysis model (BioRankings, St. Louis, MO), a measure of the difference between microbial diversity at different time points or between different samples.

Results

• Clinical efficacy results have been previously published (Figure 1).

Figure 2: Microbiota from patients with recurrent CDI shift towards the HMP profile following RBX2660 treatment.

Comparisons were made at the sample level using non-metric multidimensional scaling based on the Bray-Curtis measure. In the plot above, mean microorganisms for individual patients (points) and group mean microorganisms (triangles) are shown. Arrows highlight the shift of group means from baseline toward the cluster of HMP samples.

Figure 4: Relative abundances of Bacteroidia classes converge toward the HMP profile following successful RBX2660 treatment.

Figure 3: Patients with successful response to RBX2660 have microbiota more similar to HMP microbiota.

Conclusions

• RBX2660 restores a healthier microbiome profile among patients who responded to open-label RBX2660 treatment.
• Patient microbiota trended toward increased diversity relative to baseline following RBX2660 treatment.

Microbial diversity was analyzed by Shannon and Simpson indices. The diversity indices of RBX2660-treated patients' microbiomes were not significantly significantly, shifted after treatment, although they tended to increase.

FIGURE 1: RBX2660 efficacy is significantly higher than historical controls and consistent across patient populations (p<0.0001). Data are presented as % (N=total).

Overall Age <65 Age >=65 Females Males

Overall 79.4 (136) 79.4 (136) 79.4 (136) 79.4 (136) 79.4 (136) 79.4 (136)

Age <65 75.3 (81) 75.3 (81) 75.3 (81) 75.3 (81) 75.3 (81) 75.3 (81)

Age >=65 62.8 (55) 62.8 (55) 62.8 (55) 62.8 (55) 62.8 (55) 62.8 (55)

Females 51.8 (110) 51.8 (110) 51.8 (110) 51.8 (110) 51.8 (110) 51.8 (110)

Males 44.8 (67) 44.8 (67) 44.8 (67) 44.8 (67) 44.8 (67) 44.8 (67)

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