Janus Henderson INVESTORS

GLOBAL LIFE SCIENCES FUND

At a glance

Performance*
The Fund returned 8.07%, the Index returned 7.47% and the Sector returned 4.27%.

Contributors/detractors
Stock selection in pharmaceuticals and biotechnology aided relative performance, while positioning in healthcare services and life sciences tools and services weighed on returns.

Outlook
Stock selection in pharmaceuticals and biotechnology aided relative performance, while positioning in healthcare services and life sciences tools and services weighed on returns.

Portfolio management

Andy Acker, CFA

Daniel Lyons, Ph.D., CFA

Investment environment

- Healthcare stocks were up sharply for the quarter, nearly matching the broader market rally. This rally was driven by enthusiasm for artificial intelligence (AI), hopes that interest rates could soon be moderating, and better-than-expected economic data, especially in the US.
- Pharmaceuticals performed the best, led by surging demand for new glucagon-like peptide 1 (GLP-1) receptor agonist weight-loss drugs. Medical devices also saw strong gains as higher utilisation rates boosted revenues.
- Managed healthcare experienced losses. The flipside of higher utilisation rates has been rising costs for insurers. Lower-than-expected reimbursement rates for Medicare Advantage also contributed to headwinds.

Portfolio review

Looking at individual holdings, Sarepta Therapeutics was the top positive contributor after the US Food and Drug Administration (FDA) said it would consider Sarepta's application for expanded usage of Elevidys for all Duchenne muscular dystrophy (DMD) patients with a confirmed mutation in the DMD gene. The FDA had limited approval of the ground-breaking gene therapy to ambulatory 4 and 5 year olds, pending a confirmatory trial that concluded in October. Those results were mixed.

However, Elevidys did meet its secondary goals, and early uptake has been strong. Sarepta also reported positive phase 3 results for its next-generation exon-skipping DMD platform. (Exons are the regions of genes that code for proteins and are defective in the devastating muscle wasting disease.) The results suggest a step-change improvement over the firm's existing exon skippers, already a $1 billion franchise. The improved exon skippers could become a maintenance therapy for patients helped by the one-and-done gene therapy.

Janux Therapeutics also aided performance. Its share price rose after a pair of early phase dose-optimisation trials suggested strong (if early) best-in-class results for its innovative tumour-focused T-cell therapy. Like other T-cell approaches, Janux's masked bispecific antibodies bind to tumours and T cells to engage the immune system to destroy cancerous tumours. However, Janux's approach removes the masks primarily in the tumour environment, which seems to reduce toxicity and improve efficacy. Most patients in the study of advanced or metastatic prostate cancer saw a decline of prostate-specific antigens of at least 50%. Patients in the metastatic solid tumour trial also

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*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.

showed encouraging signs. Critically, the few broad immune responses that were observed were not severe and were quickly managed.

Conversely, other stocks weighed on performance, including Zai Lab. The China-based biotech was impacted by weakness in the Chinese equity market during the period. Even so, Zai Lab has seen double-digit revenue growth thanks to strong commercial franchises in China and recently launched Vyvgart, a treatment for adults with generalised myasthenia gravis. Zai Lab licenses the drug for sale in China, and in December, Vyvgart was added to China's National Reimbursement Drug List, dramatically widening the therapy's addressable market in the country. Vyvgart - which first launched in the US as an intravenous version in late 2021, then as a subcutaneous (under the skin) therapy in mid-2023 - has already achieved over $1 billion annual sales in the US.

An underweight position to Eli Lilly also detracted, as the stock continued to ride the craze for its GLP-1 franchise. Within weeks of FDA approval for the weight loss-specific formulation, Zepbound, the drug racked up more than $175 million in sales. (An earlier version, Mounjaro, is approved for diabetes.) The quarter's share price gains lifted Eli Lilly's market capitalisation to over $700 billion, and we have continued to add to the position in the stock given the growth potential of Lilly's GLP-1s.

Manager outlook

After falling out of favour with investors in 2023, healthcare stocks have started to rebound thanks to low valuations, innovation and recent drug launches. Sales of new GLP-1 obesity and diabetes drugs, for example, topped $20 billion globally in 2023 and are expected to continue growing rapidly. Meanwhile, the FDA approved a record number of novel medicines last year, and these drugs - some with blockbuster potential (sales of $1 billion or more annually) - are now beginning revenue cycles of 10 years or longer.

Merger and acquisition (M&A) activity has been another boon, as large biopharmaceutical firms seek to offset patent expirations with promising new technologies, such as antibody-drug conjugates, radiopharmaceuticals and cell therapies. Given discounted valuations and innovation, the deal-making is expected to continue throughout the year.

Not all areas of the sector have been as positive. Managed care companies have lagged on concerns about rising medical costs and regulation, including lower reimbursement rates for Medicare Advantage (MA), the privately administered health plan for the elderly. Furthermore, increased government scrutiny of MA could put some insurers in the spotlight during the US election. Sales of COVID-19 products also continue to decline, while supply imbalances for tools and services firms caused by the pandemic may take until mid-year to get sorted out.

With these factors in mind, the fund remains overweight small- and mid-cap biotechs with newly launching products or exciting late-stage pipelines. Many of these stocks trade at a discount following a three-year pullback in biotech - a drawdown we think could be ending now that rate hikes in the US have most likely concluded. While managed care faces near-term headwinds, we believe these companies still have a strong long-term outlook given their ability to reprice services annually. They also now have discounted valuations and retain important defensive qualities should economic growth slow amid today's tighter financial conditions.

In the end, though, we think healthcare's many medical advances and long-term growth trends will be the dominant story in 2024. In our view, these opportunities, along with still-attractive valuations, could help support the sector throughout the year.

Performance (%)

Returns	Cumulative				Annualised			
	1 Month	3 Month	YTD	1 Year	3 Year	5 Year	10 Year	Since inception (31/03/00)
A2 USD (Net)	1.56	8.07	8.07	15.99	5.68	9.56	9.50	7.33
Index	2.35	7.47	7.47	13.32	7.85	10.33	9.18	7.79
Sector	1.45	4.27	4.27	7.22	-0.28	5.59	6.23	6.21
A2 USD (Gross)	—	—	—	—	—	12.17	12.14	10.10
Target	—	—	—	—	—	12.53	11.37	9.94

12 month rolling	Mar 2023-Mar 2024	Mar 2022-Mar 2023	Mar 2021-Mar 2022	Mar 2020-Mar 2021	Mar 2019-Mar 2020
A2 USD (Net)	15.99	-0.61	2.40	39.15	-3.87
Index	13.32	-3.69	14.94	29.16	0.89
Sector	7.22	-6.50	-1.09	36.22	-2.79

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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.

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 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	4.08bn
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. 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. This is an Irish Investment Company regulated by the Central Bank of Ireland. A short-term trading fee may be applied upon exiting the fund as per the prospectus. These are the views of the author at the time of publication and may differ from the views of other individuals/teams at Janus Henderson Investors. Any securities, funds, sectors or indices mentioned within this article do not constitute or form part of any offer or solicitation to buy or sell them. The information in this commentary does not qualify as an investment recommendation. Investment into the fund will acquire units/shares of the fund itself and not the underlying assets owned by the fund. Cash balances and exposures are based on settled and unsettled trades as at the reporting date.

Investment policy

The Fund invests at least 80% in shares (also known as equities) of companies, of any size, including smaller capitalisation companies, 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 Sub-Investment Adviser 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 Sub-Investment Adviser 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 Sub-Investment Adviser 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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