Bellevue

Excellence in Healthcare Investments

Healthcare Observer

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Dear investors,
After a weak start to the year, biotech stocks have recently recovered some lost ground. Positive fundamental news flow bolsters our confidence that their upward move will continue during the second half of the year. As of mid-June, a total of 22 new drugs had been approved by the FDA since the beginning of January, which is seven more than the same period in 2022. This suggests 2023 could be an exceptionally good year for new drug approvals. Recent developments and innovations in oncology, Alzheimer's disease and metabolic disorders such as diabetes and obesity are being hailed as momentous breakthroughs. The treatment of diseases of the eye is, at first glance, an unspectacular field, but it is a vast field in terms of therapeutic sub-segments. Our latest issue of Healthcare Observer casts a spotlight on the wide variety of new treatment approaches within the field of ophthalmology. New treatments in the medtech industry such as pulsed field ablation for the treatment of atrial fibrillation are also highlighted in this issue.

We hope you find our articles informative and insightful.

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

Breakthrough treatments for major eye diseases and disorders

The first drugs that delay the progression of dry macular degeneration have been approved. Major breakthroughs have also been achieved in virtually every area of ophthalmology.

Amid the shadows of the acclaimed breakthroughs in areas such as oncology, broad progress is being made in the field of ophthalmology that is just as spectacular. From a medical point of view, the eye is a highly complex and, of course, very important sensory organ. It is the only organ where direct observation of the blood vessels and the nerve cells is possible. Many systemic diseases therefore also manifest in the eye. From a commercial standpoint, ophthalmology is a very attractive field because many eye diseases and disorders are quite common.

Focus on refractive errors of the eye
Refractive errors of the eye that can be treated with glasses, contact lenses and, increasingly, with laser-assisted refractive surgery represent the largest segment within the global ophthalmology market. J&J, Alcon, Bausch Health and Carl Zeiss Meditec are the leading listed companies in this market. Standardized refractive surgery for astigmatism correction has recently become a treatment option, along with multifocal contact lenses for age-related farsightedness, a condition characterized by the loss of flexibility of the lens in the eye and a weakening of the ciliary muscle. Alcon, J&J, Bausch + Lomb and Cooper are the leaders in this segment. So-called PresbyLASIK

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surgery permanently reshapes the cornea to correct presbyopia, much like a multifocal lens. Since this is an irreversible procedure, and because presbyopia often stops progressing around age 65, most patients opt for the latest generation of contact lenses instead.

Dry eye syndrome (keratoconjunctivitis sicca, dry eye disease) is a condition caused by abnormal tear film production or breakdown. The drugs currently prescribed for this condition primarily improve the moisture content of tear film and try to alleviate the frequent inflammatory symptoms with cortisone, cyclosporine A (Restasis) or lifitegrast (Xiidra). Miebo is a new treatment option from Bausch + Lomb / Novalik that was approved in 2023. It is the first drug that

> Miebo is a new treatment option from Bausch + Lomb / Novalik that was approved in 2023 and it is the first drug that improves the oily outer layer of the three-layered tear film.

improves the oily outer layer of the three-layered tear film. Whereas people will notice dry eye syndrome rather quickly after onset,

green star, or glaucoma, is an eye disease that can go unnoticed for quite a while. Glaucoma is the most common cause of irreversible vision loss, because the reduced range of vision is often not detected until the optic nerve has already been damaged and this damage cannot be reversed. Of all the known risk factors and influencing factors, only high intraocular pressure is treatable. Ocular hypertension occurs when the outflow of a water-like fluid is impaired. Previous drugs such as Latanoprost are prescribed to treat the non-pressure-dependent uveoscleral outflow or the pressure-dependent outflow pathway (Schlemm's canal). The latter can now be treated for the first time with Netarsudil, a Rho kinase inhibitor developed by the biotech company Aerie Pharma that was approved in 2017. Alcon bought up Aerie at the end of 2022.

Cataracts, also known as gray star, are cloudy areas that form on the eye's lens and are the leading cause of vision impairment among the elderly worldwide. Thanks to advances in cataract surgery options and in intraocular lenses, excellent results are already being achieved with lens implants. However, prismatic effects or other problems such as starbursts, halos around lights, excessive glare and blurred vision are a challenge in some situations. That said, chemical modifications of the intraocular lens materials have raised the water content of the lens implants and thereby reduced the aforementioned side effects while improving contrast ratios.

AMD, a huge market

Age-related macular degeneration (AMD) is a classic retinal disease due to aging. The macula lies at the back of the retina, opposite the lens, and has the highest concentration of photoreceptor cells. It is where the sharpest point of vision in the eye is located. In about 10% of all people affected by AMD, disease progression is swift and characterized by abnormal blood vessels that damage the retina and are susceptible to vascular leakage and fluid buildup inside the eye. Standard treatment consists of drugs that block the growth factors (VEGF) that are responsible for the blood vessel growth. However, the monthly injections into the eye are unpleasant. Nevertheless, the market for anti-VEGF therapies has expanded to more than USD 13 bn and it continues to grow as populations age. Market leader Regeneron is developing a higher-dose form of Eylea that is expected to be approved by June 27, 2023. Last year Roche received approval for Vabysmo, the first bispecific antibody approved for the eye. Both drugs can be administered at longer intervals of three to four months.

Last year Roche received approval for Vabysmo, the first bispecific antibody approved for the eye.

There were no approved treatments for dry macular degeneration (dAMD), which represents nearly 90% of cases and usually progresses slowly, until recently. In early 2023, Apellis received regulatory approval for Syfovre, the first-ever treatment for geographic atrophy, a late form of dAMD. Syfovre reduces the risk of severe vision loss by more than 50%. Apellis's competitor Iveric is developing Zimura, likewise a complement inhibitor, which is expected to be approved in August. Shortly before this approval decision, Iveris was acquired by Astellas for USD 3.8 bn, a markup of nearly 40% from the pre-announcement closing price.

The use of gene therapy to treat rare eye diseases

There are approximately 550 rare eye diseases, and many of them are monogenic, i.e. they are caused by a single gene disorder. In 2017, Spark/Roche's Luxturna became the first gene therapy to be approved for a rare form of inherited vision loss caused by biallelic RPE65 gene mutations. The therapy (RPE65 gene replacement) has already shown astonishing success in children and the number of gene therapies for eye diseases has steadily increased ever since. Regenex and Abbvie are expected to present data from their pivotal studies in wAMD during the second half of 2023. If successful, this one-time therapy could make anti-VEGF injections a thing of the past. In addition to Regenex, Adverum and 4D Molecular Therapeutics are also working on gene therapies for wAMD. Antibody therapies are now available that, for the first time, enable targeted treatment of thyroid eye disease or Graves' eye disease during the acute phase. Horizon Therapeutics has increased its sales guidance for Tepezza (anti-IGF-R1) to USD 3-4 bn. Viridian, another competitor, has now entered the final stage of clinical testing too. The Bellevue Biotech Fund's portfolio is invested in many of the above-mentioned companies; about 20% of its portfolio is allocated to the field of ophthalmology and it has benefited from the progress being made. Other Bellevue funds such as the Healthcare Strategy, the Diversified Healthcare, the Medtech & Services and the Asia Pacific Healthcare Fund have allocated up to 5% of their portfolio assets to the field of ophthalmology.

Regenex and Abbvie are expected to present data from their pivotal studies in wAMD during the second half of 2023.

Interview

Dr. Terence McManus
Portfolio Manager

Peak sales of at least USD 30 bn in the obesity area possible

The internet has come alive with stories of obesity drug Wegovy, how big could this be?

Terence McManus: We expect the market for anti-obesity drugs to become one of the most significant in medicine. Two years ago this was just a one- or two-billion dollar drug market, but the launch of GLP-1 agonist Wegovy by Novo Nordisk has been a "game-changer". The efficacy level now matches patients expectations, and there are limited side-effects. Consensus is looking for at least USD 30 bn peak sales for this drug class in obesity alone.

Why is this market taking-off now?

In the US each stakeholder has slowly moved to acknowledging that obesity is a real disease and has to be treated as such. Therefore the stars-have-aligned in the US, we have reimbursement, doctor support, patient demand, and now an effective drug. The positive effects on long-term healthcare costs are well understood, albeit with some debate remaining on what level of disease a positive pharmacoeconomic benefit is achieved.

Who can get reimbursement for these weight-loss drugs?

In the US we expect a high percentage of commercial plans to reimburse Wegovy. In some cases at a BMI of only 27 if they have one additional co-morbidity such as high blood pressure. This is a low threshold, the patient is not even technically obese! In Europe it is a more mixed picture, with maybe only half of the major countries currently reimbursing, and a higher threshold for the coverage than in the US.

Wegovy is a GLP-1 agonist, a drug class used in diabetes. What is the future for this class?

We expect the GLP-1 agonists to develop into one of the largest drug classes ever given the multiple potential diseases that could benefit from targeting metabolism. In terms of peak sales, we are talking about rivaling the PD-1 mAbs in cancer or anti-TNFs in autoimmune diseases. In diabetes, GLP-1 agonists have been available for a while, but have moved forward in the treatment algorithm. In this population, we know that they reduce weight and importantly reduce the risk of cardiovascular events. We also expect other benefits, such as reducing kidney disease or fatty liver.

What is the next big catalyst in obesity?

There is a major catalyst coming around mid-year. The positive read-out of a clinical trial called SELECT for Wegovy investigating cardiovascular benefit in the obese not-diabetic population will be very important for supporting reimbursement in the US and Europe. We see this as an important value inflection point for Novo Nordisk. Eli Lilly has a GLP-1 franchise in diabetes, and are launching in obesity by the end of the year, so this is also a catalyst for obesity.

Beyond Novo Nordisk and Eli Lilly, are there other competitors?

Both of these companies are doubling down on this disease area and working on oral formulations and different combination therapies. Beyond the big two, Amgen recently showed good early clinical data. Pfizer has two drugs in mid-stage trials. Novartis is looking at a mechanism which aims not to lose muscle tissue, but only fat. However, all of these competitors are many years behind Novo Nordisk and Eli Lilly.

Novo Nordisk or Eli Lilly – which is the more promising stock?

We like both of them, and own overweight positions in both stocks. Novo Nordisk is the number one in diabetes and obesity, so is more of a «pure-play». Eli Lilly has a more diversified pipeline which includes oncology and Alzheimer's disease.

BIOTECHNOLOGY

Despite a steady stream of good fundamental data, the biotech sector has not been able to keep up with the overall market advance since the end of January.

Viridian Therapeutics presented positive data from its Phase I/II trial evaluating low-dose VRDN-001, an antibody for the treatment of thyroid eye disease (TED, Graves' disease). Apellis received FDA approval for Syfovre in patients with geographic atrophy (GA), an advanced form of age-related macular degeneration (dry AMD). After decades of clinical trial failures, Syfovre is the first and only treatment for GA. 89Bio, Viking Therapeutics and Akero Therapeutic presented excellent clinical data in fatty liver disease (NASH). Akero's efruxifermin showed a significant benefit in obese patients with fatty liver disease who were already being treated with GLP-1 receptor agonists compared to GLP-1 therapy alone. Sensational data was also presented in blood cancer. Legend Biotech's CAR-T cell therapy Carvykti reduced the risk of disease progression in multiple myeloma by 74% compared to standard treatment. Two major acquisitions were announced during the period under review. Pfizer offered to buy Seagen for USD 43 bn and Astellas Pharma reached an agreement to buy Apellis competitor Iveric for just under USD 5 bn.

Dr. Christian Lach, Portfolio Manager

MEDTECH & SERVICES

The Medtech & Services sector (-1.7%) showed a slightly negative performance from January to May 2023, but it beat the broader healthcare market (-2.3%).

Performance by subsector diverged. Medical technology (+7.2%) began to bounce back from its weakness in 2022, while the healthcare services subsector suffered from profit-taking in US health insurance stocks (-7.6%) on the heels of their strong performance in the previous year.

First-quarter earnings announcements have been good across the board, confirming our forecast that medical procedures would bounce back in 2023 after 2 years of a severe corona-related downturn. Meanwhile US health insurers have benefited from the growing number of people enrolled in «Medicare Advantage» and «Commercial» plans as well as from the higher level of short- and medium-term yields. Thanks to their conservative earnings guidance, they have more than enough reserves to absorb a full recovery in elective procedures.

Stefan Blum, Portfolio Manager

PHARMA & GENERIKA

Strong sales reports for Novo Nordisk's Wegovy and Eli Lilly's Mounjaro continue to make big waves.

Both medicines have shown weight-loss effects in obesity, although Mounjaro has so far been approved as a diabetes treatment only. Eli Lilly also published Phase III data on its Alzheimer's drug Donanemab in May. The data wasn't jaw-dropping but still got a positive response. Of particular importance was that it confirmed the mechanism of action of this class of products, i.e. the build-up of beta-amyloid plaques in the brain was prevented with the help of antibodies, and this news was also welcome for Eli Lilly's competitors Biogen and Eisai, which have submitted a similar product called Leqembi for regulatory approval. FDA approval for the very first vaccines indicated for the prevention of lower respiratory tract disease caused by respiratory syncytial virus was also granted during the first half of the year: Arexvy from GSK and Abrysvo from Pfizer (both for adults 60 years and older). In mid-March, the Centers for Medicare & Medicaid published a memorandum on negotiating lower prices for certain drugs. This triggered little activity in the stock market; it seems investors have learned to contend with this new policy. In the generics space, the launch of the first biosimilars in the US for Abbvie's Humira made head-

Samuel Stursberg, CFA, Head Research Healthcare Funds

ASIEN & EMERGING MARKETS

Looking back over the period under review, positive news from the oncology space made headlines.

The Chinese biotech company Legend Biotech and its partner Johnson & Johnson published exciting Phase III data on their cell therapy Carvykti in multiple myeloma. In the second- to fourth-line of treatment, Carvykti reduced the risk of disease progression or death in 74% of all cases (hazard ratio of 0.26). This represents an entirely new playing field in the treatment of multiple myeloma compared to both standard therapy and the only other approved cell therapy for myeloma treatment (Abecma from BMS). Some doctors believe a complete cure is possible.

Beigene, another Chinese biotech, received FDA approval for its BTK inhibitor zanubrutinib for the treatment of CLL/SLL (chronic lymphocytic leukemia/small lymphocytic lymphoma). In two global Phase III studies, the drug demonstrated its "best-in-class" profile. The Japanese pharmaceutical company Otsuka has a potential money maker with Kisqali, which it has licensed out to Novartis. It published positive Phase III data on Kisqali, a CDK4/6 inhibitor, in adjuvant HR+/HER2 breast cancer.

Oliver Kubli, CFA, Portfolio Manager

News

Clinical progress in personalized cancer medicine

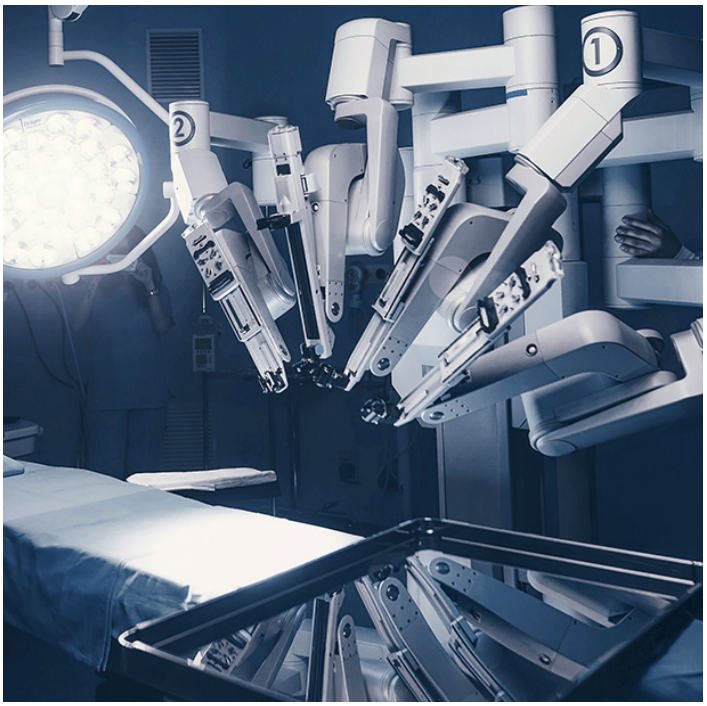
Targeted cancer therapy can have significant positive impact on cancer prognosis. This has been demonstrated by the successful outcomes of various treatment modalities ranging from cell therapy to low-molecular-weight compounds. At this year's ASCO Congress in Chicago, clinical progress and certain aspects related to the reimbursement of treatment costs sparked considerable discussion. AstraZeneca presented data from a trial of Tagrisso in certain cases of lung cancer after tumor resection. The drug cut the risk of death for patients with specific tumor mutations by an impressive 50%. Enhertu, a HER2-directed antibody drug conjugate (ADC), is another promising drug that has demonstrated broad activity across cervical, ovarian, and biliary tract cancer. Up to now the drug has been approved for the treatment of breast, gastric and lung cancers.

In bone marrow cancer, cell therapies, so-called CAR-T therapies, have cured some patients with blood cancers. In the past, CAR-T treatments were administered after patients had received multiple prior lines of therapy, but now they appear to be moving to earlier lines of therapy. Cell therapy production and administration are still the greatest challenges associated with cell therapy. Promising efficacy in bone marrow cancer has also been demonstrated by novel bispecific antibodies. This new immunotherapeutic approach is a good example of how cancer treatment options are constantly improving and expanding. That said, the financial repercussions that high-cost personalized cancer medicine have for healthcare systems remains a controversial issue.

Attractive markets beyond China

There are a growing number of interesting investment opportunities in emerging healthcare markets, particularly in India, Brazil, and Saudi Arabia, and particularly in the healthcare services segment. The pandemic led to widespread demand for better healthcare in these countries. The government has been unable to provide the level of quality demanded because of its limited resources in terms of doctors and nurses and due to a lack of hospital capacity. Saudi Arabia's government has launched numerous initiatives. Recent reforms provide previously uninsured expats and all Saudi citizens employed in the private sector and their families with private-sector health insurance plans.

We are witnessing similar developments in India's private-sector healthcare sector. There are also very promising investment opportunities in Brazil's healthcare sector. Even before the pandemic, many employees in the country's private sector had private health insurance. COVID-19 led to a huge surge in outpatient and low-margin consultations that pushed up costs for insurance providers and prevented clinics from scheduling procedures that were commercially more attractive. The situation has improved in the meantime and insurance premiums are expected to increase significantly due to the high cost ratios over the past few years. Meanwhile stock valuations are at historical lows. We significantly increased the weighting of Brazilian healthcare stocks in the Bellevue Emerging Markets Fund to almost 20% for these reasons.



Outlook

Biotechs in the valuation valley

A decoupling of the biotechnology sector from the largely positive performance of the technology sector has been witnessed so far this year. The Nasdaq 100 index was up 32% to the end of May. Its gains have been fueled by heavyweight stocks active in the fields of artificial intelligence or semiconductors. Meanwhile the Nasdaq Biotechnology Index is down 3% over the same period. Small and mid-cap biotechs that are still not generating high sales and need external capital to fund their R&D pipelines showed particularly steep losses. The same can be said about the medical technology sector, especially in the digital health subsegment.

The higher level of interest rates since 2021 complicates the financing plans of small-cap biotechs and medtechs. The drop in company valuations, which decline in step with the falling stock prices, only adds to the pressure. Companies caught in these crosscurrents are obliged to focus their financial resources even more astutely. Less promising projects are being terminated or, in the best case, licensed out. Just how risk-averse the capital market has become towards the biotech sector is evident in the shrinking number of IPOs: No less than 104 biotech hopefuls went public in 2021, but in 2022 there were only 21 biotech IPOs. As of early June of this year, a mere 7 biotechs have gone public (another 9 are in the starting gate). It is widely expected that the low valuations will prompt big pharma company to intensify their search for suitable acquisition targets. In April, for instance, Merck acquired Prometheus Biosciences, an immuno-oncology specialist, for USD 10.8 bn.

Pulsed field ablation is one of the hottest new developments in medical technology

The treatment of cardiac arrhythmias has reached a major turning point. Several pivotal studies are set to provide clinical data in 2023 and 2024, accompanied by the launch of innovative products. PFA holds great promise as a new treatment for atrial fibrillation due to its remarkable safety profile and shorter procedure duration compared to existing options.

Atrial fibrillation is the most common sustained cardiac arrhythmia. The condition can have serious consequences for sufferers, with approximately a quarter of all strokes attributed to atrial fibrillation.

The root cause is heart muscle bridges that emit disruptive electrical signals, resulting in an erratic heartbeat. The current gold standard treatment involves minimally invasive catheters that use heat or cold to ablate heart muscle fibers. In contrast, pulsed field ablation uses targeted ultrafast electric fields to create micropores in heart muscle cells, leading to their demise. Unlike thermal catheters, this technique does not damage adjacent tissue, thereby reducing complications such as esophageal or nervous system injury.

Pulsed field ablation is expected to accelerate market growth, with a projected increase in market size from the current figure of USD 7 bn to USD 12 bn in 2027. Alongside Medtronic, which has presented excellent clinical data, notable players include Boston Scientific, Abbott, and Johnson & Johnson.

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 9.4 bn as at December 31, 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

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«Investing with vision» – innovations in ophthalmology

Thanks to medical advances, exciting opportunities are opening up in ophthalmology. Treatments for age-related eye diseases and rare eye diseases are feasible for the first time. In this video feature, our experts, Dr. Christian Lach and Samuel Stursberg, inform you about this fascinating field and show investors the opportunities and risks.

Moderated by: Dr. Cyrill Zimmermann, Head Healthcare Funds and Mandates

To the Video

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