CDI has a (Prevention) Perception Problem:

Lessons from the On-going Development of SYN-004 (ribaxamase)
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The gut microbiome is a collection of ~39 trillion microbes in our GI tract (predominantly the colon)\(^1\)

A healthy gut microbiome protects the body from disease
- Antibiotics are the primary source of microbiome damage

Protecting the gut microbiome can prevent disease
- Preclude emergence of pathogens and MDROs
- Prevent detrimental changes to microbial metabolome
- Preserve healthy gut barrier function

Conceptually simple
- Validated in part by the success of antimicrobial stewardship programs\(^2,3,4\)

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Clostridium difficile Infection

The definitive gut microbiome disease

• *C. difficile* exists as toxigenic and non-toxigenic species in the colon
  • Up to 17.5% of healthy adults\(^1,2\) and 26% of hospitalized adults\(^3\-^5\) can have asymptomatic *C. difficile* colonization
    - Readily transmitted by contact with spores

• *C. difficile* infection (**CDI**) is due to secretion of an enterotoxin (toxin A; TcdA) and a cytotoxin (toxin B; TcdB)
  • Toxins can cause diarrhea and inflammation
    - Serious CDI complications include pseudomembranous colitis, toxic megacolon, colon perforation, sepsis and death

**Clostridium difficile Infection is Costly**

Epidemiological and economic burden of CDI in the USA from a modeling approach¹

- **606,058** CDI patients in the USA in 2014
- **>1 in 5** experience at least one CDI recurrence
- **~7** extra days spent in the hospital by CDI patients²
- **$5.4B** added cost to healthcare and community in 2014
- **44,500** CDI-attributable deaths (7%)

¹Desai (2016) *BMC Infect Dis* (2016) **16**:303. Overnight stays in the hospital contributed 78% of the total direct and indirect costs of CDI cases in healthcare facilities and 52% of costs for CDI cases originating in the community.
²van Kleef (2014) *J Hosp Infect* **88**:213-7
Protecting the Gut Microbiome from Antibiotics

Targeted strategy to prevent *Clostridium difficile* infection (CDI)

1 Very mixed clinical results (see Goldenberg (2017) *Cochrane Database Syst Rev.* 12:CD006095. doi: 10.1002/14651858) and current IDSA-SHEA guidelines indicate "there are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials" (see McDonald (2018) *Clin Infect Dis* 66:987-994).
Antibiotic use worldwide¹

Billions of Opportunities to Damage the Microbiome

¹Data extracted from IMS Health 2017; doses in standard units. Macrolides, fluoroquinolones and tetracyclines make up the majority of the remaining non-β-lactam antibiotics

β-Lactam Antibiotics

Some of the worst gut microbiome offenders

~64% of the World’s antibiotics
~57% of US antibiotics
100’s of millions of patients
SYN-004 (ribaxamase) to Protect the Gut Microbiome

β-lactam antibiotic excreted into the GI tract damages the microbiome

IV β-LACTAM ANTIBIOTIC

Antibiotic Excreted in Bile

β-Lactam Antibiotic

DAMAGED Microbiome
SYN-004 (ribaxamase) to Protect the Gut Microbiome

Degrading β-lactam antibiotic excreted into the GI tract

**SYN-004** (ribaxamase) degrades penicillins and cephalosporins; a separate preclinical stage product (SYN-006) degrades carbapenems

*Administered concomitantly with IV β-lactam antibiotic throughout the course of IV antibiotic therapy*
SYN-004 (ribaxamase) Phase 2b Clinical Trial

Protected the microbiome, prevented CDI, reduced emergence of VRE

- Patients admitted for treatment of LRTI at 54 sites (Europe, North America)¹
  - Reduced CDI incidence
    - Placebo (7) 3.4%
    - SYN-004 (2) 1.0%²
  - Suppressed emergence of MDROs
    - Reduced VRE colonization by 43.9%³
    - Reduced expression of multiple AMR genes
  - Preserved the microbiome
    - Reduced ceftriaxone-mediated loss of microbial diversity in stool samples

²P=0.045 vs Placebo. ³P=0.0002 vs Placebo. P-values are based on one-sided z-test (Chi-square) for the comparison of SYN-004 to Placebo.
LRTI = clinical diagnosis of moderate to severe lower respiratory tract infection. VRE = vancomycin resistant enterococci
We Began Evaluating the Path Forward...

Why Bother?
Incidence is low, drugs are cheap
Just treat the CDI
3 Key Challenges in Developing CDI Preventatives

- Low Incidence
- No Agreed Biomarkers
- Cheap Treatments

Clinical Trial Size, Cost

Market Access
1. Prevention Trials >> Intervention Trials

SYN-004 may be prescribed to a **broad range** of patients.

Most patients **won’t** get CDI (with or without SYN-004).

Potential **efficacy** can be diluted by underlying ID patient comorbidities.

**Demonstrating CDI reduction in a prevention trial means dosing a lot of patients.**

- **Low Incidence**
  - CDI rate **3.4%**
  - SAE rate **10.2%**

1 Incidence and SAE data are from the Placebo group of the SYN-004 (ribaxamase) Phase 2b clinical trial (patients with lower respiratory tract infections treated with IV ceftriaxone)
Designing a Phase 3 CDI Prevention Trial

Antibiotic Types

SYN-004 Timing

Dosing Days

Index Infections

Prior Antibiotics

Comorbidities

Demographics

HCF Exposure

Conmeds

Prior CDI

CDI Rates

CDI Assay

Study Sites

Compliance

HCF: Healthcare facility
Designing a Phase 3 CDI Prevention Trial

Can we simplify the trial with a biomarker endpoint?
SYN-004 (ribaxamase) Protected Microbial Diversity

Compared to T0, patients receiving ribaxamase demonstrated **significantly better maintenance and recovery** of microbial diversity at T1 and T2 versus Placebo.

1. Shannon Index and Chao1 represent α-diversity, a measure of the microbial community composition within a sample.
2. Size of each ball is relative to the standard error of the sample group.
2. Microbiome Endpoints Can’t Help (Yet)

No Agreed Biomarkers

Dysbiosis is **not** an approvable endpoint

- Higher incidence of dysbiosis endpoint should enable smaller clinical trials
- Having dysbiosis **doesn’t** always mean the patient will get sick
- Can’t **reliably** predict CDI occurrence using pretreatment *C. diff* colonization

*Image: Don’t Argue trimmed wood cigar box lid, Canadian Museum of Civilization #CNC 2001.185.37, Tony Hyman Collection*
### C. difficile Colonization vs CDI

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>C. difficile Colonized Pretreatment</th>
<th>Not Colonized Pretreatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>SYN-004</td>
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<tr>
<td>Baseline (n)</td>
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<td>Colonization (n) during Period 1-2</td>
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<td>CDI (n) during Period 1-2</td>
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<td><strong>CDI/New Colonization</strong></td>
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<tr>
<td>New Colonization (n), Follow-up</td>
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<tr>
<td>CDI (n) during Follow-Up</td>
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<td><strong>CDI/New Colonization</strong></td>
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<tr>
<td>Total New Colonization on Study</td>
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<td>Total CDI on Study</td>
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<tr>
<td><strong>CDI/New Colonization</strong></td>
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</table>

*P=0.0454, \*P=0.0586, \*P=0.0880 vs Placebo. P-values are based on one-sided z-test (Chi-square) for the comparison of percentages of patients in each group with CDI or C. difficile colonization at indicated time point. HCFA = healthcare facility associated.
SYN-004 (ribaxamase) Phase 3 Proposal

Lots of variables means large numbers

• On-going discussions with the FDA

• We proposed one large, global, multi-center, randomized controlled clinical trial
  • Primary efficacy endpoint reduction of CDI incidence in SYN-004 vs Placebo
  • Co-primary safety endpoint relative risk of mortality in SYN-004 vs Placebo

• Evaluate a broad range of patients who are receiving IV β-lactam antibiotics
  • Enroll patients at high risk for CDI (e.g. age, prior antibiotic, HCF/LTCF exposure)
  • Evaluate multiple β-lactam antibiotics (e.g. ceftriaxone, piperacillin/tazobactam)
  • Evaluate different index infections (e.g. LRTI, UTI, intraabdominal)

• Enroll up to 4,000 patients to balance different parameters between groups
  • Trial intended to be self-replicating

CDI: Clostridium difficile infection. LRTI: lower respiratory tract infection. UTI: urinary tract infection.
3. When You Look to Fund a 4,000 Patient Trial

“Flagyl costs $30 per course”

“There’s no reimbursement for CDI prevention”

“Preventatives should cost less than antibiotics”

 Cheap Treatments

• Who Pays?
• How Much?
Q: If an HAI occurs who bears the cost? The hospital or the plan?

“Well when you're talking about a hospital acquired infection, you're talking about a patient who's already in the hospital for another reason and their stay is extended because of the hospital acquired infection. That's all going to be incorporated into the DRG, so there's not going to be any additional cost to the managed care company.”

– Commercial Insurer - 1.55 Million Lives - 80% Commercial¹

“So, for instance, you’d mentioned about the possibility of a new medication for hospital acquired infections. Our opening position would be that that’s just a part of the DRG and you will probably have shorter hospital stays because of that

– Commercial Insurer - 9 Million Lives - 60% Commercial¹

By relying on DRGs, Medicare and Payers shift the cost of HAIs onto hospitals

¹Interviews conducted pursuant to market access study contracted by Synthetic Biologics, March 2018

DRG = diagnosis related group; medically-adjusted lump sum DRG payments are intended to cover the cost of all items and services furnished to the patient during their entire hospital stay.

HAI = hospital acquire infection; Medicare imposes reimbursement penalties on hospitals with the worst HAI scores (HACRP; Section 3008 Affordable Care Act)
How Much? Valuing Point-of-Care CDI Prevention

Simplified prevention cost-savings model based on SYN-004 Phase 2b results

![Diagram showing the process of CDI prevention and costs]

- **Infection (e.g. LRTI)**
  - IV β-Lactam Antibiotic
  - Dysbiosis
  - CDI
  - Treatment & Management
  - Recurrence
  - Transmission

**Patients (n)**
- **1,000**
- **1,000**

**Cost**
- **DRG**
- **< $570 per patient**

**CDI Prevention**

- **34 (3.4%)**
- **10**

**Cost**
- **$510,000**
- **$300,000**

**Recurrence**

- **10 (1.0%)**
- **3**

**Cost**
- **$150,000**
- **$90,000**

**Net cost saving**

- **+$810,000**
- **+$240,000**

*Not including penalties, legal liabilities, mortality

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1. Published direct and indirect costs of CDI are variable; current example uses $15,000 per patient for incident CDI and $30,000 per patient for recurrent CDI.
Factors Affecting Preventative Cost: Benefit

Cost Additive Scenario
DRG < (Index Infection + Preventative + CDI)

- Opportunity for NTAP?²
- DRG increase over time?

$128
$192
$256
$320
$384
$456
$512
$576
$640
$768

Cost Savings Scenario
DRG > (Index Infection + Preventative + CDI)

1° CDI cost = $5,000/patient
1° CDI rate = 1.7%
1° CDI preventative effect = 50% reduction

1° CDI rate = 3.4%
1° CDI preventative effect = 71% reduction
1° CDI cost = $15,000/patient

Cost Neutral Scenario
DRG = (Index Infection + Preventative + CDI)

By way of comparison...
Drug price for a course of vancomycin
125 mg t.i.d. x 14 days = $270-$570
(www.goodrx.com accessed 02Nov2018)

1 Cost sensitivity example based on simplified model in previous slide using CDI incidence and preventative effect size are from SYN-004 Phase 2b clinical trial
2 Medicare New Technology Add-on Payment (NTAP) can provide additional payment for new therapies that can demonstrate significant clinical benefit
During SYN-004 (ribaxamase) development we have encountered a bizarre CDI “prevention perception problem” that is entirely financial

- Incidence is low, treatments are cheap, **just treat the CDI**

This short-sighted approach is a function of clinical development costs and uncertain market access and ignores the comprehensive disease burden

- The need for targeted, effective CDI prevention remains acute for patients, clinicians, healthcare facilities and the community

With continued advocacy, education and strong science we should be able to eradicate these perceptions

- “Let’s say with some condition there’s a drug or some surgery and everybody seems to be doing it, then that will end up in the DRG if it changes the cost significantly (over time)”
  
  – Commercial Insurer - 0.9 Million Lives - 100% Commercial¹

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¹Interviews conducted pursuant to market access study contracted by Synthetic Biologics, March 2018.
• But beyond just the money, it’s also the morbidity and mortality that we were talking about before, right? And that, I think, from a clinician’s standpoint, our job is to heal people and to help them make it so that—so you can take care of things in the right way.”

– Chief Medical Officer - 396 Bed Community Hospital¹

¹Interviews conducted pursuant to market access study contracted by Synthetic Biologics, March 2018.