



Healthcare Observer

June 2022

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**Dear Investors,**

We are pleased to present the 20th issue of our Healthcare Observer. The very positive resonance we have received from our readers is much appreciated and inspires us to keep you to date on exciting investment trends in the healthcare sector. As we are constantly striving to grow our expertise, we have also expanded our portfolio management team in recent years. The latest persons to join our team are Teresa Vilanova, healthcare analyst, and Terence McManus, who talks about the investment strategy of our new healthcare fund in this issue's interview. Amid all the economic and geopolitical uncertainty we face today, the healthcare sector remains an anchor of stability that, thanks to its innovations, will continue to grow faster than the global economy in the coming years. As the coronavirus pandemic and its repercussions recede, investor attention is turning back to significant medical breakthroughs beyond the context of the COVID-19 pandemic and their commercial potential.

We hope you enjoy the latest issue of our Healthcare Observer.

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

Major advances outside the spotlight on Alzheimer's

New therapeutic approaches offer highly attractive potential returns – biotechnology companies active in numerous niches within the area of neurological disorders have been particularly successful in bringing new products to the market.

Of all the major disease areas, drug companies researching disorders of the central nervous system (CNS) experienced the highest clinical trial failure rates for a long time. Investigational drug candidates often showed promising results in early phase clinical trials, but then missed their primary end points in pivotal trials involving a larger number of patients. Thanks to the tremendous progress that has been made in basic research over the past two decades, the number of neurological drugs approved by regulators has steadily increased.

In view of the significant unmet medical needs, CNS disorders represent a vast universe of therapeutic and commercial opportunities for novel therapeutic approaches. According to data from the World Health Organization (WHO), there are 55 million people worldwide with dementia, 70% of whom have Alzheimer's disease. In the United States alone, the world's largest healthcare market, about a quarter of the population suffers from some kind of neurological disorder and the related economic burden adds up to more than USD 800 bn per year in terms of direct and indirect treatment costs. Not surprisingly, there is considerable demand for new treatments, especially for neurodegenerative diseases, that slow or stop disease progression rather than just provide relief from the symptoms.

Medical advancements in the fight against Alzheimer's are also catching a lot of attention from the media, the general public and the investment community. Regulatory approval of Biogen's Aduhelm pill in June 2021 has not, however, triggered much enthusiasm from doctors or investors in the meantime. Aduhelm is a monoclonal antibody that reduces amyloid beta plaques in the brain. Biogen must conduct another clinical trial to verify the clinical benefit of the drug. There are two other investigational products that could support the

viability of this therapeutic approach: Roche and Eisai Pharma will present data from trials of their anti-amyloid antibodies gantenerumab and lecanemab during the second half of this year and in 2023 Eli Lilly will present data on its investigational antibody donanemab. There are still unanswered questions regarding the interaction between amyloid beta plaques and tau protein fibrillization associated with the onset and progression of Alzheimer's disease and the decline in cognitive ability. Going forward, identifying the best molecular targets for new drug candidates for Alzheimer's disease and determining the most effective mechanisms of action for anti-amyloid therapies will be key priorities.

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From an investor's point of view, however, the most exciting developments for treating CNS diseases are happening outside the spotlight of attention on Alzheimer's disease and the most notable medical advancements here have often been made by biotechnology companies. Intra-Cellular Therapies received FDA approval of Caplyta as a monotherapy and as adjunctive therapy for the treatment of bipolar depression in December 2021. Unlike Vraylar, a rival product developed by Abbvie and Richter Gedeon, Caplyta improved depressive episodes associated with both bipolar I and II disorder. Both products could achieve blockbuster status, though, because they are the first new treatments regulators have approved for this serious neurological disorder in two decades. In addition to their rapid onset of action, Caplyta and Vraylar are characterized by high levels of tolerability. That sets them apart from older drugs, which can lead to weight gain, psychomotor disturbance, and other adverse side effects. Sector experts estimate that Caplyta can generate billions in annual peak sales.

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We added to our shareholdings of Intra-Cellular during 2021, but recently reduced our stake in Sage Therapeutics due to the lack of convincing data from its trial of zuranolone in patients with major depressive disorder (MDD). Sage has been marketing Zulresso, the first drug ever approved for the treatment of postpartum depression, since 2019. Axsome Therapeutics expects the FDA to issue a final decision on AXS-05 as a treatment of MDD during the current quarter. This product is a novel NMDA receptor antagonist, a class of drugs effective at treating major depressive disorder. Axsome was granted breakthrough therapy designation from the FDA in order to expedite the drug's development.

Axsome also plans to submit pivotal clinical data in narcolepsy, a chronic sleep disorder that causes overwhelming daytime drowsiness, for another product called AXS-12 by mid-2023. The cause of this disease, which is associated with excessive drowsiness and sudden attacks of sleep, is not lack of sleep, but abnormal brain activity. Provigil, Xyrem and Xywav, which represent the current gold standard for the treatment of narcolepsy, are not effective enough and they are also classified as controlled substances that can cause addiction. Harmony Biosciences has launched Wakix, a drug with a new efficacy profile that is suitable as monotherapy and in combination with other drugs. The active substance pitolisant is not habit-forming and is currently being tested in additional pivotal clinical studies for other conditions associated with symptoms of excessive sleepiness, such as idiopathic hypersomnia, excessive daytime sleepiness (EDS) or myotonic dystrophy.

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The treatment of acute and chronic migraine is another indication in which novel drugs have achieved a breakthrough after a prolonged period of repeated trial failures. CGRP (Calcitonin Gene Related Peptide) antagonists, the first class of migraine-specific drugs, play a key role here. They block CGRP, a peptide that is produced in neurons and induces the dilation cerebral blood vessels. CGRP plays a role in the transmission of pain signals and is considered a major factor in migraine headache and the associated sensitivity to pain, light, and noise. One of the pioneers in migraine treatment is Alder Biopharma, a company that developed eptinezumab, an antibody-based migraine treatment, and now belongs to Lundbeck. Biohaven Pharma, a company in the fund's portfolio, has developed rimegepant, a pill with the same mechanism of action that has been approved for acute and preventive treatment of migraine. In addition to a rapid onset of action with few side effects, a fundamental advantage over the currently available antibody-based treatments is that rimegepant is taken by patients as a pill for both acute and prophylactic treatment of migraine and must not be administered intravenously in an outpatient setting.

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The growing commercial success of neuroscience companies has also led to a steady increase in the weighting of these stocks in our fund portfolios over the past two years. After opening positions in Alkermes, Biogen and Neurocrine Biosciences, the Bellevue Biotech Fund is now invested in eight neuroscience specialists with innovative therapies for CNS disorders. In view of the promising clinical projects, we are confident that this exposure will continue to grow as time goes by.



Interview



Dr. Terence McManus
Senior Portfolio Manager

«Benefiting from the diverse characteristics of the healthcare sector»

Our new team member Dr. Terence McManus outlines the investment strategy of the new Bellevue Diversified Healthcare Fund.

Dr. McManus, you are the newest member of the Bellevue healthcare team. Could you describe your role and background?

Terence McManus: I am responsible for the portfolio management of the new Bellevue Diversified Healthcare Fund and support the pharmaceutical research effort. That fits perfectly with my professional background. After my Ph.D in neurophysiology I started my career as a scientist in a biotech company before working as a sell- and buy-side healthcare equity analyst in London and Zurich and most recently as a portfolio manager for a global healthcare fund. I am lucky to work in this team with its broad sector knowledge, including regional and subsector expertise, for instance in medtech or the Asian markets.

Which investor group does the Bellevue Diversified Healthcare Fund address?

We see this strategy as most attractive for institutional clients given the expected lower volatility, more defensive nature, and broad healthcare exposure. Over the long-term, our vision is that the fund could become a core holding within a client's portfolio, whether that be institutional or retail investors.

What does this mean for the investment process?

We have adopted both an bottom-up and top-down investment approach, with performance expected to be driven by allocation decisions and stock picking. For this we have developed a bespoke style matrix, and are using this as one of our pillars for allocation. Our aim is to be able to benefit from the structural growth within healthcare, but also to be supported by the defensive quality and deep value within the sector.

How is the subsector weighting in this fund?

Along with style, we are actively managing the fund using subsector allocation to take advantage of the low correlation between healthcare industries. We have a diverse exposure across subsectors, but currently hold small overweight positions in pharmaceuticals and biotech, and underweight positions in medtech & services, and life science tools.

What is the structure allocation, and what do the tail companies look like?

Our third allocation pillar is structure, this is whether a stock is within the index at a high weight (core), low weight (periphery), or outside the index. Tail companies could be small biotechs in the developed world, or quite large emerging market healthcare companies.

How are ESG criteria integrated into the investment scheme?

We include ESG criteria upfront, and also engage with our holding companies through an internally developed survey. At a portfolio level, we monitor the funds weight in the different MSCI ESG rating buckets and compare this to the healthcare index and peer funds.

In your view, which are the growth factors for the healthcare sector this year and beyond?

It is good time to take a step back. For most countries, we would continue to expect healthcare spending to outpace GDP. With broadly inelastic demand for healthcare products and services, we would expect continued growth even in a global economic slowdown. Most healthcare sub-industries are not experiencing supply issues, and demand remains elevated as we work through a backlog created by Covid. We therefore expect continued robust volume metrics in healthcare. On top of this, scientific advancements are at a high pace, and governments remain willing to pay up for innovation. These factors make the sector defensive in nature, but with strong structural and disruptive growth opportunities. We see this combination as particularly attractive for investors at present.



BIOTECHNOLOGY

Despite the positive news flow, the biotech sector has lagged the broader stock market performance since the beginning of this year.

The war in Ukraine and inflation worries have pressured the sector, along with the interest rate hikes announced by central banks. In COVID-19 vaccine news, Moderna and Pfizer/Biontech have initiated clinical trials of Omicron-specific vaccines. Sanofi and GSK presented positive results from their trial of a protein-based COVID-19 vaccine candidate. Regeneron announced it had adapted its antibody cocktail to enhance its protection against the Omicron strain and Pfizer is increasing production capacity for its COVID-19 pill Paxlovid.

Biomarin released good two-year data on its trial of roxaparvovec for severe hemophilia A, a genetic bleeding disorder. Biohaven's migraine medicine Nurtec is now also approved in Europe for acute and preventive treatment of migraine. Apellis published good 18-month data from its study of pegcetacoplan in geographic atrophy (GA), a late stage of the dry form of age-related macular degeneration (dAMD), a condition for which no treatment is currently available.

Dr. Christian Lach, Portfolio Manager



MEDTECH & SERVICES

The Medtech & Services sector (-12.3%) gave up significantly more ground during the four months from January to April 2022 than the overall healthcare market (-7.8%).

Medtech stocks tumbled 20.0%, while services stocks retreated only 0.9% thanks, among other factors, to the health insurance stocks in this subsector. Significant divergences in performance are mostly attributed to macro factors, ranging from the Omicron surge and rising interest and inflation rate expectations to the war in Ukraine.

US health insurers such as UnitedHealth, Cigna and Anthem were marked up on the solid business fundamentals of their Medicare Advantage plans (supplemental insurance coverage for seniors aged 65 and over) and the upward trends in short- and medium-term bond yields, which herald higher investment income. Non-emergency surgical procedure volumes showed a strong rebound in March and April. New product approvals were also announced, such as the Dexcom G7 continuous glucose monitoring system (Europe), the OmniPod 5 interactive insulin delivery system (USA) and the miniaturized, leadless Aveir pacemaker, which obviates the need for transvenous electrodes (USA).

Marcel Fritsch, Portfolio Manager



PHARMA & GENERICS

Large cap pharma stocks outperformed the market as a whole amid a volatile market backdrop.

The NYSE Arca Pharmaceutical Index showed a slightly positive ytd performance of 1.5% (in USD) to the end of April, easily beating the MSCI World Index (-13.0%) and the MSCI World Health Care Index (-7.8%). This outperformance can mainly be traced to the macroeconomic environment, against which pharmaceutical companies are considered a safe haven. Moreover, neither Russia nor Ukraine are very important for the pharmaceutical industry. As for product news, there were some negative reports on the oncology front: Sanofi and Roche failed to meet their goals in late-stage trials of three cancer drug candidates. Eli Lilly, on the other hand, was cheered by investors after presenting positive data from its trial of tirzepatide in participants with obesity or overweight showing a more than 20% loss in body weight. The product could be launched in the market as an antidiabetic agent already this year. However, further studies exploring its efficacy as an anti-obesity drug are required and a regulatory decision is not expected before 2024.

Samuel Stursberg, CFA, Head Research Healthcare Fonds



ASIA & EMERGING MARKETS

Political and macroeconomic developments have both had a growing impact on Asian equity markets during recent months.

The publication of several lists of sanctioned individuals and entities by the US government, for example, exposed Chinese healthcare companies to a higher level of uncertainty. Meanwhile the US also upped the pressure on Chinese companies listed as ADRs in the US to provide full access to auditing reports. This news led to some heavy selling on stock exchanges.

The growing dissimilarity between Japanese and US monetary policy reduced the value of the yen versus the dollar by well over 10% within a few short weeks. This should have a positive effect on the sales of the highly export-oriented Japanese pharmaceutical and medical technology companies. From a fundamental perspective, many Asian healthcare companies are still performing very well. Legend Biotech, for example, recently achieved a breakthrough in its multiple myeloma program. The FDA approved the genetically modified autologous T-cell therapy (CAR-T) developed by Legend Biotech and Janssen for the treatment of patients with advanced multiple myeloma in late February.

Oliver Kubli, CFA, Portfolio Manager

Internal news

We are excited about the new additions to the Healthcare team:



Dr. Teresa Vilanova
Healthcare Analyst

Teresa Vilanova is a healthcare analyst at Bellevue Asset Management. Prior to this, Teresa completed a PhD on the topic “Development of a Non-invasive Tool for the Treatment of Infertility” at the University of Oxford. After her studies she gained experience in the clinic as well as in private equity. Teresa is a member of the Medtech & Digital Health Team, where she is mainly engaged in researching life science companies, leveraging her expertise in molecular biology. “My everyday work is fascinating. Not only do I get to update my knowledge of disruptive technologies, I also get to see how the companies behind them help pave the way for future diagnostic systems.”



Dr. Terence McManus
Senior Portfolio Manager

Terence McManus is a Senior Portfolio Manager at Bellevue Asset Management. He has 12 years of experience within healthcare-specific investing and analysis in London and Zurich. Terence started his career as a scientist focused on drug discovery. He holds a PhD in neuroscience from the University of Southampton, UK.

Terence is lead portfolio manager of the recently launched Bellevue Diversified Healthcare Fund. In addition, Terence supplements the team's pharmaceutical research effort with his in-depth knowledge of this core healthcare subsector. The Bellevue Diversified Healthcare Fund aims to benefit from the healthcare sector's positive characteristics of above-average growth but largely defensive and stable end-markets. Backed by the deep pool of healthcare subsector/regional knowledge at Bellevue Asset Management, the fund aims for robust returns across market conditions through diligent active management, diverse exposure, and a tilt towards structural growth.

“The Bellevue Diversified Healthcare Fund supplements the offering here at Bellevue Asset Management and, as a relatively conservative, low volatility option, we hope it can become a core holding for a broad range of clients in the coming years.”

News

Stage is set for new products and therapies

Significant clinical progress has been made with a number of promising new therapeutic approaches, bringing them closer to market approval. This issue of our Healthcare Observer is devoted to recent groundbreaking advances in neurology. In the field of metabolic diseases, Eli Lilly will apply for regulatory approval of tirzepatide as an anti-obesity agent this year. After the release of very strong clinical data, industry experts forecast the drug could generate annual sales in excess of USD 4 bn already by 2025.

In oncology, two CAR-T therapies were recently greenlighted by the FDA. Bristol-Myers Squibb's Breyanzi was approved as a treatment for large B-cell lymphoma and Carvykti, a therapy jointly developed by J&J and Legend Biotech, was approved as a treatment for multiple myeloma. Marketing authorization in Europe should soon follow. The use of natural killer cells (NK), which represent up to 15% of all lymphocytes circulating in the human immune system, is still in the early stages of development. NK cells can attach to cancer cells or virally infected cells and eliminate them. Nkarta will present clinical data on its monotherapy candidate for acute myeloid leukemia by mid-year, while Fate has started clinical trials of four investigational agents in different blood cancers.

New cancer drugs from China

The Chinese biotech company Legend is the best example to date of the progress Chinese companies are making in oncology, having released excellent data from a pivotal trial of its blood cancer drug cilta-cel. Study data showed that 83% of patients had no signs or symptoms of cancer at median follow-up of 22 months. Beigene received EU approval for zanubrutinib for the treatment of a blood cell cancer characterized by an excess of abnormal white blood cells in the bone marrow. Both companies are among the largest biotech positions in our emerging markets fund. The Chinese government has designated biotechnology one of the country's key high-tech areas that it aims to boost during this decade.

The overall weighting of Chinese healthcare companies in our portfolio remains unchanged, but we reduced Brazil's weighting. Both the Brazilian real and the various Brazilian companies in the portfolio have made significant gains since the beginning of the year, which prompted us to realize profits. We slightly increased India's weighting in the portfolio. The fund has no exposure to Russia because there are no companies there that suit our investment strategy.

Healthcare stocks as an inflation hedge

In which sectors will company profits be eroded by prolonged high inflation and which companies will be in a position to pass rising costs through to the buyers of their products? These questions are having an impact on the sector preferences of investors and on analyst estimates of corporate earnings. The healthcare industry represents a stable investment universe in today's market environment. The innovation factor makes a crucial difference: The long-term added value associated with new products and treatments creates a monopolistic situation for the innovation leaders. This gives them pricing power and that fuels operating profit growth. In the near term, protection against inflation and relatively inelastic demand in the event of a recession are important from an investment point of view. Defensive industries are perfect candidates here, especially healthcare companies with high operating cash flows and attractive valuations. We have recently placed more emphasis on these defensive elements in our funds.



Outlook

Breakthrough results expected at oncology congress

Attendees at the annual meeting of the American Society for Clinical Oncology (ASCO) in Chicago from June 3 to 7 will gather in person for the first time in three years and Bellevue's investment specialists will also be there. Investor attention has recently shifted to advances in oncology, after having been riveted for several years on medical research efforts to bring the COVID-19 pandemic under control. As ASCO 2022 approaches, results from a number of clinical trials analyzing CAR T-cell therapies and antibody drug conjugates (ADCs) are at the top of the agenda. The advantage ADC technology offers is the antibody-mediated delivery of chemotherapeutic compounds directly to cancer cells, where they can release their cytotoxic payloads, minimizing the impact on normal, healthy cells. Trial results for ADC therapies targeting breast cancers with no over-expression of HER2 will be eagerly awaited at ASCO 2022. Gilead and AstraZeneca in collaboration with Daiichi Sankyo are the ones to watch here. Genmab and Seagen will present data for their ADC therapy for the treatment of metastatic cervical cancer. Genmab will also give an update on its trial of epcoritamab, a bispecific antibody, in patients with B-cell lymphoma, a blood cancer. Roche will present clinical data for a checkpoint inhibitor for lung cancer patients. Legend Biotech, a Chinese company, will capture attention with its presentation of data from its CAR T-cell trial in multiple myeloma. If the latest efficacy data confirms the excellent response rates in this type of bone marrow cancer, the product could be administered to patients who are unresponsive to different treatment regimens and as a second-line therapy.

Aquablation: Robot-assisted surgery for benign prostate enlargement

Many men in their later years experience benign prostate enlargement, also known as benign prostatic hyperplasia (BPH). The prostate gland is located below the bladder and produces fluid for the semen. Testosterone stimulates the growth of the prostate gland throughout a man's life. The prostate enlargement almost all men develop sooner or later can cause blockage of the urethra, the tube that carries urine out of the body. The consequences include having to get up to urinate several times a night, difficulty emptying the bladder, urinary urgency, frequent urinary tract infections, and possibly even being unable to urinate at all. In addition to medications, surgical therapies are available. These options include minimally invasive approaches like Teleflex's Urolift and Boston Scientific's Rezum, which do not require general anesthesia but may produce less durable results. The gold standard is still a procedure called TURP (transurethral resection of the prostate), which works by cutting excess tissue using a wire loop carrying an electric current. TURP's dominance is now being challenged by aquablation, a procedure that also accesses the prostate through the urethra but uses a water jet to remove excess tissue. The Aquabeam product developed by Procept Biorobotics is special for another reason, however: it's a surgical robot. The device is positioned in the area to be treated. An ultrasound image of the prostate appears on a touchscreen. The surgeon uses this screen to select anatomical landmarks, and then only has to work a foot pedal to control automatic removal of the tissue by the robotic system. This level of standardization makes treatment outcomes less dependent on the experience and manual dexterity of the surgeon and shortens procedure times, resulting in more efficient use of surgical resources.

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 12.8 bn as at December 31, 2021.

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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Register now: Bellevue Healthcare Events

Dr. Cyrill Zimmermann, Dr. Christian Lach and Samuel Stursberg are looking forward to the following events with the topic:



„Six hours' sleep for a man, seven for a woman, and eight for a fool“

Napoléon Bonaparte

Napoléon's recommendation may no longer be up-to-date or even medically verifiable - but it shows that healthy, restful sleep has always been important and its duration has always been a significant issue. But what happens when sleep disorders become chronic? Advances in medicine have provided new and interesting approaches to solving the problem.

Bellevue Healthcare Events:

23.06.22: Breakfast in Basel - bellevue.ch/healthcare-breakfast-june

24.06.22: Breakfast in Zürich - bellevue.ch/healthcare-breakfast-june

29.06.22: Lunch in Geneva - bellevue.ch/healthcare-lunch-june

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