Evaluate Vantage

December 14, 2018

Novo hopes slimmed-down bet can still win in obesity

Madeleine Armstrong

Novo Nordisk is determined to dominate obesity, but two discontinuations hint that the ride might be rocky.

Novo Nordisk knows that if it is to continue to grow it needs to be more than just a diabetes company. But obesity, the area the Danish group is focusing on after diabetes, makes for a difficult bet.

There is no doubt that obesity is a growing problem worldwide, and any drug company that cracks this would be guaranteed huge sales. But this might be easier said than done. Current obesity drugs, including Novo's own Saxenda, leave much to be desired, and the group will need better performance with its new projects if it is to achieve its obesity ambitions.

Illustrating just how tough obesity is, in August Novo discontinued two projects that it had previously talked up as potential contenders: the FGF 21 analogue NN9499 and the glucagon analogue G530L (*Interview – Novo fattens up its obesity pipeline, 7, 2018*).

Novo's clinical-stage obesity pipeline			
Project	**Mechanism**	**Obesity impact**	**Status**
Semaglutide (injectable)	GLP1 agonist	Appetite reduction	Phase III
AM833*	Amylin analogue	Appetite reduction	Phase I
GG-co-agonist 1177/NN9277	Glucagon and GLP1 co-agonist	Appetite reduction + energy expenditure	Phase I
Tri-agonist 1706/NN9423	Glucagon, GLP1 and GIP tri-agonist	Appetite reduction + energy expenditure	Phase I
PYY1562/NN9747*	Peptide YY analogue	Appetite reduction	Phase I
PYY1875	Peptide YY analogue	Appetite reduction	Phase I
G530L/NN9030	Glucagon analogue	Energy expenditure	Discontinued
NN9499	FGF 21 analogue	Energy expenditure	Discontinued
**Being tested alone and in combo with semaglutide. Source: Company website.*			

The company now seems to be pinning its near-term hopes on a combination of its diabetes therapy semaglutide and an amylin analogue, AM833 – but it has other irons in the fire, including a GLP1/GIP/glucagon tri-agonist.

Novo's chief science officer, Mads Krogsgaard Thomsen, admitted that the weight loss seen with Saxenda, the group's marketed obesity drug, was "not phenomenal". Saxenda uses the same active ingredient as Novo's diabetes drug Victoza but at a higher dose.

"Today's medications can only do around 10%, including our own Saxenda," he said in a face-to-face meeting with *Vantage* this week. Novo is aiming for a result closer to that seen with bariatric surgery; this can produce 30-40% weight loss, but is drastic and restricted to the most obese patients.

Step up

It looks unlikely that the company will hit this target with its most advanced obesity project, semaglutide; the drug is already approved in diabetes as Ozempic, and Novo is testing a higher dose in obesity, with the first data due from the pivotal Step programme in 2020.

Mr Thomsen expects weight loss of around 15% with sema, double that seen with Saxenda but still not enough to rival bypass surgery.

Getting this number higher might require a combo approach, and Novo is already planning to add the amylin analogue AM833 into the mix. Like sema, this project works on the appetite reduction side of the obesity equation, but other groups have had little luck in making this mechanism work, including Amylin Pharmaceuticals with pramlintide.


Novo's chief science officer, Mads Krogsgaard Thomsen

Mr Thomsen believes that a sema and AM833 combo should produce weight loss of at least 25%. It could be a while before this is put to the test: Novo has already carried out a phase I multiple dosing trial of AM833, but still needs to do this with the combination, and he would not say when the project might go into phase II.

He contended that Novo had made improvements to its molecule that should help avoid the nausea seen with pramlintide. Nevertheless, this might still be an issue with AM833, he admitted: “So far in the animal models AM833 has shown mostly GI side effects, and it seems to be at least as tolerable as GLP1.”

Sema itself has struggled with nausea, and any magnification of this with the sema/AM833 combo or might scupper the project’s chances. But Mr Thomsen noted that the 10% dropout rate seen with sema was similar to that with the diabetes stalwart metformin. “People tend to forget that.”

Two down

To get around this problem Novo will perhaps need to look at the other side of the obesity equation: increasing energy expenditure. But this approach has also been fraught with difficulties, a case in point being the notorious Fen-Phen, which was brought down by the cardiovascular toxicity of its fenfluramine component.

And Novo has not had much luck here either: the two projects it discontinued in August were designed to increase metabolism. At the time the company said there had been no safety issues with either candidate.

For the FGF 21 analogue NN9499, at least, the reason was more prosaic, Mr Thomsen said: “We boosted energy expenditure, but patients started eating more.” However, the project might still have life in other indications such as Nash, he added. Bristol-Myers Squibb already has an FGF 21 inhibitor, BMS-986036 or ARX618, in phase II for Nash.

This kind of approach might only work when combined with appetite-suppressing drugs – something Novo is attempting with its GLP1/glucagon-targeting doublet, and its triplet, which adds a GIP agonist.

Lilly has a GIP/GLP1 dual agonist LY3298176, which recently posted promising data from a phase II diabetes trial, including impressive weight loss.

Mr Thomsen brushed off questions about the potential threat from LY3298176. “In terms of obesity Lilly isn’t further ahead,” he said. “They’ve shown an interest in going into obesity, and I hope they will. It would be advantageous for society to have more than one big company in obesity.”

As for the future, Mr Thomsen highlighted a project targeting GDF15 as “a very exciting molecule that will enter the clinic. It’s a very different mechanism of action.” However, this also appears to work via appetite suppression.

Novo hopes that, one day, it will develop products that change the body’s “set point” for weight; this differs between individuals, and helps explain why some people find it difficult to keep weight off. The Danish group is working with an unnamed biotech on this project, but Mr Thomsen would not give any more details.

Such a drug is probably 20 years away from the market. Investors will want to see some pay-off in the shorter term if Novo is to justify its push into obesity.

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Evaluate HQ
44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754