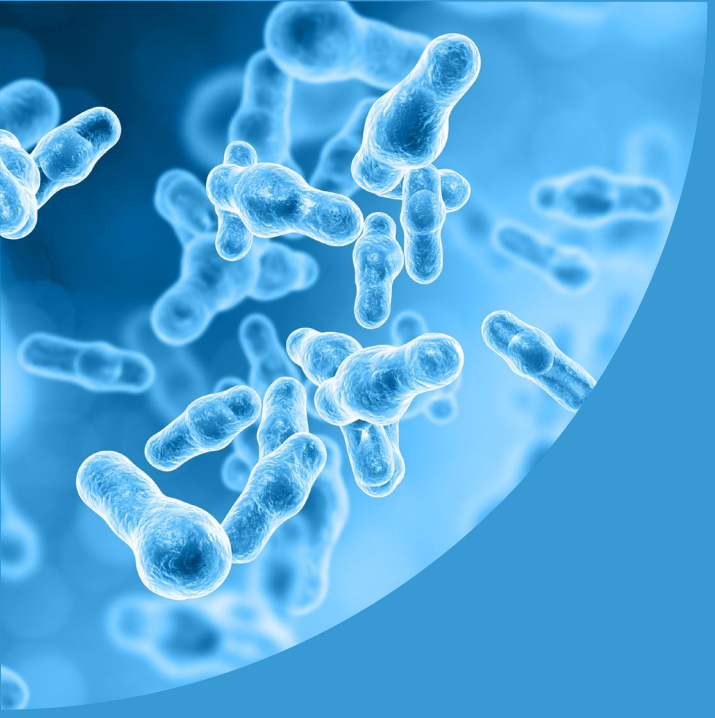


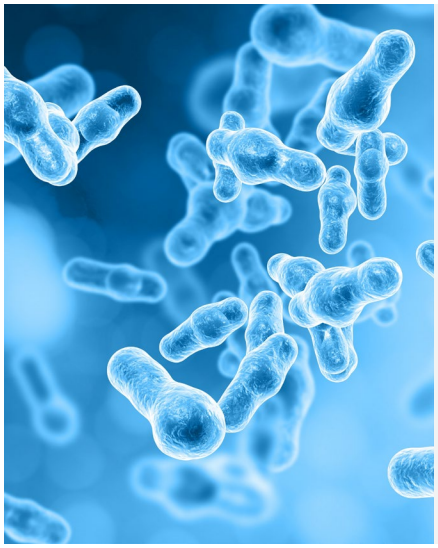
Summit therapeutics

C. difficile Infection

(CDI)

Ri-CoDIFy

CDI (*C. difficile* infection)



Est. 500,000
Cases per year in the US

Est. $5.4 billion
Annual acute care costs, with 20,000 – 30,000 deaths per year in the US

25%+ recurrence
Recurrence is a primary clinical issue in CDI, as up to 25% of initial cases of CDI result in a second episode; the risk of recurrence rises to 65% after a third episode

Urgent Threat
The highest threat designation by the US CDC; *C. difficile* is one of only four bacteria to carry that label, requiring immediate, aggressive action

C. difficile infection (CDI or *C. diff.*) is an **insidious** disease which can be **debilitating**, characterized by **watery diarrhea** and **abdominal cramping** and may be accompanied by **nausea**, **fever**, and **dehydration**. *C. diff.* can also result in more serious disease complications, including **bowel perforation** (a tear in the gastrointestinal tract), **sepsis**, and potentially **death**. It necessitates patient isolation because of its **highly contagious** nature, making it able to be passed from one person to another either in a hospital or long-term care facility setting, as well as in the community.

C. diff is a bacterial infection caused by the bacteria, *Clostridioides difficile,* that produces toxins causing inflammation of the colon. And the current standard of care is not solving the complete issue: broad-spectrum antibiotic treatment is a standard therapy for *C. diff.*, but dysbiosis of the gut microbiota due to broad-spectrum antibiotic exposure is also a major risk factor for the disease. In addition, recurrence following an initial infection is a major issue, where persistent treatment-related dysbiosis predisposes the patient to subsequent recurrence.

Ridinilazole is an investigational therapy that is being studied for the treatment of and the reduction of recurrence of *C. difficile* infection. Ridinilazole is not approved by any regulatory authority, and commercialization of ridinilazole is subject to regulatory approvals.

What is the Problem to Solve?

Clearly, *C. diff.* is a major problem that is underappreciated: it is a pernicious and insidious disease that causes an infected patient significant suffering or worse. An infected patient's immediate concern is a return to normalcy: the elimination of the cause and symptoms of their profuse watery diarrhea, painful abdominal cramping, or often severe complications that can potentially, at times, lead to death. Because *C. difficile* is a highly-contagious pathogen, isolation of the patient is required, leading to further physical as well as emotional suffering of the patient. The impact extends to society as a whole, as acute costs of care associated with cases of *C. diff.* exceed $5B annually in the US alone.

What is the Problem to Solve?

The way we *treat* CDI may be as significant of a problem. That is because, with *C. difficile i*nfection, broad-spectrum antibiotics exposure is a major risk factor for the disease. The most likely person to become infected with *C. diff.* is a person who just had the infection. Following an initial episode of *C. difficile* infection, a relentless cycle of recurrence can occur, where persistent treatment-related dysbiosis predisposes the patient to subsequent infection, having a further taxing impact on the patients, as well as additional costs for the overall healthcare economic system.

As noted in Qian *et. al.*, AJP, 2019, the standard of care, broad spectrum antibiotic for the treatment of *C. difficile* infection, can have substantial impacts on important groups of "good bacteria" that make up the healthy gut microbiome. .

Instead of finding the sought-after normalcy a *C. diff.* patient expects after a standard course of therapy, one in four patients can have one or more treatment-related episodes of this insidious, painful disease.

In that same review by Qian, *et. al.*, **ridinilazole**, was shown *not to* harm those same important groups of "good bacteria." An increasing body of evidence suggests that the health of the gut microbiome plays a critical role in reducing instances of recurrence of CDI.

Ridinilazole is our Phase 3 precision antibiotic, which is in development and testing for front-line **treatment of CDI** *and* **the reduction of recurrence of CDI**. Ridinilazole is intended to treat the first incidence of CDI, as well as those with previous episodes, and reduce the recurrence of the disease.

Broad-Spectrum Antibiotics Used to Treat *C. diff* Infection May Be a Major Problem that Leads to Significant Recurrence of *C. diff*

The standard of care for *C. difficile* infection is a broad-spectrum antibiotic, vancomycin. Broad-spectrum antibiotics are not selective for *C. diff* alone, but also kill other important bacteria in the gut, further damaging the balance of the microbiome that is so critical to our health, at times leading to a condition called dysbiosis.

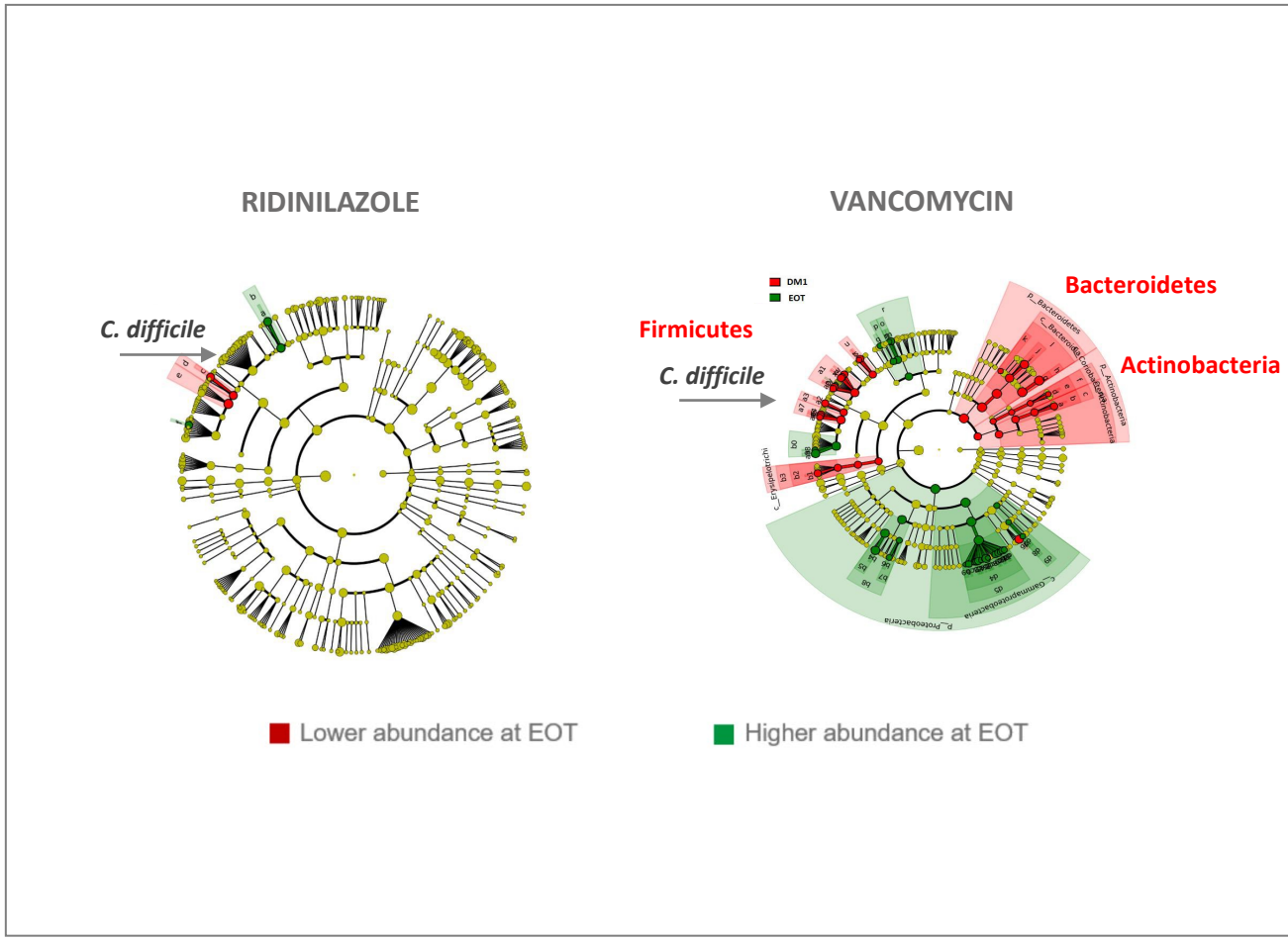
The **gut microbiome is a critical ecosystem that plays an important role in our overall health**. The microbiome consists of trillions of microorganisms that partner with our own cells throughout the body to influence functions ranging from digestion to immunity and beyond. The quantity, balance, and proportion of these microorganisms within the gut has a lot to do with its ability to perform its necessary functions.

Many of the microorganisms within the gut are bacteria: "good bacteria" such as Bacteroidetes, as well as "bad bacteria," or bacteria that can be pathogenic, such as Proteobacteria (e.g., *E. coli*). Because of the balance of the microorganisms, the presence of these bad bacteria doesn't make a person sick as they cannot overwhelm the gut; the good bacteria keep the bad bacteria in check. In a small percentage of people, *C. difficile* bacteria live within the gut, but lead to no symptoms or complications; this is because its pathogenic activity is kept in check by the rest of the microbiome. Thus, it is prevented from causing disease.

The **collateral damage caused by the use of broad-spectrum antibiotics** with their nondiscriminatory elimination of many types of bacteria is **very taxing on the patient** and may be contributing to increased risk of recurrence after treatment.

Broad-Spectrum Antibiotics Used to Treat *C. diff* Infection May Be a Major Problem that Leads to Significant Recurrence of *C. diff*

Below, the cladograms (diagrams that illustrate relative quantities, in this case, of bacteria; red indicates a reduction, green an increase) show the impact to patients' microbiomes after a course of therapy with ridinilazole or vancomycin.



On the left, we see that **ridinilazole** kills the *C. difficile* bacteria and **effectively spares the gut microbiome** from falling into dysfunction. On the right, however, **vancomycin** kills *C. diff.*, but also **substantially harms** the Bacteroidetes – good bacteria that is a critical component of a healthy, balanced microbiome and needs to be protected. This, in turn, also allows the Proteobacteria (bad bacteria) to increase in proportion as they are not all killed by vancomycin, and they are no longer held in check by the good bacteria and their related activities. This **reduces the ability of the microbiome to support the protection against overall bacterial infection, including CDI**. This imbalance of the microbiome, sometimes referred to as dysbiosis or a dysbiotic gut, can take months to return to normal – continuing to expose the patient to infection and disease, including another episode of *C. diff*.

We are Seeking to Determine if Maintaining the Integrity of the Microbiome with Ridinilazole Can Reduce the Recurrence of CDI

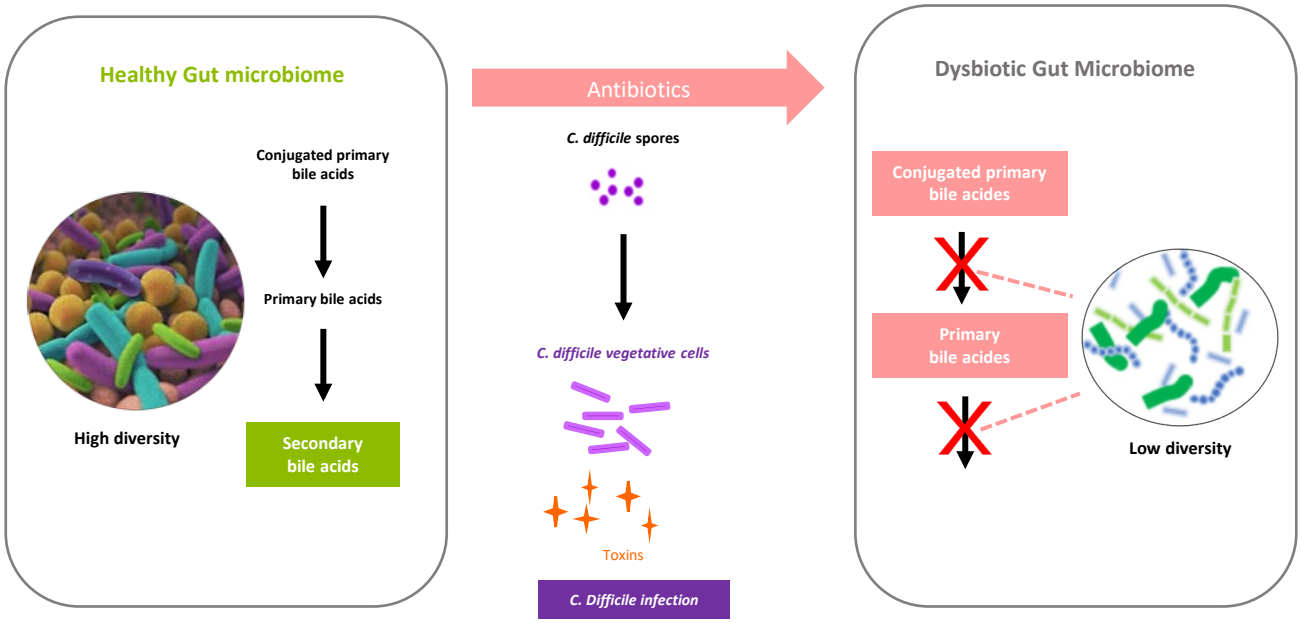
C. diff. infection most commonly occurs in patients during or shortly after a patient takes round of broad-spectrum antibiotics (antibiotics with the ability to kill wide groups of bacteria) for an infection such as pneumonia or cellulitis. The microbiome becomes damaged from the initial round of antibiotics, allowing for *C. difficile* spores to become vegetative cells that release disease-causing toxins.

Because of the lack of good bacteria, the ecosystem of the gut microbiota cannot prevent the toxins from damaging the intestinal walls, leading to CDI. The use of a **broad-spectrum antibiotic to treat the *C difficile* infection exacerbates the damage to the already-perturbated microbiome** by adding effectively a second round of non-targeted antibiotics to the gut.

A healthy diverse microbiome contains bacteria that are able to metabolize another component of the gut, bile acids. Conjugated primary bile acids are metabolized by good bacteria such as *Bacteroides* to unconjugated primary bile acids, which are subsequently metabolized further by a small number of bacterial species to secondary bile acids.

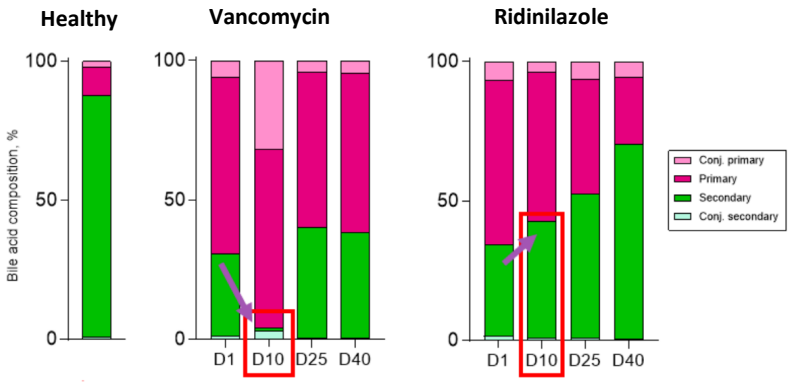
These **secondary bile acids have protective, naturally antibacterial properties which act against toxin-producing *C. difficile* bacterial cells**. Thus, **secondary bile acids have a direct effect on recurrent disease causation**, and the **protection of the bacteria that produce them is critical to recurrence reduction**.

The figure below demonstrates an example of the ecosystem nature of the microbiome: many of its components are interdependent upon one another in order for the gut to perform its wide-ranging protective functions across the human body.



We are Seeking to Determine if Maintaining the Integrity of the Microbiome with Ridinilazole Can Reduce the Recurrence of CDI

During our Phase II CoDIFy study, we found that **Ridinilazole targets the *C. diff.* bacteria**, specifically **sparing the rest of the bacterial commensals**, as shown in the charts below. The more diverse the microbiome is with its appropriate balance of its microorganisms, the better it is at performing its tasks, such as metabolizing bile acids.



As a proportion of all bile acids within the gut, a healthy person has a substantial majority of its bile acids in the form of secondary bile acids, indicating the effective metabolizing capability of conjugated and unconjugated primary bile acids. A person about to begin treatment for CDI already has a compromised gut microbiome, typically from the initial course of antibiotics therapy for an unrelated condition that caused the **dysbiotic gut and allowed for the growth of *C. difficile*** and the release of toxins that cause disease.

Through our CoDIFy Phase II clinical trial of ridinilazole, we saw that patients randomized to start either a course of vancomycin or ridinilazole each had a gut microbiome that looked roughly the same in terms of its bile acid composition. After the 10-day course of therapy, however, the results from our Phase II CoDIFy clinical trial showed notable impacts: **vancomycin nearly eradicated the gut of its naturally-antibacterial secondary bile acids**, whereas those taking ridinilazole saw the proportion of their secondary bile acids within their gut *improve during treatment*, as shown in the above charts. Simultaneously, we **saw fewer patients in our Phase II study who were randomized to ridinilazole develop recurrent *C. diff* infection (14.3%)**, as compared to those randomized to a vancomycin course of therapy (34.8%). We saw that those who experienced recurrence had statistically significantly lower levels of secondary bile acids as compared to those who did not experience recurrence.

New Opportunity

We are current engaged in our **Phase III** Program for ridinilazole. The program is designed to determine the safety and efficacy of ridinilazole for use as first-line therapy for the treatment of initial and recurrent *C. difficile* infection. The trial's primary endpoint seeks to prove ridinilazole's superiority in sustained clinical response as compared to vancomycin, seeking to provide further evidence behind the positive results from our CoDIFy Phase II clinical trial. Please visit our Clinical Trials tab for further information relating to Ri-CoDIFy, in addition to our pediatric trial, **Ri-CoDIFy 3**. The US Food and Drug Administration (FDA) has designated ridinilazole as a **Qualified Infectious Disease Product** (QIDP). The QIDP incentives are provided through the US GAIN Act and include an extension of marketing exclusivity for an additional five years upon FDA approval. We expect ridinilazole to have exclusivity through 2034 in US, Europe, and Japan. Ridinilazole has also been granted **Fast Track designation** by the FDA.

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