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The year the regulators meet the microbiome

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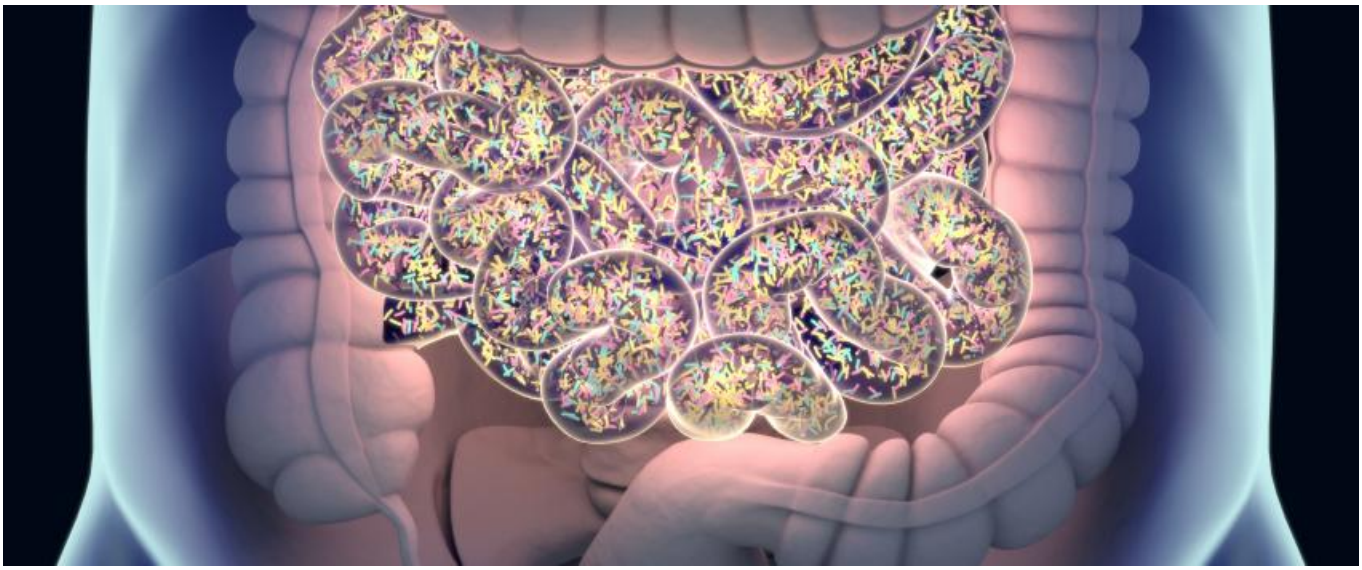

With Ferring filed and Seres preparing to do so, regulators' views on microbiome approaches to C difficile will soon be heard.

Recurrent *Clostridioides difficile* infections are a huge problem for healthcare systems, and effective solutions have been a long time coming. A phase 3 failure from Pfizer earlier this month makes it unlikely that a vaccine will arrive any time soon, and this means that microbiome approaches could reach the market first.

Ferring has already filed its enema-delivered proposition in the US, and Seres is due to follow with an oral, Nestlé-partnered project in the coming months. Full rights to the latter asset, SER-109, were secured in a substantial deal last year, though it is probably fair to say that the microbiome is still considered something of a fringe area for more traditional biopharma.

That perception could shift if another player, Destiny Pharma, manages to hook a better-known name in drug development for its phase 3-ready asset. The UK company's chief executive told *Evaluate Vantage* that he is confident a deal would be delivered by the end of year (*Destiny's date with a partner, 24 March, 2022*).

Rewilding

All the microbiome approaches in development for *C difficile* infection are based on the same idea. Toxic strains of *C difficile* can proliferate in the gut after antibiotic use and sometimes cause recurrent and very serious illness or death; *C difficile* is also incredibly infectious. Through the administration of "good" bacteria, these unwanted strains can be suppressed, allowing a patient's natural gut microbiome to be restored.

Developers claim that the projects moving through the clinic are a lot more like drugs than the faecal matter transplants that originated this approach. This is correct to some extent, although differences in the purifying and manufacturing processes, and the raw ingredients used, make it truer for some groups than others.

The three companies to have made it into phase 3 – including Finch as well as Seres and Ferring – are working on projects derived from stools donated by healthy individuals. Screening and purifying steps are taken to isolate the consortia, or collections, of bacteria to be delivered to the patients, and to inactivate potential pathogens.

The rigours of these approaches have not always impressed regulators, however. Last month the FDA slapped a clinical hold on Finch's phase 3 Prism4 trial on concerns that its donor screening protocols might be insufficient to rule out transmission of the Covid virus.

This is where projects further back in the pipeline from Destiny and Vedanta could have an advantage. These

contain defined microbial species from clonally isolated bacteria, rather than from donors. While Vedanta's VE303 contains eight types, Destiny is relying on just one bacterial strain.

These simpler approaches might be more appealing to regulators, if only from a safety perspective. Production costs should also be lower. But neither of these projects have yet entered phase 3, and it will be the consortia products from Seres and Ferring that regulators, specifically the FDA, will evaluate first.

Up first

The FDA is already reviewing Ferring's RBX2660, but the exact status of the submission is unclear. The private Swiss group told *Vantage* that it "acknowledges the submission of a BLA" but would not give any updates on the filing's timing or status.

The project, comprising mixed bacterial consortia, was originated by Rebiotix, a US biotech that Ferring bought in 2018. A large open-label study is still ongoing.

Seres is waiting for results from its own open-label trial, which are needed to complete the required safety database for a filing of SER-109. The company expects its single phase 3 trial to provide sufficient evidence of efficacy. SER-109 contains live, purified spores produced by *Firmicutes*, a naturally occurring "good" bacteria.

With phase 3 data only available on these two projects, it is hard to know whether different bacterial compositions will make a big difference on efficacy. So far, SER-109 seems to have the edge, although important differences in trial design make direct comparisons imperfect.

For example, the Ecospor 3 trial of SER-109 selected for a highly refractory population, with patients having suffered at least three recurrent *C difficile* infections in the previous 12 months, while almost half had four. In the Punch CD3 study of RBX2660, subjects only needed one or two recurrences.

Stacking up the microbiome approaches to recurrent *C difficile* infection (CDI)						
Project	**Company**	**Details**	**Status**	**Trial (setting)**	**Reduction in risk of reinfection vs control**	**% of patients with clin response (no CDI) at 8wk***
SER-109	Nestlé/Seres	Oral capsule; 4x daily for 3 days; purified *Firmicutes* spores; healthy donors	BLA planned for mid-2022	Ecospor 3 (≥3 CDI episodes within 12 mo)	Risk ratio = 0.32 (p<0.001)	88% vs 60%
RBX2660	Ferring (ex Rebiotix)	Enema; one-time dose; consortia product; healthy donors	BLA filed, status unclear	Punch CD3 (at least one recurrence after a primary episode)	Risk ratio = 0.71	70% vs 58%
CP101	Finch	Oral capsule; one-time dose; consortia product (intact microbiome); healthy donors	Prism4 on clinical hold; Prism3 (ph2) reported	Prism4 (≥3 episodes of CDI, with 2 within previous 6 mo); Prism3 (recurrent CDI)	Risk ratio = 0.79 (p<0.05)	75% vs 62%
VE303	Vedanta	Oral; ph3 dose unconfirmed; 8 bacterial clonal strains	Ph3 to start in 2022	Consortium (ph2) (post second recurrence)	Odds ratio for high dose = 0.19	86% vs 55% (high dose)
NTCD-M3	Destiny Pharma	Oral, high dose to enter ph3; one bacterial clonal strain	Preparing for ph3, in talks with licensing partners	NCT01259726 (post first recurrence)	Odds ratio = 0.28 (p=0.006)	89% vs 70%
RBX7455	Ferring (ex Rebiotix)	Oral; ph3 dose unconfirmed; consortia product, healthy donors	Ph3 stalled, details undisclosed	–	–	–
**Percentages are drug vs placebo. Source: Evaluate Pharma, company statements, publications & clinicaltrials.gov.*						

The highly refractory setting that Seres targeted is a smaller commercial opportunity than first recurrence – it has orphan drug status – but given the mortality and morbidity burden it is considered a very high need. This could shift the risk/benefit calculations for regulators.

Interestingly, however, SER-109's open-label trial does include some individuals with a first recurrence. It would be a big win for Seres and Nestlé if a broad label for recurrent *C difficile*, encompassing earlier-stage patients, were granted.

The fact that Ferring's '2660 is delivered via enema is likely to be a major commercial disadvantage, of course, and in a further blow for the company a follow-on oral project is stalled. An "unexpected issue" with third-party supplies has delayed the start of the project's pivotal Restore 3 trial, Ferring told *Vantage*, with the company denying that poor safety or efficacy were at the root of the problem.

Coming behind

Finch should be next to yield pivotal data, with Prism4 due to read out in the first half of next year. With the clinical hold still in place, however, this timeline looks certain to slip.

The private group Vedanta has pledged to move its candidate into pivotal testing by the end of the year. However, only a high dose succeeded in phase 2, where patients had to take 10 capsules a day for 14 days, clearly a big burden. No details have emerged of the phase 3 trial yet so perhaps the dosing schedule has been improved. The group has secured up to $77m in Barda funding to bring VE303 to market.

Finally, Destiny Pharma claims to have the simplest project in NTCM-M3, which contains only one strain of bacteria. But the company needs a partner to push forward.

Recurrent *C difficile* infections are thought to cause thousands of deaths a year and keep many millions in hospital, so there is clearly room for several products. Despite the undeniable need, though, this feels like a market that will face the same issues as novel antibiotics, which despite being life savers have never got support for the sort of pricing seen in cancer, for example.

Presumably this is why Seres chose to target a super-refractory setting, where arguments for a higher price could be easier to win. So while the science behind these approaches still needs proving, lack of pricing power could actually be a bigger barrier to making the microbiome mainstream.