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Will Novo’s big thinking in obesity pay off?

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Novo Nordisk has high hopes that obesity will become a major source of sales, and data on the company’s most promising projects are looming.

A sideways shift into obesity is a logical move for diabetes companies, particularly those with substantial GLP-1 agonist franchises, which have a proven metabolic impact. Novo Nordisk is the biggest player here, and has led the drive to push these drugs into the weight loss space – but the company's ambitions extend beyond this mechanism.

In the coming months several mid-stage projects are slated to yield data that variously promise to suppress appetite or increase energy expenditure; Novo believes that a combination approach will ultimately be needed to match the sort of reductions that can be achieved through bariatric surgery. The biggest pending readout is from the pivotal Step programme with semaglutide, the company's newest GLP-1 agonist, which could well form the backbone of any treatment regimen.

Phase II trials suggest that semaglutide can produce double the level of weight loss seen with liraglutide, Novo's older GLP-1 agonist, marketed in obesity as Saxenda. Saxenda is associated with 5-7% weight loss, while bariatric surgery has been shown to help patients lose 12-45% of their body weight, over three years.

Despite bestowing what appears to be a marginal benefit Saxenda, which was launched in 2015, had a 55% share of the global obesity market at the end of 2019, Novo claims. The product generated revenue of $852m last year, and the company aims to double its obesity sales by 2025. This target will be much more easily hit if semaglutide raises the game.

Data from four late-stage studies in the Step program are expected around the middle of the year. Novo has not indicated that the coronavirus pandemic has changed this timeline, noting recently that no significant delays are expected in trials already close to finalisation.

The pivotal programme tests once-weekly subcutaneous injections of 2.4mg of semaglutide. Previously in a phase II study a 0.4mg daily dose of semaglutide produced 16.2% weight loss after one year, an effect that did not show signs of plateauing. The most common adverse events were dose-related gastrointestinal symptoms, primarily nausea, something to watch for with the higher dose used in the Step program.

Bernstein analysts have written that 12% or greater weight loss would be ideal in the phase III studies, and they assume that Novo will use its priority review voucher to get semaglutide on the market as soon as possible before the Saxenda patent expires in 2022/23.

Approaching obesity readouts for Novo Nordisk					
Status	**Product**	**MoA**	**Clinical study**	**Study details**	**Data expected?**
Phase III	Ozempic (semaglutide)	GLP1 receptor agonist	Step 1 NCT03548935	Weight management: semaglutide 2.4mg vs placebo (n=1,950)	Mid 2020
			Step 2 NCT03552757	Weight management in type II diabetes: semaglutide 1mg, 2.4mg vs placebo (n=1,200)	
			Step 3 NCT03611582	Maximising weight loss: semaglutide 2.4mg + intensive behavioural therapy vs placebo (n=600)	
			Step 4 NCT03548987	Maintaining weight loss: semaglutide 2.4mg then placebo controlled phase (n=900)	
			Select NCT03574597	Cardiovascular outcomes trial, up to 2.4mg semaglutide (n=17,500)	2024
Phase II	AM833 (NN9838)	Amylin receptor agonist	NCT03856047	Dose ranging: 5 x AM833 doses, vs placebo and Victoza, primary endpoint change in body weight at week 26 (n=706)	H1 2020
Phase I	GG-co-agonist 1177 (NN9277)	GCGR & GLP-1 dual agonist	NCT03308721	Safety study, vs placebo (n=99)	H1 2020
	Tri-agonist 1706 (NN9423)	GLP-1 & GCGR & GIP tri-agonist	NCT03661879	Safety study, vs placebo (n=60)	H1 2020
	LA-GDF15 (NN9215)	GDF 15 agonist	NCT04010786	Dose escalating safety study (n=84)	H2 2020
	AM833-sema 2.4	GLP1 receptor agonist + amylin receptor agonist	NCT03600480	Dose escalation study with mainly safety endpoints (n= 96)	H2 2020
	PYY 1875 (NN9775)	Appetite-regulating hormone, PYY analogue	NCT03707990	Dose escalating safety study, mono and + semaglutide (n=88)	Primary completion was Aug 2019
Sources: EvaluatePharma, clinicaltrials.gov					

If semaglutide lives up to expectations it could provide a big improvement on currently available therapies. However, Novo ultimately wants to be able to offer a result closer to that seen with bariatric surgery, which, despite having very successful results, is a complex intervention that carries risks, and tends to be restricted to severly obese patients.

Getting up to 30-40% weight loss will involve adding in another mechanism, although of course these have to prove themselves in monotherapy first. One of the company's biggest hopes involves targeting amylin; AM833 is a long-acting human amylin analogue that in phase I demonstrated around 7% weight loss over eight weeks. A phase II dose-ranging study is expected to report in the first half of the year, and Saxenda is used an active comparator.

Other groups have had little luck in targeting amylin, including Amylin Pharmaceuticals with pramlintide,

whose development in obesity was discontinued in 2011. Previously Novo's chief science officer, Mads Krogsgaard Thomsen, told *Evaluate Vantage* that Novo had made improvements to AM833 that should help avoid the nausea seen with pramlintide.

The real potential of this mechanism could be revealed in a trial that combines semaglutide with AM833, a regimen that could generate weight loss of at least 25%, according to Mr Thomsen. A phase I combination study is due to report in the second half of the year.

Semaglutide and AM833 both serve as appetite suppressors, as do Novo's two phase I candidates LA-GDF15 and PYY 1875. Boosting energy expenditure is the other side of the coin, and this is where Novo's GLP1/glucagon-targeting doublet, and its triplet, which adds a GIP agonist, come in.

Still, as these are very early projects it is not entirely clear whether Novo will say much about the results from ongoing trials, as these are probably not considered material to the group as a whole. Progression into larger studies might be the best indication that signals have been seen.

Semaglutide is a different story, of course, and the Step readout is one of the biggest events on Novo's horizon. The sellside already has high hopes: the product is projected to become market leader in obesity by 2024, according to *EvaluatePharma.*

Biggest obesity drugs by 2024

Product	Company	Mechanism of Action	Approval in obesity	2024e obesity sales ($m)	Placebo-adjusted weight loss in pivotal trial
Ozempic (semaglutide)	Novo Nordisk	GLP-1 agonist	-	921	Step program due mid 2020
Saxenda (liraglutide)	Novo Nordisk	GLP-1 agonist	2014	823	3.7-5.2% at 56 weeks
Alli	Glaxosmithkline	Lipase inhibitor	2007	176	3% at 1 year
Qsymia	Vivus	Adrenoceptor agonist	2012	80	3.5-9.4% at 1 year

Source: EvaluatePharma; product labels.