

Bellevue Investments

Healthcare Observer

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Solutions when medication no longer works

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Dear investors,

Global COVID-19 vaccination efforts and the effectiveness of the vaccines against the various variants will shape the overall picture for the biotech and pharmaceutical industries in 2021. But there were also other remarkable breakthroughs besides all the news and developments associated with the coronavirus pandemic. On the drug development front, the FDA approved Aduhelm for Alzheimer's in a decision that was certainly controversial even within the agency. That approval decision could open the door for other therapeutics that for the first time can at least slow the progression of this previously incurable neurodegenerative disease. Read the interview with our newly hired expert Lukas Leu to find out which companies are leading the way here. The medtech industry offers neurostimulators and other solutions for other nervous system disorders such as Parkinson's or epilepsy. In this market segment, digitization is paving the way for increasingly better and smaller devices. Our feature article presents the innovation champions in this field and highlights those that are in our fund portfolios. We hope you enjoy reading the current issue of our Healthcare Observer. Be safe and stay healthy.

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

Solutions when medication no longer works

Many illnesses today can be effectively controlled and cured by drugs. However, in some conditions such as Parkinson's disease, epilepsy and chronic back pain, medication may not be effective enough. This is where neurostimulators can help – and as digital technology advances, the devices coming to market are getting better and smaller.

Medical conditions that are partly or completely unresponsive to drug treatment are far from rare. One example is Parkinson's disease, which causes slowness of movement, tremor and rigidity and leaves many patients dependent on a caregiver. Another example is epilepsy, where seizure frequency and severity may result in disability. Equally, chronic back pain may cause significant impairment of work ability. All these disorders are chronic and incurable, and most patient journeys include a series of failed treatment attempts.

Moreover, these conditions create a huge economic burden. The total cost of Parkinson's to the US economy alone is USD 52 bn. And at USD 500 bn, the economic burden of chronic pain is even higher. These figures include losses due to absence from work, social security benefits and similar, in addition to the cost of medical treatment.

Neurostimulation offers new hope

Neurostimulation is a potential therapeutic option for all these conditions because it works by delivering targeted pulses directly to the nervous system, including the brain. Amplified by the pace of digital transformation, the improvement and expansion of neurostimulation methods has been particularly impressive in the last few years – a trend likely to continue in the future. Both established corporations and start-ups are engaged in the neurostimulator market.

The neurostimulation implants approved for drug-resistant epilepsy are mainly from three companies. NeuroPace's RNS 320 system was developed specifically to treat epilepsy and comes with excellent

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medical data. For instance, patients experienced an 82% median reduction in seizure frequency at three years. The system's mechanism of action is responsive neurostimulation via two electrodes in

the brain, one of which monitors current. If this monitoring indicates that an epileptic seizure is imminent, the other electrode delivers a mild impulse to prevent it. The principle is based on a closed loop system. Data is recorded continuously, providing new insights into the condition as well as giving a more exact picture of how the epilepsy presents in the particular patient. In addition, the system enables telemedical monitoring.

Medtronic's Percept PC is suitable for use in epilepsy as well as to treat motor disorders such as Parkinson's. The platform provides deep brain stimulation according to a pre-programmed sequence. Like RNS 320, Percept PC also captures brain signals. In contrast,

Data is recorded continuously, providing new insights into the condition.

the third device, LivaNova's SenTiva & Aspire, works by vagus nerve stimulation. It was the very first neurostimulator to be approved for epilepsy but has already lost relevance.

The clear market leader in the treatment of movement disorders such as Parkinson's, with the largest number of approved therapeutic indications, is Medtronic's Percept PC, as mentioned above. Abbott's Infinity device is now also available for telemedical use and programming via the company's NeuroSphere platform. Boston Scientific's Vercise Genus boasts the highest battery capacity. Chronic back pain can also be treated by spinal cord stimulation. With all of the current devices, electrodes are implanted under the skin close to the spinal cord, the stimulator usually being located near the coccyx. Boston Scientific with its Spectra WaveWriter has replaced Intelis from Medtronic as market leader. Abbott's recently launched Proclaim is a promising new method. The real groundbreaker is a newcomer, however: Nevro's Senza Omnia, a new product on the

market, has the best clinical data and comes with innovative digital integration options to boot. As well as helping to control back pain, Senza Omnia is planned for use in other therapeutic indications including diabetic neuropathy.

The neurostimulator market as a whole is likely to experience dynamic growth, going forward. Digital transformation with the associated rise of artificial intelligence and machine learning means future devices are likely to have the capacity for continual learning and self-improvement. At the same time, it will also be possible to produce ever smaller devices and electrodes that will be all the easier to implant. All the signs point to increasing innovation in this area.

Neurostimulator suppliers in our portfolio of funds

Two of our funds are of special interest to potential investors in the field of neurostimulation. BB Adamant Medtech & Services prioritizes sustainable outperformance with a clear focus on large caps. As of August 2021, 17% of the fund’s portfolio was invested in companies involved in neurostimulation, specifically: Medtronic, Boston Scientific, Abbott, Nevro, Inspire Medical and Axonics. NeuroPace, Nevro, Inspire Medical and Axonics together account for 10% of BB Adamant Digital Health’s investment portfolio, which focuses on rapidly growing digital health companies with high expected returns.

Sector news

Stormy waters ahead for China’s healthcare industry?

A billion-dollar fine on Internet giant Alibaba, a crackdown on the booming online tutoring industry or the sudden postponement of an IPO as was the case with Ant Group – the government heads in Peking are taking drastic action to strengthen their control over the country’s private-sector tech companies. Investors are rightly asking whether or how Chinese healthcare companies could be affected by these moves or other government intervention still to come. We believe that the healthcare sector as a whole will not face the same treatment.

Raising capital through a market listing

Persisting low interest rates have fueled a growing trend in the healthcare industry of turning to financial market to raise capital. That is clearly reflected in the new listings of biotech firms via SPACs (special purpose acquisition company), or listed shell companies.

Healthcare is already one of the most highly regulated industries in China.

Such regulatory intervention is most likely to affect certain healthcare sub-sectors that, like some tech companies, are focused on data and do most of their business with consumers. It is important to recognize that healthcare is already one of the most highly regulated industries in China and it is still in the early stages of its development. Despite having made tremendous progress in recent years, China’s healthcare sector still lags its Western counterparts in terms of innovation. Viewed from the perspective of domestic policymakers, private-sector healthcare companies are crucial for delivering better healthcare at lower cost and thereby promoting common prosperity, so they belong to one of the industries that have been designated a strategic priority by the Chinese government. We do not expect stormy waters for the Chinese healthcare industry for these reasons.

Six biotech companies have been taken public via SPACs so far in

Investors raise funds by listing a SPAC on a stock exchange and then use the proceeds to finance a merger with private business. The largest biotech SPAC deal to date took place in August when CM Life Sciences III Inc. merged with EQRx Inc. in a transaction worth USD 1.8 bn. Six biotech companies have been taken public via SPACs so far in 2021. Another 22 biotech firms have announced that they intend to go public via a SPAC before the end of the year. SPAC vehicles have attracted plenty of attention as a new means of financing, but investors often don’t know what company they will ultimately be invested in. Since the SPAC segment is still lightly regulated, there is a risk that the euphoria for these vehicles will suddenly end because of some scandal. That said, we believe M&A and research partnerships in the drug development industry are here to stay. Biotech companies with proprietary technology platforms and novel treatment approaches such as mRNA, gene editing and cellular therapies, particularly in cancer, autoimmune disorders, neurological disease and rare hereditary diseases, will likely be a major focus of these trends.

Interview



Dr. Lukas Leu
Healthcare Analyst

“Best-case scenario: three products approved by the end of 2022”

Lukas Leu explains in an interview how groundbreaking the approval of Biogen’s drug Aduhelm is for research in the complex field of Alzheimer’s disease.

Is Aduhelm going to be a new Biogen blockbuster soon?

Lukas Leu: We expect initial sales of Aduhelm to be modest due to the unanswered questions regarding efficacy and the lack of clarity regarding reimbursement by health insurers. Biogen will need to convince clinics, specialists and health insurers who are still critical of reimbursement. However, positive data and initial feedback from the field could quickly build momentum and influence what are likely to be mixed opinions on the efficacy of Aduhelm.

Is the FDA decision likely to boost Alzheimer’s research?

Our team believes that this very idea was the key motivator for the approval of Aduhelm. Eli Lilly will present study results for the Alzheimer’s antibody donanemab by the end of the year. Roche is in discussions with the FDA to obtain accelerated approval for gantenerumab prior to completion of ongoing clinical trials. If both antibodies prove that they can eliminate amyloid beta plaque deposits in the brain and thus slow the progression of the disease, the validity of this therapeutic approach could be confirmed. For the beta-amyloid hypothesis and reimbursement, this is an enormously important argument.

Following a series of setbacks, targeting Alzheimer’s by clearing plaques was a highly controversial approach.

There is now consensus that some interplay between amyloid beta plaques and tau fibrils triggers onset and progression of the disease. According to current study results, certain genetic mutations promote the increase of new deposits and thus the formation of the tau fibrils. This then results in the serious damage to neurons and decline in cognitive abilities. The key question is where the better target for active substances lies and how exactly the pathological processes are connected.

Is early-stage treatment the ultimate key to success?

Thanks to ever-improving biomarkers, early stages of Alzheimer’s disease can be detected more easily, and yet the FDA will probably still rely on so-called PET scans in the near future. In particular, in the pathophysiology of tauopathies, the role of tau phosphorylation is only partially understood. To advance this understanding, accurate quantification of tau fibrils in the living brain is critical and research on new PET tracers is highly topical. Along the way, advances in blood-based biomarkers will continue to advance.

Side effects remain due to the high antibody doses.

Because only a maximum of 3% of the antibody substances cross the blood-brain barrier into the brain, higher doses are necessary. This can lead to brain edema or headaches in patients. Differentiated is the approach of Alzheimer’s vaccines, which should induce a humoral immune response against pathological tau or beta-amyloid proteins in the brain.

What developments can be expected in the next 18 months?

In the best-case scenario, Eli Lilly and Roche will receive approval for their products. Then we would probably already have three drugs on the market by the end of 2022, which would have a positive impact on access to these drugs.



BIOTECHNOLOGY

The biotech sector was buoyed by good news flow and outperformed the broader market in the period since May.

For COVID-19 vaccines, initial data indicate that heterologous vaccine schedules using different types of vaccine approaches could significantly enhance protection. This news puts the data that CureVac published for its mRNA vaccine candidate in a different light. The findings are positive for other mRNA vaccine producers such as Arcturus and for companies pursuing alternative vaccine approaches, e.g. Bavarian Nordic. Meanwhile mRNA vaccine pioneers Moderna and BioNTech continue to expand their production capacity. The FDA's approval of a new treatment for Alzheimer's disease, Aduhelm from Biogen, underscored the agency's push to promote greater innovation. In the gene-editing field, Intellia reported encouraging data from an early-stage ATTR amyloidosis trial. A single course of treatment with NTLA-2001 resulted in an 80% reduction of the misfolded clumps of TTR protein. In the field of oncology, Genmab has sustained its fast growth thanks to Darzalex, which is becoming the standard of care for first-line treatment of multiple myeloma. Chinese biotech firms were marked down due to uncertainty about potentially stricter regulatory standards for new medicines, but companies such as Beigene, Innovent or Zai Lab are still ideally positioned in such a scenario.

Dr. Christian Lach, Portfolio Manager



MEDTECH & SERVICES

The Medtech & Services sector (+7.8%) delivered a mid-tier performance in the April-August period.

As expected, the quarterly reporting season buoyed medtech sector stocks. Healthcare services providers are on a more solid footing now that standard medical treatments can again be performed despite the upturn in new coronavirus cases. US health insurers (S&P Managed Health Care +2.3%) were weak due to the double whammy of the increasing number of medical procedures and the extra COVID-19-related costs. Nevertheless, thanks to their strong performance in the first four months of the year, the year-to-date performance of US health insurance companies (+16.0%) is within range of the Medtech & Services sector's ytd performance (+17.3%) and that of the broader healthcare sector index (MSCI World Healthcare Net +17.2%).

In light of the growing momentum of vaccination campaigns around the world, we expect to see a rapid increase in vaccination rates. This should have a positive impact on the performance of medical technology stocks (strong sequential growth in elective procedures) and US health insurance stocks (decline in COVID-19-related costs). US health insurers are still trading at a significant discount of more than 30% to the total market.

Stefan Blum, Portfolio Manager



PHARMA & GENERICS

The healthcare sub-sectors pharmaceuticals and generics have developed differently on the financial markets over the last four months.

Whereas generics stocks tended to move sideways overall, large cap pharmaceutical stocks made significant gains. The NYSE Arca Pharmaceutical Index rose by a whopping 12.9% (in USD). In addition to the business performance of corona vaccines, where Pfizer, among others, is playing a leading role, a lot of attention was paid to the US approval decision regarding the Alzheimer's drug Aduhelm from Eisai and Biogen. In fact, the drug was approved on June 7, 2021, which was also received with goodwill by the markets. However, it quickly became clear that it was unlikely to be a quick commercial success due to the criteria that potential patients would have to fulfill in order to be reimbursed in a lengthy process. More commercially relevant is the drug Wegovy from Novo Nordisk, which is used for weight reduction and also received US approval in June. It is already clear that this GLP-1 receptor agonist, which we reported on in detail in the last Observer, has a good chance of becoming the most successful diabetes drug.

Samuel Stursberg, CFA, Head Research BB Adamant



ASIA & EMERGING MARKETS

Increasing regulation of China's private sector through government intervention has dragged the country's stock market lower, and in the meantime also on healthcare stocks.

However, China's healthcare industry is already highly regulated. Strict regulations have been introduced during the past ten years affecting the entire value chain, from R&D to the pricing of approved products. Access to high-quality healthcare products and services that ordinary citizens can afford is one of the Chinese government's top priorities, especially against the backdrop of a rapidly aging population.

Most of the Chinese stocks in the portfolio published excellent results for the first half of 2021. Wuxi Biologics' first-half sales jumped 127% yoy. Biotech company Innovent proved that it can generate fast growth with its leading PD-1 inhibitor Tyvyt as a cancer drug in the face of growing competition.

Due to highly anticipated FDA decision on Alzheimer's drug Aducanumab boosted the share price of Biogen/USA and Eisai Pharma/Japan. The two companies have also applied for regulatory approval in the EU, Switzerland, Canada, Brazil, Japan and Australia.

Oliver Kubli, CFA, Portfolio Manager

In Focus

A matter of the heart

Paul R. Vogt is one of the world's most renowned cardiologists and the president of the EurAsia Heart Foundation, a non-profit organization that he initiated in 2006. Bellevue entered a three-year partnership with EurAsia Heart Foundation in July of 2021. The foundation has a network of medical experts that provides professionals in developing and emerging market countries training in cardiovascular medicine, ranging from prevention and diagnostics to cardiac surgery and therapy. Cardiovascular disease represents one of the most common causes of death in developing and emerging market countries. It has a clearly detrimental impact on the economic and social development of the poor.

A group of European physicians, nurses and medical technicians provide a range of local services free of charge through the foundation. Thanks to their personal commitment, the EurAsia Heart Foundation has performed 4600 operations, advised 18000 people and treated 22600 patients. The foundation's long-term goals are reducing cardiovascular disease mortality, providing patients with adequate treatment in terms of quality and cost-effectiveness, and promoting international cooperation in this field of medicine. New projects are planned in the Ukraine, Myanmar, Kyrgyzstan and Uzbekistan. The foundation has an annual budget of CHF 2.1 mn for medical equipment and surgical procedures.

Thanks to their personal commitment, the EurAsia Heart Foundation has performed 4600 operations.

Clinical research conferences, vaccination rates and drug prices

Public attention has been focused on novel vaccines that can bring the COVID-19 pandemic under control, but this year is also distinguished by a steady flow of clinical trial data in oncology. Good progress was reported at the annual gatherings of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO). Fate Therapeutics is expected to provide an update on its cellular therapies for patients with lymphoma in December and present the latest data at the ASH 2021, the world's premier conference for hematology professionals. Data on studies of bispecific antibody-based therapeutics being conducted by Genmab, Regeneron Pharma and Roche will also be presented at that conference. New, groundbreaking anti-cancer treatment options could become reality thanks to the next-generation solid tumor cell therapies AdaptImmune is developing. Robust data will be presented at the annual meeting of the Society for Immunotherapy of Cancer (SITC) in Washington in November.

In Alzheimer's, the big surprise was the FDA's approval of Aduhelm in June, which sparked new efforts in this major field of neurological research. At the Clinical Trials on Alzheimer's Disease (CTAD) Conference in November, updated data is expected from Biogen as well as from its rival Eli Lilly. Data from AC Immune on semorinemab, the first anti-tau antibody that has produced positive results in Alzheimer's, will also be presented at the CTAD. The bush fires triggered by the debate over excessively high drug prices are no longer burning out of control, but they still flare up every now and then. However, negative surprises on this front are not expected. The general message from regulators is that drug innovation should continue to pay off, especially in untreated or poorly treated diseases. Vaccine manufacturers remain attractive from an investor's point of view. Although the delta variant continues to drive the pandemic, the COVID-19 vaccines in the market are still highly effective. Moderna and BioNtech will publish data on COVID-19 booster vaccines and other viral infections as well as other products during the months ahead.

Internal News

We recruited more specialists for our biotech and medtech teams this year



Dr. Lukas Leu
Healthcare Analyst

Lukas Leu is a Healthcare Analyst at Bellevue Asset Management. He holds a Ph.D. in biochemistry from ETH Zurich and worked for the university as a research fellow and an Equity Research Analyst covering the healthcare sector before joining Bellevue Asset Management.

Lukas is part of the «Funds & Mandates» Team and will primarily be engaged in analyzing biotech and pharma companies. He will identify the market potential of new drugs and technologies early on and assess their market potential relative to the closest competitors, Especially novel therapeutic strategies such as all forms of cell therapy, bispecific antibodies in cancer, or mRNA technology as a platform for producing vaccines. «The new technology of targeted degradation of pathogenic proteins is very exciting,» says Lukas Leu, referring to one of his current research priorities.



Mateusz Niedzwiecki
Healthcare Analyst

Mateusz Niedzwiecki holds a degree in medicine from the University of Zurich. Before joining Bellevue Asset Management, he worked in general and trauma surgery at the Horgen Hospital and most recently at the department of Urology at the University Hospital Zurich. His tasks as a member of the Medtech Team include evaluating the clinical benefit of recently introduced medical procedures in comparison to established treatment methods. Fundamental research and the perusal of scientific journals will play an important role here. «Personally, I'm fascinated by the technologies that enable minimally invasive procedures, making formerly risky procedures increasingly simpler and less risky.»

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 14.4 bn as at June 30, 2021.

One of Bellevue's core areas of expertise dating back more than 25 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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