

CORPORATE EXCELLENCE INSIGHTS

Hérens Quality AM is a specialized provider of systematic Quality Investment Solutions and one of the few providers of Quality equity investment strategies worldwide. Corporate Excellence Insight is our monthly publication that includes a brief update on markets and our thoughts about major trends that are impacting the investment management industry.

MARKET UPDATE: REALITY CHECK

The S&P 500 declined almost 5% in September, its steepest monthly drop in 2023, and extending a more modest loss recorded in August. The stock market experienced its most challenging month of the year, driven by a trio of escalating bond yields, climbing oil prices, and decelerating growth which instigated a broad sell-off, impacting even the previously favored mega-cap tech firms.

\$8bn

BIRKENSTOCK PLANS IPO AT \$8 BILLION VALUATION

German shoemaker Birkenstock has filed for an initial public offering in New York, becoming the latest European company to choose the United States as the place to raise money on the stock market.

4%

ECB RAISES KEY RATE FOR 10TH STRAIGHT TIME

The European Central Bank raised its key interest rate to a record high of 4%, with the euro zone economy in the doldrums, signalled that the hike, its 10th in a 14-month-long fight against inflation, was likely to be its last.

\$3.5bn

FORD TO PAUSE WORK ON A \$3.5 ELECTRIC VEHICLE BATTERY PLANT

Ford Motor's decision to hit the brakes on a planned \$3.5 billion battery plant in Michigan highlights a challenge for Tesla's growing crowd of rivals in the U.S. market: Tesla is pushing most of them into unprofitable, low-volume niches.

MONTHLY TOPIC: OBESITY MARKET

The wide-spread misconception around obesity is that it is a simple nutritional condition caused by excessive caloric intake or low energy expenditure. Hence, a trivial lifestyle problem due to incorrect, yet reversible, personal choices. As a result, weight-loss treatments in US are classified as lifestyle drugs and are not included in Medicare. But this is a disease that affects more and more people and puts a significant burden on the healthcare system.

According to Morgan Stanley, obesity market is expected to reach \$54 bn by 2030 globally, with US as a largest one. Already today, annual costs of obesity-related absenteeism are ranging from \$3.4 bn to \$6.4 bn, according to CDC.

Since late 90's, the developments in the obesity space - stained by tragic history of underlying health hazards incremental to treatment options back in the days - were shallow, right until June 2021 when FDA approved NovoNordisk's Wegovy. The appetite for Wegovy is so strong, that in Q2'23 drug has already passed \$1 bn sales mark, most of it generated in US.

When majority of the competitors are still exploring injectable options, NovoNordisk has already successfully completed Phase III trial for an oral version with comparable efficacy and will file for approval this year. It has also clinically proven that semaglutide has clear cardiovascular benefit, which could finally persuade insurers in US and health authorities in Europe to cover the cost of Wegovy and alternatives.

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Revolution in obesity: will it last this time?

Untapped opportunity

According to Morgan Stanley, obesity market is expected to reach \$54 bn by 2030 globally, with US as a largest one. This is an impressive number, but it comes on the back of a rather grim statistical data set – almost half of Americans are expected to be obese by 2030, according to a Harvard study, and that could account for as much as 18 percent of healthcare spending on related risk factors. Already today, annual costs of obesity-related absenteeism are ranging from \$3.4 bn to \$6.4 bn, according to CDC. In this insight, we look into controversial space of obesity and options to address the problem that gets bigger by day.

Stigmatized chronic disease

Obesity is a condition defined by excessive fat accumulation that presents health risk and is measured against Body Mass Index (BMI), which is calculated by taking weight and dividing it by square of height. For example, an individual weighing 55 kg with a height of 167 cm has a BMI of 19.7, which is within healthy range. Anything above 25 is considered overweight and above 30 - obese (Table 1). The wide-spread misconception around obesity is that it is a simple nutritional condition caused by excessive caloric intake or low energy expenditure. Hence, a trivial lifestyle problem due to incorrect, yet reversible, personal choices. As a result, weight-loss treatments in US are classified as lifestyle drugs and are not included in Medicare.

Table 1: Classification of Obesity types

	Body Mass Index (BMI)
Overweight	25 to <30
Class I (low risk)	30 to <35
Class II (moderate risk)	35 to < 40
Class III (high-risk)	40 or higher

Source: Hérens Quality AM

In reality, however, it is a chronic progressive relapsing disease that by this day lacks complete understanding. Hereditary studies calculated that contribution of genetics to the development of obesity varies between 40 and 70 percent, while genome-wide association studies found out 97 specific positions (called *loci*) of genetic markers associated with BMI, all of which affected genes expressed in the central nervous system.

The real trick to effective treatment of obesity is to address weight loss as well as weight maintenance. And while weight loss problem has been in focus since the beginning with several breakthrough therapies developed, issue of weight maintenance remains a fundamental question of the disease. The basic biological reality is such that at a certain level of obesity, the body will fight back to regain initial weight, especially if it was shed rapidly and in a short period of time. The bounce-back happens because at the end of the weight-loss journey, people's resting metabolism slows down substantially. At the same time, subjects of "crash diets" demonstrate plummeting levels of leptin, which is a hunger hormone. Together with slower metabolism, it creates a vicious cycle - people eat less, are constantly hungry, but number on scales is going up. The only effective way to maintain lost weight as of today is bariatric surgery - around 90 percent of people lose about 50 percent of weight and keep it off - but it is mostly used in Class III obesity cases.

Tragic history of treatment options

The first big craze in US around weight loss began in 1940's with discovery of amphetamine that, among other things, became a primary ingredient in weight loss drugs. These drugs were actively prescribed by physicians and nicknamed "rainbow diet pills" because they came in great variety of bright colors. Twenty years later, in 1960's, FDA removed all of them from the market after reports of numerous deaths and accumulated injuries reached congressional hearings.

Fast forward to 1990's, another wave of drugs resurrected hopes for a magic pill and so-called "fen-phen" was arguably the most popular of them. "Fen" referred to fenfluramine, an appetite depressant, while "Phen" referred to phentermine, a type of amphetamine (yes, you read that right). Separately, they have been on the market for years and considered mediocre for weight loss, but in 1979 Dr. Michael Weintraub decided to test them in combination. The study was a remarkable success, but Dr. Weintraub did not bother to do extensive research on side-effects, as he assumed drugs would be safe given that both have been on the market for more than a decade.

But they weren't. Further studies have shown that women who have been taking "fen-phen" combo have developed unusual abnormalities in the heart valves among other valvular injuries. Combo was taken off the market in September 1997.

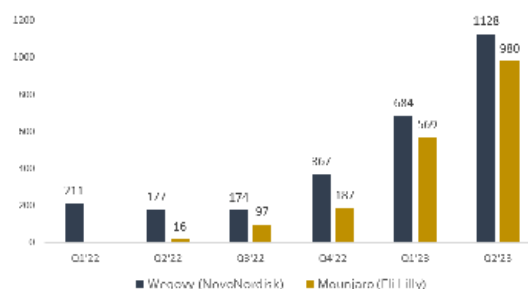
Since then, the developments in the space were shallow, right until June 2021 when FDA approved NovoNordisk's Wegovy (2.4 mg semaglutide) that in a 68 week-long study of 1'961 adults with BMI 30 or more demonstrated remarkable 14.9% weight loss on a weekly injection.

Race for dominance, but NovoNordisk to remain on top

It would not be entirely false to claim that when it comes to weight loss drugs, patients have five major things in mind, these being 1) efficacy, 2) side effects, 3) administration and ease of use (injection vs pill), 4) remission rate and 5) price tag.

Given massive stain mark in the history of obesity treatments, no wonder that initial reaction to Wegovy was that of caution, but everyone quickly figured out that the drug was indeed different. First of all, its basic compound is GLP-1, which a natural hormone that affects insulin secretion (hence, at first was developed to treat diabetes). Secondly, it is a peptide-based medication, and as peptides have very specific targeting, the side effects are moderate. The appetite for Wegovy is so strong, that in Q2'23 drug has already passed \$1 bn sales mark (Figure 1), most of which come from US. Naturally, the space became attractive for other big pharma names. Eli Lilly, as a major competitor to Novo in diabetes, expects Mounjaro (targets two obesity related hormones, GLP-1 and GIP) to be approved for obesity before the end of 2023, thus offering first tangible alternative to Wegovy.

Figure 1: Quarterly sales of Wegovy and Mounjaro (only diabetes sales) (\$ mio)



Source: Hérens Quality AM

But there are many more to come. According to Evaluate Pharma, the obesity pipeline had more than 20 Phase II/III clinical candidates in 2022, and these are just 20 percent of the entire obesity pipeline as most are still in pre-clinical stage. AstraZeneca, Pfizer, Boehringer Ingelheim are just few big names entering the game. Some of them will fail, but some will succeed for sure. As a frontrunner, however, NovoNordisk has one big advantage – when majority of the competitors are still exploring injectable options, it has already successfully completed Phase III trial for an oral version with comparable efficacy and will file for approval this year.

Another great advantage of NovoNordisk is that it is a company of remarkable quality (hence, it is a part not only of regional, but also Top portfolios), which is a direct function of its long-lasting operational excellence and robust track-record of R&D yields. It has unrivalled knowledge of the field and strong management team to support visionary decision-making. This is precisely why company has managed to retain leadership in diabetes despite decade-long competition from Eli Lilly, with whom they share the market. We expect similar trends in the obesity space.

Cardiovascular benefits to open up previously closed doors

Unfortunately, weight maintenance issue remains acute as once off Wegovy, subjects, per usual, do regain some of the lost weight. This, eventually, can lead people to question long-term benefits of the treatment and perhaps finally realize that lifestyle change is still an inevitable component to successfully overcome the disease. On the other hand, with recent study, NovoNordisk has clinically proven that semaglutide has clear cardiovascular benefit, which could finally persuade insurers in US and health authorities in Europe to cover the cost of Wegovy (\$1'300 a month) and alternatives. One thing is certain – inflection point in obesity has been reached and it will be a dynamic space going forward, one we will follow closely.