Speed Dating: Pipeline C. difficile Agents

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Investigational drug therapies currently in early-stage clinical development for the treatment of clostridioides (clostridium) difficile infection

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- ACX-362E
- DS-2969b
- LFF 571
- RBX2660
- ribaxamase *
- ridinilazole *
- SYN 006, 007
- Ramizol
- Ramoplanin
- CRS 3213
- MCB 3681
- Spores NOT included
Figure 1. Pathogenesis of *Clostridium difficile* infection and areas for emerging therapy improvement. Starting with normal microbiota, antibiotic disruption of the intestinal bacterial community results in a susceptible state, which can lead to colonization with *C. difficile*. Once germinated, vegetative *C. difficile* produces a variety of toxins to cause mucosal damage. If the damage is severe, this may lead to severe disease. With effective antibiotic therapy, *C. difficile* can be reduced and natural colonization resistance can develop over time as the natural microbial community recovers. Reinfection or recurrence may occur before this process is complete. Fecal microbiota transplant may expedite this recovery by directly replacing the missing microbial community members. Areas marked with a red circle are potential areas where new emerging therapies could improve clinical management.
CDI Problems 2019
Increasing Recurrences; Patient PTSD

Each additional episode of CDI associated with:
- Increased morbidity and mortality
- Increased healthcare cost
- Limited treatment options

Recurrent CDI associated with increased perturbation of the gut microbiota
- Mainstay therapy (metronidazole and vancomycin) associated with increased dysbiosis

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**Increasing Risk of Recurrence\(^{(1)}\)**

- **1st Infection**: Risk: ~25%
- **2nd Infection**: Risk: ~45%
- **3rd Infection**: Risk: ~65%
Novel CDI Therapies

- **ACE-362E**  novel small molecule  
  new target: DNA polymerase IIIC inhibition

- **CRS3123**  inhibits MetRS, methionyl-tRNA synthetase in Gram-positive bacteria

- **DS-2969B**  novel GyrB inhibitor

- **LFF571**  Thiopeptide that inhibits EF-TU

- **RBX2660**  commercialized, standardized  
  fecal microbiota suspension- single dose bag
**Ridinilazole**

- Non absorbable
- Does not act through cell wall inhibition
- Nor via lipid, protein, RNA or DNA synthesis
- Likely impairs cell division - elongates cells and inhibits sporulation
- Narrow spectrum

Less Microbiome change compared to vancomycin
Bactericidal with Inhibition of Toxin Production

Ridinilazole arrests *C. difficile* cell division\(^{(1)}\)

- Control
- 0.125x MIC
- 0.25x MIC
- 0.5x MIC

![Images showing cell morphology at different concentrations of Ridinilazole](image1)

Ridinilazole inhibits toxin production\(^{(1)}\)

- Toxin A
- Toxin B

![Graph showing toxin production inhibition at different concentrations of Ridinilazole](image2)

Ridinilazole is bactericidal\(^{(2)}\)

- Dose dependent inhibition of septum formation

![Graph showing bacterial quantification over time](image3)

(1) Basseres *et al.* JAC 2016
(2) Corbett *et al.* JAC 2015
Potent Growth Inhibition of *C. difficile*

*C. difficile* MIC range (≈600 clinical isolates) = 0.015 – 0.5µg/mL; MIC$_{90}$ = 0.125µg/mL

- No differences in MICs between *C. difficile* ribotypes including hyper-virulent strains
- No increase in MIC against isolates with reduced vancomycin or metronidazole susceptibility
- No cross-resistance to other classes of antibiotics
- No differences in MIC based on geographic source of isolates

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th>N</th>
<th>Ridinilazole</th>
<th>Metronidazole</th>
<th>Vancomycin</th>
<th>Fidaxomicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corbett 2015</td>
<td>UK</td>
<td>82</td>
<td>0.125</td>
<td>8</td>
<td>2</td>
<td>0.06</td>
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<tr>
<td>Freeman 2015</td>
<td>EU</td>
<td>107</td>
<td>0.125</td>
<td>2</td>
<td>2</td>
<td>0.125</td>
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<tr>
<td>Goldstein 2013</td>
<td>US</td>
<td>50</td>
<td>0.25</td>
<td>2</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>Snydman 2014</td>
<td>US</td>
<td>200</td>
<td>0.25</td>
<td>8</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>Snydman 2016</td>
<td>US Phase 2</td>
<td>142</td>
<td>0.25</td>
<td>1</td>
<td>2</td>
<td>0.5</td>
</tr>
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</table>
Ridinilazole Phase 2 Study

**Group Design**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Agent</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Ridinilazole</td>
<td>200mg BID 10 days</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Vancomycin</td>
<td>125mg QID 10 days</td>
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Significantly improved SCR vs vancomycin—Driven by a marked reduction in rCDI rates

PCR or EIA
Up to 1
Recurrence in 3 months
or 3 in 1 year

Lancet Infect Dis 2017;17:735-744.
Relative Changes in Taxonomic Composition
Reduction in rCDI potentially associated with microbiome preservation

- Cladograms showing changes in relative abundance following 10 days dosing

**RIDINILAZOLE**

**VANCOMYCIN**

- Higher abundance at baseline
- Higher abundance at EOT
Ribaxamase (SYN 004)
A Therapy to protect the Microbiome from antibiotic collateral damage

• Ribaxamase a Class A β-lactamase - single amino acid modification

• Formulated for oral pH-dependent delivery at pH > 5.5 (proximal small intestine)

• For use with selected IV beta-lactam antibiotics (Ceftriaxione)

• Intended to degrade excess antibiotics excreted into the intestine via the bile
Ribaxamase Clinical Trials

Completed two Phase 1, two Phase 2a, and Phase 2b trials

- **Well-tolerated** alone and in combination with IV ceftriaxone
- **Negligible absorption** of ribaxamase at doses up to 5x those used in Phase 2b
- **Degraded** ceftriaxone in chyme
- Was effective with proton pump inhibitors
- **Did not alter PK** of IV ceftriaxone

Phase 2b Proof of Concept Study

Patients received IV ceftriaxone for a lower respiratory infection + ribaxamase or placebo

- **Met primary endpoint** of significant reduction in *C. difficile* disease
- **Significantly reduced** new colonization by vancomycin-resistant enterococci
- **Protected the gut microbiome** from antibiotic damage
- Reduced emergence of antibiotic resistance

Ribaxamase: Phase 2b Proof-of-Concept Study

84 Multinational Clinical Sites

Patients admitted to the hospital for treatment of a lower respiratory tract infection

Modified intent to treat = 412 patients

1:1

Ceftriaxone + Ribaxamase (plus a macrolide)

Ceftriaxone + Placebo (plus a macrolide)

Primary Endpoint:
- Prevention of C. difficile infection (CDI)

Exploratory Endpoints:
- Evaluate ability to limit disruption of the gut microbiome
Phase 2b-Proof of Concept Study

Study Design

- Randomized 1:1, 150 mg ribaxamase or placebo

<table>
<thead>
<tr>
<th>Treatment Period 1</th>
<th>Treatment Period 2</th>
<th>Follow-up Period</th>
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<tr>
<td>5-14 days</td>
<td>72 hrs</td>
<td>6 weeks</td>
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- IV Ceftriaxone + Study Drug (qid dosing)
- Study Drug (qid dosing)
- Monitor for diarrhea and *C. difficile* infection
- 4 week follow-up visit

- Fecal microbiome and fecal colonization samples taken for analysis

- **206** patients per group in mITT
- Average age of patients ~70 years old
- ~2/3 males in each group
- ~1/3 of patients in each group also received macrolides
- ~1/3 patients received concurrent drugs for stomach acidity (PPIs)

**Adverse Events**

- Percentage of subjects reporting at least one treatment emergent adverse event (TEAE) was similar between ribaxamase and placebo groups (40.8% vs. 44.2%)
**Clostridium difficile Infection (CDI)**

**Primary Endpoint**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ribaxamase</th>
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<tbody>
<tr>
<td><strong>Number of Subjects with CDI</strong></td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td><strong>P=0.045</strong></td>
<td>3.4%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>71% relative risk reduction</strong></td>
<td></td>
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<tr>
<td><strong>5 x RT 027 001, 014, 198</strong></td>
<td></td>
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<tr>
<td><strong>P=0.028</strong></td>
<td>3.9%</td>
<td>1%</td>
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<tr>
<td><strong>RT 027</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients Treated for CDI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(oral vancomycin, metronidazole and fidaxomicin)</td>
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- No CDI patients reported previous CDI
- P-values are 1-sided based on the pre-specified Z-test
- The study was powered at 80% with 1-sided alpha=0.05
Ribaxamase Pipeline Products

Ribaxamase is intended for use with selected IV penicillins and cephalosporins

Use with oral antibiotics \(\rightarrow\) SYN-007

- Delayed-released formulation of ribaxamase
- Intended for release distal to site of oral antibiotic absorption
- Tested in canine model

Use with carbapenems \(\rightarrow\) SYN-006

- Novel metallo-beta-lactamase with broad antibiotic degradation activity
- Formulated for oral delivery (enteric coating)
- Potential to protect gut microbiome from all classes of beta-lactams
- Tested in pig model
**SYN-006 Preserves Pig Gut Microbiome Diversity**

*Student T-test, 2 tailed, unpaired, unequal variance*

**Shannon Alpha Diversity**

Post/Pretreatment ratios significantly different with ertapenem alone and ertapenem + SYN-006.
Ribaxamase Represents a Paradigm Shift

In the Use of Intravenous β-lactam Antibiotics

Current paradigm

- Bile
- Treat Infection

Current paradigm:

- Stomach
- Duodenum
- Jejunum
- Ileum
- Cecum
- Colon

Ribaxamase paradigm:

- Stomach
- Duodenum
- Jejunum
- Ileum
- Cecum
- Colon

- Ribaxamase
- No Drug Release

- Antibiotic
- Degraded

Oral antibiotics

- Healthy, diverse microbiome
- Suppresses secondary infections
- Limits emergence of resistant species

- Disrupted microbiome
- Secondary infections such as *C. difficile*
- Selects for resistant species
Lessons Learned from Cadazolid & Surotomycin for Future Trial Design

• **Endpoint definitions matter**
  – Investigator assessment is important; not all diarrhea needs to be treated (single day, other cause identified). If not treated, should not be considered a failure
  – Method of imputation for missing data needs to be considered carefully

• **Diagnostic method matters (PCR and/or EIA)**
  – Diagnostic uncertainty could lead to an underestimate of efficacy magnitude

• **Patient population matters**
  – If goal is to improve the rate of sustained cure/prevent recurrences, it is important to enroll patients at risk for recurrence to increase the power to show difference vs standard of care