Platinum International Health Care Fund

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Performance

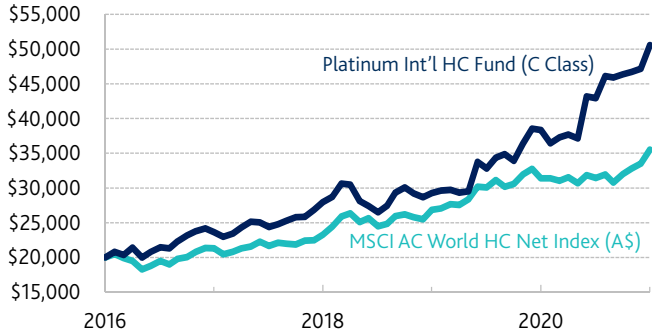
(compound p.a.⁺, to 30 June 2021)

	QUARTER	1YR	3YRS	5YRS	SINCE INCEPTION
Platinum Int'l HC Fund*	9%	32%	22%	20%	12%
MSCI AC World HC Index^	11%	13%	15%	12%	10%

⁺ Excludes quarterly returns.
* C Class – standard fee option. Inception date: 10 November 2003.
After fees and costs, before tax, and assuming reinvestment of distributions.
^ Index returns are those of the MSCI All Country World Health Care Net Index in AUD. Source: Platinum Investment Management Limited, FactSet Research Systems.
Historical performance is not a reliable indicator of future performance.
See note 1, page 4. Numerical figures have been subject to rounding.

Value of $20,000 Invested Over Five Years

30 June 2016 to 30 June 2021



After fees and costs, before tax, and assuming reinvestment of distributions. Historical performance is not a reliable indicator of future performance. Source: Platinum Investment Management Limited, FactSet Research Systems. See notes 1 & 2, page 4.

The Fund (C Class) returned 9.1% over the quarter and 31.9% over the year.[1]

It was an eventful three months for the biotech sector, one that will be etched in history we expect.

In a stunning move, the aducanumab antibody (sold under the brand name Aduhelm and developed by Biogen and Eisai) gained accelerated approval for Alzheimer's disease. This accelerated approval has wide-ranging ramifications for neurodegenerative diseases, given it was based on a measurable surrogate marker versus the more traditional cognitive benefits measure (discussed in more detail below in the Commentary).

Gene editing took centre stage. **Intellia Therapeutics** (+102% over the quarter) presented positive results for NTLA-2001, a therapy based on the Noble-prize winning CRISPR/Cas9 technology.[2] The technology essentially edits the mutated gene that causes hereditary Transthyretin Amyloidosis (ATTR), a rare disease where the liver produces misfolded proteins that deposit on organs, causing damage. Intellia has shown that by using lipid nanoparticles (LNPs), a "guide RNA" and "mRNA" encoding, the Cas9 enzyme (which acts like a pair of molecular scissors, capable of cutting strands of DNA) can be delivered systemically to the liver.

Apart from showing successful editing, it is exciting to see that Intellia is applying mRNA technology to achieve enzyme expression. Intellia has been our investment in the CRISPR gene editing space for some time, we liked the company's non-viral delivery approach and the gradual optimisation of the therapy. Targeting the liver first is smart, given LNPs naturally travel to the liver, however, extrapolating the recent data to other organs/tissue is not linear and further optimisation will be required. While the long-term safety of gene editing needs to be further explored, Intellia's progress marks a significant step in the next generation of therapeutic modalities.

1 References to returns and performance contributions (excluding individual stock returns) in this Platinum International Health Care Fund report are in AUD terms. Individual stock returns are quoted in local currency terms and sourced from FactSet Research Systems, unless otherwise specified.

2 A more detailed explanation of CRISPR/Cas9 technology can be found here: https://www.livescience.com/58790-crispr-explained.html

Drug developers may be making big strides, but tool companies and manufacturers are also gearing up for genomic medicines. During the quarter, Danaher acquired Aldevron, a manufacturer of plasmids, mRNA and proteins (with annual sales of ~US$500 million), for around US$10 billion. Earlier this year, Merck KGaA acquired AmpTec to expand its mRNA manufacturing capabilities.

There are various industry and investment ramifications emanating from the above activities. New "genomic" therapeutic modalities have arrived and precision neurology is at a key inflection point (as we discuss below). We are invested in several companies in this exciting space including **Eisai** (+47%), **Prothena** (+105%) and **Denali Therapeutics** (+37%), three companies that have been good performers for the Fund over the quarter and indeed, the year.

Elsewhere in the portfolio, our Chinese biotech holdings also advanced nicely. **CStone Pharmaceuticals** (+85%) is a less-known China biotech that is rapidly progressing to becoming a commercial company. Its partnership with Pfizer and EQRx is progressing well. EQRx is a very interesting US-based private company that has secured the rights to both of CStone's oncology antibodies. EQRx seeks to make medicine more affordable for those who need it, and as such, is looking to disrupt the product pricing dynamics in the US, particularly in the oncology space.

Changes to the Portfolio

Small commercial US biotech **Esperion Therapeutics** continues to refine its sales approach for its non-statin cholesterol-lowering products. While its partner Daiichi-Sankyo has been successful in Germany, Esperion is only making gradual progress in the US. Broad cardiovascular drug launches have been difficult, particularly for a small biotech with limited resources. However, we do believe the products have significant value for patients who have high cholesterol, but cannot tolerate the more-traditional cholesterol-lowering medications (i.e. statins), or simply cannot reduce their cholesterol levels despite intensive treatment. The stock fell 25% over the quarter due to disappointing sales figures, however, we took advantage of the price weakness and continued to add to our position.

During the quarter, we gradually increased our holding in German biotech **Centogene**. The stock fell 14% over the quarter as worries persist about Centogene's SARS-CoV-2 testing business. To us, these worries distract from Centogene's core business, which is rare disease genetic testing, so we viewed the share price weakness as a buying opportunity. We also increased our holdings in a number of commercial biotechs.

Disposition of Assets

REGION	30 JUN 2021	31 MAR 2021	30 JUN 2020
North America	36%	34%	39%
Europe	21%	24%	27%
Asia	12%	10%	6%
Australia	10%	9%	10%
Japan	4%	5%	7%
Other	1%	1%	0%
Cash	16%	17%	10%
Shorts	-1%	-3%	0%

See note 3, page 4. Numerical figures have been subject to rounding.
Source: Platinum Investment Management Limited.

Net Sector Exposures

SECTOR	30 JUN 2021	31 MAR 2021	30 JUN 2020
Biotechnology	53%	49%	50%
Pharmaceuticals	22%	23%	26%
Life Sciences Tools & Services	7%	5%	9%
Health Care Equip & Supplies	0%	0%	2%
Machinery	0%	1%	0%
Health Care Technology	0%	0%	1%
Health Care Providers & Serv	0%	1%	1%
TOTAL NET EXPOSURE	83%	81%	89%

See note 4, page 4. Numerical figures have been subject to rounding.
Source: Platinum Investment Management Limited.

Top 10 Holdings

COMPANY	COUNTRY	INDUSTRY	WEIGHT
SpeeDx Pty Ltd	Australia	Biotechnology	4.6%
Takeda Pharmaceutical	Japan	Pharmaceuticals	3.7%
Sanofi SA	France	Pharmaceuticals	3.3%
CStone Pharmaceuticals	China	Biotechnology	2.8%
Bayer AG	Germany	Pharmaceuticals	2.5%
Telix Pharmaceuticals Ltd	Australia	Biotechnology	2.4%
Quanterix Corp	US	Life Sciences Tools	2.1%
Syneos Health Inc	US	Life Sciences Tools	2.0%
Gilead Sciences Inc	US	Biotechnology	1.9%
Almirall SA	Spain	Pharmaceuticals	1.9%

As at 30 June 2021. See note 5, page 4.
Source: Platinum Investment Management Limited.

For further details of the Fund's invested positions, including country and industry breakdowns and currency exposures, updated monthly, please visit https://www.platinum.com.au/our-products/pihcf.

Commentary

As mentioned above, Aduhelm was approved because a surrogate endpoint (reduction of beta-amyloid plaques in the brain of Alzheimer patients) was positive. This is a measurable effect using a positron emission tomography (PET) scan, while measuring cognitive abilities remains more difficult and in the case of Aduhelm, the drug's cognitive benefits are widely debated (regulators have asked for additional confirmatory trials). The fact that the antibody was approved on the basis of a biomarker is akin to firing a starting gun. Eli Lilly has announced it is now looking to file for approval of its Alzheimer's antibody donanemab, while Roche is also considering an expedited filing with the US Food and Drug Association (FDA) for gantenerumab. Importantly, this will result in significant investment in this space, which we are very excited about.

We are believers in precision medicine and are confident that neurology will follow oncology's targeted therapy pathway. Oncology once had chemotherapy as its only weapon at its disposal. Today, we can classify cancer by its molecular profile rather than its location and treat it accordingly.

Many biotechs focus on deciphering the tumour microenvironment to guide drug development and subsequently drug therapy. There is no reason why neurology will be any different in years to come. Currently, we talk about Alzheimer's and Parkinson's disease at a high level but we already know there are subsets within these diseases. There are toxic protein deposits, like tau and beta-amyloid, that cause damage to neurons. The ratio of the two proteins can define if a patient responds to therapy. There are inflammatory processes causing nerve damage as well, opening another pandora's box of therapeutic targets.

These diseases are complex and they take years to manifest clinical symptoms. There are genes that when mutated can cause or put you at risk of developing neurodegenerative diseases. In the case of Alzheimer's disease, there are 35 known genetic associations and many are linked to the brain's immune system, while in the case of Parkinson's disease, there are over 95. Denali Therapeutics, a US biotech in the Fund, calls these genes degenogenes. Denali's lead drug DNL151, an inhibitor of the leucin-rich repeat protein kinase 2 (LRRK2) is being tested on patients with Parkinson's disease that harbour mutations in the LRRK2 gene. This is similar to targeting kinases that are troublemakers in cancer.

Besides these large neurodegenerative diseases there are other rare neurodegenerative diseases that are getting more attention like frontotemporal dementia (FTD), a form of dementia, or amyotrophic lateral sclerosis (ALS). These diseases are heterogeneous but we are gaining a greater understanding about the underlying genetic mutations, the molecular biology and clinical manifestation of these diseases. Alector, a US biotech we are invested in, is developing antibodies that can restore progranulin levels in FTD patients that harbour mutations in the progranulin gene and hence have an imbalance in progranulin. In early July, GSK announced an alliance with Alector to co-develop Alector's progranulin antibodies.[3]

There are other examples whereby genetic mutations are being uncovered to classify subsets of neurodegenerative diseases and allow for targeted therapies to be developed. Identifying patients with these mutations and building out a database of relevant phenotypes and molecular profiles is crucial in this space and here our research has led us to the small German company Centogene. It is this broad analysis that assists us in building out our neurodegenerative puzzle and discover new long-term investment opportunities.

Outlook

Consolidation in the therapeutic biotech space has been limited for now, while fund raising in the private market continues unabated and valuations have never been as high as they are today. It seems all the action is in unlisted biotechs, while public markets are drifting, and in some cases feel abandoned. Some recently listed biotechs were 'hot' not that long ago and are now trading at very exciting valuations. While we follow and engage with private companies regularly, we find it hard to fully comprehend valuations that are being paid. We know that patience is an absolute virtue in this space and we will remain very disciplined.

3 The two companies will co-develop these antibodies for various neurodegenerative diseases and co-commercialise in the US and share profits. Outside of the US, GSK will have exclusive rights. GSK will pay US$700 million upfront and a potential US$1.5 billion in milestone payments along with royalties.

Notes

Unless otherwise specified, all references to "Platinum" in this report are references to Platinum Investment Management Limited (ABN 25 063 565 006, AFSL 221935).

Some numerical figures in this publication have been subject to rounding adjustments. References to individual stock or index performance are in local currency terms, unless otherwise specified.

1. Fund returns are calculated by Platinum using the net asset value unit price (i.e. excluding the buy/sell spread) of the stated unit class and represent the combined income and capital returns over the specified period. Fund returns are net of fees and costs, pre-tax, and assume the reinvestment of distributions. The MSCI index returns are in AUD, are inclusive of net official dividends, but do not reflect fees or expenses. MSCI index returns are sourced from FactSet Research Systems. Platinum does not invest by reference to the weightings of the specified MSCI index. As a result, the Fund's holdings may vary considerably to the make-up of the specified MSCI index. MSCI index returns are provided as a reference only. The investment returns shown are historical and no warranty is given for future performance. Historical performance is not a reliable indicator of future performance. Due to the volatility in the Fund's underlying assets and other risk factors associated with investing, investment returns can be negative, particularly in the short term.
2. The investment returns depicted in the graph are cumulative on A$20,000 invested in C Class (standard fee option) of the Fund over the specified period relative to the specified MSCI index in AUD.
3. The geographic disposition of assets (i.e. other than "cash" and "shorts") shows the Fund's exposures to the relevant countries/regions through its long securities positions and long securities/index derivative positions, as a percentage of its portfolio market value. With effect from 31 May 2020, country classifications for securities were updated to reflect Bloomberg's "country of risk" designations and the changes were backdated to prior periods. "Shorts" show the Fund's exposure to its short securities positions and short securities/index derivative positions, as a percentage of its portfolio market value. "Cash" in this table includes cash at bank, cash payables and receivables and cash exposures through derivative transactions.
4. The table shows the Fund's net exposures to the relevant sectors through its long and short securities positions and long and short securities/index derivative positions, as a percentage of its portfolio market value. Index positions (whether through ETFs or derivatives) are only included under the relevant sector if they are sector specific, otherwise they are included under "Other".
5. The table shows the Fund's top ten positions as a percentage of its portfolio market value taking into account its long securities positions and long securities derivative positions.

Disclaimers

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