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Lilly and Pfizer fight for new territory in obesity and diabetes

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Both developers lay out ambitious plans for oral projects to rival injected GLP-1s, while Lilly strives to build on Mounjaro.

Lilly's Mounjaro is unrivalled when it comes to promoting weight loss, an attribute that is likely to make this GIP/GLP-1 agonist one of biopharma's best-selling drugs. The developer this week laid out plans to do better still, firing the starting gun on pivotal development of two novel diabetes and obesity agents and signalling a substantial ramp in R&D spend.

Retatrutide, also known as triple G, is a tri-agonist that the group reckons could push weight loss into the mid-to-high 20% range and prove highly effective at dissolving liver fat; the untapped Nash market is clearly in its sights. The second asset is orforglipron, an oral GLP-1 agonist with the potential to be just as effective as injected drugs against this target, Lilly executives forecast.

Pfizer also threw its hat into this ring at an R&D update this week, detailing two oral GLP-1 projects, one of which it will take into phase 3. This will not happen until late 2024 at the earliest, forcing executives to brush off concerns about how late the big pharma would come to this market.

There is plenty to play for, in Pfizer's eyes. The company expects the GLP-1 space to be worth $90bn in sales by 2030, and reckons it can take a $10bn slice with an oral agent. This implies a much bigger market than current expectations: based on consensus sellside forecasts, *Evaluate Pharma* shows the incretin market, as this is also known, being worth around $50bn by 2028.

The Pfizer number is not far off the $100bn that Bank of America recently estimated Mounjaro could be make in 2032, if it gets approved in all the settings that Lilly is gunning for. This suggests that many see a big market out there, for whoever succeeds. Amgen is another contender, with plans to put a GLP-1 receptor agonist/GIP receptor antagonist into phase 2.

A separate consideration for Pfizer is whether it can really compete here without an injected product, with greater efficacy, to round out its offering. On a call executives did not rule out adding such a product. If the orals progress successfully, watch this space for business development, perhaps.

Sitting duck?

When it comes to oral agents both Lilly and Pfizer are taking aim at Novo Nordisk's Rybelsus, the only oral GLP-

1 currently available for type 2 diabetes. Despite a strict administration regimen – the once-daily drug must be taken on an empty stomach with a specific amount of water – sales are seen hitting almost $6bn by 2028, according to *Evaluate Pharma*.

Such dosing requirements will not be necessary with their agents, Lilly and Pfizer contend. Both also aim at obesity, thanks to signs of much greater weight loss than with Rybelsus. This still has to be shown in phase 3, of course, although early data released by both companies are promising.

Lilly said it had almost completed orforglipron's phase 2b programme, and presented "estimated" data at an investor update that look competitive with Novo Nordisk's Wegovy. This contains semaglutide, a GLP-1 agonist that forms the active ingredient of the Danish group's incretin franchise.

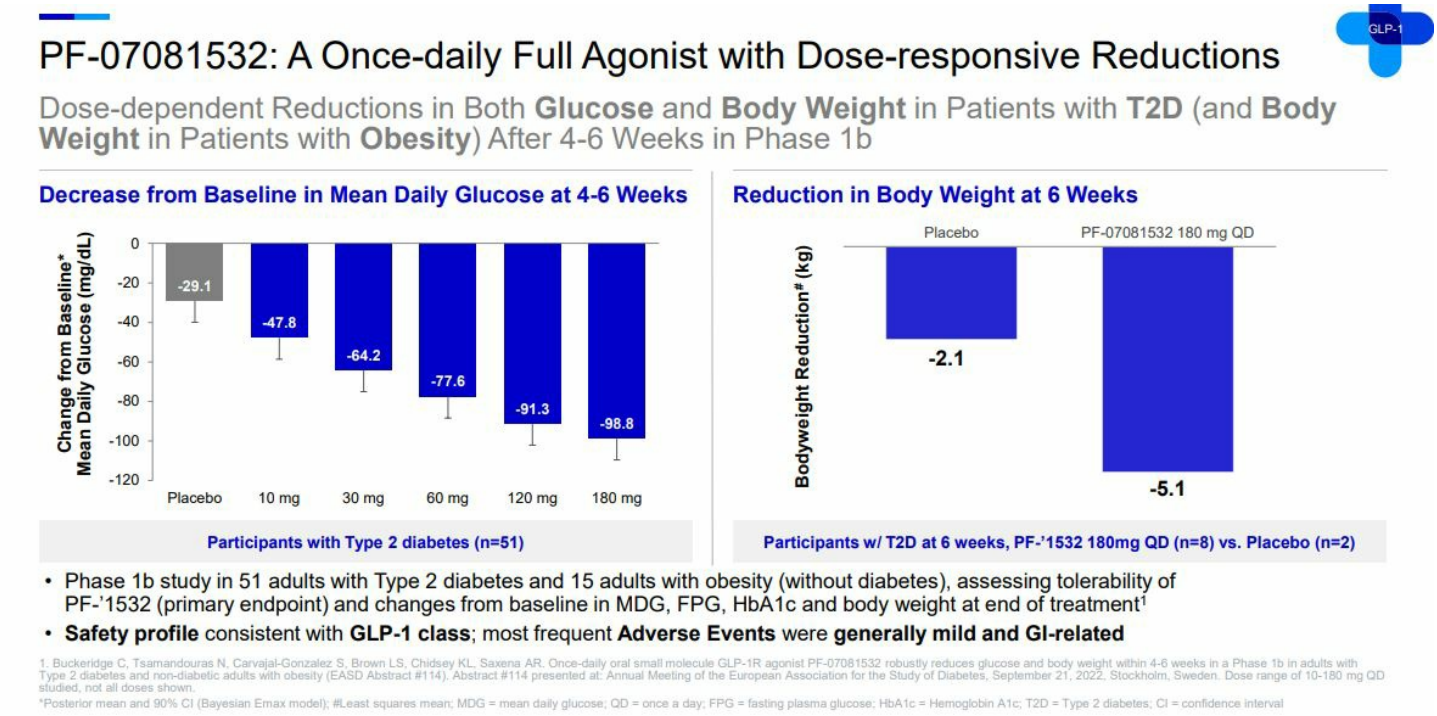
Stacking up Lilly's new contenders: cross-trial comparisons

	Orforglipron (at week 36, oral)	Retatrutide (at highest dose, injected*)	Mounjaro (injected**)	Wegovy (at week 68, injected)	Rybelsus (at week 26, oral)
Weight loss in obesity	~14-15%	~22-24%	15-21%	15%	-
Weight loss in T2D	up to 9.6%	~15-17%	6.3-7.8%	9.6%	3-4%
HbA1c reduction in T2D	up to 2.1%	~2%	1.7-1.8%	-	1.2-1.4%

*Notes: *at 48 weeks for obesity, and 36 weeks for T2D; **at week 72 for obesity, and week 40 for T2D. T2D = type 2 diabetes. Source: Lilly presentation, NEJM & drug labels.*

Pfizer said this week that it would only move forward with oral projects in this space and, like Lilly, it reckons it can beat Rybelsus and match the efficacy of injected GLP-1 agents. The two agents in contention are danuglipron, dosed twice daily and on which some data have previously been released, and PF-07081532 once a day. Both looks similar at this stage, although data are very early.

Pfizer must hope that PF-07081532 wins out – it is hard to believe that a twice-daily offering has much of a commercial future. Either way, both generated weight loss of more than 5kg at six weeks; this is better than Rybelsus, which promoted 2-4kg at 26 weeks, though Lilly's orforglipron is probably already the target here.



Source: Pfizer investor presentation.

In terms of efficacy, however, it will take another combination product like Mounjaro to provide a further "step change in efficacy", as Lilly described it.

Phase 2b data with retratrudide show weight loss pulling away from the trajectory seen with Mounjaro, Dan

Skovronsky, Lilly’s chief medical officer, said, “which gives us some degree of confidence we can exceed that in phase 3”.

For now, this project is not being taken forward in type 2 diabetes, although that has not been ruled out, Lilly said. The company highlighted its activity against liver fat which suggests a push into diseases like Nash and NAFLD, settings with huge potential but where developers have struggled.

Weight loss in the upper 20% range would certainly be a game changer, but safety will have to be very closely watched as studies progress. The company already highlighted increases in heart rate seen with retratutide.

A final question here is what Novo Nordisk is doing about all this. The group is for now the biggest player in the incretin market, but some huge Mounjaro forecasts put that under threat – some banks are pencilling in $30bn by 2030 for the Lilly drug.

Novo is developing its own combination, cagrisema, which is also moving into phase 3, and it has a couple of oral projects in early development. Consensus for sales of Ozempic, its injected GLP-1, are $16bn for 2028. That is a big number to protect, and the Danish group's investors will be keen to see pipeline progress next year.