Forward-Looking Statements

Statements in this presentation, other than statements of historical fact, constitute forward-looking statements within the meaning of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include statements regarding Summit’s clinical trials supporting the safety and efficacy of its product candidates and the potential novelty of such product candidates as treatments for disease, plans and objectives for preclinical studies, clinical trials, product development and regulatory filings, Summit’s collaboration with Eurofarma Laboratorios SA, Summit’s awards from BARDA and CARB-X, Summit’s Discuva Platform, strategies, future performance, expectations, assumptions, financial condition, liquidity and capital resources. These forward-looking statements may be preceded by, followed by or otherwise include the words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions. Actual results or events may differ materially from those expressed or implied in any forward-looking statements due to various factors, including the risks and uncertainties inherent in clinical trials and product development and commercialization, such as the uncertainty in results of clinical trials for product candidates, the uncertainty of whether the preliminary results from a clinical trial will be predictive of final results of that trial or whether the results of clinical trials will be predictive of results in later stages of product development, the risk of delays or failure to obtain or maintain regulatory approval, the risk of failure of the third parties upon whom Summit relies to conduct its clinical trials and manufacture its product candidates to perform as expected, the risk that any third-party collaborator, including Eurofarma, terminates or fails to meet its obligations to Summit, the risk that Summit’s discovery and development platform may not identify new potential drug development candidates, the risk of increased cost and delays due to delays in the commencement, enrollment, completion or analysis of clinical trials or significant issues regarding the adequacy of clinical trial designs or the execution of clinical trials and the timing, cost and design of future clinical trials and research activities, the timing of expected filings with the FDA or other regulatory agencies; and the other risks and uncertainties described in Summit’s public filings with the Securities and Exchange Commission.

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Urgent Need for New Antibiotics Provides Major Opportunity
Poor Patient Outcomes & Increasing Resistance with Existing Classes of Antibiotics

THE CHALLENGE

Recent launches have disappointed

• No new classes of antibiotics: incremental changes fail to combat emerging drug resistance
• Failure to address clear unmet patient needs
• No compelling medical evidence: non-inferiority trials don’t show clear patient benefit
• No economic data to justify use of premium priced treatments over cheap generics

THE SUMMIT SOLUTION

Focus on differentiation

• Develop new classes of antibiotics with distinctive features and benefits
• Target the infection or pathogen to restore health and protect the microbiome
• Address measurable unmet medical need
• Show superiority in patient outcomes to establish compelling use case
• Demonstrate value of new antibiotics through economic data
Past Commercial Success Associated with Innovation

1920s-1980s
- Multiple novel mechanisms & classes
- Multiple examples of significant commercial success
  - Ciprofloxacin; azithromycin; ceftriaxone
- Resistance not clinical issue

Since 1990
- Few new mechanisms; only incremental benefits
- Niche market positioning with low commercial return
- Resistance is a clinical issue

Adapted from ReAct Group 2015
## Only Two Novel Late Stage Antibiotics in the Global Pipeline

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Company</th>
<th>Phase</th>
<th>Drug Class</th>
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<tbody>
<tr>
<td>Ceftobiprole</td>
<td>Basilea</td>
<td>3/ Marketed (ex-US)</td>
<td>Cephalosporin</td>
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<tr>
<td>Plazomicin</td>
<td>Achaogen</td>
<td>Marketed (US)</td>
<td>Aminoglycoside</td>
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<tr>
<td>Eravacycline</td>
<td>Tetraphase</td>
<td>Marketed (US)</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Omadacycline</td>
<td>Paratek</td>
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<td>Tetracycline</td>
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<td>Lefamulin</td>
<td>Nabriva</td>
<td>Marketed (US)</td>
<td>Pleuromutilin</td>
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<td>Iclaprim</td>
<td>Motif Bio</td>
<td>CRL received</td>
<td>2,4 diaminopyrimidine</td>
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<tr>
<td>Fusidic acid</td>
<td>Melinta</td>
<td>3</td>
<td>Fusidane</td>
</tr>
<tr>
<td>WCK771/WCK2349</td>
<td>Wockhardt</td>
<td>3</td>
<td>Fluoroquinolone</td>
</tr>
<tr>
<td>Cefilavancin</td>
<td>Theravance</td>
<td>3</td>
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<td>Contezolid</td>
<td>MicuRx</td>
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<td>Oxazolidinone</td>
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<td>Sulopenem</td>
<td>Iterum</td>
<td>3</td>
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<tr>
<td>SPR994</td>
<td>Spero</td>
<td>3</td>
<td>Carbapenem</td>
</tr>
<tr>
<td>Imipenem &amp; relebactam</td>
<td>Merck</td>
<td>3</td>
<td>Carbapenem/BLI</td>
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<tr>
<td>Cefiderocol</td>
<td>Shionogi</td>
<td>3</td>
<td>Cephalosporin</td>
</tr>
<tr>
<td>Cefepime &amp; AAI101</td>
<td>Allecra</td>
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<td>Cephalosporin/BLI</td>
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<tr>
<td>Cefepime &amp; tazobactam</td>
<td>Wockhardt</td>
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<td>Cephalosporin/BLI</td>
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<tr>
<td>EXT2514SUL</td>
<td>Entasis</td>
<td>3</td>
<td>BLI</td>
</tr>
<tr>
<td>Zoliflodacin</td>
<td>Entasis</td>
<td>3</td>
<td>Novel; spiropyrimidinetrione</td>
</tr>
<tr>
<td>Ridinilazole</td>
<td>Summit</td>
<td>3</td>
<td>Novel; C. difficile specific</td>
</tr>
</tbody>
</table>

Source: Pew Trust

R&D Day
Oct. 7, 2019
Summit’s Approach: Innovations for Patient Betterment
Translating Novel Science into Differentiated Products Delivered to the Patient

DISCOVER
- New classes of antibiotics
- Distinctive features and benefits
- Targeted spectrum preserves microbiomes
- Less prone to rapid resistance development

DEVELOP
- Clinical trial designs to test for unmet need
- Outcomes to show superiority over standard of care
- Health economic measures to demonstrate value of improved outcomes

COMMERCIALIZE
- Patients offered solution to unmet need
- Physicians have data to switch therapy
- Payors have data showing economic value
- Strong stewardship case to use new drugs
Our New Class Targeted Antibiotic Pipeline

<table>
<thead>
<tr>
<th></th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<td>CDI (Ridinilazole)¹</td>
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<td>Urgent (CDC)</td>
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<td>Gonorrhea (SMT-571)</td>
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<td>Urgent / High (CDC / WHO)</td>
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<tr>
<td>Gonorrhea (Target #2)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Urgent / High (CDC / WHO)</td>
</tr>
</tbody>
</table>

Discuva Platform

A portfolio created with assistance: BARDA, CARB-X, Innovate UK & Wellcome Trust

1. We own worldwide rights to ridinilazole, outside of certain Latin American countries and Caribbean islands.
Ridinilazole Designed to be Patient-Friendly
Clear Phase 2 Trial Differentiation Supports New Standard of Care Potential

Cured CDI and sustained cures over 40 days
- 60% reduction in recurrences, the key unmet need
- Superiority over standard of care vancomycin in sustained cures
- Discharged from hospital earlier

Improved physical & mental effects of CDI compared to VAN
- Resolved diarrhea earlier
- Significantly reduced pain/discomfort
- Significantly reduced anxiety/depression

Gut-friendly
- Treatment preserved microbiome and allowed good bacteria to recover
- Generally well-tolerated, as treatment targeted to gut

Initiated global Phase 3 clinical trials Feb. 2019
Expect top-line data H2 2021
With positive results, expect NDA filing 2022

Source: CoDIFy Phase 2 clinical trial
Agenda

8:00am  Welcome and Opening Remarks  
        David Roblin, MBBS, BSc, FRCP, FFPM

8:15am  Impact of the Microbiome/Metabolome on CDI  
        Casey Theriot, PhD

8:40am  Ridinilazole  
        Richard Vickers, PhD

9:00am  Economics of CDI  
        Kevin Garey, PharmD, MS, FASHP

9:25am  Commercialization of Ridinilazole  
        Daniel Elger, PhD  
        Anna Diaz Triola, MBA  
        Kevin McDermott

9:50am  Q&A

10:15am  Break

10:30am  Precision Antibiotic Pipeline – Killing the bad bugs, preserving the good bugs  
         Dave Powell, PhD

11:10am  Q&A

11:35am  Closing Remarks  
         Glyn Edwards
Alterations to the microbiota and metabolome in *C. difficile* infection

Casey M. Theriot, PhD
Assistant Professor in Infectious Disease
NC State University College of Veterinary Medicine
October 7, 2019
Targeted manipulation of the gut microbiota and metabolome to alter GI diseases

Interaction of *C. difficile* with gut commensals, gut derived bile acids, and other metabolites *in vitro*

Interaction of *C. difficile* with gut commensals, engineered gut bacteria, and gut derived bile acids in a mouse model

Characterization of gut environment using omic approaches: microbiomics, transcriptomics, and metabolomics

Translational research to determine the mechanism behind fecal transplantation therapy at UNC hospital
Using metabolomics to investigate the interaction between the host, gut microbiota, and the pathogen

Alterations in the gut microbiota and metabolome leads to *C. difficile* infection

Britton and Young, *Gastroenterology* 2014
Theriot et al. *Nature Comm* 2014
Theriot and Young, *Annual Rev Microbiology* 2015
Antibiotic-induced shifts in the mouse gut microbiome and metabolome increase susceptibility to *Clostridium difficile* infection

Casey M. Theriot\(^1\), Mark J. Koenigsknecht\(^1\), Paul E. Carlson Jr\(^3\), Gabrielle E. Hatton\(^1\), Adam M. Nelson\(^1\), Bo Li\(^4\), Gary B. Huffnagle\(^2\), Jun Z. Li\(^4\) & Vincent B. Young\(^1\),

Monitor animals for weight loss, inappetence and hunched posture

Days -12

Cefoperazone in drinking water (0.5 mg/ml)

Switch to regular water

Susceptible CDI

Resistant to CDI
Multiple structures of the gut microbiome are resistant to CDI
Susceptibility to CDI is associated with alteration of the gut metabolome

*Untargeted metabolomics
Bile acid metabolism

- Steroid carboxylic acids derived from cholesterol in mammals
- Aid in fat absorption and modulate cholesterol levels
- Primary bile acids that reach the large intestine are converted to secondary bile acids by bacterial enzymes:
  1. Deconjugation: $\text{taurocholate} \xrightarrow{\text{microbiota}} \text{taurine} + \text{cholate}$
  2. $7\alpha$-dehydroxylation: $\text{cholate} \xrightarrow{\text{microbiota}} \text{deoxycholate}$
Gut microbial derived secondary bile acids


\[
\text{taurocholate} \xrightarrow{\text{microbiota}} \text{taurine + cholate} \\
\text{cholate} \xrightarrow{\text{microbiota}} \text{deoxycholate}
\]
Susceptibility to CDI is associated with an increase in bile acid taurocholate
Susceptibility to CDI is associated with an increase in bile acid taurocholate.

*Targeted bile acid analysis
Taurocholate can induce germination of *C. difficile* spores *in vitro*.

- Tc = Taurocholate
- Dc = Deoxycholate

**Diagram:***

- **x-axis:** Tc and Dc (0.1% - 0.5hr and 0.01% - 6hr)
- **y-axis:** Percent germination
- **p-values:** 0.00006 and 0.008

**Legend:**

- C. difficile spores
- Bile acids
- Germination
C. difficile life cycle and metabolites

- Bile acids
- Spores
- Vegetative cells
- Carbohydrates
- Amino acids
- Toxin production
- Germination
- Outgrowth
- Sporulation
- Toxin production

Toxin
Susceptibility to CDI is associated with an increase in simple sugars and sugar alcohols

*Untargeted metabolomics*
Susceptibility to CDI is associated with an increase in sugar alcohols.

*Targeted sugar analysis

![Graph showing the comparison of sugar levels pre- and post-antibiotics with Mannitol and Sorbitol](chart)

- **Pre-antibiotics**
  - Mannitol
  - Sorbitol

- **Post-antibiotics**
  - Mannitol
  - Sorbitol

- **C. difficile**
  - Spores
  - Taurocholate
  - Germination/Outgrowth
  - Carbohydrates, Amino Acids
  - Vegetative C. difficile

*p = 0.0286*
Simple sugars and sugar alcohols enhance growth of *C. difficile* in vitro
C. difficile life cycle and metabolites

- Spores
- Bile acids
- Vegetative cell
- Carbohydrates
- Amino acids
- Vegetative cells
- Toxin production
- Toxin
- Germination
- Outgrowth
- Sporulation
Gut microbial derived secondary bile acids and *C. difficile*

Sorg and Sonenshein 2008, 2010; Francis et al. 2013
Ramirez et al. 2010; Weingarten et al. 2015, 2016

Thanissery, et al. *Anaerobe* 2017
Translating CDI in mice to humans: Fecal Transplants

Figure 2. Sampling timeline for recurrent CDI patients treated with FMT.

- FMT
- Pre-FMT (vanco)
- Post-FMT

Seekatz, Theriot, Young et al. *Anaerobe* 2018
Restoration of members of the Lachnospiraceae and Ruminococcaceae after fecal transplantation

Seekatz, Theriot, Young et al. Anaerobe 2018
Secondary bile acids are associated with recovery from CDI post fecal transplant.
Translating from mice to humans: Fecal Transplants
Alterations to the fecal metabolome before and after FMT

• Untargeted mass spectrometry detected 924 compounds of known identity

• Pairwise comparisons revealed >400 metabolites to be varying across groups (p<0.05)

• Key differences in:
  • **Lipid metabolism**
    • Includes endocannabinoids, polyunsaturated and other fatty acids, and **bile acids**
  • Amino acid metabolism
  • Nucleotide metabolism
  • Xenobiotics

*Unpublished data: Theriot, Gulati, McGill, Dougherty, Callahan*
Alterations in the fecal metabolome before and after FMT

Pre-FMT:
• Primary bile acids
• Secondary bile acids

Post-FMT:
• Primary bile acids
• Secondary bile acids

*Unpublished data: Theriot, Gulati, McGill, Dougherty, Callahan
Secondary bile acids biggest predictor of post FMT samples

- Lithocholate
- Deoxylcholate
- Dehydrolithocholate
- Tauroursodeoxycholate
- Taurocholenate sulfate
- Lithocholate sulfate 1
- Glycocholate sulfate
- Glycochenodeoxycholate 3-sulfate
- 7-ketodeoxycholate
- Glycodeoxycholate
- Hyocholate
- Glycohyocholate
- Chenodeoxycholate
- Glychocholate
- 3-dehydrocholate
Working model of how antibiotics decrease colonization resistance against *C. difficile*

1. Can restoring microbial-mediated secondary bile acid metabolism in the large intestine restore colonization resistance against *C. difficile*?

2. Can restoring bacteria that are able to compete for the same nutrients (amino acids and sugars) as *C. difficile* requires for growth reestablish colonization resistance against *C. difficile*?

---

Theriot and Young, *Annual Rev Microbiology* 2015
Other papers supporting this

Metabolomic networks connect host-microbiome processes to human *Clostridioides difficile* infections

John I. Robinson, …, Peter J. Mucha, Jeffrey P. Henderson

*J Clin Invest.* 2019. [https://doi.org/10.1172/JCI126905](https://doi.org/10.1172/JCI126905).

Human fecal metabolomic profiling could inform *Clostridioides difficile* infection diagnosis and treatment

Casey M. Theriot and Joshua R. Fletcher

Department of Population Health and Pathobiology, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, USA.
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Ruth Parsons
Garrison Allen
Gracie Vestal
Shayla Kim

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Sarah O’Flaherty, PhD: *NC State University*
Ben Callahan, PhD: *NC State University*
Ajay Gulati, MD: *University of North Carolina*
Sarah McGill, MD: *University of North Carolina*
Michael Dougherty, MD: *University of North Carolina*
Clinical coordinators: Holly Cirri and Ariel Watts

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NIH NIGMS R35 GM119438
NIH NIGMS K01 GM109236

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theriotlab.org  @TheRiotMicrobe
Ridinilazole: The Story So Far...

Richard Vickers, SVP, Chief Scientific Officer, Antimicrobials
Reducing Recurrence Is a Key Unmet Need in CDI

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

<table>
<thead>
<tr>
<th>Infection</th>
<th>Risk</th>
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</thead>
<tbody>
<tr>
<td>1st</td>
<td>~25%</td>
</tr>
<tr>
<td>2nd</td>
<td>~45%</td>
</tr>
<tr>
<td>3rd</td>
<td>~65%</td>
</tr>
</tbody>
</table>

Ridinilazole designed to treat CDI and reduce the recurrence of CDI

Targeting \textit{C. difficile} while preserving the gut microbiota

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 (vancomycin and metronidazole) associated with increased dysbiosis

\(^{(1)}\)Kelly, Clin Micro Infect, 2012: 18:12-17
Ridinilazole Potent Growth Inhibition of *C. difficile In Vitro*

*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>
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<td>82</td>
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<td>Freeman 2015</td>
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<td>Goldstein 2013</td>
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Targeted Spectrum of Activity *In Vitro*

Potentially Reduced Gut Microbiota Perturbation

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Genus/species</th>
<th>Ridinilazole</th>
<th>Fidaxomicin</th>
<th>Vancomycin</th>
<th>Surotomycin</th>
<th>Metronidazole</th>
<th>Cadazolid</th>
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<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(2)</td>
<td>(1)</td>
<td>(3)</td>
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<td>Actinobacteria</td>
<td><em>Bifidobacterium</em> spp.</td>
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<td>2</td>
<td>128</td>
<td>0.25</td>
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<tr>
<td></td>
<td><em>Eggerthella</em> lenta</td>
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<td>≤0.03</td>
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<td>8</td>
<td>0.5</td>
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<td>Firmicutes</td>
<td><em>Lactobacillus</em> spp.</td>
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<td>&gt;512</td>
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<td>4</td>
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<td>0.5</td>
<td>&gt;512</td>
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<tr>
<td></td>
<td><em>Enterococcus</em> faecium</td>
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<td>&gt;512</td>
<td>0.5</td>
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<td></td>
<td><em>Streptococcus</em> spp.</td>
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<td>128</td>
<td>1</td>
<td>-</td>
<td>&gt;512</td>
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<tr>
<td></td>
<td>Various Gram positive rods</td>
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<td>-</td>
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<td><em>Finegoldia</em> magna</td>
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<td>0.5</td>
<td>1</td>
<td>0.25</td>
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<td><em>Veillonella</em> spp.</td>
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<td>256</td>
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<td>&gt;512</td>
<td>2</td>
<td>16</td>
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<td>Bacteroidetes</td>
<td><em>Bacteroides</em> fragilis</td>
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<td>&gt;512</td>
<td>64</td>
<td>&gt;512</td>
<td>2</td>
<td>4</td>
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<tr>
<td></td>
<td><em>Bacteroides</em> ovatus</td>
<td>&gt;512</td>
<td>&gt;512</td>
<td>256</td>
<td>&gt;512</td>
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<td>8</td>
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<tr>
<td></td>
<td><em>Bacteroides thetaiotaomicron</em></td>
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<td>128</td>
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<td></td>
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<td>128</td>
<td>&gt;512</td>
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<td>&gt;32</td>
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<tr>
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<td><em>Parabacteroides</em> spp.</td>
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<td></td>
<td><em>Prevotella</em> spp.</td>
<td>&gt;512</td>
<td>&gt;512</td>
<td>512</td>
<td>&gt;512</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Fusobacteria</td>
<td><em>Fusobacterium nucleatum</em></td>
<td>64</td>
<td>&gt;512</td>
<td>512</td>
<td>&gt;512</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td><em>Fusobacterium</em> spp.</td>
<td>&gt;512</td>
<td>&gt;512</td>
<td>&gt;512</td>
<td>&gt;512</td>
<td>0.5</td>
<td>16</td>
</tr>
</tbody>
</table>

(1) Goldstein *et al.* AAC 2013
(2) Snydman *et al.* AAC 2012, Citron *et al.* AAC 2016
(3) Tyrrell *et al.* Anaerobe, 2016, # PIII-16
Bactericidal with Inhibition of Toxin Production

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

- **Control**
- **0.325x MIC**
- **0.25x MIC**
- **0.5x MIC**

Ridinilazole inhibits toxin formation

- **Toxin A**
- **Toxin B**

% of toxin level compared to control

Ridinilazole is bactericidal

- **Drug free control**
- **Ridinilazole 2xMIC**
- **Ridinilazole 10xMIC**
- **Vancomycin 5xMIC**

Dose dependent inhibition of septum formation

\(^{(1)}\) Basseres et al: JAC 2016
\(^{(2)}\) Corbett et al. JAC 2015
CoDIFy: Phase 2 Proof of Concept Trial
Randomized, Double Blind, Active Controlled 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>
</tr>
</tbody>
</table>

**Primary Endpoint**
- Sustained Clinical Response (SCR)
- Defined as clinical cure at end of therapy and no recurrence in the 30 days after treatment

**Key Secondary Endpoint**
- Clinical response at Test of Cure (TOC)

**Exploratory analysis**
- Clinical microbiology
- Inflammatory markers
- Detailed examination of the microbiome during and after therapy

EOT – End of Treatment; TOC – Test of Cure; EOS – End of Study
Ridinilazole therapy resulted in significantly improved SCR compared to vancomycin
• Driven by a marked reduction in rates of recurrent CDI

Δ8.1

<table>
<thead>
<tr>
<th>Proportion of Patients (%)</th>
<th>Clinical Cure</th>
<th>Recurrence</th>
<th>Sustained Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ridinilazole</td>
<td>77.8</td>
<td>14.3</td>
<td>66.7</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>69.7</td>
<td>34.8</td>
<td>42.4</td>
</tr>
</tbody>
</table>

90% CI: -9.3, 25.8
90% CI: -35.5, 3.0
90% CI: 3.1, 39.1

Vickers, et al., 2017
Consistent Trend for Improved SCR with Ridinilazole
Prespecified Subgroups at Higher Risk of Recurrence

**Subgroup** | **Estimated Improvement and 90% CI** | **Responders/N** | **Estimate (90% CI)**
--- | --- | --- | ---
Overall | | | 21.1 (3.1, 39.1)
Age Group 1:
<75 Years | | | 12.0 (-9.4, 33.5)
≥75 Years | | | 42.7 (9.7, 75.7)
Age Group 2:
<65 Years | | | 15.9 (-12.3, 44.0)
≥65 Years | | | 20.8 (-3.0, 44.7)
Baseline Severity (ESCMID):
Non-Severe | | | 22.3 (1.9, 42.7)
Severe | | | 15.9 (-29.8, 61.6)
Recurrent CDI History:
None | | | 21.4 (1.6, 41.3)
1-3 Previous Occurrences | | | 19.9 (-22.8, 62.5)
Concomitant Antibiotics at BL:
No | | | 21.6 (1.8, 41.3)
Yes | | | 18.9 (-29.7, 47.5)
Ribotype 027:
No | | | 19.9 (-22.8, 62.5)
Yes | | | -4.6 (-51.3, 42.1)
Hospitalization:
Inpatient | | | 13.3 (-23.0, 49.6)
Outpatient | | | 19.5 (-1.2, 40.2)
Relative Changes in Taxonomic Composition
Reduction in rCDI Potentially Associated with Microbiome Preservation

Cladograms Showing Changes in Relative Abundance of Microbiome Following 10 Days Dosing

RIDINILAZOLE

VANCOMYCIN

Reduced relative abundance
Increased relative abundance

Source: Thorpe et al., *PLOS ONE*, 2018
Quantifying Fold Shifts in Relative Abundance
Vancomycin Significantly Decreased Firmicutes and Bacteroidetes

Firmicute families Ruminococcaceae, and Lachnospiraceae reduced to below detection (2-3 log)
• Bacteroidetes decreased by over 3 logs, to <0.05% relative abundance
• Ridinilazole's impact restricted to modest decreases in selected Firmicutes families

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Fold change</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAN</td>
<td>RDZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actinobacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteroidetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firmicutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteobacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Taxa</th>
<th>Fold Change BL to EOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Bacteroidetes</td>
<td></td>
</tr>
<tr>
<td>Bacteroides</td>
<td>1773.5</td>
</tr>
<tr>
<td>Porphyromonadaceae</td>
<td>6274.8</td>
</tr>
<tr>
<td>Firmicutes</td>
<td></td>
</tr>
<tr>
<td>Lactobacillaceae</td>
<td>113.5</td>
</tr>
<tr>
<td>Clostridaceae</td>
<td>9.0</td>
</tr>
<tr>
<td>Lachnospiraceae</td>
<td>1415.8</td>
</tr>
<tr>
<td>Peptostreptococcaceae</td>
<td>17.9</td>
</tr>
<tr>
<td>Ruminococcaceae</td>
<td>570.2</td>
</tr>
<tr>
<td>Veillonellaceae</td>
<td>5.5</td>
</tr>
<tr>
<td>Erysipelotrichi</td>
<td>46.6</td>
</tr>
</tbody>
</table>

Decrease: 
- <5
- >5<10
- >10
- >100
- >1000

Increase: 
- <5
- >5<10
- >10
- >100
- >1000
Quantifying Fold Shifts in Relative Abundance
Vancomycin Resulted in Significant Expansion of the Proteobacteria

Primarily observed in the Enterobacteriaceae with ≈220 fold increase by EOT
- *Citrobacter, Enterobacter* and *Serratia* increased 10 fold from below detection at baseline
- *Klebsiella spp.* abundance expanding by over 3 logs.
Beneficial Impact on β-Diversity

Minimal Impact with Ridinilazole

Significant Loss of Diversity with Vancomycin

β-diversity at baseline significantly different to healthy controls

Minimal impact on community structure during ridinilazole dosing

Significant shift in vancomycin treated patients cluster at EOT compared with baseline

By EOT, vancomycin treated patients cluster further from healthy controls than observed at baseline
Bile Salt Metabolism and CDI
One of the Main Mechanisms of Colonization Resistance to C. difficile
Following ridinilazole treatment, there is normalization of bile acid composition

- Vancomycin disruption persists diminishing the return of colonization resistance
- Data provide functional rationale for reduced recurrences with ridinilazole
Metabolome Wide Changes By EOT

Tyrosine Metabolites

Amino Sugars

Oligosaccharides

C

Tyrosine

1.0E+03
1.0E+03
8.0E+02
8.0E+02
6.0E+02
6.0E+02
4.0E+02
4.0E+02
2.0E+02
2.0E+02
0.0E+00
0.0E+00

Indole-5,6-quinone

4.0E+02
4.0E+02
3.0E+02
3.0E+02
2.0E+02
2.0E+02
1.0E+02
1.0E+02
0.0E+00
0.0E+00

Kynurenate

D

Tyramine

8.0E+02
8.0E+02
6.0E+02
6.0E+02
4.0E+02
4.0E+02
2.0E+02
2.0E+02
0.0E+00
0.0E+00

N-acetyl-muramate

2.0E+03
2.0E+03
1.0E+03
1.0E+03
5.0E+02
5.0E+02
0.0E+00
0.0E+00

N-acetyl-D-mannosamine

2.0E+04
2.0E+04
1.0E+04
1.0E+04
5.0E+03
5.0E+03
0.0E+00
0.0E+00

D-glucosamine

8.0E+02
8.0E+02
6.0E+02
6.0E+02
4.0E+02
4.0E+02
2.0E+02
2.0E+02
0.0E+00
0.0E+00

E

Raffinose

8.0E+03
8.0E+03
6.0E+03
6.0E+03
4.0E+03
4.0E+03
2.0E+03
2.0E+03
0.0E+00
0.0E+00

Stachyose

4.0E+03
4.0E+03
3.0E+03
3.0E+03
1.0E+03
1.0E+03
0.0E+00
0.0E+00

Lactose

2.0E+04
2.0E+04
1.0E+04
1.0E+04
5.0E+03
5.0E+03
0.0E+00
0.0E+00

RID

VAN
Ridinilazole Improved Patient Quality of Life

- Patients’ quality of life assessed during the course of the study using the EQ-5D
- 5 domain questionnaire assessing patients’ welfare
- Greater improvements across all domains with ridinilazole - particularly anxiety and pain

EQ-5D-3L – Pain/Discomfort

EQ-5D-3L – Anxiety/Depression
Oral Administration for Topical Action in Gut Lumen

Ridinilazole is Associated with Negligible Systemic Exposure

PK assessed in healthy volunteers (Phase 1) and CDI patients (Phase 2)

- Inflammation of GI Tract does not result in increased exposure
- No effect on exposure due to concomitant medications, disease severity, age, food or gender
- Peak plasma concentrations >1,000 fold lower than NOAEL concentration in toxicology studies

### Concentration

<table>
<thead>
<tr>
<th></th>
<th>Phase 1 (200mg BID 10 days)</th>
<th>Phase 2 (200mg BID 10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 10</td>
</tr>
<tr>
<td>Plasma (ng/mL)</td>
<td>Day 1</td>
<td>Day 10</td>
</tr>
<tr>
<td>Median (Min, max)</td>
<td>0.09 (&lt;0.05, 1.3)</td>
<td>0.14 (&lt;0.05, 1.06)</td>
</tr>
<tr>
<td>Faeces (µg/g)</td>
<td>Day 5</td>
<td>Day 10</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1,466 (547)</td>
<td>1,364 (446)</td>
</tr>
</tbody>
</table>

Plasma (ng/mL) Day 1 Day 10 Day 5 Day 10

Median (Min, max) 0.126 (<0.10, 0.24) 0.09 (<0.05, 1.3) 0.14 (<0.05, 1.06)

Faeces (µg/g) Day 5 Day 10 Day 5 Day 10

Mean (SD) 1,466 (547) 1,364 (446) 1,298 (1,302) 1,373 (1,390)
Favorable Tolerability Data
Comparable Rates of Adverse Events Across the Two Treatment Groups

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Ridinilazole n patients (%)</th>
<th>Vancomycin n patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>180</td>
<td>183</td>
</tr>
<tr>
<td>TEAEs</td>
<td>41 (82)</td>
<td>40 (80)</td>
</tr>
<tr>
<td>Severe drug related TEAEs</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>SAEs</td>
<td>8 (16)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>TE SAEs</td>
<td>8 (16)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Drug related TE SAEs</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Withdrawals due to AEs</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

**SOC Preferred Term**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Ridinilazole n patients (%)</th>
<th>Vancomycin n patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>20 (40)</td>
<td>28 (56)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>12 (24)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>12 (24)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>11 (22)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>10 (20)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>9 (18)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>6 (12)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>5 (10)</td>
<td>5 (10)</td>
</tr>
</tbody>
</table>
Phase 3 Clinical Trials Designed to Evaluate Clinical and Economic Evidence

**Primary Endpoint**
- SCR to 30 days after end of therapy (EOT)
- Test for superiority (>95% power)

**Important Secondary Endpoint**
- Clinical cure at AOC
- Test for non-inferiority (90% power)

**Secondary & Exploratory Endpoints**
- SCR rates to 60 and 90 days post EOT
- Impact on microbiome/metabolome
- Safety and tolerability

**Health Economic Outcomes Endpoints**
- Include readmission rates, length of hospital stay

**Global Studies**
- North & South America, Europe, Asia Pacific

---

**Group Design for Each Trial**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Agent</th>
<th>Regimen</th>
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<td>1</td>
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<td>2</td>
<td>340</td>
<td>Vancomycin</td>
<td>125mg QID 10 days</td>
</tr>
</tbody>
</table>

**Screening**

- D12 (AOC): Key 2° Endpoint
  - Clinical Response at the AOC Visit

**Treatment**

- D40 (AOC): 1° Endpoint
  - SCR to 30 days post EOT

**Follow-Up**

- D70: 2° Endpoint
  - SCR to 60 days post EOT

- D100 (EOS): 2° Endpoint
  - SCR to 90 Days Post EOT
Statistical Assumptions

**Primary endpoint is Sustained Clinical Response to 30 days post-End of Treatment (EOT)**

- Test for superiority; >95% power, 2-sided test, 5% significance level
- Assumes 55% SCR rate for vancomycin and a 15% improvement with ridinilazole
- Looking for consistent trend on SCR to 60 and 90 days post-EOT

**Important secondary endpoint is Clinical Cure at AOC**

- Test for non-inferiority; 90% power, 1-sided test, 2.5% significance level
- Established NI margin of 10%
- Assumes conservative 80% response rate for vancomycin and ridinilazole

…the treatment of CDI and reducing the recurrence of CDI
Potential Path to Regulatory Approvals for Ridinilazole

Planned Milestones

- **Feb. 2019**
  - Phase 3 clinical trials initiated

- **H2 2021**
  - Phase 3 clinical trials top-line data

- **2022**
  - File NDA with the FDA
Ri-CoDIFy: Landmark Trials Designed to Make a Difference

Ridinilazole designed to specifically treat CDI, preserve the microbiome and prevent recurrence

If trials are successful, ridinilazole will have the opportunity to:

- Bring a clear difference and benefit to patients though the immediate and long term benefit of cure and recurrence prevention
- Address the key unmet need in CDI – preventing recurrence
- Show the significant deleterious effect of vancomycin on the microbiome
- Provide a better treatment option for physicians
- Align with stewardship – right drug, right patient. Replace inappropriate broad spectrum antibiotics
- Reduce health care costs through prevention of reoccurrence and hospital readmissions

“The best way to prevent the 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th}… recurrence is to prevent the 1\textsuperscript{st}”
Professor Yoav Golan, Tufts University, Ri-CoDIFy 1&2 US Investigator Meeting
The Economics of C. difficile Infection

Kevin W. Garey, PharmD, MS, FASHP
Professor and Chair
Dept of Pharmacy Practice and Translational Research

UNIVERSITY of HOUSTON | COLLEGE OF PHARMACY
The Impact of *Clostridium difficile* Infections (CDI)

Of patients with CDI given metronidazole or oral vancomycin, 25% will experience recurrent CDI.

There is a lot of *C. difficile* all around us

**Hospital-onset CDI:**

- Exposure to healthcare
- No exposure to healthcare

**Community-onset CDI**

- 24.2%
- Total cases: 453,000; recurrences: 83,000; mortality: 27,300 (inpatient), 2000 (outpatient)

**Community-acquired CDI**

- 34.2%
- Total cases: 606,058; recurrence: 166,821; mortality: 44,500


2Desai et al. BMC ID 2016;16:303
*C. difficile* is the main contributor to gastroenteritis-associated deaths in the USA

Analysis of National Center for Health Statistics (NCHS) multiple-cause-of-death mortality data for the years 1999–2007, a 5-fold increase in mortality attributed to CDI was noted

Hall et al. CID 2012;55:216-23
Mortality risk is especially pronounced in the elderly

Mortality rate per 100,000 population

CA-CDI: community-associated CDI; HCA-CDI: Health-care associated CDI

Recurrent CDI: Common and increases likelihood with each CDI episode

- Recurrence is present when CDI re-occurs within 8 weeks
  - Provided the symptoms from the previous episode resolved
  - May occur within days

Risk of Recurrence of CDI

Rate of infection

- After initial exposure: 2%
- After initial infection: 18%
- After first recurrence: 45%
- After second recurrence: 65%

Risk of recurrent infection increases with each treatment failure

Adapted from Jiang et al. *Am J Gastroenterol.* 2006;101:112.
The financial economics of CDI (& recurrent CDI) is driven (85%) by one variable

Hospitalizations (or re-hospitalizations)
Costs of CDI will involve initial hospitalization costs + (re-)admission costs

- Hospital-onset CDI: Exposure to healthcare
- Community-onset CDI
- Community-acquired CDI: No exposure to healthcare

Costs of CDI

Most important cost considerations:

<table>
<thead>
<tr>
<th>Extended LOS due to CDI</th>
<th>Likelihood of re-admission</th>
<th>Likelihood of admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-onset CDI:</td>
<td>Community-onset CDI</td>
<td>Community-acquired CDI</td>
</tr>
</tbody>
</table>

Methods to decrease CDI incidence (costs)

Antibiotic exposure

Primary CDI

Continued dysbiosis

Recurrent CDI

Methods to decrease CDI incidence

Antibiotic stewardship to decrease global use of antibiotics (hard)

Choose an anti-recurrent CDI strategy
How much does CDI increase your length of stay (red lines) and hospitalization costs (blue bars)

Recurrent CDI is costly:
Healthcare utilization for recurrent CDI

* Of disease-attributable readmission, 85% returned to the initial hospital for care

Aitken, DuPont, Garey. PLOS One 2014 July 24;9(7)
Increased healthcare utilization = increased healthcare costs

Cost in US dollars; median (IQR)

<table>
<thead>
<tr>
<th>Cost in US dollars; median (IQR)</th>
<th>Without recurrent CDI</th>
<th>With recurrent CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI-attributable hospitalization^</td>
<td>$13,168 (7,525 - 24,455)</td>
<td>$28,218 (15,049 – 47,030)</td>
</tr>
<tr>
<td>Total hospitalization^</td>
<td>$20,693 (11,287 - 41,386)</td>
<td>$45,148 (20,693 - 82,772)</td>
</tr>
</tbody>
</table>

What is the likelihood of CDI re-hospitalization and what does this cost?

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Patient</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Design</th>
<th>Data source</th>
<th>Outcome</th>
<th>CDI cost or cost reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins, 2015</td>
<td>USA</td>
<td>CDI Medicare pts</td>
<td>Pts rehospitalized</td>
<td>Pts not rehospitalized</td>
<td>Cohort</td>
<td>Medicare data</td>
<td>Rehospitalization rate</td>
<td>9%</td>
</tr>
<tr>
<td>Aitken, 2014</td>
<td>USA</td>
<td>CDI pts</td>
<td>CDI with recurrence</td>
<td>1st episode CDI only</td>
<td>Cohort</td>
<td>Pt evaluation</td>
<td>Rehospitalization rate</td>
<td>12%</td>
</tr>
<tr>
<td>Magee, 2015</td>
<td>USA</td>
<td>Hospitalized pts</td>
<td>Pts with CDI</td>
<td>Pts without CDI</td>
<td>Hospital DC analysis</td>
<td>Premier database</td>
<td>Hospitalization costs</td>
<td>$7,286</td>
</tr>
<tr>
<td>Levy, 2015</td>
<td>Canada</td>
<td>Canada population</td>
<td>Pts with CDI</td>
<td>Pts without CDI</td>
<td>Simulation</td>
<td>Canada population estimates</td>
<td>Hospitalization costs</td>
<td>$11,930-15,330</td>
</tr>
<tr>
<td>Le Monnier, 2015</td>
<td>France</td>
<td>CDI pts</td>
<td>Pts with index CDI</td>
<td>Pts with R-CDI</td>
<td>Cohort</td>
<td>Hospital databases</td>
<td>Hospitalization costs</td>
<td>6,183-11,366 Euros</td>
</tr>
<tr>
<td>Shah, 2016</td>
<td>USA</td>
<td>CDI pts</td>
<td>Pts with index CDI</td>
<td>Pts with R-CDI</td>
<td>Cohort</td>
<td>Pt evaluation</td>
<td>Hospitalization costs</td>
<td>$15,050</td>
</tr>
</tbody>
</table>

Pubmed: 2014-2019; Search terms: *Clostridium difficile* and economics
Pts: patients; CDI: C. difficile infection; R-CDI: recurrent CDI
## Putting it all together: Best estimates for national economic burden (USA)

<table>
<thead>
<tr>
<th>Population</th>
<th>CDI cases (N)</th>
<th>Total costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>US population (decision analysis)</td>
<td>606,000</td>
<td>$5.4 billion</td>
</tr>
<tr>
<td>Medicare (&gt;65)</td>
<td>240,000</td>
<td>$6 billion</td>
</tr>
<tr>
<td>CDC Epicenter (US population)</td>
<td>500,000</td>
<td>$4.8 billion</td>
</tr>
</tbody>
</table>

Desai et al. BMC ID 2016; Shorr et al. ICHE 2016; Lessa et al. NEJM 2015
Bottom line: expensive

• Any data that an antibiotic that reduces CDI recurrence could decrease these costs?
Real-world evidence that an anti-recurrent antibiotic (fidaxomicin) can reduce healthcare costs

USA: Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for select patients.

**CDI-related re-admissions:** Fidaxo: 20.4%; Vanco: 41.3%
UK experience with narrow-spectrum antibiotic and reduction in healthcare costs?


- A (n=98)
- B (n=162)
- D (n=127)
- C (n=511)
- E (n=209)
- F (n=178)
- G (n=278)

90-day hospital recurrence rate

- First line, all episodes
- First line, R-CDI
- Select episodes only

Before Fidaxo | After fidaxo
---|---
A (n=98) | 10.6 3.1
B (n=162) | 16.3 3.1
D (n=127) | 21.1 12.5
C (n=511) | 7.7 8.3
E (n=209) | 12.9 11.8
F (n=178) | 16.9 9
G (n=278) | 5.4 5.8

Real-world evidence that fidaxomicin may reduce these costs?

UK, 2012-13: seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% and 17.3% to 3.1% and 3.1% in hospitals A and B, respectively (p<0.05, each)

Many phase III CDI studies are incorporating economics into their study design. Example bezlotoxumab (European population)

Prabhu et al. CID 2017
Before we leave the costs. Will we be able to use the recurrence results from the ridinilazole phase III trials to predict CDI recurrence in the real world (and build an economic model?)?

<table>
<thead>
<tr>
<th>Recurrence rates from phase III studies&lt;sup&gt;1-2&lt;/sup&gt;</th>
<th>O27</th>
<th>Other ribotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidaxomicin</td>
<td>23.2</td>
<td>7.8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>30.8</td>
<td>25.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison of phase III results to observed results&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Expected**</th>
<th>Observed</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidaxomicin</td>
<td>10.88</td>
<td>3.1-12.5</td>
<td>7.65</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>26.56</td>
<td>5.4-21.1</td>
<td>12.98</td>
</tr>
</tbody>
</table>

**Assuming 20% of UK strains during time period were 027<sup>4</sup>

**ANSWER: Probably!**

There are other costs associated with CDI: the patient perspective
I wonder if we should consider other endpoints?

Aitken et al. ICAAC 2014 Poster #K-360, Sat, Sept 6, 2014
The driver for decreased Quality of Life (QOL) is not so much physical as a worry/anxiety of transmissibility or symptom persistence.
QOL goes down considerably with recurrent CDI

“It was a little over a year ago I was diagnosed and treated with metronidazole, then treated again in April with vancomycin for it as tested positive again, and am 50 years old and otherwise healthy except for hypertension issues. I think I acquired it as a caretaker for my elderly mother (who has since passed away), and having antibiotics for dental issues. I wouldn't wish this illness on my worst enemy, and it's been a life changer for me.”
Final conclusions

• C. difficile is costly
  – US estimates: $4-6 billion dollars per year
• Prevention of CDI recurrence is likely the most feasible way to decrease costs
  – Therapeutic modalities have decreased CDI recurrence with decreased associated costs
• Other patient reported outcomes (QOL) should become part of the consideration to choose an anti-recurrence CDI strategy
Acknowledgements

Research grant support paid to the University of Houston
State/Federal: Texas Department of State Health Services, Houston Health Department, NIH (NIAID 1U01 AI24290-01)
For profit: Merck & Co, Summit PLC, Healthy Sole
Ridinilazole – Planning for Commercial Success
Daniel Elger, Chief Commercial Officer
Differentiated Benefits Underpin Commercial Strategy

Aiming to:

- Provide step-change in patient benefit captured in label
- Offer major healthcare cost savings through improved Rx
- Deliver on each stakeholder’s goals - outcomes, QOL, value, microbiome, stewardship, quality

Clear value proposition:
Avoid clinical and economic burden of CDI recurrence

→ Positioning of ridinilazole as the appropriate front-line therapy for CDI
Large Market Opportunity in CDI

\[ \text{BIG PATIENT POOL} \times \text{LARGE UNMET NEED} = \text{LARGE MARKET OPPORTUNITY} \]

\[ \text{BIG PATIENT POOL} \times \text{CLEARLY SUPERIOR TREATMENT AND RIGHT COMMERCIAL STRATEGY} = \text{COMMERCIAL SUCCESSFULL THERAPY} \]
Clear Addressable Population

- CDC + published recurrence data suggest ~600K US patients
- Range of care and reimbursement settings
  - Significant ex-DRG component
- 75%+ are front-line patients
Obvious Unmet Need

- Almost all patients get generics with unacceptable outcomes
- Vancomycin use dominates
- Marked lack of branded competition, especially in front-line

⇒ CLEAR TASK – BEAT VANCOMYCIN
Avoidable Economic Burden

COST OF CDI RECURRENCE OVER ONE YEAR

$34,000
$40,000, 2023

What if ALL front-line patients receive an agent that reduces recurrence by 15%?

Number Needed to Treat = 6.7

$6,000 saving per treated patient

~$2.7B saving

US Healthcare System, 2023

1 - Costs adjusted to 2023 pricing using US CPI for years to 2018 and assumed 2% inflation 2019-2023
2 - Based on NNT of 6.7 associated with 15% recurrence delta; 3 – Based on front-line population per Lessa et al, 2015

2013 DATA
Rodrigues et al.

~$34,000
~$40,000, 2023

~$6,000 saving per treated patient
Goal to Win with Evidence in CDI

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Economic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superiority vs standard therapy = step change in patient care</td>
<td>Substantial cost savings</td>
</tr>
<tr>
<td>Differentiated label</td>
<td>Robust Health Economic Outcomes Research support from launch</td>
</tr>
<tr>
<td>Unique connection to microbiome</td>
<td>Justification for premium price</td>
</tr>
<tr>
<td>Patient-friendly safety profile</td>
<td>Demonstrable value</td>
</tr>
</tbody>
</table>

AVOID RECURRENCE BURDEN
Goal to Win with Application in CDI

- Learn lessons from history
- Understand market barriers and levers at granular level
- Act early enough
- Hire great people

CLEARLY SUPERIOR TREATMENT AND RIGHT COMMERCIAL STRATEGY
Ridinilazole – Planning for Commercial Success

Anna Diaz Triola, MBA, VP, Marketing
History Can Inform the Future for the Betterment of Patients
Summit Marketing Launch Imperatives
Building Transition of Care Pathways for Patients with C. difficile

- Focus on the microbiome
- Make recurrence matter
- Create ecosystems of clinical and patient advocacy
- Build strategic launch plans and great teams
- Execute thoughtfully and nimbly
Headwinds are Lessening

- Increased + attention in Washington / globally
- New policies support launches
  - QIDP agents only need to meet “newness” criteria
  - NTAP raised to 75% of WAC (up from 50%)
- Pro-innovation incentives have moderate bi-partisan support
- Recognition by guideline organizations to act quicker¹

¹ The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), February 2018
## Market Access Today
Why the Reduction of Recurrence Matters

<table>
<thead>
<tr>
<th>Top Comorbid Conditions of CDI Population</th>
<th>Estimated Annual US Costs of Management Efforts*</th>
<th>Leverageable Interests / Care Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic heart disease</td>
<td>$329 B</td>
<td>Cardiothoracic surgeons (nearly 8 M life saving procedures in 2014)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>$237 B</td>
<td>Endocrinologists (those with diabetes 2-3 times more likely to develop depression)</td>
</tr>
<tr>
<td>Cancer</td>
<td>$175 B</td>
<td>Oncologists (patient friendly, progression free survival compromised)</td>
</tr>
</tbody>
</table>

Why Would **Anyone** Knowingly Introduce An Additional “Chronic” Condition to an Already Fragile and Costly Population that is on a path to a defined outcome?

* Sources: direct costs: CDC, NIH, CDC

Oct. 7, 2019

R&D Day
Oct. 7, 2019

Summit therapeutics
Our Plan: Launch with Payers, Not Against Them
Building Payer Alignment without Compromising Margins

- Kindle Action Ecosystems
- Establish Case for Actual Savings
- Advocate Role of Microbiome on Co-Morbidity Outcomes
- Improve Site of Care / Transition Quality
- C. difficile Market Access Leadership
- Be at the Policy Table (not on the menu)
- Innovate Distribution Model
- Maintain “Kill the Bug” as objective #1

R&D Day
Oct. 7, 2019
Summit Market Access Launch Imperatives
Ideas into Action

**EDUCATE**
Educate! Dislodge “Old Stories” of acceptable C. difficile management

**EVIDENCE**
Build evidence package that drives rapid review, superior access and optimum net price

**RECRUIT**
Recruit launch geniuses

**ACCESS**
Build our access plan:
- Quickly turn off new-to-market blocks
- Adeptly navigate Medicare exceptions
- Process secure measured health system access

…and execute impeccably!
Precision Antibiotic Pipeline: Killing the Bad Bugs, Preserving the Good Bugs

David Powell, PhD, SVP Research
Discovery Agenda

- Discuva Platform (our discovery engine)
- Targeted DDS-04 series for Enterobacteriaceae infections
- Targeted SMT-571 series for *Neisseria gonorrhoeae* infections
Discovery Engine
Discovering New Mechanism Antibiotics with our Discuva Platform
Summit Discovery is Precision Targeted, Microbiome Protecting and Patient Centric

Unmet need & Indication focus

Novel MOA/ Escapes resistance

Pathogen targeting / microbiome sparing

Mission to discover new mechanism antibiotics with targeted activity against a specific pathogen(s) for indications of high unmet need
We Believe the Future is Targeted Spectrum Antibiotics

1. Broad spectrum antibiotics are becoming less desirable as the health benefits of the microbiome become more understood.

2. The discovery of broad spectrum antibiotics over the past 30 decades has been an acknowledged failure, a new approach is needed.

3. Most antibiotic discovery over the past 30 years has focused on broad spectrum hits, narrower compounds often discarded from screens.

4. Targeted Spectrum allows precision approach:
   - Kills bad bugs
   - Preserves microbiome
   - Drives patient betterment
   - Promotes good stewardship
Summit Discovery is Primed for Success
Aligning Strategy and Technology

- DDS-04 series
- SMT-571 series
- DDS-03 series
- Roche
Bioinformatics Drives our Antibiotic Discovery

- RDZ MICROBIOME
- AMRita PIPELINE
- NETWORK SUPPORT
- OTHER PROJECTS
Studies on the microbiome continue to show its importance for human health.

New microbiome companies are seeking to preserve and enhance human health or target disease causing mechanisms.

Our microbiome sparing strategy is well exemplified in our C. difficile program and continues in earlier discovery efforts.

We are creating a new position to better characterize our microbiome preserving agents to further highlight the benefit of targeted approaches vs less discriminating broad spectrum agents.
The Discuva Platform Integrates Many Functions

A combination of technologies and different functional expertise groups drives the Discuva Platform.

- Library of mutant engineered bacteria
- Next-generation sequencing
- Genome map of mutation insertions
- Outward-facing promoters

AbR Transposon
Proprietary Transposons Drive the Discuva Platform

1. Gene activating Insertion
2. Gene disruption
3. Gene down-regulating Insertion

Outward-facing promoters

Bacterial gene

WT

AbR

Transposon

1 2 3
Killing the Bad Bugs: Proprietary Libraries Enable Discovery Across Pathogens of High Unmet Need

**CDC Urgent / WHO Critical Threats**
- **K. Pneumoniae**
- **N. gonorrhoeae**
- **E. coli**
- **P. aeruginosa**
- **A. baumannii**

**CDC Serious Threats / Other ESKAPE Pathogens**
- **S. pneumoniae**
- **E. faecalis**
- **E. faecium**
- **S. aureus**

**Gram negative**
**Gram positive**

*Current Summit preclinical programs*
Data Interpretation Supported by Summit’s Bioinformatics Interface (AMRita)

*Escherichia coli*

- High density insertion
- 550k different mutants across 4.1Mbp of non-essential genome
- 1 Tn insertion every 7 bp

- Essential gene identification
- Target ID for ABx
- Validation of phenotypic MOA
The Platform Elucidates Mechanism of Action and Optimizes Against Resistance

Promoted genes = transposon in promoter region (250)

Disrupted genes = transposon inside gene body

Downregulated genes = transposon after gene body on the reverse orientation
Fosfomycin’s Mechanism of Action and Resistance in *E.coli*

murA upregulation

phnG-P upregulation

Scale: +/- 10000

Scale: +/- 5000

R&D Day
Oct. 7, 2019
Resistance Mechanisms are Direct and Indirect

- cyaA disruption
  - Scale: +/- 50

- ptsl disruption
  - Scale: +/- 50

- uhpT,A,C disruption
  - Scale: +/- 100

COMPOUND INCREASING CONCENTRATION

Oct. 7, 2019
The Platform has Validated Many Known Mechanisms and has Discovered New Potential Mechanisms


<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>ptsI</td>
<td>Large deletion</td>
<td>Regulation of cAMP levels</td>
</tr>
<tr>
<td>ptsI</td>
<td>Large deletion</td>
<td>Regulation of cAMP levels</td>
</tr>
<tr>
<td>cyaA</td>
<td>CCTTCG−289 [del 371 bp]113GCCGAC</td>
<td>Regulation of cAMP levels</td>
</tr>
<tr>
<td>glpT</td>
<td>ATGGCCTTGTGAT, Pro (CC865T)→ Leu (CT865T)</td>
<td>Regulation of cAMP levels</td>
</tr>
<tr>
<td>cyaA</td>
<td>Insertion IS1, insertion point GCA536</td>
<td>Transporter</td>
</tr>
<tr>
<td>cyaA</td>
<td>TTGCTATAACGTGA, Gln (C400AA)→ stop (T400AA)</td>
<td>Regulation of cAMP levels</td>
</tr>
<tr>
<td>uhpT</td>
<td>CGTTTCTAGGAAC, Gln (C862AG)→ stop (T862AG)</td>
<td>Transporter</td>
</tr>
<tr>
<td>cyaA</td>
<td>AAGTCA454[del 1 bp]456CTTCTT</td>
<td>Regulation of cAMP levels</td>
</tr>
<tr>
<td>cyaA</td>
<td>GCTGGG430[del 7 bp]438GTTGGA</td>
<td>Regulation of cAMP levels</td>
</tr>
<tr>
<td>uhpT</td>
<td>Insertion IS1, insertion point 628CTG</td>
<td>Transporter</td>
</tr>
<tr>
<td>uhpT</td>
<td>CGTTACAGCAGCG, Gly (G637GC)→ Ser (A637GC)</td>
<td>Transporter</td>
</tr>
<tr>
<td>uhpT</td>
<td>Insertion IS200 AAAC1434 (insertion point 42 bp downstream of stop codon for uhpT)</td>
<td>Transporter</td>
</tr>
<tr>
<td>uhpA</td>
<td>Large deletion</td>
<td>Transporter</td>
</tr>
<tr>
<td>uhpT</td>
<td>GCCGCG1299[CTGGATATCGCCGCG]1300ATGGT 15-bp duplication</td>
<td>Transporter</td>
</tr>
<tr>
<td>uhpT</td>
<td>Large deletion</td>
<td>Transporter</td>
</tr>
<tr>
<td>uhpA</td>
<td>Large deletion</td>
<td>Transporter</td>
</tr>
<tr>
<td>uhpA</td>
<td>GCCGCG140[del 8 bp]149TGTGTA</td>
<td>Transporter</td>
</tr>
<tr>
<td>glpT</td>
<td>CCTCCTAGGCCCTA, Trp (TG878G)→ stop (TA878G)</td>
<td>Transporter</td>
</tr>
</tbody>
</table>

All described genes identified via transposon profiling
DDS-04 Series Program
Lead Optimization Program for the
Treatment of Enterobacteriaceae Infections
Enterobacteriaceae Infections Represent a Significant Area of Unmet Medical Need

- CRE have been characterized as an urgent threat by the CDC
- Some CRE bacteria have become resistant to almost all available antibiotics

CRE/ESBL producing Enterobacteriaceae cause a wide range of infections such as urinary tract infection/complicated urinary tract infection, bacteremia and hospital acquired pneumonia

*Data from CDC Antibiotic Resistance Threats in the United States, 2013*
Drug Resistant Enterobacteriaceae Infections Are Rising
A Growing Cause of Healthcare-Associated Infections

<table>
<thead>
<tr>
<th>Healthcare Associated Infection</th>
<th>EU incidence (‘000s) †</th>
<th>US incidence (‘000s) †</th>
<th>% Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia / Lower Respiratory Tract</td>
<td>861</td>
<td>250</td>
<td>27-30 a,b</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>313</td>
<td>249</td>
<td>19-20 c,d</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>888</td>
<td>562</td>
<td>62-75 e-h</td>
</tr>
</tbody>
</table>

Distribution of Carbapenemases in Enterobacteriaceae are a Global Threat

![Map showing the distribution of Carbapenemases in Enterobacteriaceae across different countries.](image)

<table>
<thead>
<tr>
<th>Distribution Type</th>
<th>IMP</th>
<th>KPC</th>
<th>NDM</th>
<th>OXA</th>
<th>VIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endemic/nationwide distribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant outbreaks/ regional spread</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporadic outbreak/ occurrences</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Logan & Weinstein, The Journal of Infectious Diseases, Volume 215, Issue suppl_1, 15 February 2017, Pages S28-S36*
The Summit DDS-04 Series Seeks to Treat Three Potential Indications with One Drug

- **Respiratory Infection**
- **Blood Stream Infection**
- **Urinary Tract Infection**
DDS-04 is a Novel LolC/E Lipoprotein Transport Inhibitor Series

**HTS Hit**

**Discuva Platform**

- **Control**
- **0.125x MIC - 1x MIC**

- *lolCDE genes upregulated*

---

<table>
<thead>
<tr>
<th>LolICDE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Essential inner membrane ABC transporter in Gram negative bacteria</td>
</tr>
<tr>
<td>• Releases lipoproteins into the periplasm from the bacterial inner membrane</td>
</tr>
</tbody>
</table>
Sequence Homology Gives Enterobacteriaceae Specific Activity

![Graph showing sequence homology and MIC for different bacteria species.](image-url)
# DDS-04 Exhibited Low Levels of Activity Outside Enterobacteriaceae

<table>
<thead>
<tr>
<th>Bacterial Strain</th>
<th>MIC (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>8 - &gt;64</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>&gt;16</td>
</tr>
<tr>
<td><strong>Enterobacter cloacae</strong></td>
<td>0.06 - 0.25</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>0.03 – 0.5</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>0.12 - 1</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>
DDS-04 Series Exemplar (DDS-04a) was Well Tolerated with Exposure at Key Infection Sites \textit{In Vivo}

- Kidney: 239,414 ng/g
- Urine: 189,000 ng/mL
- Lung: 24,549 ng/g
- Blood: $C_{\text{max}}$ 16,667 ng/mL

MIC$_{90}$ UPEC: 1 µg/mL

Exposure across key body sites:
- IV 40mg/kg
- 200x MIC
- 150x MIC
- 25x MIC
- 15x MIC

Oct. 7, 2019
R&D Day
Summit therapeutics
**In Vivo Proof-of-Concept Achieved in a Murine UTI Model**

Route/Regimen – IV TID over 3 days

Significant reduction in bacterial burden in the urine

**E. coli** uropathogenic strain
**In Vivo Proof-of-Concept Achieved in a Murine UTI Model**

Route/Regimen – IV TID over 3 days

Significant reduction in bacterial burden in the urine

Data generated by Evotec, United Kingdom
In Vivo Proof-of-Concept Achieved in an Intraperitoneal Mouse Sepsis Model

Route/Regimen – IV TID

Significant reduction in bacterial burden in blood
In Vivo Proof-of-Concept Achieved in a Murine Pneumonia Model
Route/Regimen – IV TID

K. pneumoniae ATCC 43816
## DDS-04 – Series Profile

<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiology/MIC90</td>
<td></td>
</tr>
<tr>
<td>Cidality and FoR</td>
<td></td>
</tr>
<tr>
<td>Microbiome sparing profile</td>
<td></td>
</tr>
<tr>
<td>PK – Infection (x3) site exposure</td>
<td></td>
</tr>
<tr>
<td>ADMET – human metabolism</td>
<td></td>
</tr>
<tr>
<td>PD – Translational Models</td>
<td></td>
</tr>
<tr>
<td>Safety/Tox/MTD</td>
<td></td>
</tr>
<tr>
<td><strong>TBC</strong></td>
<td><strong>Human Dosing Regimen</strong></td>
</tr>
</tbody>
</table>

Oct. 7, 2019
Three Potential Indications in One Drug

**RESPIRATORY INFECTION**
- PNEUMONIA

**BLOOD STREAM INFECTION**
- BACTERAEMIA/SEPSIS

**URINARY TRACT INFECTION**
SMT-571 Program
Our Preclinical Candidate for Neisseria gonorrhoeae

Powered by CARB-X

Summit therapeutics
Neisseria gonorrhoeae is an Ancient and Global Disease

Gonorrhea is an ancient human disease

- In 1161 English parliament passed a law to reduce the spread of "...the perilous infirmity of burning"
- Albert Neisser discovered the bacterium Neisseria gonorrhoeae in 1879

... gonorrhea was becoming untreatable and reported cases were on the rise

Early treatment options were barbaric ....
Early Success Fighting *Neisseria gonorrhoeae*

The Birth of a Wonder Drug

*In the 1940s a new antibiotic entered the market….*

….. *Problem solved!?*
But *Neisseria gonorrhoeae* is Incredibly Adaptable

The Bugs Always Win

Over the following decades *N. gonorrhoeae* evolved …

… eventually overcoming all known classes of antibiotics
Gonorrhea Represents a Continuing Healthcare Challenge

Untreated gonococcal infection can cause health problems including:

- Increased incidence of pelvic inflammatory disease & epididymitis
- Infertility in men and women
- Ectopic pregnancy, spontaneous abortion, stillbirths and premature deliveries
- Severe eye infections following childbirth which can lead to blindness
- Significantly increased risk of HIV infection and transmission

Disseminated gonococcal infections occur in 1-3% of cases:

- Septic arthritis
- Endocarditis
- Meningitis

Gonorrhea is often asymptomatic further exacerbating the problem.
Neisseria gonorrhoeae – A Global Disease

Impending Healthcare Disaster

Reduced susceptibility to ceftriaxone – the global picture

The nightmare scenario....

There are no other approved options.....
SMT-571: A Targeted Potential New Treatment Option for the Treatment of *Neisseria gonorrhoeae*

Excellent microbiological profile against all *N. gonorrhoeae* strains

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<tbody>
<tr>
<td>MIC (µg/mL)</td>
<td>0.08</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
<td>2.8</td>
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</tbody>
</table>

SMT-571 exhibits excellent activity across >262 *N. gonorrhoeae* clinical isolates

SMT-571 confirmed to have a targeted spectrum of activity - including the microbiome
SMT-571 Has a Targeted Spectrum of Activity

- JMI laboratories performed panel assay exploring a broad geographical collection of 232 strains
- SMT-571 confirmed to have a narrow spectrum of activity - including microbiome related strains

<table>
<thead>
<tr>
<th>Organism</th>
<th>SMT-571</th>
</tr>
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<tbody>
<tr>
<td>Acinetobacter baumannii</td>
<td>16-32</td>
</tr>
<tr>
<td>Actinomyces spp</td>
<td>8-32</td>
</tr>
<tr>
<td>Bacteroides spp</td>
<td>2-4</td>
</tr>
<tr>
<td>Bifidobacterium spp</td>
<td>32-&gt;64</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>1</td>
</tr>
<tr>
<td>Clostridium spp</td>
<td>1-4</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>16-&gt;32</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>32-&gt;32</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>8-32</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>0.03-0.25</td>
</tr>
<tr>
<td>Haemophilus parainfluenza</td>
<td>0.25-1</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>16-&gt;32</td>
</tr>
<tr>
<td>Lactobacillus spp</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>0.06</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>0.06-0.25</td>
</tr>
<tr>
<td>Neisseria spp</td>
<td>0.06-0.5</td>
</tr>
<tr>
<td>Porphyromonas spp</td>
<td>0.25-1</td>
</tr>
<tr>
<td>Prevotella spp</td>
<td>1-2</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>32-&gt;32</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1-4</td>
</tr>
<tr>
<td>Streptococcus spp</td>
<td>32-&gt;32</td>
</tr>
</tbody>
</table>
SMT-571 Shows Rapid Killing and Low Frequency of Resistance

- SMT-571 shows no cross resistance with mutants raised against ceftriaxone
- The compound is bactericidal with a 5 Log reduction in CFU/mL after 4-8 hours

Low potential for resistance development
No spontaneous *N. gonorrhoeae* resistant mutants isolated *in vitro*

<table>
<thead>
<tr>
<th>Frequency of Resistance</th>
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<tbody>
<tr>
<td>WHO-M</td>
<td>&lt;8.2 x 10^{-10} @ 4 x MIC</td>
</tr>
<tr>
<td>WHO-V</td>
<td>&lt;3.1 x 10^{-10} @ 4 x MIC</td>
</tr>
<tr>
<td>WHO-X</td>
<td>&lt;8.7 x 10^{-10} @ 4 x MIC</td>
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</tbody>
</table>
A Predictive *In Vitro* PK/PD Model of *Neisseria gonorrhoeae* Infection

Translational models highly challenging for *N. gonorrhoeae*

Hollow Fiber Model of *N. gonorrhoeae* (Institute of Clinical Pharmacodynamics)

- SMT-571 has demonstrated activity at 5mg/kg using human ADME data
SMT-571 Aligns well with *Neisseria gonorrhoeae* TPP

WHO preferred target product profile (TPP) for a new treatment for gonorrhea:

- Single oral dosing regimen
- Novel mechanism of action with no cross resistance to current standard of care
- No drug-drug interactions

SMT-571 is an advanced molecule from a new and promising chemical series with:

- Consistently high activity against *Neisseria gonorrhoeae*
- Exceptionally low levels of mutational frequency
- Bactericidal profile
- Good oral pharmacokinetics
- Novel mechanism of action

Programme identified through the Discuva Platform

- Ongoing product development supported by CARB-X
### SMT-571 – Summary and Series Profile

<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
<td>Microbiology/MIC90</td>
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<tr>
<td>Cidality and FoR</td>
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<tr>
<td>Microbiome sparing profile</td>
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<tr>
<td>PK – Infection site exposure</td>
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<tr>
<td>ADMET – human metabolism</td>
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<tr>
<td>PD – Translational Models</td>
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<tr>
<td>Safety/Tox/MTD</td>
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<tr>
<td>Human Dosing Regimen</td>
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</tbody>
</table>
Summit Discovery has industry-leading capabilities to drive its patient centric, microbiome sparing, new MOA antibiotic strategy.

The highly targeted, new mechanism DDS-04 series has great potential against one of the most urgent unmet need areas, Gram-negative Enterobacteriaceae infections.

With a promising TTP profile, the precision antibiotic candidate SMT-571 is being further developed to treat ever-challenging Neisseria gonorrhoeae infections.
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