the older patients that I would view as excellent candidates for fecal microbiota transplantation (FMT) were either screened out of the study or did not wish to participate," Hohmann says. They may not have wanted to take the risk of getting placebo instead of drug, resulting in a patient group that "might not have been sick enough," she says, which could explain a lower than expected rate of recurrence in the placebo group. "I think many of the people who ended up in the study may not have needed FMT." Fecal transplants are fast-becoming a treatment of choice for multiply recurrent *C. difficile* infections (*Nat. Biotechnol.* **32**, 401, 2014).

SER-109 is a mixture of gut flora taken from stool donors that is designed to be a scaffold, which over time, and without additional treatment, will come to resemble a normal gut microbial population, increasing the mass of the microbiome and crowding out harmful *C. difficile*. Using microorganisms as drugs may be less elegant than trying to modulate biology with a small molecule, but "if you don't know enough about the disease pathology, put the bugs in and let them do what they know how to do," says William Tanner, biotech analyst at Guggenheim Securities in New York. "If you believe FMT helps prevent recurrent *C. difficile* infections, SER-109 makes abundant sense," Tanner says, to try to restore normal gut biology. The difference between SER-109 and the administration of a fecal transplant "is not that great," he says.

Differences in patient management among the sites in the trial could also have contributed to the high overall success rate in the placebo group. "There is evidence for center-specific variability (in the trial)," Boston-based Leerink Swann analyst Joseph Schwartz said in a note to investors. "Physicians' judgment call falls on a blurry line that may have contributed to higher [placebo] response," he said. That notion is supported by a recent trial of fecal transplants that used an active microbiome control—returning participants' own microbiome-abnormal (dysbiotic) stool to them by transplantation, a sham procedure that is close to using a placebo.

In that trial, the rates of cure in the control groups varied greatly between the two study sites. Plus, a surprising number of people in both control groups got better, "which speaks primarily to the power of placebo," Hohmann says.

Seres will look at the microbiomes of the phase 2 participants before, during and after treatment to better understand the degree and type of spore engraftment observed in phase 2 and how this may have differed from the microbiome changes observed in phase 1b. The company is also eager to analyze the microbiome composition from phase 1b and compare it to samples from patients in Phase 2, using both 16S ribosomal sequencing and full shotgun sequencing. "How different microbiomes are going to engraft or morph is unknown," Hohmann says. "Seres has a great opportunity to study some of those issues," she says. Participants' age may also affect their response to SER-109. Most patients who get recurrent *C. difficile* infections are over 65, and it was in this group where SER-109 had the best effect in the phase 2 trial. The microbiome directly interdicts with the immune system and the gut-associated lymphoid tissue and people over 65 also have a microbiome senescence, Pomerantz said, adding that, "whether this is important we don't know and I'm not going to speculate."

Seres will also consider the potential effect of changes in manufacturing and dosing. The drug in the 1b trial was given in a larger number of capsules, whereas the phase 2 doses were more concentrated.

The complexity of looking at the microbiome as a biomarker is a significant factor in doing this kind of drug development—both for bacteria-derived drugs and also small-molecule modulators of the microbiome. Looking at a balance of many things and not a set of discreet things makes drug development a lot more difficult, Hohmann says.

Seres's next product is a synthetic microbiome drug made from 12 cultured microbiome species, designed for treating primary *C. difficile* infections. A phase 1 trial of that drug is open. With its sights set on synthetic microbiome drugs, the fate of SER-109 may ultimately serve to gain a better understanding of how to do discovery and development of a microbiome drug. "Maybe they are just going to use these data as science and proceed with their defined (synthetic) mixture," Hohmann says. Pomerantz recalled the industry's drug development experiences in other fields—gene therapy, immuno-oncology, the development of monoclonal antibodies in the 1980s—where the first trials led to data that made the next trials more mechanism-based and better understood. Seres's competitive advantage may lie in having proprietary knowledge—the ability to grow anaerobic bugs and having the resources to spend on applying methods to characterize the microbiome.

Seres may also be planning a dual-pricing strategy for treating *C. difficile* infections, Tanner says, charging a lower price for primary *C. difficile* infections with its synthetic drug and more for treating multiply recurrent episodes, which is a greater cost to the system, with SER-109. In the long run, he says, the failure of SER-109 may not matter much because the scope of the opportunity to understand how to manipulate the microbiome could create significant value.

Mark Ratner *Boca Raton, Florida*

Allergan enriches skin portfolio

Last month Allergan announced its plan to acquire Fort Washington, Pennsylvania–based Vitae Pharmaceuticals for $639 million or about $21 per share—a 159% premium over the autoimmune drug developer's close of $8.10 the day before the announcement. Dublin-based Allergan said that adding Vitae's lead product, VTP-43742, will strengthen the company's dermatology product pipeline. A first-in-class, oral retinoic-acid-receptor-related, orphan nuclear receptor gamma (RORγt) inhibitor for treating psoriasis and other autoimmune disorders, VTP-43742 acts by inhibiting interleukin 17 secretion from T-helper 17 cells and blocking the action of IL-23. Vitae recently completed a phase 2 proof-of-concept trial in patients with moderate to severe psoriasis with the small-molecule inhibitor, and is expected to start a larger, longer phase 2 study this year, with results due in the second half of 2017. The acquisition also adds VTP-38543, a topical liver X receptor beta (LXRβ) selective agonist currently in a phase 2a proof-of-concept clinical trial for treating atopic dermatitis, as well as Vitae's Contour structure-based drug design platform for discovering product candidates for challenging therapeutic targets. Allergan's medical dermatology franchise currently includes Tazorac (tazarotene) for acne and psoriasis, Botox (onabotulinumtoxinA) for hyperhidrosis and acne vulgaris gel Aczone (dapsone). Such treatments make up one of the drug industry's biggest markets, worth nearly $49 billion in worldwide sales last year.

"I am a believer in cell therapy. These products will most certainly save lives. Based upon what I have seen I recommend the industry remain optimistic." David Epstein, former Division head of Pharmaceuticals at Novartis, who spearheaded the company's move toward cell-based cancer treatment in 2014, including in-licensing of U Penn's CAR-T platform, comments on the company's announcement that it would be shutting down their cell- and gene-based therapy unit. (*FierceBiotech*, 6 September 2016)

"We haven't invented anything yet." Jerry Hayes, Monsanto's "honeybee health lead" points out that the company's RNAi therapy to combat the varroa mite, a vector for multiple bee pathogens, about to enter field trials, is at least seven years from market. (*Wired*, 8 August 2016)