LSP Life Sciences Fund – 2019 Review
The end of a year, the end of a decade

The end of 2019, but also the end of a decade – it's time to review what has happened. The decade brought us Trump in the White House and Brexit in Europe. We have started booking our holidays on AirBNB, travelling with UBER and watching Netflix instead of TV.

We have also seen considerable developments in healthcare, medical science and research. Gene therapy was a big promise at the turn of the century but really came of age in the past few years. Scientists have made great strides in harnessing the power of the immune system to fight disease. A deeper understanding of the checks and balances of the immune system have led to the development of so-called checkpoint inhibitors, to activate the patient's natural defenses to target and kill cancer cells. These discoveries spawned a whole new area of medical science – cancer immunotherapy. This new class of drugs, which include Opdivo and Yervoy (owned by pharma company Bristol Myers Squibb, a strategic partner of LSP) and Keytruda (owned by pharma company Merck) are fast becoming the fundamental treatments for several forms of cancer. New cell-based treatments, which re-engineer cells from the patient and re-train them to fight cancer, have even cured patients. Something that was science fiction only a decade ago. And still, we are only beginning to understand the real potential of cancer immunotherapy and cell therapy. It is definitely an area that we consider to be one of the prime areas of investment in the coming decade.

Biotechnology is no longer the future of medicine – it has arrived. For example, monoclonal antibodies (laboratory produced antibodies directed at a specific disease target) were considered niche science a few decades ago, but now account for over $100 billion in *annual* product revenues. These new medicines have transformed the treatment of cancer and autoimmune diseases, as well as diagnostics. A whole range of next generation antibodies are in development which should enable more precise targeting, expand the range of disease targets, improve safety and move away from the necessity for intravenous administration.

We have also seen great advances in the treatment of a wide range of rare or orphan diseases. Treatments have moved from 'simply' replacing missing proteins such as pioneered by Genzyme (now Sanofi), to far more complex, cutting edge genetics such as used by **Spark Therapeutics** (now part of Roche). Spark was the first to develop a gene therapy which could restore sight to patients with a rare form of blindness – with a single injection into the eye. A concept which was unimaginable just a few years ago.

Cystic fibrosis has been (almost) conquered! In 2012, Vertex Pharmaceuticals won approval for Kalydeco, the first direct-acting drug against cystic fibrosis. Two more drugs followed in 2015 and 2018. Then, in October 2019, a fourth Vertex drug called Trikafta reached the market. Collectively, these drugs significantly improve lung function, and by doing so, provide dramatic, life-extending benefits to 90% of cystic fibrosis patients.

Curing some patients with Hepatitis C was possible before the start of the decade but it required a year of weekly injections, plus an additional weekly pill and terrible side effects – with only a 50% chance of success. Improvements came in 2011 with the launch of new treatments but the real breakthrough came in 2014 with the approval of the first all-oral treatment regimen for hepatitis C developed by Gilead Sciences. The once-daily pill, called Harvoni, demonstrated a nearly 90% cure rate for the most common form of hepatitis C, and did that in just 12 weeks of treatment. By the end of 2015, Harvoni was generating nearly $14 billion in sales for Gilead, making it one of the most successful drugs in history curing millions of patients around the world. It was the first time a viral infection could be cured, and the infectious agent cleared, by a drug.

And just before the turn of the decade – the FDA approved **Amarin**'s cardiovascular drug Vascepa for the treatment of patients with high triglycerides (fat) in their blood. Vascepa has been demonstrated to reduce the risk of a severe cardiovascular event (such as a heart attack or stroke) by as much as 25% on top of the benefits of statins. This is the biggest news in the field of cardiovascular disease – the largest pharmaceutical market of all - since the introduction of statins in the late 1980's.

These are just a few of the advances made in the past decade, but it gives a sense of the pace of progress. We expect to witness many more dramatic developments in the year and decade ahead. Science never stops, no matter what.

Through the LSP Life Sciences Fund, our investors have participated in many of these positive developments. The fund has invested in many of the orphan disease, oncology and cardiovascular success stories to return +541% or an annualized +20% to investors over the past 10 years. The big success story of 2010/2011 was **Amarin Corporation** which was also a winner in 2018 and again in 2019.

We have written extensively about **Amarin** in past notes, as it continues to be a favorite of ours. **Amarin** developed a method to purify the therapeutic component from fish oil. Whereas several smaller studies have demonstrated some benefits of fish oil on lowering fat in the blood (triglycerides), larger studies by other companies to demonstrate an impact on the clinical outcome of patients, had all failed in the past. **Amarin** was a successful investment for the fund in the 2010/2011 time period due to positive Phase 3 studies, which demonstrated dramatic reduction in triglycerides. We no longer held the position when FDA changed course and requested – unexpectedly and contrary to what they had agreed before - a clinical outcome study (CVOT) which not only caused a dramatic drop in the share price but cost tens of millions of dollars and took about 5 years to complete. We reinvested just ahead of the CVOT data – which exceeded all expectations by demonstrating a dramatic 25% benefit, on top of statins, in reducing the risk of cardiovascular events, such as stroke or myocardial infarction. The benefits were even higher in some patient groups. Vascepa, which was already on the market for patients with ultra-high triglyceride levels is now available for all patients with high triglycerides at risk of CV disease. A true breakthrough in the field.

The fund invested in cutting edge cell therapies for the treatment of cancer. In 2011, the renowned researcher Dr. Carl June first published promising results from a small study of three advanced chronic lymphocytic leukemia patients. The findings, which detailed how June's personalized immune cell therapy wiped out all signs of leukemia in two of the three patients, showed the first successful gene transfer therapy to create T cells aimed at battling cancerous tumors. This was the start of the CAR-T revolution. Dr. June and his team have been collaborating with Novartis. The two leading biotech companies to emerge were **Juno Therapeutics** and **Kite Pharmaceuticals** – the fund invested in both companies as each technique had its own merits. Both companies have since been acquired (Celgene acquired Juno for USD 9 billion and Gilead acquired Kite for USD 12 billion). The FDA has since approved Kymriah (Novartis) and Yescarta (Gilead) as the first personalized cell-based treatments with the potential to cure some forms of leukemia.

While these treatments are successful – they are also incredibly complex and expensive. The race is on to develop the next generation of cell therapies. There are several different approaches being used and we view **Precision BioSciences** as well **as Fate Therapeutics** as particularly promising. These companies have very different technologies, but both aim to develop off-the-shelf cell based products to overcome the limitations of the first generation CAR-Ts (that are patient specific). **Precision BioSciences** uses a proprietary gene editing platform to engineer cells using the same target as Kymriah and Yescarta but in a cell which has been stripped of its identity. The idea is to generate large quantities of cells in the laboratory, which will not be recognized as foreign (and then rejected) by the patients. Early data presented in late 2019 looks encouraging, with additional proof of concept data expected in 2020.

Fate Therapeutics uses a very different approach. FATE is a pioneer in the development of iPSC-based off-the-shelf therapies for the treatment of cancer. iPSC or induced pluripotent stem cells are a relatively recent discovery. It is a technique whereby differentiated cells such as skin or blood cells can be reverted back to an undifferentiated state. These stem cells can then be directed to become a different cell type. Fate

is using this Nobel prize winning technology to make NK or natural killer cells. **Fate Therapeutics** is the first to initiate human clinical studies with a product based on iPSC. While still in early stages of development, investor excitement around **Fate therapeutics'** platform stems from its broad applicability. In 2020, data will begin to emerge and with that we think investors will assign greater probability to the platform as it becomes de-risked.

Cell therapy is just one of the areas of excitement for the year ahead. Gene therapy has finally come of age as mentioned above. Our top pick in this segment remains **uniQure**. This Company was a great performer for the fund in 2019 and we remain optimistic about the potential for 2020. This is a company which has been around for a long time. As is often the case with cutting edge science – it takes time to convert the science into medicine. We believe that the expertise **uniQure** has built over the past few decades, in terms of the science but equally importantly in terms of manufacturing know how, will prove of tremendous benefit. Exciting early data from the hemophilia B program has transformed the share price in the past 1 to 2 years. The pivotal data from the HOPE study will be available by the end of 2020 – potentially giving the Company the first gene therapy product to cure hemophilia B. But that it not all. **UniQure** has a pipeline of other exciting gene therapy programs in development. The program to treat Huntington's disease (HD) is causing the most excitement. After years of preclinical work – the company has the green light to start treating patients and we may have initial data in the coming months. HD is a very large opportunity, so proof of concept in this indication will be impactful.

As can be expected with cutting edge, first in class technologies – there are failures. Over the years we have seen many, we were investors in a few of them. For instance, in the past year, we were an investor in the US biotech company **Marinus Pharmaceuticals** who failed to define a therapeutic dose for its treatment for depression. The Company was adopting a fast follower strategy to another biotech's drug called Brexanalone (developed by Sage Therapeutics) by developing Allopregnanolone as a more effective, easier formulation for the treatment of post- partum depression. While the Phase 2 studies did demonstrate efficacy, they fell short of the bar set by Sage and indicated that additional studies would be needed to define the optimum dose. The shares suffered badly and did not recover, even with subsequent positive data in a different indication, severe refractory status epilepticus.

Obseva is another example of a company that had some setback. A Swiss, women's health company, with a very experienced management team – **Obseva** has three products in development. Most of the value was considered to be attributable to linzagolix, which is in late stage development for uterine fibroids and endometriosis. The second product, nolasiban is being developed to improve the birth rate in fertility treatments. Despite positive read out in previous Phase 3 studies – nolasiban failed to demonstrate a statistical benefit in the final Phase 3 study – with dramatic impact on the share price. Despite subsequent positive linzagolix data – the shares have not recovered.

Sometimes, companies underperform not because they are experiencing a setback but rather because investors shy away simply because there is a *lack* of data and newsflow. Both **CytomX** and **Cocrystal** suffered from such a lack of data in the past year. In particular, the fundamental investment thesis on **CytomX** has not changed at all. The Company is developing a technique to mask the active region on monoclonal antibodies, such that they are only activated at the site of the tumor. This reduces side effects and allows doctors to potentially give higher doses of treatment. The technology can also be used to specifically hit previously undruggable targets. The market lost interest in the story when initial data was not stellar, and it has taken time to generate real proof of concept. In contrast, 2020 should be a year of data for the company and provide evidence of the uniqueness of the technology platform.

Antiviral drug discovery company **Cocrystal**, also suffered from lack of data and delays to clinical studies being conducted in Hong Kong. This, combined with lack of funding – and thus a financing overhang – made the company lose a lot of its market value. At the time of our investment, Prof. Ray Schinazi, who was the leading figure in the development of antiviral drugs for the treatment of HIV and the first cure for Hepatitis C mentioned above, was chairman and leading investor in the company. He has since taken a back seat to the management team, which in hindsight was a mistake. Data from the long-awaited Hepatitis C Hong Kong study should still come in 2020 and despite our misgivings about management, should the Nobel prize winning science translate into medical benefit – the share price will respond.

The Fund has benefited from its ability to invest in both Europe and the US and indeed two of our best performing stocks of 2019 are Benelux based: **argenx** and **Galapagos**. A long-term investment of the fund – **Galapagos** had a fantastic 2019. The Company announced the final positive Phase 3 results for its innovative new oral treatment for arthritis in late March. Then in July they signed a unique deal with Gilead Sciences. The companies were already partnered on Galapagos' lead arthritis program, filgotinib, that it had developed in-house from scratch. They have now embarked on a 10-year collaboration that will allow Gilead to leverage **Galapagos**' team of more than 500 scientists and its drug discovery platform to develop a portfolio that includes six molecules currently in clinical trials. Gilead will invest $5.1bn including an upfront payment of $3.95bn and a $1.1bn equity investment. Why didn't Gilead just buy the company? The deal value was over 60% of the Market Cap of **Galapagos** at the time of the deal. According to Gilead CEO, Daniel O'Day; "*Innovation, particularly in the early stages of our value chain, is about engaging people, motivating them correctly, getting the very best scientists and keeping a certain independence*". Galapagos has a huge stockpile of cash and the freedom to develop its growing pipeline of drugs independently – at least for the remainder of this decade.

Belgian antibody company **argenx**, is an excellent example of next generation monoclonal antibody technology platforms. **Argenx**' proprietary SIMPLE antibody development platform leverages the llama immune system, which produces a broad set of antibodies with human-like antibody fragments which are combined with its engineering technologies to produce antibodies with enhanced features, such as potency and tissue penetration. Ultimately, it is all about the treatments developed with the technology. The leading program, efgartigimod, is set to become the first of a new class of treatments for a range of autoimmune diseases. Pivotal data for the lead indication will be available in 2H20. While there was no big news item from **argenx** in 2019, management spent the time engaging with US investors following the September 2018 NASDAQ IPO. The Company has attracted the A-list of US specialty healthcare funds which have increased their holdings with each financing round. **Argenx** now has a market cap of $6.3bn and is very well financed with over USD 1.5 billion in cash on its balance sheet to advance additional products into clinical studies. In contrast to 2019, 2020 promises to be a year of big news.

For the LSP Life Sciences Fund it was a year of some companies that did very well (**Amarin, Galapagos, argenx, uniQure** amongst other) and some that have (so far) been underperforming (**Cocrystal, CytomX, Obseva, Marinus**), to end the year with a return of +11.5%[1]. Although we would have wished to see a higher return for the year (as we do every year in fact, no matter the number), we know that investing in this sector, carries volatility risk in the short term. Certain periods will be better than others. So, what will 2020 look like in terms of return? We have no idea of course. We simply endeavor to invest in some of the most innovative companies. This does involve taking risk, which we try to mitigate by applying stringent investment criteria and following an intense due diligence process for every investment we make. An important component of that process is to assess the likelihood of certain clinical trials to read out positively

[1] *Gross of fees – LSP Public*

in terms of safety and efficacy. Companies in our sector – both big and small - are required to run clinical trials because that is the only way to know for sure if a drug is safe and effective. Our society demands this and rightfully so. Looking back over our 12-year track record, we have averaged a larger than 70% success rate of picking the winners. This has contributed to our entire track record of returning over 500% since 2010. In fact, since 2007, our total return adds up to more than +850%. Over the entire period 2007 - 2019 we have had some years in which we underperformed – the performance in 2016 was negative - but also many great years where we outperformed. Clearly, our most important message to our investors – and to investors in general – is that investing in biotech is not a short-term game – drug development takes time and there will be both breakthrough successes and disappointments along the way. Importantly, we remain as committed as ever to select for the most promising innovations in healthcare for the coming decade with a view to generating solid returns for our investors as we have done over the past.

We wish all our investors a Happy New Year, a prosperous 2020 and we thank them for the trust they have placed in us over these past 10 years or longer.

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