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05 Dec 2023 | **Analysis**

Time For Oral Incretins To Prove Their Worth

by Elizabeth Cairns

Several crucial trial readouts in diabetes and obesity will come this year and next, and the stakes are high.

Pfizer Inc.'s decision late last week to shelve the twice-daily form of its oral GLP-1 danuglipron means the US giant has slipped down the rankings of companies trying to bring oral forms of incretin drugs – the wildly successful therapies for diabetes and obesity – to market.

And this week a new player entered this space: *Roche Holding AG* obtained a Phase I-stage oral incretin, CT-996, through its acquisition of *Carmot Therapeutics Inc.* yesterday. (Also see "*Roche Looks To Muscle Into Obesity Market With $2.7bn Carmot Buyout*" - Scrip, 4 Dec, 2023.) But several companies are ahead of Roche. As so often in the metabolic space the charge is led by *Novo Nordisk A/S* and *Eli Lilly and Company*, but another group, *Structure Therapeutics, Inc.*, will be the next to reveal crucial data, with a Phase II readout coming in the next few weeks.

Key Takeaways

- Several groups, including recent entrants Roche and AstraZeneca, are pursuing oral incretins for diabetes and obesity
- Novo Nordisk and Lilly are the most advanced in this space
- But the next few months will see important data on at least eight others

Novo has the first and only oral incretin on sale. Rybelsus, a once-daily pill formulation of the GLP-1 agonist semaglutide, was approved for diabetes in 2019 and the group is now devoting great effort to getting the drug approved for obesity too.

Novo is waiting for data from the final study in the OASIS program before seeking approval in obesity. Data from the OASIS-4 study, examining a 25mg daily pill, ought to arrive in the first

half of next year. If weight loss and side-effects are acceptable – and a 50mg dose has already hit these benchmarks – Rybelsus could be approved for obesity a year or so later, though probably under a different brad name.

How successful it might be is a different question. Rybelsus's launch for diabetes was initially fairly slow, though admittedly the COVID-19 pandemic arrived almost immediately. And the pills must be taken carefully: on an empty stomach, and patients must wait at least 30 minutes before having their first meal or drink of the day or taking other oral medicines. Presumably these restrictions would also be in place for Novo's obesity equivalent.

Still, Rybelsus is forecast to sell $2.6bn this year and some of that is almost certainly off-label use for obesity.

Novo's great rival, Lilly, has taken a different tack. It has not developed an oral form of its blockbuster subcutaneous incretin tirzepatide, a GIP/GLP-1 agonist, instead developing an oral single-mechanism GLP-1, orforglipron.

Orforglipron is currently in no fewer than eight Phase III trials: four in diabetes, two in obesity and two in patients with both disorders. In all, more than 10,000 patients have been enrolled across these trials, all of which are scheduled to complete in 2025. Interim data from some of them could come next year, but it would be unwise to bet on orforglipron's approval for either indication before 2026. According to consensus data from *Evaluate Pharma*, the sellside forecasts orforglipron sales of $1.3bn in diabetes and $525m in obesity by 2028.

It is not clear why Lilly opted for this molecule over an oral form of tirzepatide. This might be because Lilly believes that the dose required might be such that the side effects are different from the injected form. Alternatively, it could be related to manufacturing, if the GIP/GLP-1 combo is more difficult to synthesize. Another theory is that production is simply too expensive: tirzepatide must be made via chemical synthesis, whereas semaglutide is made in yeast recombinantly, a cheaper process.

Imminent

The next most advanced product comes from Structure Therapeutics. Its lead product, the peptide GLP-1 GSBR-1290, is in a Phase I/II trial in obese or overweight patients with type 2 diabetes, and topline data from the Phase IIa diabetes cohort are imminent.

In the Phase I, 28-day multiple ascending dose part of the trial, GSBR-1290 yielded a dose-dependent reduction in weight, with statistically significant placebo-adjusted weight loss of 4.9% at the highest dose of 90mg with weekly titrations. Treatment-emergent adverse events were mild to moderate, and no discontinuations or down-titrations due to adverse events were reported.

This weight loss looks modest compared with the 15% Rybelsus achieved in its Phase III OASIS-1 study. But OASIS-1's data came at 68 weeks – around 1.3 years – and the GSBR-1290 data came after just a month's treatment. On the other hand, just 22 patients were treated, 17 with Structure's incretin, so the finding is not enormously robust.

Topline data from the Phase II obesity cohort of the GSBR-1290 study are due in the first half of 2024.

Swiss biotech *BioLingus AG* is developing not an oral but a sublingual formulation of a GLP-1 – liraglutide, the same molecule in the subcutaneous diabetes drug Victoza, sold by Novo Nordisk. A Phase I/II trial in patients with type 2 diabetes could report next year, and in the meantime BioLingus hopes to go public, having filed for a $47m NASDAQ IPO.

Two recent deals are also worth noting. The main asset Roche obtained on Monday by buying Carmot for $2.7bn is CT-388, a once-weekly injectable GIP/GLP-1 which has shown promise for obese patients with or without type 2 diabetes in Phase I (Also see "*Roche Looks To Muscle Into Obesity Market With $2.7bn Carmot Buyout*" - Scrip, 4 Dec, 2023.). But the deal also gets Roche CT-996, an oral GLP-1 currently in a Phase I trial in overweight/obese patients and patients with type 2 diabetes. Data could come in a year or so.

And less than a month earlier, *AstraZeneca PLC* had taken a license to ECC5004, *Eccogene (Shanghai) Co., Ltd*'s once-daily peptide GLP-1, paying $185m upfront (Also see "*AstraZeneca Moves Into Obesity With Eye On Combinations*" - Scrip, 9 Nov, 2023.). Astra does not just intend to move this forward in diabetes and obesity; it also has a plan to combine the therapy with an oral PCSK9 inhibitor as a therapy for high cholesterol.

The Future

All these mid- and late-stage programs are years from market, of course, and the risk for their developers is that Novo and Lilly will by then have sewn the oral market up, just as they largely have the subcutaneous space. So how might the future look?

Bill Coyle, global head of biopharma at the consultancy ZS, said that as the supply of incretin drugs finally grows enough to satisfy demand, price might play a part in market positioning.

"As more and more assets come to the marketplace, one of the grounds for competition might be price," he told *Scrip*. "Some of the later entrants, which could include orals, might target a lower price."

Other factors could play a role. "Maybe you pay premiums for the drugs that have shown cardiovascular outcomes," he said. "Perhaps you see a premium for drugs with higher efficacy. Perhaps in the future, if there's drugs with [milder] side effects, perhaps you see a premium for

that."

First, though, these assets will have to prove themselves in the clinic, and the next readout to watch for will come from Structure.

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