Bellevue

Excellence in Healthcare Investments

Healthcare Observer

February 2023

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Dear investors,
With the coronavirus pandemic now in the rear view mirror, the healthcare sector will return to normal in the current year, regardless of the uncertainty and worries regarding inflation and recession risks. Normality for the sector means that company fundamentals will take center stage and drive stock prices again, more so than the general macroeconomic environment. This explains our optimism that healthcare investments will deliver a better performance in 2023 than they did last year. Numerous innovative drugs, ranging from gene therapies to oncology medicine, are nearing approval. The first big headline came in January when the US FDA approved the very first treatment for Alzheimer's that significantly slows the progression of this disease. The feature article in this issue highlights the better treatment options. In the interview with Terence McManus you can read about the most promising subsegments within the healthcare industry at different market phases. And last but not least, persisting low valuations are a strong buy argument.

We hope that you had a good start to 2023 and you enjoy reading our latest Healthcare Observer.

Yours sincerely, Dr. Cyrill Zimmermann, Head Healthcare Funds & Mandates

Major breakthrough in Alzheimer's treatment

The very first drugs that actually slow the progression of this as yet incurable disease have been approved. Novel approaches are already being investigated too.

The FDA's decision announced January 6 marked a milestone for Alzheimer's patients. A scientific advisory panel of the FDA recommended approval of lecanemab, an antibody that is sold under the brand name Leqembi. A corresponding marketing authorization has been accepted by the European regulators in recent days. After several other trials of antibody treatments for Alzheimer's had failed, lecanemab, an antibody co-developed by Eisai and BioArctic and co-commercialized with Biogen, is the first drug to demonstrate a slowing down in the progression of Alzheimer's in a Phase III trial. Lecanemab reduces amyloid beta plaques in the brain. These protein deposits are thought to play a primary role in the pathogenesis and progression of Alzheimer's disease. In the confirmatory study with 1795 participants, lecanemab was found to have slowed cognitive decline by 27% compared to the placebo group at 18 months.

The FDA granted lecanemab accelerated approval, which is an approval pathway in which the US health agency relies on a substitute for a clinically meaningful endpoint. This so-called surrogate endpoint is not itself a direct measure of a specific, clinically relevant treatment benefit, but it is thought to predict a clinical outcome, much like the temperature curve of patients with influenza. The FDA may grant full approval at a later date upon submission of additional data that confirms a clinical benefit. In the case of Alzheimer's medicines, full approval is a requirement for full reimbursement of patient treatment costs by payers. The Centers for Medicare and Medicaid Services (CMS), a US government agency, sets treatment reimbursement rates in the US. The current consensus is that full FDA approval for lecanemab for the US market will be given late in 2023.

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Eli Lilly will also publish data from its trial of donanemab, an amyloid beta antibody, sometime this year. Its Phase III data should be published by mid-2023. This timeline does not put Eli Lilly at a major disadvantage because the FDA agreed to a rolling submission process for donanemab in 2021. In this process, individual sets of clinical data

relevant to the approval process are submitted at relevant intervals rather than in one single filing at the end of the study, as is the case in traditional approval pathways. Based on available information to date, donanemab is thought to reduce amyloid beta plaques more quickly and effectively than lecanemab. Patients in the highest dosage arm showed a 93% reduction in plaque load. Besides clinical efficacy, the side effect profiles of the two antibodies could be a key differentiation factor. If the data released to date is confirmed in subsequent readouts, donanemab is likely to also be granted an approval pathway sometime in 2024.

Gantenerumab, the antibody developed by Roche, is definitely out of the race after producing disappointing results in two clinical trials. It failed to significantly slow the decline in cognitive performance and the reduction in beta amyloids was also less than expected. In addition, side effects such as cerebral edema and intracerebral hemorrhages were more serious than with donanemab and lecanemab.

The two Alzheimer's medicines will not have an impact on the sales and profits of Eisai and Eli Lilly in the current year. How much the drugs achieve in peak sales will depend above all on how much of the treatment costs are covered by payers and for which patient groups the drug can be used. While conservative estimates forecast that annual drug revenues can reach the high, single-digit billions, optimistic scenarios forecast peak revenues of USD 15 to 20 bn. In view of the high medical need, the drug developers will have considerable pricing power for both products. Eisai has said the annual treatment cost for Leqembi would be priced at USD 26 500. Eli Lilly is likely to set a similar price for donanemab.

Next-generation Alzheimer's therapies are already slowly progressing through R&D pipelines in the wake of these two pioneer drugs. Most products are still focusing on amyloid beta plaques and tau fibrils. In addition to pharmaceutical companies, selected biotech firms are among the front runners and they are also in our fund portfolios. One of them is BioArctic, the Swedish company that developed and outlicensed lecanemab. Alnylam and Ionis have early-stage programs targeting amyloid precursor protein (APP) and tau protein, respectively. These programs are based on the two companies' proprietary RNA technology platforms, which regulate the gene sequences responsible for the production of the disease-causing protein.

The two genes ApoE4 and TREM2 represent a new approach in Alzheimer's research. People carrying the ApoE4 gene may develop protein abnormalities resulting in the buildup of fatty deposits in neurons, promoting the death of these nerve cells. Other research projects are investigating plaques as part of the brain's immune response to bacterial infections. Research is also ongoing into

The two genes ApoE4 and TREM2 represent a new approach in Alzheimer's research.

inflammatory components, synaptic neuronal activity and the impact of metabolism in causing Alzheimer's disease. Machine learning and AI methods are being tested for the identification of new gene markers to diagnose Alzheimer's.

Given today's demographic trends, investors stand to benefit from breakthrough therapies and diagnostics in coming years.

Machine learning and AI methods are being tested for the identification of new gene markers to diagnose Alzheimer's.

According to a recent forecast by the World Health Organization (WHO), for instance, 139 million people worldwide are expected to have dementia by 2050, and around 70% of them are expected to have Alzheimer's. After decades of clinical failures, this area is being viewed with renewed optimism.

Interview

Dr. Terence McManus
Portfolio Manager

«Obesity could become the story in 2023»

In a tough year for stocks, healthcare held-up well, was this a classic shift to defensives?

Terence McManus: Last year healthcare stocks fulfilled their role as safe havens within investors diversified portfolios, with the sector outperforming the broader equity markets on a relative basis. Demand for healthcare products and services are broadly inelastic, and therefore very resilient. Investors recognized this in 2022, with relatively solid performances from the defensive parts of the sector, such as large cap biopharma and managed care. We look for a more positive absolute performance for the sector in 2023, aided by a more constructive macro environment for stocks.

After the strong relative performances, are valuations stretched?

Healthcare ended the year at a small premium valuation versus the broader markets. This is not the top-limit on a relative or absolute basis, there are multiple periods in history where the sector has traded at a much higher premium. Specifically during periods of high economic uncertainty, but low healthcare reform risk. In addition, we expect some significant clinical and commercial developments in 2023, which should help keep momentum for the sector.

With multiple economic scenarios possible, can healthcare stocks remain relevant?

We have seen strong factor rotations in the market and within healthcare already in early January, this volatility could continue. However, healthcare offers solutions across equity market style-factor leadership. In the case of a shallow recession or goldilocks soft-landing in the US we will see a strong switch to growth-style stocks. In that scenario, investors can adapt, and switch more allocation towards growth- or cyclical-related healthcare subindustries such as molecular diagnostics, genomics, animal health, and dental.

In your view, which are the most important value inflection points for 2023?

We will see a combination of important commercial markets opening up, and exciting new modes of action making it to the mainstream. The approval of the first clinically proven disease-modifying Alzheimer's disease drug is a positive step-forward for patients, and could open-up a large market over the long term. I would say, the emergence of obesity as a large commercial opportunity is likely to be the story of 2023. In terms of clinical developments, drugs based on complex technologies such as gene therapy, cell therapy, RNA technologies, which have been approved in niche indications, are set to advance in the clinical into more mainstream disease areas with bigger patient populations.

How about the prospects outside of biopharma?

We expect hospital utilization to finally recover back to at least pre-COVID levels in 2023 after labor shortages delayed the rebound, this would be positive for medtech. Life science tools are more trickly to predict given COVID-related tough-comps, and a high correlation with macro factors. However, early indicators suggest continued strong underlying end-markets. Across subsectors, China reopening should prove a nice tailwind in the mid-term once this current COVID wave passes.

Would you expect a significant uptick in M&A activity in the sector?

Yes, with significant firepower for the large companies, and more moderated small and mid cap valuations, we expect increased M&A activity in 2023. We also expect the trend for divestments and re-structuring to continue.

What is the impact of these developments on your portfolio strategy?

For the Bellevue Diversified Healthcare Fund we enter the year fairly balanced across subsectors and style factors, but are looking at specific key performance indicators, or KPIs, to signal allocation shifts. With multiple clinical developments expected in the year, we expect bottom-up stock selection, aided by the depth of expertise here at Bellevue, to drive performance. As for investing themes we have two major disease areas on our radar, which are obesity, and Alzheimer's disease.

BIOTECHNOLOGY

The performance of biotech stocks beat the total market again by a wide margin in the period since autumn.

Many clinical conferences were held during this time and most of the related news flow was positive. At the CTAD conference (Alzheimer's), study results were presented that demonstrated a significant slowdown in disease progression for the first time ever in this therapeutic area. Lecanemab, an antibody developed by Eisai/BioArctic/Biogen, showed a positive treatment effect that increased over time and the side effect profile was relatively benign, leading to accelerated approval by the FDA in early January. At the American Society of Hematology (ASH), exciting new data from trials of bispecific antibodies were presented, Regeneron's linvoseltamab antibody for the treatment of multiple myeloma for example. This class of medicines has already been established in lymphoma (HL/NHL) with products from Genmab/Abbvie and Roche. Progress was also widely reported in cell and small-molecule therapies; Beigene in particular reporting convincing data for its BTK inhibitor. In the field of gene therapy, Uniqure/CSL's treatment for hemophilia B patients was the first gene therapy ever to be approved by the FDA for the rare bleeding disorder. Of no less significance for the sector was Amgen's takeover of Horizon Therapeutics for nearly USD 28 bn, a premium of 36% over the pre-announcement closing price.

Dr. Christian Lach, Portfolio Manager

MEDTECH & SERVICES

The medtech & services sector (+4.3%) delivered a positive performance between August and December 2022 but was unable to beat the broader healthcare market (+8.7%).

Performance for the full year was negative (-12.5%), although subsector performance was highly divergent. Medtech corrected (-24.8%), for example, while the services subsector gained 7.4%, driven by US health insurers. The divergent subsector performance can mostly be traced to macro factors such as rising interest rates and a shortage of qualified personnel in the healthcare industry.

Generally speaking, the valuation multiples of fast-growing companies were pressured the most by the sharp increase in interest rates. This process of adjustment seems to be over and these companies consistently reported pleasingly good results nevertheless. Not only that, they also have little exposure to the economic cycle. The overall positive data and projections that many companies announced at the J.P. Morgan Healthcare Conference in January confirmed this trend.

Stefan Blum, Portfolio Manager

PHARMA & GENERICS

Pharma benefited yet again from its status as a safe haven during the September to December period.

This was especially evident in September, when equity market volatility spiked again. The NYSE Arca Pharmaceutical Index gained 14.4% (in USD) over the four-month period and helped to fuel the broad healthcare market's advance (MSCI World Health Care: +8.1%). Stocks were moved by sector and subsector activity as well as by non-company-specific news flow. At the company level, strong sales reports on Wegovy from Novo Nordisk (+26.1%) and Mounjaro from Eli Lilly (+19.5%) were clearly positive triggers. Both products have shown weight-loss effects in obesity, although Mounjaro has so far been approved as a diabetes treatment only. The Japanese pharmaceutical company Eisai and its US partner Biogen laid the groundwork for the preliminary approval of their Alzheimer's drug lecanemab when they presented strong Phase III data. Roche, on the other hand, terminated its study of its Alzheimer's drug candidate, gantenerumab, due to disappointing data.

Samuel Stursberg, CFA, Head Research Healthcare Fonds

ASIEN & EMERGING MARKETS

In October, Chinese President Xi cemented his power at the 20th Party Congress.

Against all expectations China lifted almost all of its COVID restrictions in November and December. That sparked a rally on China's stock market that also lifted healthcare stocks. This situation drew attention to the systemic importance of the Chinese telehealth providers JD Health and Alibaba Health. Online consultations, digital drug prescriptions and online distribution are being encouraged and are crucial in this huge country.

The Japanese pharma company Eisai presented detailed data from its Phase III study of lecanemab at the CTAD Alzheimer's conference. The drug demonstrated efficacy also at the 18-month mark and met all the second endpoints of the study as well. The US FDA granted the drug accelerated approval on January 6, 2023 (refer to the main article of this Healthcare Observer for more details) and it will be marketed under the brand name Leqembi.

Oliver Kubli, CFA, Portfolio Manager

News

Transcatheter mitral valve repair system from Edwards Lifesciences a winner

At the 2022 Transcatheter Cardiovascular Therapeutics (TCT) conference in Boston, Edwards Lifesciences presented data from a clinical study of its Pascal Precision mitral valve repair system for patients with severe degenerative mitral valve regurgitation. In this heart valve disease, the mitral valve does not seal well so blood flows backward into the pulmonary veins. Pascal is an implant that is positioned between the mitral valve's two flaps via catheter. It is then used to clip them together, creating two smaller openings that form a tighter seal than the previous orifice.

Edwards Lifesciences' randomized CLASP IID US pivotal trial evaluated the safety and efficacy of the Pascal system with Abbott's already approved MitraClip system. The interim results demonstrated that Pascal is as good as the MitraClip in terms of safety and effectiveness. At 30 days, 3.4% of the Pascal patients experienced a primary safety endpoint event (which included cardiovascular mortality and stroke) compared with 4.8% in the MitraClip group. Pascal also appeared to show a small benefit in terms of durability. Pascal Precision received US marketing authorization later in 2022. We estimate that the market volume for transcatheter mitral valve repair systems will more than double to USD 2.2 bn between 2021 and 2026.

New treatments for lymphoma and leukemia

Promising data readouts from clinical trials of several drugs targeting lymphoma and multiple myeloma, a malignant tumor of the bone marrow, were presented at the annual gathering of the American Society of Hematology (ASH) in New Orleans. Epcoritamab, a bispecific antibody developed by Genmab and Abbvie, demonstrated promising clinical efficacy in several B-cell lymphomas. Bispecific antibodies are increasingly becoming a more competitive treatment option versus cell therapy, especially in lymphoma.

Johnson & Johnson and Roche presented additional clinical data for their bispecific antibodies targeting GPRC5D, a new antigen, in the area of multiple myeloma. In a direct comparison, it appears that Johnson & Johnson has the better antibody in this area. The efficacy data presented by the Chinese biotech firm Beigene for Brukinsa in chronic lymphocytic leukemia (CLL) also caused quite a stir. The efficacy profile of Brukinsa, classified as a BTK inhibitor, demonstrated superiority over the currently approved drugs for CLL patients – Johnson & Johnson's Imbruvica and AstraZeneca's Calquence. Brukinsa, which has been approved in the EU since November 2021, has a very good chance of becoming the new standard of care for CLL in China and the USA.

Healthcare Outlook 2023 – Market commentary

Read more here

China's healthcare sector shifts into post-pandemic gear

The corona pandemic and the zero-COVID policy response hardly left a mark on China's biopharmaceutical industry. Clinical studies experienced few delays. Legend Biotech and Beigene achieved major clinical breakthroughs on the international stage with their cancer therapies. After an initial wave of biotech IPOs in 2020, we expect the wheat to be separated from the chaff during the next few years. Up to ten companies could succeed in bringing a product to market. Business in cyclical areas of the healthcare sector that had struggled in the face of pandemic-related restrictions will bounce back very strongly during the current year. These areas include hospitals, clinical service providers and medtech subsegments such as hip implant solutions and orthopedic devices.

We have raised the China weighting of our Emerging Markets and Asia-Pacific funds to 60% and 40%, respectively. We bought shares of biotech companies, clinical services providers, hospital operators and medtech firms. We realized profits in the digital health space and afterwards selectively bought some of these same stocks. Two of the new additions to the portfolio are Microport, which is benefiting from the growing number of elective procedures, and Jinxin, a specialist for in vitro fertilization.

Outlook

New blockbusters on the verge of regulatory approval

A total of 37 new drugs were approved by the US FDA in 2022. Gene therapy will dominate the first half of 2023. The first news flow will come in May when Biomarin reports on its trial of Roctavian in hemophilia A. If successful, Biomarin expects Roctavian and Voxzogo, a treatment for achondroplasia that was approved in 2022, could account for 50% of its total 2025 sales target of USD 5 bn. In May Krystal Biotech hopes to receive regulatory approval for B-Vec, a topical gene therapy for a rare genetic condition called butterfly skin, for which there is no cure. Sarepta and Roche expect the FDA to announce its decision on their gene therapy for Duchenne muscular dystrophy (DMD) on May 29.

In oncology, attention centers on the pipeline progress of two therapeutic approaches. In bispecific antibodies, the market is anticipating new data on Regeneron's linvoseltamab therapy for multiple myeloma, which should be submitted for marketing authorization sometime in 2023 too. At Genmab, data on its HexaBody-CD38 antibody and its bispecific antibodies in solid tumors are eagerly awaited. In lung cancer, Gilead Sciences and its partner Arcus Biosciences are hoping to bring a combination immunotherapy (anti-TIGIT/anti-PD1) to the market. Their data readouts have attracted plenty of attention and details will be presented at the ASCO conference in June.

Another drug with blockbuster potential is cariprazine from Abbvie and Gedeon Richter, a schizophrenia medication that was approved for major depressive disorder in December. After receiving accelerated approval in January, full approval of lecanemab in Alzheimer's is anticipated in the summer of 2023. It will also be exciting to see whether add-on therapies for GLP-1 receptor agonists, a class of therapeutic agents for diabetes – Wegovy from Novo Nordisk for example – will be effective in obesity treatment.

Fundamentals are moving medtech stock prices again

The valuations of fast-growing, innovation powerhouses in the medtech sector were generally battered the most in 2022 as interest rates moved sharply higher. This phase of readjustment appears to be over now, and we are optimistic that the fundamental progress medtech companies have made and are making will capture investor attention again once the macroeconomic environment becomes less volatile. A recession cannot be ruled out yet, but in the past medtech & services stocks tended to perform relatively better than the broader market during periods of recession.

We expect medtech stocks to benefit from the normalization of procedure volumes for two reasons. COVID-related hospital shortages will resolve amid high population immunity and the hospital workforce situation will continue to normalize through 2023. We see additional growth potential due to the backlog of treatments that had to be deferred during peak COVID. In addition, improved pricing power, active cost management and strong sales growth are likely to widen profit margins. Major company-specific catalysts include new product launches (e.g. TriClip, Dexcom G7, Omnipod 5 and Pascal Precision), successful clinical trial results and cost reimbursement decisions, for example for CGM sensors for type 2 diabetes patients that only need basal insulin.

Large cap medtech names are trading at a 14% premium to the S&P 500, which looks attractive compared to the historical premium range of 15-25%. The stock-market performance of healthcare services, especially managed care stocks (US health insurers) will also be influenced by macroeconomic developments (interest rates, recession). At the same time they offer good downside protection in a potentially bumpier stock market. As was already the case in 2022, managed care could prove to be a defensive refuge with better relative performance if interest rates remain high for longer than expected and the economy weakens more than forecast. But more important than macro factors is the observation that the underlying insurance business is showing solid growth, especially in Medicare Advantage and in commercial plans.

Moreover, health insurance premium pricing for 2023 has been a favorable factor because health insurers were able to pass on core price inflation and they also factored in some conservative assumptions. Procedure volumes remain manageable as COVID caseloads decline while non-COVID caseloads rebound. US health insurers are trading at a 16% discount to the S&P 500, which looks attractive to us. We believe hospital operators may benefit from the recovery in elective procedures and a return to pre-pandemic revenue growth. Profitability could be further enhanced through strict cost-cutting programs.

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 9.6 bn as at June 30, 2022.

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

Dr. Cyrill Zimmermann
Head Healthcare Funds/Mandates

Dr. Christian Lach
Portfolio Manager

Alexandra Keller
Office Manager/ Assistant

Christina Wirz
Event Manager/ Sales Assistant

T +41 44 267 67 00
info@bellevue.ch

www.bellevue.ch/healthcare

Latest video updates from our portfolio managers

Biotech (Lux) team: US Food and Drug Administration grants accelerated approval for Alzheimer's drug

To the video

Asia-Pacific und Emerging Markets Healthcare team: Regional healthcare strategies: China in focus

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Bellevue Asset Management AG
Seestrasse 16 | 8700 Küsnacht
T +41 44 267 67 00
info@bellevue.ch | www.bellevue.ch