Platinum International Health Sciences Fund

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Overview

- The first half of 2025 was a difficult one for the Health Sciences space as pharma companies grappled with the Trump administration's drug pricing proposals. By the end of the year regulatory risk had receded, we saw more corporate action across the biotech and pharma space, and good clinical data from a number of firms.
- The Fund was not immune to this volatility but generated a +34% return for investors in 2025 and is now beating its benchmark index across one, three and ten-year periods, and since inception.

Performance

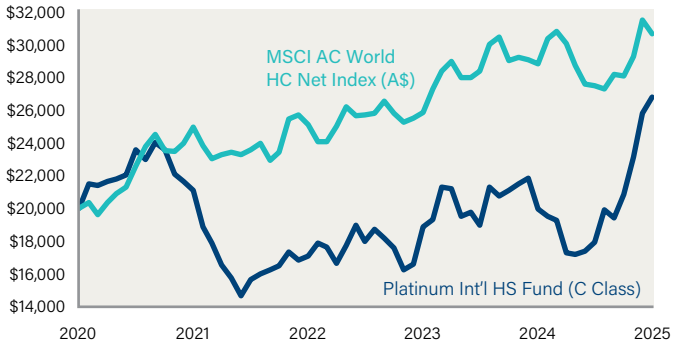
compound p.a.+, to 31 December 2025

	QUARTER	1YR	3YRS	5YRS	SINCE INCEPTION
Platinum Int'l HS Fund*	28%	34%	16%	6%	10%
MSCI AC World HC Index^	9%	6%	7%	9%	9%

+ 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 5. Numerical figures have been subject to rounding.

Value of $20,000 invested over five years

31 December 2020 to 31 December 2025



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 5.

2025 was a year of two halves. In the first half, regulatory and pricing uncertainty dominated and Chinese biotech companies stepped up their out-licensing activity. In the second half, pharma companies negotiated clarity with President Trump's administration and the Chinese biotech threat became part of doing business. By year-end positive clinical data helped sentiment and we saw the return of deal activity. A slew of equity raises and some IPOs added the finishing touches. Fund holdings **Arrowhead** and **Bright Minds** raised money even as I was writing this report.

To give investors clarity on the performance of our listed holdings I note the net performance of the C-class Fund over Q4 was 28.4% with the listed holdings up 31.9%, while the private holdings declined 2.9%. The net annual performance of the listed only section of the portfolio was 40.6%. The unlisted portfolio had a return of -3.4% for one year.

For the Fund, we have had a smorgasbord of news items this quarter. The clinical data for **Terns Pharmaceuticals'** allosteric inhibitor for CML was the standout for us (see commentary below for more detail).

Cogent Biosciences (+150% over the quarter) continued to report positive data for bezuclastinib, a kit inhibitor for gastrointestinal stromal tumors (GIST) and Advanced and NonAdvanced Systemic Mastocytosis. The company submitted a New Drug Application for NonAdvSM in the last week of 2025.

On the obesity front, we had solid data from **Structure Therapeutics** (+160% over the quarter), a holding we have had since the company's IPO in February 2023. Over time we trimmed or added but have kept it as a core position. We believe the obesity market will evolve with next generation therapies providing different remedies. This quarter **Wave Life Sciences** reported very early data for its INHBE siRNA that indicated weight loss but preserved lean body mass. This is exciting but very early. On the downside, Danish company **Zealand Pharma's** performance was negative (-6% over the quarter), not due to negative data but to a sentiment shift and pricing pressure on obesity therapies.

Arrowhead Pharmaceuticals had an interesting year, marked by the uncertainty of its partner Sarepta, who faced serious safety issues for its Duchenne Muscular Dystrophy gene therapy. This quarter Sarepta made good progress addressing these challenges, while Arrowhead got its first product approved and received a milestone payment from Sarepta for progress with an asset from their collaborations. This allowed for solid share price appreciation.

On the downside, **Syntara** was unable to move straight into late-stage testing with its lox inhibitor for myelofibrosis, while **Bicycle Therapeutics** has had mixed progress (-15% over the quarter).

During the quarter we trimmed some holdings due to performance and are gradually building positions in new investments that are building momentum in their pipeline (**Absci**) or commercial product (**Hansa Pharma**).

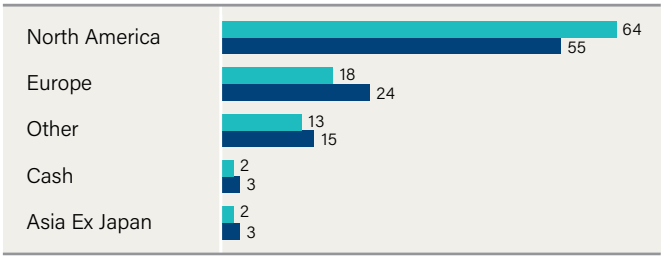
Commentary – blood cancer and precision medicine

Some 25 years ago, imatinib (brand name Glivec/Gleevec), a tyrosine kinase inhibitor (TKI), revolutionised the treatment of chronic myeloid leukemia (CML).

What was once a deadly blood cancer is today a chronic disease.[1] The development pathway and the approval of imatinib was a milestone for precision medicine. At the time, primary care and cardiovascular diseases dominated development, while targeted cancer medicines were seen as outliers and 'not profitable enough'. Fast forward to today and the oncology landscape has changed tremendously.

1 Chronic diseases are long lasting and can be controlled but typically not cured.

Disposition of Assets %



31 DEC 2025 30 SEP 2025

See note 3, page 5. Numerical figures have been subject to rounding.
Source: Platinum Investment Management Limited.

Net Sector Exposures %

31 DEC 2025 30 SEP 2025

See note 4, page 5. Numerical figures have been subject to rounding.
Source: Platinum Investment Management Limited.

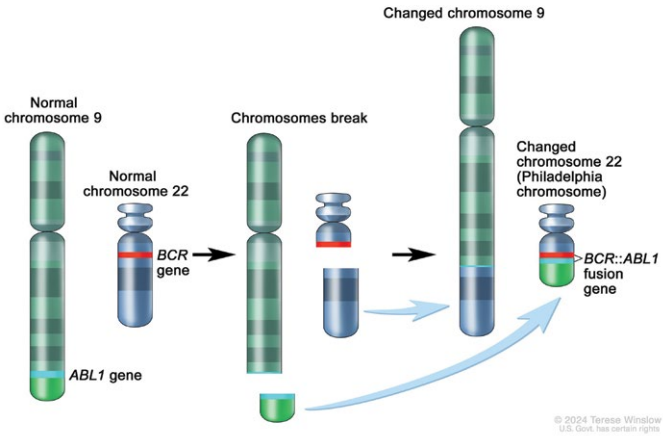
Top 10 Holdings

COMPANY	COUNTRY	INDUSTRY	WEIGHT
SpeeDx Pty Ltd	Australia	Health Care	4.7%
Imricor Medical Systems Inc	US	Health Care	4.3%
Structure Therapeutics Inc	US	Health Care	4.2%
Vera Therapeutics Inc	US	Health Care	4.2%
Arrowhead Pharmaceuticals Inc	US	Health Care	4.1%
Roche Holding AG	US	Health Care	3.8%
Apogee Therapeutics Inc	US	Health Care	3.6%
Immunovant Inc	US	Health Care	3.2%
Terns Pharmaceuticals Inc	US	Health Care	3.1%
Amplia Therapeutics Ltd	New Zealand	Health Care	3.1%

As at 31 December 2025. See note 5, page 5.
Source: Platinum Investment Management Limited.

CML is a poster child for precision medicine thanks to a cytogenetic abnormality[2] (the Philadelphia chromosome, identified in 1950) that drives the uncontrolled growth of immature white blood cells.

The Philadelphia chromosome has pieces from chromosome 9 and chromosome 22, essentially swapping places (see illustration below[3]).



In the 1980s, scientists further characterised the translocation, showing that the ABL-proto oncogene (ABL1, a protein tyrosine kinase[4]) forms a fusion protein with the BCR gene[5]. This fusion protein results in a permanently active enzyme leading to uncontrolled cell growth causing CML.

Kinases are enzymes that catalyse the transfer of phosphates from ATP[6] to proteins, mediating cell signaling. Kinases have been classic drug targets for many, many years, most often by directly targeting the active site that mediates the ATP transfer.

In the '90s, scientists at Ciba-Geigy (today known as Novartis) developed an active site kinase inhibitor that shut down the activity of the bcr-abl fusion protein described above. I was fortunate to be in the lab next door at Ciba at the time! After the approval of imatinib, additional active site kinase inhibitors targeting kinase mutations were approved.

2 A cytogenetic abnormality is a chromosomal alteration that is visible on a karyogram, which is a visualization of our chromosomes. Humans have 23 pairs of chromosomes, encoding our DNA.

3 See https://www.cancer.gov/publications/dictionaries/cancer-terms/def/philadelphia-chromosome

4 ABL1 also known as Abelson murine leukemia viral oncogene homolog 1.

5 Breakpoint cluster Region gene.

6 ATP: Adenosine triphosphate, the main energy carrier in a cell.

The challenge with active site inhibitors is the emergence of resistance and side effects or intolerance. This dynamic has been playing out in CML, highlighting the need for next generation therapies with a different mode of action. This is where 'allosteric' inhibitors will make a difference. Allosteric comes from the Greek *allos* meaning 'other or different,' and *stereos* or 'space.' Proteins (enzymes are proteins) are dynamic molecules, they change shape and hence change their function, e.g. from active to inactive.

Over the past decade, thanks to computational science, machine learning and better biophysical tools, scientists have focused on understanding these 'shift changes' and mapping the allosteric sites that play a role in changing protein confirmation and how proteins interact. These sites are often hidden but play a crucial role and hence are attractive therapeutic targets.

The abl kinase has one of these allosteric sites. Normally, this kinase self-regulates by modifying this allosteric site via a fatty acid attachment. A so-called myristoyl group (14-carbon fatty acid) is attached to this 'myristoyl binding pocket' changing the shape of the kinase and hence turning the kinase inactive.

The bcr-abl fusion protein, however, has lost the myristolation capability and hence the active site is always open for business. The myristoyl binding pocket is hence a formidable drug target. In 2021 Novartis received approval for asciminib, an allosteric inhibitor that mimics myristoylation.

Commercially the drug has been a success, confirming our assumption that there is a need for new mechanisms of action for CML patients. However, asciminib requires a couple of hours fasting prior to taking the drug which is not very convenient. Furthermore, a third of first line patients fail to achieve a deep response.

Terns Pharma has also been busy working on a more selective allosteric inhibitor for the myristoyl binding pocket. We invested in Terns in early 2025 given its compelling valuation and the profile that was emerging for Tern-701, including high selectivity for the target site and deepening responses in treatment failure patients.

This quarter, clinical data showed that the drug is very effective in patients who have tried the Novartis allosteric inhibitor and also on patients who have tried other experimental therapies. Importantly, there is no need for fasting or signs of hypertension or pancreatitis. This is, albeit in a small set of patients, outstanding data. We know there is a good readthrough from early data to approval and earlier lines of treatment. This drug has a solid chance to set a new bar for the treatment of CML.

It is very gratifying to see this progress, particularly as Glivec started my passion for drug development when I met the scientists behind the drug while working at Ciba-Geigy.

Outlook

We continue to expect more M&A as the executives at pharma and large medical tool companies get a firmer understanding on pricing and hence are willing to deploy capital. A number of our holdings have mid to late-stage assets with solid data, hence we expect deal activity in the not-so-distant future.

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. Country classifications for securities reflect Bloomberg's "country of risk" designations. "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.

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