Rebiotix:
Overcoming Business, Regulatory, and Clinical Challenges to Develop New Microbiome Restoring Drugs

June 2017
Why We’re Here: Incredible Importance of the Human Microbiome

Established Clinical Value:
• Restoring a healthy microbome can effectively prevent recurrent *C. difficile* infections (rCDI)

Enormous Upside Potential:
• GI, liver, cardiovascular, metabolic, infectious diseases and immuno-oncology linked to microbiome

Proper Growth of the Field is Critical:
• Need for carefully regulated products and trials
• Essential to provide statistically qualified and clinically actionable data
**Drug development:** the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery

- Manage expectations vs reality for a new pharma model
- Develop a standardized drug product
  - What kind of product? Manufacturing? Controls?
- Establish safety/efficacy through controlled trials
- Understand and demonstrate microbiome restoration
  - Statistical tools. Clinically actionable data/conclusions
- Determine optimal delivery route, dose
  - Safety, efficacy, patient experience, cost
- Identify indications most likely to benefit
  - Clear proof-of-concept and careful trials needed needed
A New Drug Development Model

**Traditional Drug Development**

- Identify a single active component and advance through established preclinical/clinical models
- Metrics, timelines, resourcing, IP, and risk well vetted and understood

**Microbiome Drug Development**

- Is it too early to confidently identify a single/narrow active
- Metrics, models, timelines…not well established, involves risks that aren’t well vetted

Diverse microbiota community

Multi-omics and preclinical models for microbiota restoration still rapidly evolving

Limited Consortium

Paradigm for Narrowing?
Solution: Focus on Clinical Benefit from the Beginning

A very different paradigm (Rebiotix):
- Get to market with what works, then create next product
  - Create biorepository of donor, drug, and product samples
  - Use clinical outcomes and microbiome analysis to develop next product

Rapid Clinical Entry
- CDI
- IBD
- HE
- others

Fast learning
- Patient samples
- Clinical outcomes
- Quality metrics
- Genetic analysis

Additional Products
- RBX7455
- RBXxxxx

Disease-specific formulations
- Full microbiota
- Defined group

Controlled input
- Quality metrics
- Release assay
- Manufacturing processes
Rebiotix Established the Standard for Microbiota Restoration Therapies with FDA

• Used Quality by Design methodology
  – Rigorous test methods for purity/potency
  – Established design space for product after thousands of tests
  – Developed robust/reproducible manufacturing processes
  – Established product release criteria

• Created Quality System
  – Validated analytical test methods

• Developed patient friendly packaging
  – Real time two year inventory shelf life for lead candidate RBX2660
  – No colonoscopy required for delivery
  – Room temperature-stable oral product RBX7455

• Fast Track, Orphan Drug, Breakthrough Therapy designation
Rebiotix: Microbiota Restoration Therapy (MRT) Platform

- **Uniquely diverse:** proprietary platform therapy to rehabilitate dysbiotic gut microbiome
- **Standardized, Scalable & Stable:** designed for commercial viability from the beginning
- **Proven effectiveness:** therapy shown to be effective in randomized controlled clinical trials

**RBX2660**

**Phase 3 Ready**
- Demonstrated safety & efficacy in >300 patients treated
- Data show 55% reduction in CDI recurrence

**RBX7455**

**In Feasibility Trial**
- Room-temp stable
- Expands accessible market
- Enables easy repeat dosing for chronic diseases

**Pipeline**

**Advanced & Diverse**
- Four novel programs in development
- Ability to rapidly expand into new disease targets
- Partnering with leading clinical/microbiome researchers
- Leverage both enema & oral delivery methods
Defining a Regulatory Pathway

• No precedent with regulatory agencies
  – Rebiotix was first company to submit IND to FDA

• No controlled clinical data until recently
  – Mostly anecdotal data, no controlled studies
    • First published randomized controlled trial in 2013
  – Lack of safety data
  – No trial design precedent
  – Strong consumer belief in efficacy (>90% in recurrent CDI)

• Completed three successful rCDI trials
  – >300 rCDI patients treated to date
  – Clear benefit demonstrated
  – Randomization demonstrated no donor effect on efficacy
# RBX2660: Established Safety and Efficacy in Controlled Trials

<table>
<thead>
<tr>
<th>Study Design Criteria</th>
<th>PUNCH™ CD (Phase 2)</th>
<th>PUNCH™ CD2 (Phase 2b)</th>
<th>PUNCH™ Open Label</th>
<th>PUNCH™ CD3 (Phase 3)</th>
</tr>
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<tbody>
<tr>
<td>Inclusion: Multi-recurrent CDI (*no positive CDI stool test for enrollment)</td>
<td>✓*</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Under symptomatic control post antibiotic tx (24-48 hr washout)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Success: Freedom from Recurrence @ 8 weeks</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Consistent RBX2660 Dose &amp; MFG</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Controlled Trial</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Total Treated Patients (Active + Control)</td>
<td>34</td>
<td>127</td>
<td>242 (at data lock)</td>
<td>3Q17</td>
</tr>
<tr>
<td>Treatment Effect Delta (Tx-Control)</td>
<td>n/a</td>
<td>+21 points. (p&lt;0.05)</td>
<td>+27 points (p&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Learnings: Placebo Response Rates in Controlled rCDI Studies

- No published RCT data prior to 2013
- Response rates in placebo-treated arms of rCDI trials are higher than observed in traditional drug development

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo treatment</th>
<th>% Response in placebo cohort</th>
<th>Forest Plot</th>
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</thead>
<tbody>
<tr>
<td>Rebiotix Phase 2B</td>
<td>Saline/PEG enema</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>SER-109 Phase 2</td>
<td>Oral capsule</td>
<td>47</td>
<td></td>
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<tr>
<td>Kelly, FMT vs autologous FMT*</td>
<td>Autologous FMT</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Bezlotoxumab/actoxumab</td>
<td>IV vehicle</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Surawicz, S. boulardii</td>
<td>Oral vehicle</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Aggregate</td>
<td>NA</td>
<td>49</td>
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</tr>
</tbody>
</table>

*Patients from Miriam Hospital, RI

- Placebo responses are consistent across studies and due to prior antibiotic treatment
- Statistical plans must account for ~50% placebo response rate
RBX2660: Demonstrating Microbiome Restoration

The only company with a proven microbial therapy that rehabilitates the gut microbiome and reduces CDI recurrence

Healthy Donor → C. diff Patient → Follow-up → Healthy Patient

RBX2660 Analysis

C. diff Patient @ Baseline

Patient @ 60 Days
RBX2660 Restores a Normal Microbiome in Phase 2B

- Over 17,000 patient samples collected to date from Rebiotix’ clinical trials
- Phase 2B: patients were dysbiotic at study entry
  - Key question: what does a healthy microbiome look like? (HMP, RBX2660…)
- After RBX2660 treatment, patient microbiomes progressively shifted closer to a healthy range

Multidimensional Similarity Analysis

- Over 17,000 patient samples collected to date from Rebiotix’ clinical trials
- Phase 2B: patients were dysbiotic at study entry
  - Key question: what does a healthy microbiome look like? (HMP, RBX2660…)
- After RBX2660 treatment, patient microbiomes progressively shifted closer to a healthy range
Developing Biostatistical Tools: Patient Microbiomes Significantly Improved by Treatment

- Kullbeck-Liebler analysis and Wald-type tests demonstrate increasing and **statistically significant** divergence from baseline after treatment.
- These analyses provide quantifiable microbiome endpoints for future clinical trials.

![KL Divergence Diagram](image)

**KL Divergence**

(** indicates P < 0.001 for Wald test)**

- More divergent
- Less divergent
Key Taxonomic Changes Toward Healthy Microbiome

- At study entry, key Gram negative and Gram positive taxa are highly divergent from a healthy microbiome (HMP) and from RBX2660.
- After successful treatment, patient microbiomes significantly diverge from baseline and converge toward RBX2660 and HMP.
- These data confirm that RBX2660 restores a healthier microbiome.

Additional microbiome analyses to be presented 3/4Q17.
Diversifying the Dose and Delivery Route: RBX7455
First Room Temperature Stable Oral Capsule

- Lyophilized formula
  - Broad spectrum microbiota
    - Includes non-spore forming Bacteroides
  - Room temperature stability
  - One dose = $1 \times 10^9$ CFU (8 capsules or less)
  - Capsule releases contents in intestine

- Easier application for repeat dosing for chronic conditions/indications

- Leveraging clinical/regulatory program with RBX2660 precedent for rCDI

- Phase 1 Dose Ranging Study Initiated – Dec. 2016
  - 18/20 pts enrolled, Promising early results
## Expanding the Clinical Benefits: Broadening Pipeline

<table>
<thead>
<tr>
<th>Indication</th>
<th>Phase 1</th>
<th>Dosing</th>
<th>Phase 2a / b</th>
<th>Phase 3</th>
<th>Next Milestone</th>
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<tbody>
<tr>
<td><strong>RBX2660 - Enema Formulation</strong></td>
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<tr>
<td>Recurrent CDI Prevention</td>
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<td></td>
<td></td>
<td></td>
<td>• Confirmatory Phase 3 study: H2 2017</td>
</tr>
<tr>
<td>VRE Elimination</td>
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<td></td>
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<td></td>
<td>• Completed Proof-of-Concept</td>
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<td></td>
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<td></td>
<td></td>
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<td>• Published results</td>
</tr>
<tr>
<td>Pediatric Ulcerative Colitis</td>
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<td></td>
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<td></td>
<td>• In progress; multicenter</td>
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<td></td>
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<td></td>
<td></td>
<td>• Clinical data readout expected 2017</td>
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<tr>
<td>Multi-Drug Resistant UTI</td>
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<td>• Proof-of-concept</td>
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<td></td>
<td></td>
<td></td>
<td>• In progress; multicenter</td>
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<tr>
<td>Hepatic Encephalopathy</td>
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<td>• Proof-of-concept</td>
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<td></td>
<td>• Clinical data readout expected 2017</td>
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<tr>
<td><strong>RBX7455 - Oral Formulation</strong></td>
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<tr>
<td>Recurrent CDI prevention</td>
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<td></td>
<td></td>
<td>• Dosing Proof-of-concept</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>• Data mid-2017</td>
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Expectations, Hype, and Reality in a Rapidly Growing Field

<table>
<thead>
<tr>
<th>Company</th>
<th>Preclinical</th>
<th>Phase 2</th>
<th>Phase 2b</th>
<th>Phase 3</th>
<th>Clinical Review</th>
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<tbody>
<tr>
<td>Diverse Consortium</td>
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<td></td>
<td></td>
<td></td>
<td>• Efficacy demonstrated in multiple, controlled Phase 2 studies</td>
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<td>• Phase 3 ready</td>
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<td>• Preparing for Phase 2</td>
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<td>• No Phase 1 publication</td>
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<td>• Preclinical</td>
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<tr>
<td>Finch Therapeutics</td>
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<td>• Completed one Phase 2</td>
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<td>• Enrolling Phase 3</td>
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<td>• Preclinical</td>
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<tr>
<td>Limited Consortia</td>
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<td>• Phase 1 Jan 2017</td>
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<tr>
<td>VEDANTA BIOSCIENCES</td>
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<td>• Preclinical</td>
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<td>• Preclinical</td>
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<tr>
<td>Single Strain / Synthetic / Metabolites</td>
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<td></td>
<td>• Preclinical</td>
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Summary: Solving Challenges for Microbiome Restoration Therapy

• “Early and often” to establish development path with FDA

• Standardized drug product and process
  – Starting with known efficacious formulation leads to early success
  – Two dosing routes, easy delivery, first RT-stable oral formulation
  – Phase 3 ready product for preventing rCDI

• Established safety and efficacy
  – Multiple successful clinical trials; key learnings to power future trials for success

• Demonstrated improvement of patient microbiome after treatment
  – Key biostatistics tools developed to strengthen future analyses

• Established product/process facilitates rapid expansion to additional indications
  – Phase 1 proof-of-concept trials ongoing, with continued portfolio expansion
Thank you

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203-676-2367