

GLOBAL LIFE SCIENCES FUND

At a glance

Performance*

The Fund returned 7.81%, the Index returned 5.87% and the Sector returned 7.16%.

Contributors/detractors

Stock selection in biotechnology and pharmaceuticals aided relative performance, while positioning in health care equipment and supplies weighed on returns.

Outlook

Although health care lagged the broader market in 2023, attractive valuations, accelerating innovation and mergers and acquisitions could propel the sector in the months ahead.

Portfolio management



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Daniel Lyons, Ph.D., CFA

Investment environment

- Health care stocks were positive for the quarter, benefiting from optimism that the interest rate-tightening cycle in the US was ending. In addition, worries about the potentially negative impacts of GLP-1 weight-loss drugs on the sector eased.
- Biotechnology saw some of the biggest gains, as these companies are especially sensitive to interest rates. Positive clinical data and merger and acquisition (M&A) activity were additional tailwinds for the group.
- Devices and medical technology firms and tools makers also outperformed due to the improved rate outlook, as well as from strong post-Covid procedure volumes.

Portfolio review

Looking at individual holdings, Cytokinetics was the top positive contributor. The firm's lead drug candidate, aficamten, is a small molecule myosin inhibitor being studied for hypertrophic cardiomyopathy (HCM), a condition that causes a thickening of the heart muscle and restricts blood flow. The stock soared after Cytokinetics reported positive phase 3 results for aficamten, which showed a statistically significant and clinically meaningful improvement in exercise capacity in patients. Big pharma has demonstrated interest in novel targeted therapies for cardiovascular disease (such as Bristol-Myer Squibb's \$13

billion acquisition of a rival drug in 2020), which has prompted market participants to speculate that Cytokinetics could be an acquisition candidate.

ImmunoGen also aided performance. Its shares surged when AbbVie announced plans to buy it for \$10 billion, representing a 95% premium to the prior closing price. (Janus Henderson was among the top active holders. ImmunoGen develops antibody drug conjugates (ADC), which is among the hottest areas of cancer research. One can think of an ADC as a precision-guided missile that brings chemotherapy directly to cancer cells with less collateral toxicity. Earlier this year, ovarian cancer patients taking ImmunoGen's Elahere saw a 33% reduction in mortality risk compared to chemotherapy - the first time an overall survival benefit had been achieved in chemo-resistant ovarian cancer. AbbVie said it expects to complete the acquisition by mid-2024.

Conversely, Akero Therapeutics weighed on performance. The biotech firm is developing efruxifermin for non-alcoholic steatohepatitis (NASH), a fatty liver disease that affects over 10 million adults in the US and is a leading cause of liver failure. The company reported phase 2 data in the most severe NASH patients and failed to hit statistical significance on the main endpoint, in this case for fibrosis reversal. Despite achieving statistical significance on other disease markers and prior trials that prove the drug's benefit in moderate NASH patients, investors beat a retreat. We believe this had a lot to do

Marketing communication

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Past performance does not predict future returns.

*For benchmark and sector, if applicable, refer to Fund details on page 3. For relevant descriptions, risks and the Fund's investment policy statement, refer to Additional fund information on page 4.

with the recent perception that GLP-1 receptor agonists will crowd out the rest of the NASH market.

Sarepta Therapeutics was another detractor. We have been long-term holders of the company, a leader in the field of Duchenne muscular dystrophy with a marketed exon-skipping franchise approaching \$1 billion in sales and a novel gene therapy, Elevidys, that could be game-changing for patients. The process of bringing Elevidys to market has had its ups and downs. In June, the US Food and Drug Administration (FDA) granted accelerated approval for four- and five year olds, pending a confirmatory trial. In October, that trial missed on its primary endpoint, although it did show benefit on multiple key secondary endpoints. As such, the FDA could allow Elevidys to stay on the market and even broaden the indication given the clinical benefits observed and high unmet medical need.

Manager outlook

Enthusiasm for artificial intelligence, increased optimism for an economic 'soft landing' and declining sales of COVID-19 products pressured the health care sector for much of the year. As such, many stocks were trading at a discount to the broader market and/or their long-term averages at the time of writing. We believe this creates an attractive set-up for investors as we close out the year.

For one, discounted valuations could make health care - a traditionally defensive sector - even more appealing in the event of an economic slowdown or recession in 2024, a risk that remains given higher interest rates, an inverted yield curve and a rapidly declining money supply. Historically, the sector has outperformed during market

downturns, and discounted valuations improve the odds of that pattern continuing.

Second, despite recent negative sentiment, innovation within the sector has been accelerating. The FDA approved a record number of novel therapies in 2023, with many drugs targeting large disease categories such as obesity, autoimmune disease, cancer, and Alzheimer's. These drug launches could represent the start of major product cycles, driving revenue growth through the next decade.

Given these factors, we continue to take a barbell approach, seeking to balance the sector's defensive qualities with potential new growth opportunities. To that end, we favour large-cap biopharma and managed care firms that generate strong free cash flow and which we think can hold up well in a recession. The fund is also overweight small- and mid-cap biotechs with newly launching products or exciting late-stage pipelines. Some of these stocks were impacted by worries over higher yields and new GLP-1 drugs in the second half of 2023, which weighed on valuations and created, in our view, an opportunity to invest in biotech's long-term growth potential at attractive levels.

We believed the weakness could also drive increased M&A activity, as we started to see with AbbVie's announcement that it would buy ImmunoGen, as well as Roche's recent acquisition of obesity drug-maker Carmot Therapeutics. In our view, such deals could help improve sentiment in the health care sector broadly and catalyse a longer-term recovery in small- and mid-cap biotech stocks after a multi-year drawdown.

Performance (%)

| Returns | Cumulative | | | | Annualised | | |
|----------------|------------|------------|------|-----------|------------|-----------|------------|
| | 1 Month | 3 Month | YTD | 1 Year | 3 Year | 5 Year | 10 Year |
| A2 USD (Net) | 7.42 | 7.81 | 5.44 | 5.44 | 1.84 | 10.62 | 9.44 |
| Index | 4.42 | 5.87 | 3.76 | 3.76 | 5.55 | 10.47 | 9.01 |
| Sector | 5.75 | 7.16 | 2.68 | 2.68 | -1.81 | 6.81 | 6.38 |
| A2 USD (Gross) | — | — | — | — | — | 13.26 | 12.08 |
| Target | — | — | — | — | — | 12.68 | 11.19 |

| Calendar year | 2023 | 2022 | 2021 | 2020 | 2019 | 2018 | 2017 | 2016 | 2015 | 2014 |
|---------------|------|--------|-------|-------|-------|-------|-------|--------|------|-------|
| A2 USD (Net) | 5.44 | -4.35 | 4.72 | 23.41 | 27.06 | 2.01 | 20.55 | -13.79 | 5.69 | 32.75 |
| Index | 3.76 | -5.41 | 19.80 | 13.52 | 23.24 | 2.51 | 19.80 | -6.81 | 6.60 | 18.10 |
| Sector | 2.68 | -13.91 | 7.12 | 20.53 | 21.80 | -3.40 | 21.68 | -9.37 | 5.90 | 18.33 |

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Fund charges will impact the value of your investment. In particular, the ongoing charges applicable to each fund will dilute investment performance, particularly over time. For further explanation of charges please visit our Fund Charges page at www.janushenderson.com.

Investment objective

The Fund aims to provide capital growth over the long term. Performance target: To outperform the MSCI World Health Care Index by at least 2% per annum, before the deduction of charges, over any 5 year period.

For the fund's investment policy, refer to the Additional fund information on page 4.

Past performance does not predict future returns.

Fund details

| | |
|--------------------|------------------------------|
| Inception date | 31 March 2000 |
| Total net assets | 3.70bn |
| Asset class | Equities |
| Domicile | Ireland |
| Structure | Irish Investment Company |
| Base currency | USD |
| Index | MSCI World Health Care Index |
| Morningstar sector | Sector Equity Healthcare |
| SFDR category | Article 8 |

In accordance with the Sustainable Finance Disclosure Regulation, the Fund is classified as Article 8 and promotes, among other characteristics, environmental and/or social characteristics, and invests in companies with good governance practices.

Additional fund information

Tax assumptions and reliefs depend upon an investor's particular circumstances and may be subject to change. Please note the performance target is to be achieved over a specific annualised time period. Refer to the performance target wording within the objective. With effect from 1 January 2023, the Key Investor Information document (KIID) changed to the Key Information Document (KID), except in the UK where investors should continue to refer to the KIID. Availability of share classes shown may be limited by law in certain jurisdictions. Performance records/scenarios are detailed within the fund's specific KIID/KID; fees and charges, and the respective risk rating may vary. Further information can be found in the fund's prospectus and KIID/KID, which must be reviewed before investing. Please consult your local sales representative and/or financial adviser if you have any queries. As of 31 January 2023, Daniel Lyons Ph.D., CFA also manages this fund. Note that any differences among portfolio securities currencies, share class currencies and costs to be paid or represented in currencies other than your home currency will expose you to currency risk. Costs and returns may increase or decrease as a result of currency and exchange rate fluctuations. Investment into the fund will acquire units/shares of the fund itself and not the underlying assets owned by the fund. The ongoing charge is calculated using the PRIIP methodology. The PRIIP methodology differs to the UCITS ongoing charge methodology, as the PRIIP methodology captures additional recurring charges, including but not limited to: Interest paid on borrowing (e.g. bank interest); Any fees incurred in relation to stock-lending activity (i.e. the fee paid to the lending agent); Any costs associated with holding closed-ended vehicles. References made to individual securities do not constitute a recommendation to buy, sell or hold any security, investment strategy or market sector, and should not be assumed to be profitable. Janus Henderson Investors, its affiliated advisor, or its employees, may have a position in the securities mentioned.

Investment policy

The Fund invests at least 80% in shares (also known as equities) of companies, of any size, with a life sciences orientation, in any country. Up to 20% may be invested in developing markets. The Fund may also invest in other assets including cash and money market instruments. The investment manager may use derivatives (complex financial instruments) to reduce risk, to manage the Fund more efficiently, or to generate additional capital or income for the Fund. The Fund is actively managed with reference to the MSCI World Health Care Index, which is broadly representative of the companies in which it may invest, as this forms the basis of the Fund's performance target. The investment manager has discretion to choose individual investments for the Fund with weightings different to the index or not in the index, but at times the Fund may hold investments similar to the index.

Investment strategy

The investment manager looks to identify innovative healthcare companies addressing high unmet medical needs across fields including biotechnology, pharmaceuticals, healthcare services and medical technology. The team understands that success of drug development is binary in nature, creating wide disparities between winners and losers. The investment process leverages proprietary statistical models to analyse the probability of a company's success, focusing on products they believe can overcome the rigours of clinical development. Additional tools, such as physician surveys and prescription models, attempt to more accurately predict commercial viability.

Fund specific risks

When the Fund, or a share/unit class, seeks to mitigate exchange rate movements of a currency relative to the base currency (hedge), the hedging strategy itself may positively or negatively impact the value of the Fund due to differences in short-term interest rates between the currencies. The Fund could lose money if a counterparty with which the Fund trades becomes unwilling or unable to meet its obligations, or as a result of failure or delay in operational processes or the failure of a third party provider. Shares/Units can lose value rapidly, and typically involve higher risks than bonds or money market instruments. The value of your investment may fall as a result. Shares of small and mid-size companies can be more volatile than shares of larger companies, and at times it may be difficult to value or to sell shares at desired times and prices, increasing the risk of losses. If a Fund has a high exposure to a particular country or geographical region it carries a higher level of risk than a Fund which is more broadly diversified. The Fund is focused towards particular industries or investment themes and may be heavily impacted by factors such as changes in government regulation, increased price competition, technological advancements and other adverse events. The Fund may use derivatives to help achieve its investment objective. This can result in leverage (higher levels of debt), which can magnify an investment outcome. Gains or losses to the Fund may therefore be greater than the cost of the derivative. Derivatives also introduce other risks, in particular, that a derivative counterparty may not meet its contractual obligations. If the Fund holds assets in currencies other than the base currency of the Fund, or you invest in a share/unit class of a different currency to the Fund (unless hedged, i.e. mitigated by taking an offsetting position in a related security), the value of your investment may be impacted by changes in exchange rates. Securities within the Fund could become hard to value or to sell at a desired time and price, especially in extreme market conditions when asset prices may be falling, increasing the risk of investment losses.

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— INVESTORS —

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Source: Janus Henderson Investors, as at 31 December 2023, unless otherwise noted.

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