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CDI Market Snapshot: Microbiome Therapies Begin Descent On Landscape

by David Wild

The recent US approval of Ferring's microbiome-targeting Rebyota is set to change the treatment landscape for recurrent *Clostridioides difficile* infection and could be the proving ground for this class of agents. Rebyota is the first microbiome-targeting treatment to reach the market, but several promising candidates for the same indication are waiting in the wings.

Clostridioides difficile infection (CDI) is a billion-dollar problem that microbiome-targeted companies are keen to solve. CDI is arguably the lowest-hanging fruit for microbiome-focused companies as there is a clear rationale for treating a dysbiotic gastrointestinal tract through a microbial restoration approach, and there is a history of doing so effectively with fecal microbiota transplantation (FMT). What's more, clinicians, patients and regulators are hungry for an equally effective but safer and more palatable alternative to FMT.

Now, the US Food and Drug Administration has approved the first such therapy, giving the green light to *Ferring Pharmaceuticals*'s Rebyota on 30 November 2022 (Also see "*Ferring Makes Important Milestone For Microbiome With Rebyota Approval*" - Scrip, 1 Dec, 2022.). The agent is the first in a line of competitors seeking to enter the estimated $1bn market for CDI – as well as a range of indications beyond – and there could be two additional treatments by the end of 2023.

What the current pipeline shows is an increasingly refined approach to developing microbiome-based treatments for CDI, with improvements in convenience of administration, reductions in potential safety issues, and an enhanced ability to manufacture at scale without the need for human feces.

Recurrent C. difficile A Stubborn Clinical Challenge

The need for effective CDI management, particularly recurrent CDI (rCDI), is significant. CDI affects roughly 500,000 people in the US annually and an estimated 124,000 individuals in

Europe. The illness's human and economic toll is severe, with an estimated 30,000 related deaths annually in the US and an annual economic burden of anywhere from $796m to $6.3bn in the US and €300m in European countries.

Because CDI most often occurs after a course of antibiotics given in health care settings, it disproportionally affects the most vulnerable older individuals. The incidence of CDI is expected to rise along with an aging global population, making the introduction of more effective treatments for CDI and rCDI even greater.

The cause of hospital-acquired CDI is most often attributed to the use of broad-spectrum antibiotics, which disrupt the normal intestinal flora and open the door to resistant *C. difficile* to colonize the intestines, leading to infectious diarrhea and possibly pseudomembranous colitis. While antibiotics are the source of the problem, they are also the current mainstay of treatment for CDI. Perhaps unsurprisingly, 15-35% of CDI patients experience rCDI, defined as a re-infection within eight weeks of symptom resolution of a previous episode.

More recent clinical guidelines have introduced non-antibiotic options for treatment of rCDI, including *Merck & Co., Inc.*'s Zinplava (bezlotoxumab), a monoclonal antibody against the *C. difficile* toxin. However, the biologic comes with a price tag of roughly $4560 US per 1000 mg vial.

After demonstrating a cure rate of 80-90% in treating rCDI or refractory CDI, FMT was also inserted into clinical guidelines as a possible treatment for rCDI. However, it too comes with limitations: the treatment is most effectively performed via colonoscopy, an invasive procedure, and it costs an estimated $3,000 per treatment. Most concerning for regulators, there have been cases of lethal pathogen transmission (*See timeline below*).

Thus, increasing attention has been paid to possible standardized and closely regulated microbiome-targeted treatments for rCDI.

Is Fecal Microbiota Transplantation On Its Way Out?

300 CE

Ge Hong, a physician in the Eastern Jin Dynasty of China, describes using “yellow soup” to treat food poisoning and severe diarrhea. The soup is

administered orally.

1958

Eiseman et al. publish the first report describing use of FMT. The treatment was given to four patients with antibiotic-associated diarrhea via rectal enemas and led to prompt recovery.

1966

Luo et al. successfully treat two patients with pseudomembranous colitis using fecal enemas from healthy donors.

1978

Clostridium difficile is discovered as the cause of pseudomembranous colitis and FMT becomes known as a quick and permanent cure for associated diarrhea.

2013

- Els et al. carry out the first randomized controlled trial of FMT, showing duodenal infusion of donor feces in patients with recurrent CDI after antibiotics is significantly more effective in treating recurrent CDI than antibiotics alone.
- FMT is introduced into the American College of Gastroenterology clinical guidelines for treatment of recurrent CDI.
- FDA issues guidance stating it intends to exercise enforcement discretion under limited conditions regarding the investigational new drug requirements for use of FMT to treat recurrent CDI in patients not responding to standard therapies.

2016

FDA issues guidance narrowing its 2013 enforcement discretion to exclude stool banks.

2018

FDA cautions about the potential risk of life-threatening infections with FMT following reports of transmission of multi-drug resistant organisms causing death in one individual.

2019

FDA receives reports of two immunocompromised adults who developed invasive infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* after being administered investigational FMT. One patient dies. FDA requires screening of all donor specimens for multi-drug resistant organisms and requires use of other measures to preserve safety of stool specimens. The agency also requires that informed consent forms mention the risk of multi-drug resistant organism transmission.

2020

Another FDA missive cautions of the risk of serious or life-threatening infections with use of FMT following reports of transmission of enteropathogenic *E. coli* and Shigatoxin-producing *E. coli* in six patients after investigational use of FMT supplied by stool bank OpenBiome. FDA also requires additional protections, including use of nucleic acid amplification tests (NAAT) of both new stool and already-banked stool products for enteropathogenic and Shigatoxin-producing *E. coli*

NOVEMBER 2022

FDA finalizes 2016 guidance and approves first fecal-derived therapeutic, accelerating the market shift away from FMT (Also see "*New FDA Fecal Transplant Guidance Should Ease Ferring's Path To Commercialization*" - Pink Sheet, 29 Nov, 2022.).

Rebyota First-To-Market

On 30 November 2022, Ferring subsidiary *Rebiotix, Inc.* received FDA approval for Rebyota (fecal microbiota, live-jslm) for the prevention of rCDI in adults, when given following a course of

antibiotics.

The agent is first-to-market, but it is a less-than-perfect offering. The Phase III PUNCH study submitted as part of the New Drug Application failed to meet the specified statistical criterion that the FDA asked for, with a non-significant recurrence-free rate of 70.6% at eight weeks among Rebyota recipients, compared to 57.5% of placebo recipients. There were also more deaths in patients receiving Rebyota than placebo (Also see "*Ferring's Fecal Transplant Gets Through AdComm, Aided By Preference For Standardized Product*" - Pink Sheet, 22 Sep, 2022.).

The FDA's approval of the agent despite these limitations demonstrates the agency's eagerness to move away from FMT and its attendant risks. While Rebyota represents a step forward in that it is administered through a single enema and the company conducts thorough donor screening and testing for a panel of transmissible pathogens, the treatment still carries a risk of transmitting infectious agents since it is stool-derived.

More broadly, Rebiotix, acquired by Ferring in 2018, has developed a proprietary microbiota-based MRT drug platform for delivering human-derived microbes into the gastrointestinal tract. The company is developing another rCDI treatment, RBX7455, which is a room-temperature stable oral capsule, and that product is currently undergoing Phase III study for the treatment of rCDI, and is also being investigated for other indications.

Ken Blount, CSO at Rebiotix and vice president of microbiome research at Ferring, said that "we can easily envision 50,000 patients within the first year benefiting from this therapy, if you look at the current treatment paradigms." (Also see "*Ferring Favorite To Get First Approval For Microbiota-Based Therapy* " - Scrip, 8 Jul, 2019.)

With SER-109, A More Convenient Mode of Administration

Not far behind Rebyota on the pathway to approval is SER-109, *Seres Therapeutics, Inc.*'s lead microbiome candidate. The agent is widely expected to receive approval by the Prescription Drug User Fee Act (PDUFA) date of 26 April 26 2023.

Seres's proprietary platform focuses on uncovering consortia of bacteria that interact with host cells and tissues to treat diseases and prevent infections, CDI being one of them. However, like most microbiome-based companies, it is also extending trials to other conditions, including additional infectious and inflammatory conditions.

SER-109 has a significantly more attractive mode of administration, as it is given as an oral capsule. The product consists of purified Firmicutes spores derived from healthy donor stool and like Rebyota, still carries a risk of pathogen transmission. However, the company's manufacturing process is meant to inactivate vegetative organisms.

SER-109 has stronger data supporting its use. In the Phase III ECOSPOR 3 trial, it met its primary endpoint of reducing recurrence eight weeks after treatment, with 88% and 66% of SER-109 and placebo recipients, respectively, recurrence-free after eight weeks, and a continued benefit through 24 weeks. ECOSPOR IV, a Phase III single-arm trial of 263 patients, added some evidence, showing a recurrence rate of 8.7% at eight weeks, regardless of the number of prior CDI infections.

Enthusiasm regarding Seres's product yielded a partnership with Nestlé Health Science in July 2021, with the two companies agreeing to jointly commercialize SER-109 in the US and Canada. Nestle is providing license payments of $175m up front and an additional $125m upon FDA approval, in addition to milestone-dependent payments of up to $225m. Seres will be entitled to 50% of commercial profits as well, with HC Wainwright forecasting $315m in worldwide sales in 2023 (Also see "*Seres Banks Serious Cash To Drive Microbiome Therapy To Market*" - Scrip, 2 Jul, 2021.).

Finch Therapeutics, A Single Pill

Further down the industry pipeline is *Finch Therapeutics Group, Inc.*'s CP101, a single oral capsule consisting of consortia of microbes from healthy donors. At the core of the company's "Human-First Discovery" platform is access to granular data from hundreds of human FMT studies spanning dozens of conditions. These data are analyzed to uncover conditions that might be driven by microbial dysbiosis and to uncover key microbial dynamics associated with successful clinical outcomes.

Finch was established by two pioneers of the microbiome industry, having founded OpenBiome, a stool bank that supplies FMT specimens to clinicians, researchers and biopharma companies.

Promising CP101 data resulted in Breakthrough Therapy and Fast Track designations from the FDA and provides the basis for a 64% likelihood of approval by Biomedtracker. The agent's Phase III PRISM 3 trial found CP101 led to sustained clinical cure in 73.5% of patients with rCDI 24 weeks after treatment, compared to 59.4% with placebo at the same time. Among patients with microbial engraftment one week after treatment, 96% were recurrence-free at eight weeks. Data from the PRISM-EXT open-label extension study further supported these findings, and a topline readout of PRISM4 is expected in first half 2023.

Other Finch Therapeutics pipeline in various stages of development are targeting inflammatory bowel disease and autism spectrum disorder.

VE303 Not Donor-Derived

While Rebyota, SER-109, and CP101 are all donor-derived agents, *Vedanta Biosciences, Inc.*'s VE303 consists of a defined consortium of eight strains of live bacteria grown from pure clonal cell banks. This is a major advantage as it averts the risk of pathogen transmission that accompanies donor-derived products.

Since VE303 does not rely on human-derived stool specimens, the company can manufacture it under cGMP conditions and can easily scale up manufacturing.

The Phase II CONSORTIUM study looked at 79 patients at high risk of rCDI who were randomized to one of two doses of the orally-administered product for two weeks, or to placebo. At eight weeks, 86.2% and 56.5% of the high-dose treatment and placebo groups, respectively, were recurrence-free, which is among the highest absolute risk reduction rates for a microbiome-based treatment.

The promising results led to a $23.8m contract option from the Biomedical Advanced Research and Development Authority (BARDA), part of the US Health and Human Services' Office of the Assistant Secretary for Preparedness and Response. BARDA sees antibiotic-resistant CDI as an urgent public health threat as broad-spectrum treatment of secondary infections that might occur during an influenza pandemic, a chemical, biological, radiological, nuclear (CBRN) threat, or an emerging infectious disease can increase the incidence of CDI. The funds are being used to support a phase III clinical trial of VE303 and are part of a larger contract valued at $76.9m, to be paid out according to achievement of pre-specified milestones.

Vedanta's pipeline also includes product candidates for inflammatory bowel disease, Gram-negative infections, solid tumors and food allergy.

A Novel Mechanism Of Action With NTCD-M3

Destiny Pharma plc's NTCD-M3 (formerly VP20621) is notable for following a separate mechanistic rationale. Rather than using commensal bacteria to rebalance the gut microbiome, the treatment consists of an oral nontoxigenic strain of *C. difficile* that acts as a temporary "ground cover," colonizing the gut and crowding out toxigenic *C. difficile*. The company published Phase II data in 2015 showing the agent's promise, with a recurrence-free rate of 95% among NTCD-M3 recipients, and a Phase III trial is set to start in the second half of 2023.

Use of a single strain not derived from feces translates to a potential safety advantage, and simpler and lower-cost manufacturing.

Destiny's microbiome pipeline is not as full as its competitors and includes only one another agent aimed at preventing COVID-19 and influenza.

Microbiome Treatments A While Away in Europe

While the US market looks to be filling up gradually with microbiome-based treatments for rCDI, Europe will have to wait an estimated 5-10 years for EU-wide approval of microbiome-based treatments. The European Medicines Agency (EMA) is still developing a regulatory pathway for fecal microbiome-derived products and currently there are no microbiome therapies under evaluation by the EMA's human medicines committee. It is also unclear what therapeutic categories each microbiome treatment would fall under, with some possibly considered medicinal products, others potentially classified as Tissue and Cell products, while still others falling into the category of advanced therapy medical products, if they include genetically modified organisms.

Companies are working with European regulators to carve out a path towards approval of these agents. Destiny has reached an agreement with the EMA on the shape of its proposed Phase III development program for NTCD-M3, and Carl Bilbo, senior vice president and head of Microbiome Franchise at Ferring, said his company is in consultations to help establish European Directorate for the Quality of Medicines and Healthcare guidelines. He hopes to see a Europe-wide harmonized classification and submission pathway, given the variance in regulatory and clinical approaches to FMT-based therapies across individual countries.

Need For More Clinical Data

The approval of the first microbiome-targeting treatment opens the door wider not only for other microbiome therapeutics for CDI, but possibly for a range of other possible indications. However, as Keay Nakae, an analyst at Chardan Capital Markets, emphasized, the field remains relatively early in its development.

"There's been success in *C. difficile*, which we view as a low-hanging fruit, but there have been failures in other indications, ulcerative colitis for one," Nakae told *In Vivo*.

With relatively few microbiome treatments at the commercial stage, publicly traded microbiome companies have been under a level of financial pressure in some cases greater than the challenges the average biopharma has been facing as of late. The Catch-22 is that being low on funds could impact a company's ability to generate the kind of data that would make them more a more attractive investment target.

"What we'll need to see from the space [for these companies to fare better] is more human clinical data across the indications that the different companies are going after," said Nakae.

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