SCRIP
CITELINE COMMERCIAL

14 Jul 2023 | **Analysis**

Obesity Market Potential Is Huge, But Access To Drugs An Increasing Challenge

Novo's SELECT Readout For Wegovy May Answer Payer Questions

by Mandy Jackson

Despite double-digit weight loss across several drugs presented at ADA, experts note access to obesity therapies will be constrained without outcomes data to justify their widespread use and cost.

While the GLP-1 agonists have been hailed for their double-digit percentage weight reductions in clinical trials presented at the recent American Diabetes Association (ADA) annual meeting, data on how significant weight loss can improve or prevent cardiometabolic comorbidities may be what is needed to improve payer coverage. Given the numbers of people eligible for treatment and the costs of new medicines, there are growing concerns that many who could greatly benefit from obesity drugs will not be able to access them.

Accessibility already is a problem for *Novo Nordisk A/S*'s Wegovy (semaglutide), which the company has struggled to manufacture at a pace that keeps up with demand. The US Food and Drug Administration approved Wegovy – a higher-dose version of the injectable GLP-1 agonist Ozempic (semaglutide) for diabetes – for obesity in 2021 and the drug launched at a wholesale acquisition cost (WAC) of $1,297 per year. (Also see "*Novo Nordisk Hopes To Gradually Build US Access To Obesity Therapy*" - Scrip, 7 Jun, 2021.) Novo could have an oral version of semaglutide on the market for obesity in 2024, pending US and EU filings for oral semaglutide later this year, but the timing of its launch may depend on whether the company's manufacturing for injectable semaglutide can catch up with US demand.

Cardiovascular outcomes data may go a long way to justifying the cost of chronic treatment with obesity therapies in a large patient population that mostly has

With Competition Closing In, Novo

SCRIP
CITELINE COMMERCIAL

gone without pharmaceutical options. The SELECT cardiovascular outcomes trial (CVOT) of Wegovy, from which results are expected within the next few months, will go a long way to boosting the drug's profile, Novo executive vice president of development Martin Lange noted in a recent interview with *Scrip* (*see sidebar*). The CVOT data may also provide needed evidence for why weight loss induced by a GLP-1 agonist is worth widespread use.

Details Oral Semaglutide Weight Loss At ADA

By Mandy Jackson

25 Jun 2023

Novo's oral semaglutide generated 15.1% weight loss at 68 weeks in the Phase IIIa OASIS 1 study, but Lilly's orforglipron provided up to 14.7% weight loss at 36 weeks in Phase II without reaching a plateau.

Read the full article here

Lange said SELECT "has the potential to become a landmark study. We still see a lot of biases around obesity and having interventional data suggesting that we can improve outcomes in these patients will basically inform the dialogue much better." He asserted that SELECT could help change the way obesity is discussed in health care systems in the way that the United Kingdom Prospective Diabetes Study (UKPDS) changed the dialogue around type 2 diabetes almost 40 years ago. UKPDS was designed to show how improved glucose control reduces diabetes complications.

"The next important data readout in obesity is Novo Nordisk's SELECT study in mid-2023 (based on NVO's guidance), which could show a survival benefit in patients using GLP-1s," Cantor Fitzgerald analyst Louise Chen said in a 28 June note about the investment bank's interview with two key opinion leaders. "Both of our physicians expect a positive outcome. One physician said that he thinks a 20%-25% risk reduction is possible. This would be upside to Street expectations, which are in the low-teens."

Huge Market Potential With Many New Drugs Coming

Nevertheless, given mega-blockbuster predictions for the obesity drug market despite manufacturing, pricing and other access challenges, many players are competing to bring new weight loss therapies forward for the large and growing market. Morgan Stanley analysts said in a 30 June note following the ADA meeting in San Diego that they expect the obesity therapeutics market to achieve greater than $50bn in sales by 2030. Barclays analysts forecast a $100bn obesity drug market within the next decade in a 28 June note.

The need for obesity interventions is large and expanding. The most recent statistics on obesity from the National Institute of Diabetes and Digestive and Kidney Diseases show that as of 2018 42.4% of US adults are obese and 30.7% are overweight, while the World Obesity Atlas 2022 published by the World Obesity Federation predicts that more than 1 billion people globally will be obese by 2030.

SCRIP
CITELINE COMMERCIAL

Eli Lilly and Company may bring a new injectable GLP-1 drug to the US market for obesity in late 2023 – its dual agonist of GLP-1 and GIP, Mounjaro (tirzepatide), which was approved in 2022 for diabetes. (Also see "*Lilly's Mounjaro Diabetes Approval Is First Challenge To Novo's GLP-1 Franchise*" - Scrip, 13 May, 2022.) Lilly also has an oral GLP-1 agonist, orforglipron, that moved into Phase III this year and showed impressive weight reduction in Phase II results presented at the ADA meeting.

Here again, however, Lilly is behind Novo, which plans to file its oral semaglutide 50mg – a high-dose version of its oral GLP-1 drug Rybelsus (semaglutide) – for approval to treat obesity in the US and EU before the end of 2023. Data from the Phase IIIa OASIS 1 clinical trial of oral semaglutide 50mg presented at the ADA meeting showed 15.1% mean weight loss versus 2.4% for placebo at 68 weeks, while in Lilly's Phase II study of orforglipron mean weight loss was 14.7% at the highest dose tested versus 2.3% for placebo at 36 weeks; both drugs were tested in overweight and obese adults with at least one additional cardiometabolic comorbidity, excluding type 2 diabetes.

Wegovy, Mounjaro, oral semaglutide and orforglipron all may go up against another formidable competitor in the GLP-1 agonist class from Lilly's incretin agonist portfolio. The company presented Phase II results at ADA for its "triple G" or GGG agonist – targeting GLP-1, GIP and glucagon – retatrutide, which delivered up to 24.2% weight loss at 48 weeks at its highest dose; one investigator noted this was the greatest weight loss ever observed in a trial of less than one year duration (*see sidebar*).

Lilly Wows ADA Crowd With Obesity Data Across Three-Drug Incretin Portfolio

By Mandy Jackson

26 Jun 2023

Lilly may gain its first US approval in obesity with Mounjaro before the end of 2023, but presented data at ADA for it and two other drugs – retatrutide and orforglipron – that also yielded significant weight loss.

Read the full article here

But along with gasps and applause from audience members at ADA during presentations of double-digit weight loss results across the GLP-1 drug class, there were concerns about how health care systems around the world would be able to deliver medicines impacting not only weight but blood glucose levels and markers of cardiovascular health to all of the patients who need them.

Determining Who Gets Access To Which Drugs

University College Dublin professor Carel Le Roux, principal investigator of the Phase II obesity trial for survodutide (BI 456906), a GLP-1 and glucagon receptor agonist co-developed by *Boehringer Ingelheim GmbH* and *Zealand Pharma A/S* and presented at the ADA meeting, said

obesity needs to be recognized as a chronic disease that should be managed chronically. But given the high volume of patients that need to be treated, Le Roux said predictors of those at greatest risk from obesity and with the greatest potential response to new medicines are needed to help the health care system prioritize patients for treatment.

"What we want to do is we want to be equitable," he told *Scrip* in an interview. "We want to treat those patients at the highest risk of the complications of obesity, and patients who will have the biggest response to these therapies."

Yale School of Medicine associate professor Ania Jastreboff, who is director of the Yale Obesity Research Center and co-director of the Yale Center for Weight Management, also noted during a press conference at the ADA meeting that "we don't yet know who will respond to what therapies, and just like for other diseases, like diabetes, we don't have one medicine to treat everybody."

That means treatment for obesity will have to be individualized based on patients' responses to different drug mechanisms as well as based on a particular treatment's effects on an individual's comorbidities, Jastreboff explained. "It's not one medicine – one magic injection or one magic pill – it's all the different therapies," she said. "It's pairing it with bariatric surgery, it's pairing the therapies together using combination therapy and investigating all that."

Boehringer Ingelheim, Novo, Lilly and other industry and academic participants are working together on a €16m project in the EU called Stratification of Obesity Phenotypes to Optimize Future Therapy (SOPHIA), funded by government, industry and diabetes organizations to identify patient subpopulations most likely to respond to different obesity treatments.

"There's no country in the world that can afford today to treat all the people living with obesity," Le Roux said. "I think payers, be it public payers or private payers, want to treat the disease of obesity. The problem is just that it's so big that nobody can afford it, so how do we ultimately segment the market to be able to have a better health economic outcome as well?"

He noted that ADA and the European Association for the Study of Diabetes (EASD) have each identified both the treatment of obesity and glycemic control as keys to managing diabetes. "And it turns out that type 2 diabetes as a complication of the disease of obesity is probably the complication that's the most sensitive to the treatment of obesity, so we have the most bang for our buck when we treat people with obesity who also have type 2 diabetes," he said.

About a third of patients treated at the top dose of Boehringer/Zealand's obesity drug survodutide in the companies' Phase II trial achieved 25% or more weight loss. "At that level, you're really able to put diabetes into glycemic remission and obesity [remission] in many patients," Le Roux said, although he pointed out that survodutide was tested in non-diabetic

overweight and obese adults.

NASH And Other Comorbidities Improved With Weight Loss

Survudotide is being developed specifically for obesity and not for diabetes, although a Phase II trial is under way in non-alcoholic steatohepatitis (NASH), a complication of obesity, with results expected in the fourth quarter of 2023. *Merck & Co., Inc.* and *Altimmune Inc.* each have GLP-1/glucagon receptor agonists in development for NASH – efinopegdutide (MK-6024) and pemvidutide, respectively – and Lilly's Phase II trial of the GGG agonist retatrutide included a substudy in obese and overweight patients with non-alcoholic fatty liver disease (NAFLD) or NASH. (Also see "*Merck And Altimmune Vie To Be Leaders In NAFLD And NASH*" - Scrip, 15 Jun, 2023.)

Harvard Medical School associate professor Lee Kaplan, director of the Obesity, Metabolism and Nutrition Institute (OMNI) and founding director of the Weight Center at *Massachusetts General Hospital*, presented the retatrutide data in NASH during an ADA press conference. Kaplan noted that "30% liver fat reduction is associated with an improvement in NASH in those patients who have NASH, and what you see here is 100% of people at the two highest doses had at least a 30% reduction in their liver fat."

Boehringer/Zealand Dual Agonist Achieves Promising Level Of Weight Loss

By Mandy Jackson

24 Jun 2023

Survodutide provides another obesity treatment option, albeit with gastrointestinal side effects that will need to be managed with slow titration to maintenance dosing, which will be tested in Phase III.

Read the full article here

In addition, he explained that 95% to 100% of patients treated with retatrutide had a 50% reduction in liver fat, 80% to 86% had a 70% reduction in liver fat, and 79% to 86% achieved greater than 95% reduction of liver fat at 24 weeks. Kaplan pointed out that a normal liver has less than 5% liver fat.

"What has been found so far is that when you add … glucagon activity the liver fat clearance goes up tremendously," he said. "To my knowledge, there is no GLP-1 mono-agonist that causes significantly more than 50% clearance of liver fat on average. Whereas, again, to my knowledge, all of the published and reported data for those that have glucagon in them are in the range of 70% to 80%. This is the first one that has 100%."

Jeff Emmick, senior vice president of product development at Lilly Diabetes, said the company is studying its incretin agonists – including Mounjaro, orforglipron and retatrutide – in multiple comorbid conditions, since obesity has been associated with about 200 comorbidities.

“Some of those comorbid conditions require greater weight loss and perhaps the more weight you lose, the better the improvement in those comorbid conditions,” Emmick said. “We think that's going to be important to payers as well to continue to show the value of these medicines.”

Lilly has shown improvements in cardiometabolic parameters in patients who have lost significant weight in clinical trials of Mounjaro and it is seeing even greater improvements in blood pressure, triglycerides and lipid levels with retatrutide.

Within the Phase III TRIUMPH clinical trial program for retatrutide in obese and overweight patients, Lilly is conducting trials in obstructive sleep apnea (OSA) and osteoarthritis (OA), including TRIUMPH-1 in people without type 2 diabetes, including participants with OSA and OA; TRIUMPH-2 in participants with type 2 diabetes, including people with OSA; TRIUMPH-3 in patients with Class II or III obesity and established cardiovascular disease; and TRIUMPH-4 in patients with OA.

“We worked across three divisions of the FDA to get alignment to do that,” Emmick said. “And we have alignment that if we see benefits in those subpopulations, then at initial approval we can have an indication not only for chronic weight management, but also osteoarthritis and sleep apnea, rather than coming behind with what we call NILEX studies, which is what we've done with tirzepatide. We have a sleep apnea program with tirzepatide, we have a heart failure program with tirzepatide, but in this case, we're embedding some of that within the chronic weight management program.”

Lilly’s Phase III studies of Mounjaro in obese patients with sleep apnea and in obese patients with or without diabetes who have heart failure with preserved ejection fraction will read out in 2024, and the primary completion date for a recently initiated Phase III trial in patients with type 2 diabetes and NAFLD is September 2024. The company’s CVOT for Mounjaro in obese patients, SURMOUNT-MMO, has an October 2027 primary completion date.

Glucose Effects Observed Even In Non-Diabetic Patients

Jastreboff noted in her ADA presentation of Lilly’s Phase II retatrutide data that the mean baseline hemoglobin A1c level in the study’s non-diabetic population was 5.5%, but there was a decrease of nearly half a percent during the trial. Also, among the 36% of participants who had pre-diabetes at baseline, 72% of them reverted to normal glycemia in the retatrutide treatment groups.

Cardiometabolic parameters also were significantly improved in obese and overweight adults treated with oral semaglutide in the OASIS 1 trial. Filip Knop, professor and director of the Center for Clinical Metabolic Research at Herlev-Gentofte Hospital, *University of Copenhagen*, said in his presentation of the Phase III data at ADA that there were significant reductions at week 68 in both systolic and diastolic blood pressure compared with placebo and “quite a robust

reduction in high sensitivity CRP, indicating the anti-inflammatory effect of semaglutide." There also was "a small but nevertheless statistically significant reduction in HBA1c," Knop said.

University of Alabama at Birmingham (UAB) professor Timothy Garvey, who is a senior scientist at UAB's Nutrition Obesity Research Center, said during his ADA presentation of the Phase III SURMOUNT-2 data for Mounjaro in obese and overweight adults who had type 2 diabetes that more than 90% of patients with diabetes are overweight or obese.

The mean body mass index (BMI) on the maximum dose of Mounjaro decreased by more than five BMI units in SURMOUNT-2, which represents a change of a whole class of obesity, Garvey noted. The change in hemoglobin A1c, a key secondary outcome measure in the trial, was about 2.1% on average over the course of the trial for Mounjaro-treated patients and about half of patients treated with the drug achieved normal A1c levels. In addition, blood pressure, triglyceride and lipid levels improved.

Endocrinologist Ildiko Lingvay, a University of Texas Southwestern professor, as the discussant for the SURMOUNT-2 presentation remarked that many long-term safety and efficacy questions remain for Mounjaro, which will be partly answered by the SURPASS and SURMOUNT outcomes trials in diabetic and obese patients, respectively. Those questions include durability of weight loss beyond a year and a half of treatment and longer-term cardiovascular outcomes.

"Insurance companies now are dropping coverage for obesity medications, so we will have to have this data in order to support ongoing coverage and hopefully cost savings in the long run," Lingvay said.

Garvey noted in a 23 June press conference at the ADA meeting that 15% weight loss has been shown to be sufficient for treating and preventing a broad array of obesity-related complications, so Mounjaro could help fill a gap in the treatment of obese adults, with and without diabetes.

"These medicines are very expensive, in the $1,000-$1,400 [per year] range," he said. "These costs, I think, limit access. Health care systems and insurance coverage folks, obesity is such a common disease, they don't want to open the dam up and let all the water out. If everybody starts being treated – a third of Americans are obese, another third are overweight – you can't treat everybody with these kinds of therapeutic interventions."