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THE OBESITY REVOLUTION

Beyond Wegovy and Ozempic: Biotechs vie for piece of red-hot weight loss market with novel strategies

This is part of a series about new obesity drugs that are transforming patients' lives, dividing medical experts, and spurring one of the biggest business battles in years.

By Elaine Chen and Allison DeAngelis

For nearly a decade, Novartis aggressively pursued a drug candidate for muscle disorders, testing it on people with chronic inflammation, elderly people with frailty, hip surgery patients, and other groups.

Time and again, the trials failed to show that the drug, bimagrumab, led to a significant enough improvement in patients' physical function. But researchers noticed something else: The patients lost body fat.

In 2017, Novartis decided to run one more trial in people with obesity and diabetes. It found the drug caused an average loss of 21% in fat mass and also a 4% gain in lean mass — a combination that had not been seen before in any weight loss drug.

Despite the findings, Novartis set bimagrumab up for sale. Even though investors were flocking to the biotech sector, the obesity field was a drug development desert, with investment actually dropping, according to data from PitchBook. Weight loss treatments had a checkered history of being ineffective or unsafe, and the few that did make it to market were commercial flops.

But Joe Jimenez, the CEO of Novartis through much of bimagrumab's development, and some other ex-Novartis employees saw potential. They launched a new startup called Versanis Bio to license the drug in 2021.

Now, as the new weight loss drug Wegovy surges in popularity and turns



MOLLY FERGUSON FOR STAT

the industry's focus back on obesity, Versanis sees potential for bimagrumab to become a key contender in the obesity market and leapfrog competitors with its ability to build muscle.

Other startups, too, are now betting on novel mechanisms to treat obesity, hoping that their products will have a unique edge, like having fewer side effects or helping maintain long-term weight loss, that will resonate with patients and insurers.

Nick Williams, a partner at Medicxi, a venture firm that invested in Versanis, told STAT he's seeing 10 times more startup pitches with an obesity bent, compared to a few years ago. "We've seen this incredible resurgence of interest in the space, and it has also happened extremely quickly," he said.

Novo Nordisk's Wegovy, along with its similar diabetes drug, Ozempic, have jolted the obesity market awake after proving more potent and safe than any previous weight loss drug. The injectable is in a class of GLP-1-based drugs, which mimic the effects of the glucagon-like peptide-1 hormone that helps regulate insulin and hunger.

With Wegovy's success, pharma giants are racing to develop newer drugs in this class that could be taken orally, or that target more hormones. Eli Lilly, for example, has developed tirzepatide, an injectable sold as Mounjaro. It mimics both GLP-1 and another hormone, and it's shown even greater weight loss in people than Wegovy.

This class of drugs, though, often causes severe nausea in early weeks and

doesn't lead to significant weight loss in everyone. There's growing concern that in addition to fat loss, the drugs lead to muscle loss that could prove detrimental for older patients. And for most people, the costly drugs may need to be taken forever to sustain the effects.

That's where Versanis and other startups think they can offer an advantage with novel approaches. It'll be some time before it's clear whether these small players can siphon any fans from the current "it" drugs for obesity. But the growing number of companies in the space indicates how fierce the competition in the obesity market is becoming, and what options could be in store next for patients.

"Any time we see sea-change data with a particular class of medicine, you see pharma reconsider their pipeline priorities and you see biotech start to consider different mechanisms into these indications as well," Williams said.

Homing in on fat, while building muscle

Versanis' bimagrumab, which increases muscle while cutting fat, stands out because all currently available obesity drugs lead to muscle loss. In a trial for Wegovy, for example, about 40% of the weight that people lost was lean mass. Some doctors worry that elderly people taking the drug could become frailer and more vulnerable to accidents.

Bimagrumab works by blocking proteins from binding to receptors called activin type II. When certain proteins in the body bind to those receptors, they inhibit muscle growth and are thought to also promote fat accumulation.

As an added benefit, building muscle may lead to more durable weight loss.

Typically when people lose weight, their metabolism slows down. But because bimagrumab grows muscle, which burns more energy than fat, the drug may help people maintain a faster metabolism and be more resistant to weight regain, said Lloyd Klickstein, president of Versanis and a former Novartis employee who was involved in bimagrumab's development.

Data from earlier trials of bimagrumab show that people maintained weight and fat loss for 12 weeks after stopping the therapy. In contrast, people tend to quickly regain weight after they stop taking Wegovy.

The data on bimagrumab so far also show side effects included muscle spasms and diarrhea, and they occurred

early in treatment and were mostly mild.

Versanis isn't the only startup that believes it can target fat specifically. Resalis Therapeutics, a startup out of Italy, is developing an RNA-based treatment designed to inhibit microRNA called miR-22. In turn, that changes the metabolism of fatty compounds known as lipids, increases energy expenditure, and more. In preclinical studies, company executives said they saw a reduction only in fat deposits, not lean muscle. Both Versanis and Resalis are developing their drugs to be injections.

The Food and Drug Administration currently relies on draft guidance that was introduced roughly 15 years ago in approving or rejecting obesity drugs, which focuses on changes in overall weight, not muscle gain or loss. "I joke that with the FDA, it's weight loss or bust," Versanis CEO Mark Pruzanski said.

Versanis plans to push the FDA to reconsider the metrics it relies on. But for now, Versanis is using weight loss as the main endpoint for a Phase 2b trial.

"Obesity — we always talk about weight as a surrogate for it, but it's not a weight problem, it's a fat problem," Klickstein said. It seems like now, "finally, there is a drug that specifically is well-matched to the illness."

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MARK PRUZANSKI, VERSANIS CEO

Investors may be buying into the idea, but experts aren't so quickly convinced. Daniel Drucker, a professor at the University of Toronto who helped discover GLP-1, said it's too early to say if bimagrumab will offer an advantage. More data is needed, and it's also not yet clear if muscle loss on drugs like Wegovy actually poses problems for patients, he said.

"It's very early for bimagrumab, it's a very innovative observation, it's a very unique molecule," said Drucker, who has served as a consultant or speaker for companies including Novo and Kallyope. "But to me, it's not yet clear that there's a real unmet need that needs to be fulfilled."

Causing weight loss without the nausea

One of the other mechanisms that is gaining traction could help overcome a common complaint for people taking

Wegovy: nausea and vomiting. The side effects can become intolerable for some, and led about 5% of the participants in a large trial to stop taking the drug.

Wegovy takes a synthetic approach to target GLP-1 receptors and mimic the effects of the hormone, which stimulates insulin production, reduces hunger signals in the brain, and slows the emptying of the stomach, making people feel full earlier and longer.

Many obesity drug developers are following that lead. Among roughly 80 obesity treatments that are in development, over half are GLP-1-based, according to tallies by STAT and analysts at TD Cowen.

But Aphaia Pharma, a startup based in Switzerland, is developing what it calls a "natural" approach that it hopes will lead to fewer side effects.

When cells in the lower part of the small intestine are triggered with food nutrients, they're thought to release a wide range of hormones that signal to people's brains that they're full, along with other metabolic effects, said Steffen-Sebastian Bolz, Aphaia's chief scientific officer. In people with obesity, however, nutrients don't reach that area, but instead get absorbed higher up in the intestine, which also leads to high blood sugar levels, he said.

Aphaia's drug is taken orally and uses coated beads to transport glucose into the lower intestine, stimulating the cells that release hormones, including GLP-1, GLP-2, glicentin, and others. The approach is thought to be so harmless that Bolz and others at the company tried taking very early formulations of the drug years ago, he said.

The startup expects its drug to be more tolerable because it stays in the gut and stimulates natural hormone production, "only using what's already there," rather than inducing a synthetic process, Bolz said.

But because Aphaia's drug triggers hormone secretion at naturally occurring levels, it's possible it won't lead to significant enough weight loss, said Randy Seeley, director of the Michigan Nutrition Obesity Research Center, who has consulted for Novo, Lilly, and Kallyope.

Drugs like Wegovy are so effective because they introduce high levels of synthetic compounds into people's bloodstreams, Seeley said, and the compounds circulate to target receptors in different parts of the body like the brain and the pancreas.

Nonetheless, approaches similar to

Aphaia's are gaining momentum: New York-based Kallyope is also focused on stimulating natural hormones, but declined to compare its technology to Aphaia's. The company is joined by Aardvark Therapeutics, a San Diego-based startup that targets so-called bitter taste receptors in the gut that it has found trigger hormones such as GLP-1, PYY, and CCK.

Executives highlighted how these approaches mirror the effect of bariatric surgery, a procedure that makes changes to a person's digestive system and leads to weight loss. "One of the consequences of the surgery is elevated levels of multiple appetite- and glucose-regulating hormones, like GLP-1, PYY, and CCK," said Kallyope's Chief Medical Officer Brett Lauring.

Lilly and Novo are also looking at targeting other hormones such as PYY, glucagon, and amylin, but are once again focusing on synthetic versions.

Many of the startups didn't set out with explicit plans on obesity. Kallyope, which launched in 2015, didn't publicly mention any work in weight loss until 2018, when it began a research partnership with Novo Nordisk. It disclosed its own plans to develop two obesity treatments last year.

"It's been a graveyard of failed clinical programs and commercial products," said Nancy Thornberry, Kallyope's head of R&D. She had spent more than a decade working in Merck's metabolic drug unit, helping to launch blockbusters like the diabetes drug Januvia, but she also then saw pharmaceutical companies step back from the metabolic field.

"It wasn't until Novo and Lilly ... got past that magic 10% weight loss with semaglutide and tirzepatide that gave everyone a reason to believe this is doable," she said, referring to the generic drug names for Wegovy and Mounjaro.

Combining forces for greater effect

The startups face a difficult battle going up against big companies like Novo and Lilly that are already dominating the space, and have much bigger budgets — as well as a steady flow of cash coming in from commercial products.

The FDA will likely require obesity drug developers to run larger, more expensive clinical trials than for other disease areas like cancer, in part due to higher standards for safety, said Tien Lee, Aardvark's chief executive.

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NANCY THORNBERRY, KALLYOPE HEAD OF R&D

Not only that, but "the bar is now set very high" after the success of drugs like Wegovy, said Seeley, the University of Michigan obesity research director. New drugs will probably have to show at least 20% weight loss and some benefit to heart health in order to compete, he said. Novo is currently testing Wegovy to see if it protects or boosts cardiovascular health, but its underlying ingredient has already been shown to cut the risk of heart attacks and strokes in people with diabetes.

"I have seen an uptick just in the companies reaching out to me that are exploring novel approaches, and I think that's because now people understand that there's money to be made," Seeley said. "But the flipside is — now you have to put together a really good drug."

It's likely that novel drugs will have to be amenable to being taken in combination with big pharma's products, said Michael Nedelcovych, vice president of equity research at TD Cowen who covers pharmaceutical companies. It's a tried-and-true approach in oncology, a field that shifted monumentally when immunotherapies like Keytruda were introduced in the 2010s.

The Aardvark team views the combination therapy route as a pragmatic approach — there are already so many people who are on Wegovy and Mounjaro. But on top of that reasoning, one of the hormones that the biotech's drug appears to stimulate, the CCK hormone, may enhance the effect of GLP-1 to help regulate metabolism, Lee said.

The biotech also believes its drug may offset some effects of standalone GLP-1 drugs. Some research suggests that patients taking standalone GLP-1 drugs can experience an increase in another gut hormone called ghrelin, which is often referred to as the hunger hormone, and that may drive weight regain after stopping treatment, Lee said. In Phase 2a studies of Aardvark's lead drug, ARD-101, there have been signs that the treatment decreased ghrelin levels, he said.

"Like the other paradigms of treatment, it'll ultimately require a cocktail for optimal response," he said. "Right now, there seems to be more interest in terms of chasing next-generation GLP-1s, but

there's a lot more beyond that in terms of facilitating therapeutic benefit."

Resalis, the Italian startup targeting miR-22, is also testing its drug in combination with semaglutide. So far, it's finding the combination leads to better weight control over time in preclinical trials. Executives attribute it to the fact that, while semaglutide dampens appetite, leading to a quick drop in weight, Resalis' lead drug, RES-101, is rewiring metabolism and energy expenditure.

CEO Alessandro Toniolo likened it to how medical professionals treat inflammatory diseases today: Physicians used to rely on painkillers to numb the discomfort of rheumatoid arthritis and other inflammatory diseases, but can now prescribe medications that address the underlying biological problems behind the conditions. But many still prescribe both, to address patients' short- and long-term needs.

"The market will become more and more crowded, so I think the time is now to develop something orthogonal to GLP-1s," Toniolo said. Resalis hopes to start clinical trials next year.

Versanis is also currently running a nine-arm study testing its drug, bimagrumab, alone and in tandem with semaglutide. Because it works differently than drugs like Wegovy — targeting fat and muscle cells, not hormone receptors — executives anticipate that pairing two drugs will lead to greater and longer-term weight loss.

The company expects to report topline data from that trial, dubbed BELIEVE, by mid-2024 and be ready for a Phase 3 trial by 2025. For Versanis to get to this point, "a lot of it was luck, but a lot of it was having the conviction that this drug could work in obesity and not really caring about the fact that the rest of the world didn't really want to invest in obesity," said Jimenez, the former Novartis CEO.

It's yet to be seen if any of these startups will make it to market and succeed. But if they can catapult themselves into the fray, it would signal that the success of Wegovy and Mounjaro wasn't just a fleeting trend.

"The marketplace needs to be built first for these biotechs to have a prayer," said Cowen's Nedelcovych. "Having a thriving obesity marketplace, even if it is dominated by large competitors, is probably a better thing for a small company as long as they have a differentiated offering."