DEVELOPING MICROBIOME REHABILITATION BIOMARKERS FOR *CLOSTRIDIUM DIFFICILE* INFECTIONS: EVALUATION OF A PROTOTYPE MICROBIOME HEALTH INDEX™ (MHI)

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Rebiotix® Microbiota Restoration Therapy

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BACKGROUND

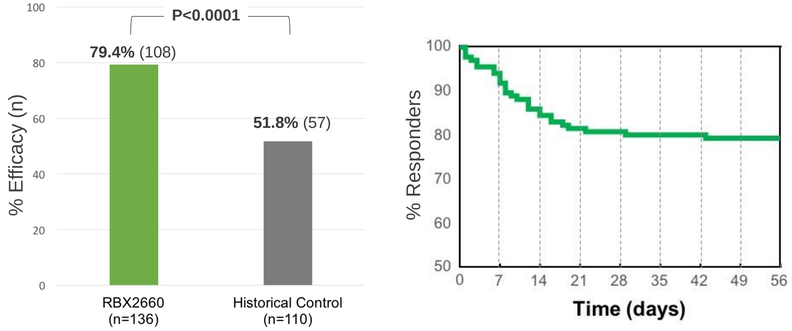
- Dysbiosis, or disruption of a healthy microbiome, is strongly associated with *Clostridium difficile* infections (CDI).
- There are several clinical development programs in progress to develop FDA-approved microbiome-based drugs. However, quantitative biomarkers for microbiome dysbiosis and/or restoration have not been established.
- In a recent Phase 2 open-label trial, a single dose of RBX2660, a standardized microbiota-based product, performed significantly better than historical controls. Microbiome analysis indicated that RBX2660 restored a healthier microbiome, as defined by the RBX2660 product profile and the Human Microbiome Project (HMP).
- Herein, we outline and evaluate a unidimensional index, the Microbiome Health Index (MHI), that describes microbiome rehabilitation among patients from that Phase 2 open-label trial.

METHODS

- Included in this analysis are 47 RBX2660 product samples and 254 stool samples collected at the indicated time points from 122 patients with recurrent CDI who received at least one dose of RBX2660 as part of the PUNCH Open Label Phase 2 trial (NCT02589847). Success was defined as the absence of CDI at 8 weeks after the last blinded treatment.
- Stool samples were sequenced using BoosterShot (CoreBiome, Minneapolis, MN), an ultra-shallow shotgun sequencing that generates taxonomic profiles with species-level resolution.

PHASE 2 OPEN-LABEL EFFICACY & MICROBIOME PROFILING

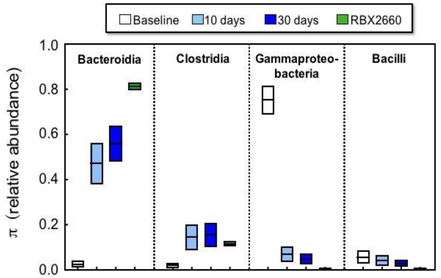
RBX2660 is efficacious in preventing recurrent CDI



RBX2660 efficacy is higher than historical controls treated with standard of care antibiotics and consistent across patient populations. Data are presented as % (n)(left). Kaplan-Meier plot (right) showing response over 8-week follow-up.

Taxa levels from patients with successful response to RBX2660 approach product profile levels over time

Taxa comparisons were made at the class level using Dirichlet multinomial parameter (pi) representing the group's mean relative taxa abundance, at each time point.

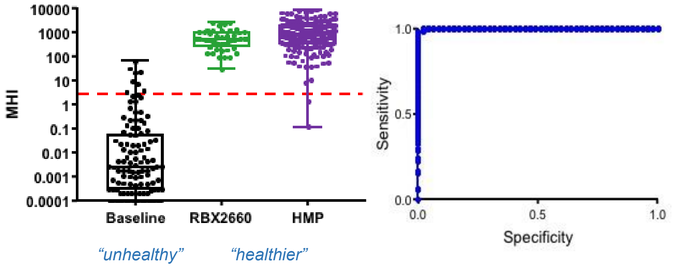


Microbiome Health Index (MHI)

a unidimensional algorithm which captures changes in the relative abundance of taxonomic classes known to have relevance to microbiome health and colonization resistance

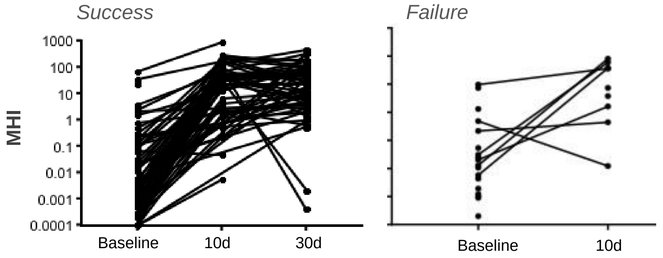
MICROBIOME HEALTH INDEX (MHI) ANALYSIS

MHI can distinguish between baseline "unhealthy" and "healthier" microbiota

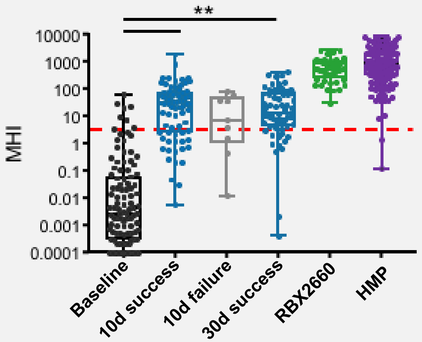


Receiver Operating Characteristic (ROC) analysis of baseline (BL) vs RBX2660 yielded an area under the curve (AUC) of 0.996 and an optimal cut-off point of MHI=31 (red dotted line; sensitivity=0.96, specificity=0.99, likelihood ratio=0.8).

Successful patients show continual MHI increase



MHI differs among successful and failed response to RBX2660



*** p <0.001 by Sign pairwise test compared to baseline*

	n	Median MHI	Fraction of patients >31	p vs BL
BL	111	0.0026	0.02	NA
10d success	73	30.1	0.49	<0.001
30d success	61	12.8	0.38	<0.001
10d failure #	9	7.4	0.44	NA
RBX2660	47	522	0.98	<0.001

 # Treatment failures prior to 56d primary endpoint did not provide additional samples for this analysis

CONCLUSIONS

- MHI can effectively distinguish patients with dysbiosis from healthier patients, as defined by the RBX2660 product profile and the Human Microbiome Project. MHI significantly increases at 10 days after treatment among RBX2660 responders. This outcome is consistent with MHI results from a prior RCT of RBX2660 for rCDI.
- Future efforts will determine whether more specific taxonomic characterization below the class level and/or inclusion of diversity metrics provide a more precise index. Also, we will evaluate MHI prospectively in ongoing clinical trials as an exploratory endpoint.