Placebo Response in a Randomized Controlled Trial of a Microbiota-based Drug Targeted at Recurrent *C. difficile* Infection: Results of the PUNCH CD 2 Trial

Sahil Khanna, MBBS, MS;[a] Julie Messer, BS;[b] Matt Adams, MS[b]

[a]Division of Gastroenterology and Hepatology Mayo Clinic, Rochester, MN; Rebiotix Inc., Roseville, MN

Background: The challenge of treating recurrent *C. difficile* infection (CDI) has prompted interest in microbiota-based drugs. Clinical results, largely uncontrolled single center studies, have demonstrated very good efficacy. A recent controlled study found a higher than anticipated placebo rate. We assessed predictors of placebo response in PUNCH CD 2, a randomized, controlled, doubled-blinded trial of RBX2660 for the prevention of recurrent CDI.

Methods: Patients were randomized to receive either: 2 doses of RBX2660 (a microbiota-based drug produced from live human-derived microbes); 2 doses of placebo (normal saline and cryoprotectant in the same proportions as RBX2660); or 1 dose of RBX2660 and 1 dose of placebo. All therapies were administered via enema; doses were 7 days apart. Failure was defined as recurrence of CDI symptoms; positive stool test; need for CDI retreatment; and no other cause for CDI symptoms within 56 days. Failures could cross over to open-label treatment and receive up to 2 doses of RBX2660.

Results: Of the 127 patients treated in the study, a total of 44 (median age: 44, range: 19 to 92 years; 68.2% female) were randomized to the placebo arm. Of the patients treated with placebo, 45.5% (20/24) responded and 54.5% (24/44) failed. There were no significant differences in median age (61.5, range: 19-90 vs. 63.5, range: 19-90 years); sex (75.0% vs. 62.5% female); median prior CDI episodes (3.0, range: 3-11 vs. 3.5, range: 2-5); median prior metronidazole courses (0.5, range:0-3 vs.1.0, range:0-6); median prior vancomycin courses (2.0, range:1-4 vs. 2.0, range: 1-5) of which (25.0% vs. 17.6%) were tapers- between patients who did and did not respond to placebo. Of the patients who responded to placebo, 90% received vancomycin just prior to study enrollment vs. 87.5% of the non-responders. All 24 patients who experienced recurrence went on to receive open-label treatment with RBX2660 and experienced an 87.5% (21/24) treatment success – consistent with previously reported results for open-label PUNCH CD study.

Discussion: The placebo response in PUNCH CD 2 and a similar recent study were higher than originally anticipated. There were no differences in the patient profiles; prior history of CDI and its treatment between the patients who responded to placebo and those who did not. Further studies are needed to explore reasons for the placebo response.