Bellevue

Excellence in Healthcare Investments

Healthcare Observer

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Dear investors,
After the disappointing performance of healthcare stocks last year, an exciting new year with plenty of attractive investment opportunities lies before us. Many biotech and pharma companies will present clinical data, shedding more light on the potential success and commercial prospects of new treatments for cancer and other diseases. New vaccines and treatments for COVID-19 infections will still be needed on a global scale – regardless whether the COVID-19 pandemic will move soon into the endemic phase or not. Positive factors for the medtech sector include a decline in coronavirus-related medical emergencies at hospitals and primary care practices, orders for medtech equipment that had been held back are being placed again, medical procedures that had been postponed are being restarted, and overall healthcare system efficiency is improving. Companies with the most promising prospects in the areas covered by this issue of Healthcare Observer were added to our funds at opportune moments.

We wish you an enjoyable read and hope you are staying safe and healthy.

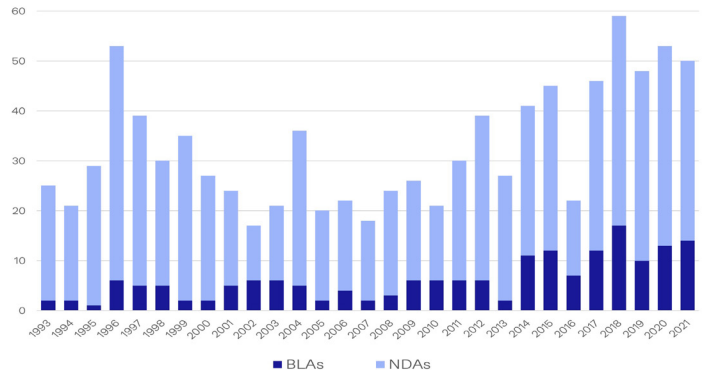
Sincerely, Dr. Cyrill Zimmermann, Head Healthcare Funds & Mandates

Plenty of triggers for higher prices

Many drug makers and medtech companies are on the verge of commercial breakthroughs, particularly in non-COVID-19 indications.

A glance at the list of new drugs approved in the US, the world's largest healthcare market, in 2021 reveals that the wave of drug R&D innovation that set in seven years ago is still moving.

New approvals



Nature Reviews Drug Discovery, January 2022

Although the number of new drugs approved by the FDA in 2021 did not match the highs from previous years, it was still above the historical average number of approvals granted. Market-moving commercial breakthroughs for treatments in COVID-19 and other indications will attract even more investor attention to the biopharmaceutical industry in 2022.

> The biopharmaceutical industry will attract even more investor attention in 2022.

COVID-19 remains a focal point

Among the many novel therapeutic modalities nearing the marketplace, the coronavirus pandemic clearly paved the way for mRNA technology's big breakthrough. We addressed this development early on in the portfolio of our biotech fund by opening positions in BioNTech and Moderna. Both companies will use the billions of dollars in revenues they have generated with their COVID-19 vaccines to accelerate the clinical development of new mRNA-based products for other therapeutic areas. At BioNTech the R&D activities are focused on personalized mRNA cancer vaccines, while Moderna will soon present decisive data from ongoing studies of its cytomegalovirus, RSV and flu vaccine candidates.

> Moderna and BioNTech will use the billions in revenues they have generated with their COVID-19 vaccines to accelerate the clinical development of new mRNA-based products for other therapeutic areas.

The astonishing spread of the new, highly transmissible Omicron variant is also a reminder that the research, development and commercialization of COVID-19 vaccines could play out over a longer-than-expected period. In 2022, we are also banking on the clinical success of two other biotech companies whose vaccine candidates could play an important role in COVID-19 booster vaccination programs. Bavarian Nordic's ABNCoV2 vaccine has elicited a robust immune response and the company is preparing for a Phase III trial of ABNCoV2 as a universal COVID-19 booster vaccine. Arcturus Therapeutics is another biotech company in the fund's portfolio that is developing mRNA-based therapeutics and vaccines. A big advantage with Bavarian Nordic and Arcturus is that their vaccines are effective at lower doses, which means they are cheaper to produce. If their ongoing studies are successful, BioNTech/Pfizer and Moderna will have to rethink their previous pricing policy.

Billion-dollar oncology and orphan disease markets

In oncology, we expect market-moving news about clinical trials, cell therapies and bispecific antibodies in particular, in 2022. China's Legend Biotech recently submitted impressive efficacy data for its cell therapy in multiple myeloma. Genmab and Abbvie are working on a potential blockbuster drug that targets hematologic malignancies with their bispecific antibody for non-Hodgkin lymphoma patients. In solid tumors, Roche made headlines when it received regulatory approval for Tecentriq, the first and as yet only cancer immunotherapy available for adjuvant treatment of lung cancer. Roche is developing Polivy in collaboration with Seattle Genetics, an add-on therapy could set a new gold standard in the first-line treatment of lymphomas.

Beyond COVID-19, rare hereditary diseases remain a lucrative field from both a medical and a commercial perspective. The recent mark-up in Biomarin's share price after it received regulatory approval of its Voxzogo enzyme replacement therapy shows just how attractive the market for very rare diseases (orphan diseases) is. Two-year data for valoctocogene roxaparvovec, Biomarin's investigational gene therapy for the treatment of severe hemophilia A, will be very important in 2022. Krystal Biotech's shares recently doubled in price after the company published positive clinical trial data on its topical gene therapy for so-called butterfly skin, a rare hereditary disease that causes blisters and wounds on the skin and mucous membranes. There is no effective treatment for this disease and Krystal Biotech's gene therapy could be granted regulatory approval before the end of 2022. Important events on the horizon for Genmab are its anticipated filing of epcoritamab, a bispecific antibody targeting malignancies in lymph nodes, and data readouts from its trials of bispecific antibodies in solid tumors. Alnylam and Ionis Pharma are developing an improved therapy against ATTR amyloidosis, a rare hereditary disease in which misfolded TTR protein fragments accumulate in the heart, nervous system and digestive tract, damaging these organs and tissues over time. Since transthyretin is a protein made in the liver, liver transplantation has been the only established treatment option for ATTR amyloidosis patients up to now. The therapies under development at Alnylam and Ionis block production of transthyretin in the liver.

> Our attitude towards treatments for Alzheimer's disease is still wait-and-see.

In neurology, our attitude towards treatments for Alzheimer's disease is still wait-and-see. Biogen's decision to slash the price of Aduhelm, its Alzheimer's drug that the FDA approved with certain limitations, confirmed our stance. Marketing this drug will remain difficult as long as there is no new positive trial data. From an investor's perspective, major market moves can be expected if Eli Lilly and Eisai Pharma/Roche receive regulatory approval for their investigational antibody treatments for Alzheimer's during the coming years and if Biogen can present convincing data from its Alzheimer's studies.

Pent-up demand in medtech

Turning to the medical technology industry, medtech innovation beyond pandemic-related applications stands to attract increasing investor attention in 2022. Certain companies that are about to receive approval for diabetes treatments, minimally invasive heart valve replacement and repair solutions, neurostimulation treatment and robotic surgery systems have substantial upside potential. In the last-mentioned application area, the approval of Medtronic's Hugo robot-assisted surgery system will likely be one of the highlights of the new year.

In cardiology, the TriClip heart valve system developed by Abbott is poised for a commercial breakthrough. TriClip is a transcatheter-based tricuspid valve reconstruction device. This clip-based system is a proven safe, simple and effective option for treating patients with tricuspid regurgitation, a life-threatening disease in which flaps of the tricuspid valve, which control the flow of blood between the two chambers on the right side of the heart, the right atrium and the right ventricle, no longer function properly. Two major product upgrades are also expected in the diabetes care devices market. Dexcom's G7 CGM blood glucose monitor will be a fully disposable, less expensive unit with significantly smaller sensors compared to its G6 predecessor. An approval decision for Insulet's Omnipod 5 insulin pump is expected during the first half of the year. This is a hybrid closed loop system in which a sensor, algorithm and pump can automatically adjust basal insulin delivery, but users must still input carbohydrate intake for meals manually.

> In the case of U.S. healthcare providers, ongoing privatization, vertical integration and efficiency gains through digitization are providing positive impulses.

As for healthcare services providers, we believe US health insurers offer the most upside potential. Progressive privatization (Medicare advantage, Medicaid), the greater pool of insured US citizens, vertical integration within the services segment (primary care and outpatient care centers) as well as efficiency gains driven by digitalization represent a wide range of positive factors, which, together with the boost to growth from non-emergency treatments that had been postponed because of the pandemic, is why we believe 2022 will be a good year.

Interview

Marvin Ng
Healthcare Analyst

«Steady growth in times of uncertainty»

New products in the wake of the coronavirus pandemic and long-term triggers: Analyst Marvin Ng talks about the growth prospects of Asia's healthcare sector.

The Chinese government's recent regulatory crackdown on tech companies has irritated international investors. Could similar actions also be taken against its healthcare industry?

Marvin Ng: I don't think so. China's healthcare sector is already highly regulated. A number of government reforms aimed at improving healthcare were already implemented over the past decade. With these reforms, the government has balanced accessible, affordable, and effective healthcare for all Chinese with a regulatory environment that encourages innovation and growth.

How has the biopharmaceutical industry in China changed in recent years?

Company priorities have shifted from „growth matters most" to „quality matters most". This shift can be seen in the tremendous clinical progress that many companies are making. Some have even achieved international market breakthroughs. Legend Biotech serves as a good example here. Through its partnership with Janssen, Legend is producing and commercializing biopharmaceutical products in the US and Europe. The next milestone event for Legend will be the FDA decision on whether to approve its cell-based CAR T-cell therapy for patients with multiple myeloma.

What do investors stand to gain over the long term by investing in Asian healthcare stocks?

First of all, Asia's healthcare industry offers steady growth even during uncertain times like with today's pandemic. Population aging is another argument in favor of Asian healthcare stocks. Lifestyle-related changes in the wake of increasing prosperity that are making chronic disease more prevalent are another trigger. Medical advances and national healthcare system reforms are also creating opportunities for novel products and services.

What role does Asia play in the fight against COVID-19?

Asian companies develop and produce many diagnostic tools, vaccines, and treatments for COVID-19. For example, South Korea diagnostics companies were among the early movers in developing SARS-CoV-2 test kits. Asian healthcare companies will continue to play a crucial role in this global battle.

Is the pandemic a new catalyst for drug development and could Asia benefit from this?

The new products and treatment approaches that have been developed in Asia since the outbreak of the pandemic are a clear indication that Asia's healthcare industry is becoming more competitive in a global context. At the same time, more and more Asian companies are joining forces with Western companies and concurrently expanding their capacity to produce medicines for regional markets. All these developments are making Asian healthcare systems more self-reliant and internationally competitive in terms of healthcare quality and delivery.

BIOTECHNOLOGY

The biotech sector underperformed the broader market during the September to December period despite a mostly positive reporting season.

In the last quarter, the biotech index declined by 7.0% while the S&P 500 gained 10.65% in USD terms. Although effective COVID-19 vaccines are widely available, the Delta and Omicron variants have made investors skeptical that the pandemic will be overcome anytime soon. In oncology, promising clinical data were presented at three annual conferences – the San Antonio Breast Cancer Symposium, the ESMO Immuno-Oncology Congress, and the American Society of Hematology (ASH) Meeting. A lot of interest was gained by Arvinas/Pfizer's ARV-471, representing a new class of SERDs for breast cancer patients, and Daiichi Sankyo/Astra Zeneca's Enhertu, an antibody with a chemotherapy payload. At the ASH meeting, Regeneron, Genmab and Roche presented convincing data from their trials of bispecific antibodies in lymphomas. Legend/Janssen presented excellent efficacy data for their cell therapy in multiple myeloma (see sector news section), while Fate Therapeutics presented promising efficacy data for its cell therapy for B-cell lymphoma. In neurology, Biohaven's Nurtec is increasingly becoming the new standard of care for chronic migraine, while Intra-Cellular Therapeutics' Caplyta was also approved for the treatment of bipolar depression.

Dr. Christian Lach, Portfolio Manager

MEDTECH & SERVICES

The medtech & services sector (-2.9%) was an underperformer during the August-December period.

The emergence of the Omicron variant and the related angst that hospitals would be overwhelmed due to the lack of sufficient capacity for standard medical treatments weighed heavily on the medtech sector. Meanwhile US health insurers (S&P Managed Health Care +21.9%) benefited from the recent developments because additional coronavirus-related treatment costs were more than offset by the decline in costs for non-COVID medical procedures. The full-year performance of the medtech & services sector (+14.9%) lagged that of the broader health market (MSCI World Healthcare Net +19.8%), while the US health insurance sector (+41.4%) was a strong outperformer. The outlook for the 2022 investment year is attractive. The sector is moderately valued and offers huge opportunities for investors. We also expect takeover activity to increase in the wake of the sharp declines in the valuation multiples of many small and fast-growing companies in 2021. Even without a normalization of the coronavirus situation, the sector-specific structural growth factors such as rising life expectancy and high rates of innovation will sustain the medtech & services sector's above-average growth versus the overall economy and lead to above-average profit growth.

Stefan Blum, Portfolio Manager

PHARMA & GENERICS

Stocks of generic drug companies showed a mixed performance during the final four months of 2021.

Large-cap pharma names managed to change course and trade higher again during the final month of the year. The NYSE Arca Pharmaceutical Index gained 5.7% over the entire period (in USD). Its constituent companies certainly did not move in unison though: Pfizer (+29%) clearly stood out in a positive sense after publishing strong data for its antiviral COVID-19 pill Paxlovid, which was subsequently granted emergency use authorization in the US. A competing product from Merck & Co., molnupiravir, was also approved for emergency use, but the related data was not as compelling and so the price of Merck's shares hardly moved over the period (+2.3%). The news that the US president and his fellow Democrats would not be to able pass their „Build Back Better" Act in December as originally planned gave a boost to the stocks of drug developers in general. The act's failure was viewed as a positive signal for drug manufacturers because it included significant drug pricing measures. The proposed legislation is not yet officially dead, but extreme pricing reforms are very unlikely in the current political environment.

Samuel Stursberg, CFA, Head Research Healthcare Fonds

ASIA & EMERGING MARKETS

Chinese healthcare stocks came under pressure in December after the Financial Times published an article.

The article was speculating that some Chinese biotech companies could soon be blacklisted by the US government. When the updated list of companies sanctioned by the US government was later published, there weren't any Chinese healthcare names on it. We believe the market's initial reaction was overblown and that the fundamental outlook for the companies in question is still as good as it was before the sell-off. Legend Biotech published impressive updated data for its cell therapy for multiple myeloma at the annual gathering of the American Society of Hematology (ASH). The first patients enrolled in the trial had received treatment about 23 months earlier. More than 60% of those patients were still progression-free and 74% were still alive, which is without precedent in this indication. FDA approval is expected in late February. Takeda, conversely, experienced a harsh setback. It had to stop two Phase II trials of its TAK-994 narcolepsy drug due to safety signals. On the other hand, Shionogi announced that its investigational COVID-19 medication appeared to also be effective against the Omicron variant.

Oliver Kubli, CFA, Portfolio Manager

In Focus

A comeback for bispecific antibodies

Oncology remains the disease area with the greatest number of drugs in development. 15 of the 50 new drugs approved in the US in 2021 were cancer drugs. There hasn't been much news about bispecific antibodies since 2014, when Amgen's Blincyto was approved, but several other candidates from this class of targeted therapeutics that activate the immune system to fight tumor cells are on the verge of a clinical breakthrough. The most promising candidates in multiple myeloma are being developed by Johnson & Johnson and Regeneron Pharma and they both target BCMA, a cell surface protein expressed on malignant plasma cells. Genentech/Roche presented very positive data on their bispecific antibody targeting the CD20 antigen on B lymphocytes and the CD3 surface receptor on T lymphocytes. If all three products are approved, CAR T-cell therapies could in the long run become the standard of care for advanced-stage multiple myeloma. The Chinese firm Legend Biotech could soon be in the vanguard of this new treatment approach. On February 28 an FDA advisory committee will discuss and vote on the company's CAR T-cell therapy for multiple myeloma.

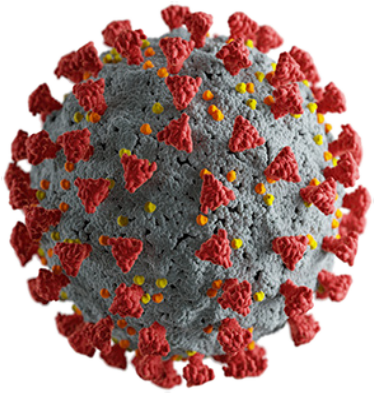
Breakthroughs in heart valve treatment

For interventional cardiologists, the annual TCT conference in November is a major event where companies present the latest clinical results for cardiology diagnostics, devices and procedures. New products for heart valve repair and replacement procedures were among the highlights of the last conference in Orlando, Florida. Some of the companies in our portfolio stood out at the conference. Medtronic presented very good safety data for its minimally invasive CoreValve and Evolut R solutions for transcatheter aortic valve replacement (TAVR). Five years after valve replacement, the safety profiles for both systems were as good as the data for patients who had undergone open heart surgery. The FDA has now approved the time- and cost-effective TAVR systems for all patients with severe aortic stenosis regardless of their surgical risk profile. Initially, the minimally invasive procedures were only approved for treating patients at high surgical risk. Edwards Lifesciences presented promising data for EVOQUE TR. This tricuspid valve replacement solution reduced the backward flow of blood in 98% of the patients enrolled in its study. Data from a larger study for which recruitment is now under way will be available in 2024. After incurring delays due to the coronavirus pandemic, Medtronic presented convincing 30-day data for Intrepid, a transcatheter mitral valve replacement system. Pivotal long-term data should be available in October 2023.

Outlook

Califf to lead the FDA

The chances that Robert M. Califf will serve a second term as head of the US FDA after already holding the position in 2016 have risen significantly. After a hearing, both Democratic and Republican senators expressed positive views of the candidate nominated by US President Joe Biden. The 70-year-old cardiologist, a co-founder of the renowned Duke Clinical Research Institute, is considered one of the country's most experienced experts for regulatory issues in clinical research. That makes Califf a very good choice to lead the FDA. He is well qualified to oversee approval processes for treatments and new vaccines that are effective in bringing the pandemic under control and vast expertise will be helpful in determining the regulatory requirements for the approval pathways for drugs enabled by new technology platforms. Critics of Califf's nomination, argue that he received consulting fees from many pharmaceutical companies, so he could face potential conflicts of interest as the new FDA Commissioner. Califf previously headed the FDA from February 2016 to January 2017.



New products to fight COVID-19

More than two years after it broke out, the coronavirus pandemic iis making towards its endemic stage – still being far from over. For vaccine and drug developers, this means that there are still plenty of market opportunities for other players to join the fight against COVID-19 apart from major protagonists like BioNTech, Moderna and Pfizer. Danish-German biotech company Bavarian Nordic published encouraging Phase II results last December for its booster vaccine candidate ABNCoV2, whose mechanism of action is geared at providing longer-lasting protection. The results of the pending Phase III study and possible subsequent approval are not expected before 2023. We believe ABNCoV2 will play a major role as part of UNICEF's COVAX vaccination campaign to supply poorer countries. Arcturus Therapeutics is also poised to launch a global pivotal trial with its mRNA vaccine. As a low-dose vaccine, the product could be produced at lower cost. Arcturus is now seeking emergency use authorization in Vietnam.

Novavax has already moved one step further ahead, having recently received EU approval for Nuvaxovid, a vaccine made of particles containing the SARS-CoV-2 spike protein. The body identifies these protein particles as foreign and activates the immune system to produce antibodies and T cells. More than two-thirds of the contracts Novavax has already signed to deliver two billion doses of Nuvaxovid were negotiated with the WHO. Topline results of clinical trials in adolescents aged twelve to 17 will be published by Novavax during the current quarter and are likely to lift its share prices, as previous readouts have demonstrated greater efficacy against the Delta and Omicron variants in this population than in adults. Final Phase III trial results are expected this quarter for Sanofi`s vidprevtyn, another protein vaccine recently showing encouraging booster data.

In the category of drugs to treat COVID-19 infection, Pfizer's Paxlovid is in pole position after receiving emergency use authorization. Paxlovid blocks the main protease necessary for the activation of viral enzymes in infected cells. In the case that governments want to stockpile the drug for future pandemic waves, Pfizer is all set to ramp up production. However, Paxlovid might start encountering drug resistance problems even before the end of the year. This scenario raises the market potential of new therapeutics like the clinical candidate being developed by Japanese company Shionogi, which selectively inhibits the same target molecule. In the category of antiviral agents that prevent the virus from entering the upper respiratory tract, a cocktail of two antibodies developed by Roche and Regeneron Pharma is the clear leader following emergency authorization. Regdanvimab, a monoclonal antibody developed by Celltrion/South Korea, has also received European Medicines Agency (EMA) approval. However, it appears that Regeneron and Lilly will need to adjust their antibody cocktails for Omicron. Only the GlaxoSmithKline-Vir Biotechnology antibody seems to be able to stand up to Omicron so far.

Already approved drugs designed to prevent virus replication in the cell have proven to be less effective. Gilead Sciences' remdesivir and Merck & Co's molnupiravir block enzymes that read the virus's genetic information and use it to make a copy. As with vaccines, future waves of infection will leave room for new therapeutic drugs to treat the disease.

Bellevue – Excellence in Healthcare Investments

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Interested in further information?

We are at your disposal at any time

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