



Bellevue

Excellence in Healthcare
Investments

Healthcare Observer



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Dear investors,

Looking at equity returns for 2023, there’s no denying that this was a disappointing year for healthcare sector investments. Biotech and medtech stocks showed the biggest losses. The financial market pushed down the prices of small and mid-cap stocks the most as interest rates moved higher, because many of these companies are still dependent on external capital. We believe investor sentiment towards the healthcare sector is worse than the fundamental developments within the sector. New drug approvals in the US will again number more than 50 this year, which is in line with the average annual number of FDA approvals for the past five years. New diabetes drugs could significantly improve treatment options and outcomes for obesity and cardiovascular disease. In the medtech business, new products incorporating digital technology are poised for a commercial breakthrough. A variety of innovations that offer attractive returns are again spotlighted in this issue.

We hope you enjoy reading this latest issue of the Healthcare Observer and wish you a restful Holiday Season.

Sincerely, Dr. Cyrill Zimmermann, Head Healthcare Funds & Mandates

Obesity: An increasingly weighty issue for investors

Obesity and its associated comorbidities have long since become a globally prevalent health crisis. Thanks to recent breakthroughs with a new class of medicines, a lasting and successful treatment for this public health issue appears possible for the first time ever, creating a market opportunity worth billions.

Obesity is a medical condition that has surged to unprecedented levels worldwide. Unlike in the past, however, awareness of this problem has clearly increased. About 40% of the world’s population is overweight or obese. According to a forecast by the WHO, this figure will rise above 50% by 2035. Obesity is a complex disease that manifests as an accumulation of fat due to the chronic overconsumption of calories and it is often associated with a strong emotional component and elements of addiction. The economic impact of obesity is tremendous. It is expected to grow to more than USD 4 tn dollars globally by 2035, which is comparable to that of the COVID-19 pandemic in 2020.

Breakthrough achieved with new solutions

Government campaigns targeting obesity are a reflection of the economic relevance of this disease, especially its immense indirect costs. Solutions that address the problem of obesity are therefore one of if not the most effective means of tackling spiraling healthcare costs, because obesity is associated with more than 200 comorbidities. In addition to metabolism disorders such as diabetes or fatty liver, comorbidities include cardiovascular disease and a great

treatment options have emerged for patients and doctors and have presented new opportunities to investors too. Given its ability to improve blood sugar control, GLP-1 drugs are setting new standards for the treatment of obesity and diabetes. Their effectiveness as a treatment for other conditions is also being studied. Long-term treatment success in obesity necessitates a broad approach.

Thanks to technology advances, such as the GLP-1 drug class, new treatment options have emerged for patients and doctors and have presented new opportunities to investors too.

Solutions that address the problem of obesity are one of the most effective means of tackling spiraling healthcare costs, because obesity is associated with more than 200 comorbidities.

ter risk for certain cancers and even depression. Despite the scale and scope of this health crisis, only about 2% of all affected people are currently receiving treatment from medical professionals. The WHO, UNICEF and other organizations have designated this health problem as a matter of utmost urgency and have launched various initiatives and programs to address it.

Thanks to technology advances, such as the GLP-1 drug class, new



Data from SELECT study marked a milestone

GLP-1 analogs are not new. What is new are the many positive health effects that the latest members of this class of medications have demonstrated. GLP-1 or glucagon-like peptide-1 is an endogenous hormone that aids in digestion and is mostly produced in the lower gastrointestinal tract. GLP-1 also stimulates the activity of the liver and the pancreas, slows gastric emptying, induces a sensation of satiety in the hypothalamus and improves muscle insulin sensitivity. The first GLP-1 analog to reach the market was Byetta (exenatide), which was developed by the biotech firm Amylin Pharmaceuticals and approved by regulators for the treatment of diabetes back in 2005. The latest GLP-1 analogs work better and are longer acting and are now also being used as a treatment for obesity.

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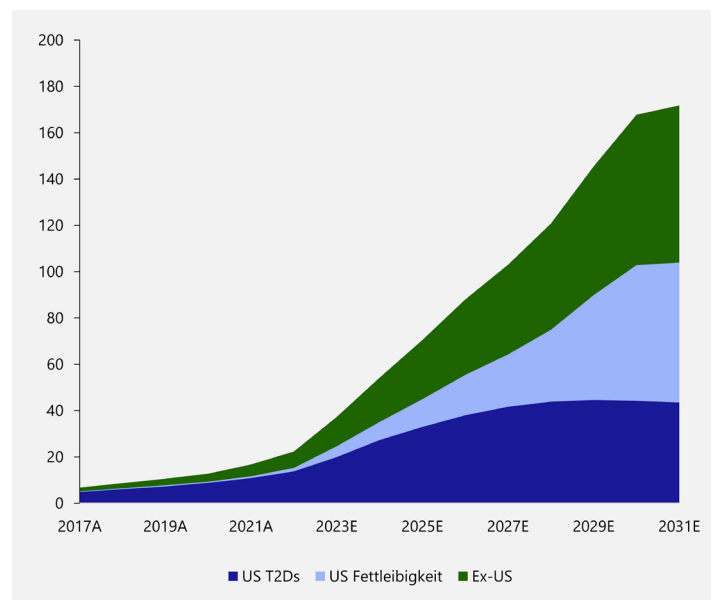
Until recently it was not known exactly what benefits GLP-1 analogs offered. That question was answered quite clearly in Novo Nordisk's SELECT study, the findings of which had been eagerly awaited. The data presented at the AHA (American Heart Association) meeting have created quite a stir. Semaglutide not only reduced the incidence of major adverse cardiovascular events (MACE – cardiovascular death, non-fatal heart attacks or strokes) by 20% in overweight and obese people with pre-existing cardiovascular disease, it also demonstrated a consistently positive effect across all measured endpoints, regardless of the baseline weight or age, and the drug was well-tolerated. Obese patients without diabetes showed a reduction not only in weight loss and blood sugar levels, as had been expected, but also in blood pressure, bad cholesterol, and blood lipids, as well as in hsCRP, a marker of inflammation.

Particularly impressive was the finding that the positive effects



were evident shortly after treatment initiation, even before weight loss occurred. Although the only significant reduction in risk among the primary endpoint data pertained to non-fatal heart attack, the data also showed a significant 19% reduction in all-cause mortality as a secondary outcome. Most of the semaglutide-treated participants reached normal blood glucose levels and also showed an improvement in kidney function. The significance of the trial readout goes beyond the realm of weight loss: there was also a significant reduction in comorbidity risk. These trial results are expected to have an impact on the recommended treatment options for people with obesity and established cardiovascular disease and lead to the widespread use of GLP-1 analogs in persons without diabetes. The market for this class of medications is projected to grow at an annual rate of more than 20% to well over USD 100 bn during the coming years. This is the fastest rate of market growth among the largest treatments areas within the healthcare system, faster than the projected growth rates for cancer and cardiovascular disease.

Market size (USD bn) indications



Note: For comparison; spending on cancer drugs of all types in 2022 was around USD 196 bn. T2Ds: type 2 diabetes. Assumption in average 10% penetration in obesity.

Source: Jefferies, JP Morgan, Bellevue Asset Management

Investing in the entire value chain

Long-term successful weight control must also integrate healthy lifestyle practices and will therefore also lead to greater demand for constructive solutions in the fields of nutrition and fitness. The value chain for obesity management thus extends from the prevention, diagnostics and treatment of obesity to the management and treatment of related medical conditions. For investors, this means a broad approach is recommended to capture the full potential of this growth story.

The recently launched Bellevue Obesity Solutions Fund, an actively managed global equity fund with a portfolio of 40 to 60 stocks, is exclusively focused on this mega trend. Under its new investment approach, investments in the healthcare industry (approx. 80% portfolio weighting) are rounded out with investments in nutrition or fitness companies (max. weighting 20%). Target companies are distinguished by high sales growth, high gross margins, an attractive product pipeline and a solid financial profile. The portfolio structure is designed to cover the entire obesity value chain.

Interview



Dr. Cyrill Zimmermann
Head Healthcare
Funds/Mandates

An exceptional stunning combination of low valuations and commercial breakthroughs

In his outlook for 2024, Cyrill Zimmermann explains why investors are likely to re-discover the upside potential that biopharma and medtech companies offer.

2023 was not a great year for healthcare sector investments. What happened?

Dr. Cyrill Zimmermann: Sales growth at numerous companies, in diagnostics for example, returned to normal levels after the pandemic ended. The second major factor was the sharp upturn in long-term interest rates, which led to a likewise sharp increase in the risk premiums and discount rates that are factored into cash flow models. That is a problem for companies that aren't making a profit yet. This interest rate effect impacted the biotech sector and companies that are developing or marketing digital healthcare products and services the most. Meanwhile the recent drug approvals in oncology, Alzheimer's disease and metabolic disorders impressively demonstrate that sector innovation is as strong as ever.

Diabetes and obesity are two themes that have recently attracted a lot of attention from the entire investment community.

Our two longstanding investments, Eli Lilly and Novo Nordisk, have clearly benefited here. Recent clinical trial results have truly been impressive. Treated participants in several studies lost a substantial 15% to 17% of their body weight and their risk of serious cardiovascular disease was reduced by 15% to 20% compared to the placebo group. There was a downside to this positive news, though, because it led to uncertainty about the future prospects of medtech companies that generate a large chunk of their sales in diabetes care and management.

Many generalist investors think medical technology is less exciting than drug development.

What makes medical technology companies so charming from an investor standpoint is that their development costs and risks are so much lower compared to the drug developers. And as digitalization continues to march across the healthcare landscape, medtech products are becoming an increasingly important tool for disease management and prevention as well as cost optimization. Big data now plays a key role in the field of surgery. Intuitive Surgical's biopsy device is one example here. Images taken by a miniature camera during the biopsy are sent to the cloud, where they are reviewed by a pathologist in real time, who then recommends whether to proceed immediately with resection. Stryker is moving down the same path in orthopedic surgery.

The sector's innovation power is undisputed. So what do you think could trigger a change in investor sentiment in the near term?

We're in an extraordinary situation. The entire healthcare universe, in developed countries and throughout the entire Asia-Pacific region, is valued at historically low levels. The MSCI World Healthcare Index trades on a forward P/E of 16 and its PEG ratio, i.e. the P/E ratio divided by forecast earnings growth, is around 1.8. The corresponding values for the S&P 500 are 18 and 2.5. Combined with the latest commercial breakthroughs, this situation offers investors lucrative entry points.

What role do emerging markets play as future markets in general?

A continuously growing one. China is a drastic example of how diabetes and lung/ colon cancer occur in emerging countries with increasing prosperity after a few decades as a result of an unhealthy lifestyle with a significant increase in the consumption of tobacco and unhealthy foods. Demographic trends – 500 million Chinese will reach retirement age by 2050 – are increasing the pressure to bring their own medical innovations to market. Among the emerging markets, China is also setting the pace in the development of innovative medicines. One example is Legend Biotech, which has developed a drug against bone marrow cancer with blockbuster potential that is also being sold in the USA. India, on the other hand, is increasingly making a name for itself as a low-cost production site for medicines. At the same time, private hospital chains such as our position Apollo Hospital are on the rise.

But the reality is that most investors are sticking to the sidelines.

Stock prices in the healthcare sector are sometimes caught in a cyclical pattern. The general euphoria triggered by the coronavirus pandemic was followed by a brutal sell-off during the past two years. We're confident that it'll only be a matter of time before healthcare stocks start trading higher again. We think mid and small caps have the most rebound potential as they have experienced excessive selling pressure.



BIOTECHNOLOGY

A steady flow of positive news attests to the biotech sector’s strong fundamentals.

Argenx continued to shine with its subcutaneous version of efgartigimod (Vyvgart) in patients with CIDP, a rare autoimmune disease of the peripheral nervous system. BridgeBio released impressive data from its study of acoramidis in ATTR cardiomyopathy, a rare heart disease. Ionis reported solid results for olezarsen, an investigational antisense medicine for the treatment of familial chylomicronemia syndrome (FCS). Novo Nordisk’s GLP-1 analog semaglutide (Wegovy) showed an impressive 20% reduction in adverse cardiovascular events (MACE) in obese patients in the company’s SELECT trial, and improved cardiovascular fitness among obese patients with heart failure (HFpEF) in the STEP trial. Structure Therapeutics presented initial data on its oral GLP-1 agonist and Eli Lilly received regulatory approval of its drug tirzepatide for weight loss (GLP-1 and GIP). At the CTAD Alzheimer Conference, Biogen/Eisai/Bioarctic announced that the subcutaneous version of its lecanemab antibody for Alzheimer’s is at least as effective as intravenous administration.

Dr. Christian Lach, Portfolio Manager



MEDETECH & SERVICES

The year-to-date performance of the medtech & services sector is slightly positive (+1.6%) and slightly better than the ytd performance of the broader healthcare market (-0.2%).

Subsector performance was not too far apart. Medtech (+1.4%) recovered from its summer sell-off and staged a strong comeback, while the services subsector (+2.0%) benefited from the stable performance of US health insurers.

It was pleasing to see that virtually all medtech companies reported strong quarterly results and a good increase in surgeries and other medical procedures, ending a 2-year pandemic-driven slump. US health insurers benefited from the growing number of people enrolled in „Medicare Advantage“ and „Commercial“ plans as well as from an increase in short- and medium-term bond yields.

Stefan Blum, Portfolio Manager



PHARMA & GENERIC

In the second half of the year, the pharmaceutical industry was characterized by medical improvements in diseases that occur as a result of obesity.

The focus was on the GLP-1 agonists from Novo Nordisk and Eli Lilly. At the annual meeting of the American Heart Association (AHA) in November, Novo Nordisk presented clinical trial results for Wegovy showing a 20% reduction in cardiovascular disease. In oncology, the drug class of antibody drug conjugates (ADCs), which address the target molecule TROP2, delivered very good efficacy data for various tumor types at the annual conference of the European Society of Medical Oncology (ESMO). The drug Dato-DXd from AstraZeneca and Daiichi Sankyo was convincing in lung and breast cancer. We see a key role for ADCs in the treatment of various types of cancer in the future. Novartis, on the other hand, completed its transformation into a pure biopharmaceutical group with the spin-off of its generics division Sanofi.

Dr. Terence McManus, Portfolio Manager



ASIA & EMERGING MARKETS

Two groundbreaking studies of Novo Nordisk’s semaglutide medication in obesity have drawn more attention to incretin-based therapies.

Incretin hormones control pancreatic beta cell secretion of insulin in response to food. Innovent, Wuxi Apptec and Chugai are three leading Asian players in this field. Innovent published impressive Phase II data on its obesity drug candidate at the end of October. Treated study patients lost 18% of their body weight at 48 weeks. Chugai discovered orforglipron and later licensed it out to Eli Lilly. Estimates of this oral GLP-1’s peak annual sales potential range as high as USD 20 bn. Wuxi Apptec is engaged in the development and production of no less than eleven GLP-1 active pharmaceutical ingredients, including six oral substances.

China’s crackdown on corruption in the healthcare sector was widened in August. Investigations have been launched against hundreds of hospital and pharma executives in the meantime. Solid quarterly earnings announcements have shown, however, that the anti-corruption campaign has not slowed the growth of healthcare companies offering top-quality products and services.

Oliver Kubli, CFA, Portfolio Manager

News

Long-term outcomes of transcatheter aortic valve replacement in low-risk patients and a breakthrough in the treatment of tricuspid regurgitation

Five-year follow-up findings from the PARTNER 3 study were presented at the TCT conference in October 2023. In this long-term study, about 1000 low surgical risk patients with severe symptomatic aortic stenosis were randomly assigned to undergo either transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR). In the first five-year follow-up, 27.2% of patients who underwent SAVR experienced at least one adverse event (death, stroke, or rehospitalization) compared to only 22.8% for patients in the TAVR group. TAVR outcomes were numerically better but not statistically superior. The trial data was very well received by doctors because it demonstrated the long-term durability of TAVR valves, which is likely to help TAVR procedures widen their share of the market.

Clinical data on the first 150 patients in the TRISCEND II pivotal trial were also published at the TCT conference. This randomized trial is designed to compare the safety and effectiveness of the EVOQUE system (Edwards Lifesciences' transcatheter tricuspid valve replacement system) and optimal medical therapy versus optimal medical therapy alone in patients with severe tricuspid regurgitation (TR). The major adverse event rate among the EVOQUE-treated patients was 27.4%, less than the expected rate of 43.8%. After 6 months of treatment, 98.8% of EVOQUE patients had mild or moderate TR compared to 21.6% of the patients in the control arm. The safety and efficacy of EVOQUE were statistically better.

More progress in Alzheimer's therapy

The Clinical Trials on Alzheimer's Disease (CTAD) conference held in Boston in October revealed yet again that the knowledge of the root causes of the disease is continually expanding and at an ever-faster pace. Eli Lilly is expected to receive US FDA approval for its Alzheimer's drug Donanemab in the next few weeks, which would make it the second therapeutic antibody in the market that removes amyloid plaque from the brain. Like the already approved drug Leqembi, jointly developed by Biogen, Eisai and Bioarctic, Donanemab is administered intravenously. Biogen and Eisai Pharma are working on a subcutaneous version so patients do not have to be hospitalized for the IV infusion.

Promising clinical trial results were presented in Boston. Biogen also presented positive data from a Phase Ib study at the CTAD conference that showed a significant reduction in neurofibrillary tangles of protein called tau fibrils. These tau fibrils, like amyloid beta plaques, lead to cognitive impairment. Biogen's investigational therapy BIIB080, which it licensed in from Ionis Pharma, is based on antisense technology. It is designed to silence the gene coding for tau protein. Biogen has begun recruiting patients for the first Phase II study. Axsome Therapeutics presented results from a trial of AXS-05 for the treatment of agitation in people with Alzheimer's disease. Currently, more than 140 therapeutic agents for Alzheimer's disease are in clinical development – a new record high.

New product: Bellevue Obesity Solutions Fund

New ways to treat obesity

As a healthcare investment company, we aim to make megatrends accessible to our investors as early and efficiently as possible. The treatment of overweight/obesity benefits more than almost any other area from strong political tailwinds and above-average growth potential. The Bellevue Obesity Solutions Fund is a completely new approach to investing in health.

Find out more



Outlook

Focus on M&A and clinical data

The valuations of many biotech companies have declined significantly during the past few months. Meanwhile big pharma companies are still reliant on outside innovation to strengthen their product portfolios and they remain on the lookout for product acquisitions that could cushion the impact of expiring patents. Against this backdrop, we expect mergers and acquisitions to play an important role in shaping sector sentiment in 2024. Oncology is one therapeutic area that will continue to attract considerable interest in this regard. Another focus of takeover activity will be autoimmune and inflammatory diseases, where more effective products targeting multiple indications can be developed simultaneously.

Other potential price triggers in the coming months will be the data readouts from anti-obesity drug trials. Structure Therapeutics will publish results from its Phase Ia/IIb study of an oral GLP-1 agonist. Boehringer Ingelheim, Pfizer, Amgen, Novo Nordisk and Eli Lilly will also be publishing new trial data. In the antisense/siRNA therapeutic area, Alnylam, Ionis and Arrowhead will be publishing data from their clinical trials in lipid metabolism disorders, hypertension and rare genetic diseases.



Tailwind for the medtech & services sector in 2024

2023 was an eventful year for investors. From a fundamental standpoint, medtech companies, hospital operators and health insurers have been on a steady above-par growth path since the summer of 2023 and they are likely to stay on this path in 2024.

Many medtech companies are anticipating high surgical procedure growth for the final quarter of 2023. A few have already made positive comments about 2024, which supports our scenario of a continued recovery in procedure volumes in 2024. Fast sector sales growth will be sustained by the approval and launch of relevant new products. Examples here are Abbott's TriClip, AVEIR and Libre products, Boston Scientific's Farapulse PFA system and the next generation Da Vinci robotic surgery system from Intuitive Surgical. Medtech's renewed pricing power, in the low single-digit percentage range, appears to be intact going forward while the negative effects of supply chain disruptions are petering out, creating additional margin improvement potential.

We expect hospitals operators to benefit from the ongoing recovery of surgical procedure volumes and slower wage growth in the nursing field. As for the health insurers, we expect premium volumes to show very good growth, fueled by a steady increase in the number of insured people and above-average premium growth in 2024. Furthermore, continued high government bond yields on a yearly comparison basis could have an accretive effect on earnings. Political risks remain low. We presume Joe Biden will be re-elected and that no party will have a solid majority in either chamber of Congress.

As the 2023 investment year has clearly shown, outstanding sector fundamentals can be overridden by macroeconomic developments and shifting investor tastes. Unlike in 2023, we are anticipating tailwinds for our investment vehicle in 2024: Rate cuts by the Fed (with a 12-month time lag), attractive valuation levels (valued at a discount despite above-average earnings growth), a general repositioning as investors turn away from high-flying stocks ("Magnificent 7") and buy up quality stocks, and a ho-hum outlook for global economic growth (which in the past has been kind to non-cyclical sectors). All of these factors argue for an investment in the medtech & services sector.

More rays of hope in the fight against new public health enemies

The healthcare sector in Asia will continue to grow faster than the region's national economies next year thanks to increasing life expectancy and high levels of innovation. A persisting soft economy is likely to encourage Chinese officials to ease restrictions to international trade in an effort to revive the country's economic growth. In 2024, companies engaged in the research and development of GLP-1-based diabetes and obesity therapies are likely to attract considerable attention from investors in Asian healthcare stocks, as has recently been observed in Europe and the US.

Chugai will present Phase III data for orforglipron. This medication is taken as a daily pill. Wuxi Apptec could sign some agreements with Western companies to produce diabetes medicines. Innovent hopes to launch a 6-mg dose of its weight-loss drug candidate, which it licensed in from Eli Lilly, towards the end of 2024. It might be able to present Phase III data for a 9-mg dose in 2024 too. The expected approval of an injected version of Eisai Pharma's Alzheimer drug Leqembi at the end of 2024 could be a major trigger for the company's shares. Donanemab, a rival product, is only available as an intravenous therapy.

Bellevue – Excellence in Healthcare Investments

Bellevue is a specialized asset manager listed on the SIX Swiss Exchange with core competencies covering healthcare strategies, entrepreneur investments and selected niches strategies. Established in 1993, Bellevue, a House of Investment Ideas staffed by 100 professionals, generates attractive investment returns and creates value added for clients and shareholders alike. Bellevue managed assets of CHF 8.1 bn as at June 30, 2023.

One of Bellevue's core areas of expertise dating back almost 30 years is the global healthcare sector. Besides the investment company BB Biotech AG Bellevue offers a diversified range of investment funds covering medical technology, digital health, biotechnology and emerging markets healthcare themes. Bellevue ranks as one of Europe's largest investors in the healthcare sector.

Independent – entrepreneurial – committed.

Interested in further information?

We are at your disposal at any time



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«Healthcare Investments in East & West – Developments and Trends»



Are we at a turning point in the healthcare sector? What investment opportunities are emerging in the USA and Asia after the pandemic?

Cyrill Zimmermann, Head Healthcare Funds & Mandates, explores these and other questions in the conversation with our long-standing experts from Boston and Singapore, Prof. Michael Mullen and Marvin Ng.



To the video