COMMENTARY

Janus Henderson Global Life Sciences Fund

Q2 2023

Marketing communication - For professional investors only
Past performance does not predict future returns

Fund Manager Name

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Investment environment

Health care stocks underperformed the broader market as moderating inflation, the prospect of slower US Federal Reserve (Fed) rate hikes, and enthusiasm around artificial intelligence (AI) continued to see investors switch into large technology stocks (especially in the US). Within the health care sector, surging demand for obesity drugs and a post-Covid recovery in procedure volumes helped health care distributors and facilities. Conversely, a drawdown of inventories (built up during Covid-related supply-chain disruptions) hurt life sciences tools companies, while biotechnology stocks felt the chilling effects of a US Federal Trade Commission lawsuit seeking to block Amgen's multibillion-dollar acquisition of Horizon Therapeutics. The suit overshadowed the ongoing momentum from smaller deals, favourable clinical trial results and drug approvals. As of quarter end, the US Food and Drug Administration (FDA) had issued 33 approvals for the year, with more than 50 applications pending. At this rate, the agency could break its previous record of 59 approvals (in 2018).

Portfolio review

The fund (A2 share class, US dollars) outperformed its benchmark, the MSCI World Health Care Index℠, over the quarter. Stock selection in biotechnology contributed positively to relative performance, while an underweight position to pharmaceuticals weighed on returns.

Looking at individual holdings, ImmunoGen was the top positive contributor. In early May, the company reported highly positive confirmatory trial data for its ovarian cancer drug, Elahere, sending the stock up 135% in one day. Elahere is an antibody-drug conjugate (ADC) that targets folate receptor alpha, a protein expressed at high levels in 35% to 40% of all ovarian cancer cases. One can think of an ADC as a precision-guided missile that brings chemotherapy directly to cancer cells. The ADC tricks the cancer cell into allowing it inside the cell (internalisation), where it releases a cytotoxin that kills the cell and neighbouring tumour cells. Patients in the confirmatory trial saw a 33% reduction in the risk of death compared to chemotherapy, the first time an overall survival benefit was achieved in chemo-resistant patients. In June, ImmunoGen also delivered a positive update to Phase 2 trial data for another ADC, pivekimab sunirine, in patients with a rare and aggressive blood cancer, suggesting the firm may be on track to building a winning platform of ADC therapies.

Apellis Pharmaceuticals was another top contributor. In April, reports emerged noting that the rare disease and ophthalmology specialist was being eyed as a possible takeover target. The stock had already been on an upswing after Apellis won FDA approval in February for its therapy for geographic atrophy (GA), an advanced form of dry age-related macular degeneration and the leading cause of blindness in the elderly. The drug, Syfovre, is the first FDA-approved treatment for GA. With two-year data demonstrating increasing treatment benefit over time and an every-other-month dosing profile, the drug was an immediate hit as first quarter sales were $18.4 million, with just a few weeks on the market - far ahead of consensus expectations.

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Janus Henderson Global Life Sciences Fund

Sarepta Therapeutics detracted from performance. The stock fell despite the FDA issuing accelerated approval for Elevydis, the first gene therapy for Duchenne muscular dystrophy (DMD). Investors were disappointed that the approval was limited to 4- and 5-year-olds, pending confirmatory trial data due later this year. To some, the wording of the decision suggested that the FDA might reconsider approval altogether if the Phase 3 trials do not achieve statistical significance. We think that's unlikely and remain optimistic about this approach to the devastating muscle-wasting disease. We are also encouraged by another Sarepta DMD drug in late-stage trials that uses a different mechanism known as exon skipping. With DMD, genetic mutations cause errors in the instructions for making dystrophin, which helps strengthen muscle fibers and protect against injury. These drugs act on RNA to skip over parts (ie. exons) of the genetic sequence, enabling production of a potentially more functional version of the protein. Previous exon skippers from Sarepta produce only small improvements in functional dystrophin yet generate nearly $1 billion of annual sales. We believe the newer candidates could be five to 10 times more effective, as well as more convenient (as the infusions are only required monthly rather than weekly).

The fund's underweight position to Eli Lilly was another detractor. Positive developments in two of the hottest areas of drug discovery - obesity and Alzheimer's - powered Eli Lilly to become the world's largest drugmaker by market value. In obesity, its drug Mounjaro delivered market-beating weight-loss benefits in clinical trials, while a next-generation therapy nicknamed "triple G" (the drug targets three obesity-related hormones) shows potential for even better results. Eli Lilly also has an inside track on developing an effective once-daily pill for obesity (most new treatments require injections). Mounjaro could win FDA approval for obesity later this year, while in Alzheimer's the company announced in May that it would seek approval for donanemab. In late-stage trials, donanemab demonstrated it could slow progression of the disease, which would make it only the second therapy able to do so. While we added to the position during the quarter, our holding still fell short of Eli Lilly's growing benchmark weighting.

Manager outlook

Optimism around AI and a slower pace of interest rate hikes led some tech-heavy equity indices to outperform during the first half of the year. Health care lagged by comparison. But we believe the risk of recession remains elevated into 2024, as higher rates and tighter lending standards take effect. In a slowing economy, health care's defensive characteristics could help lift the sector relative to peers, especially as many health care stocks now trade significantly below the market average.

Meanwhile, innovation continues to be robust. Nearly 90 new drugs are up for review by the FDA this year, with dozens already receiving approval. Many therapies target large disease categories with high, unmet medical needs, including Leqembi, the first drug to show clear evidence of slowing cognitive decline in Alzheimer's patients and the first-ever medicine for dry age-related macular degeneration. These, and other newly approved drugs, could represent the start of major product cycles, driving revenue growth for a decade or more.

With our excitement about industry innovation and our concerns for a slowing economy, 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, which typically generate strong free cash flow and can hold up well in a recession. We are also overweight small- and mid-cap biotech firms with newly launching products or exciting late-stage development opportunities, which we believe offer growth potential with reduced clinical risk.

As seen recently, some of these biotechs have been acquisition targets. In fact, 12 deals of $1 billion or more have been announced so far this year, putting 2023 on track to surpass that of any year in the past decade (a high of 14 deals was reached in both 2019 and 2021). In our view, these acquisitions will likely continue given looming patent expirations for large-cap biopharma and antitrust concerns that could drive companies to pursue smaller but more frequent deals - potentially favouring the fund's overweight position to small- and mid-cap biotech firms.

Source: Janus Henderson Investors, as at 30 June 2023

Janus Henderson Global Life Sciences Fund

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Fund information (Investment policy is on the next page)

Index	MSCI World Health Care
Morningstar sector	Europe OE Sector Equity Healthcare
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.

Performance in (USD)

Performance %	A2 (Net)	Index	Sector	A2 (Gross)	Target (Gross)
1 month	3.0	3.2	2.9	-	-
YTD	2.5	0.8	1.6	-	-
1 year	13.7	6.3	4.7	-	-
3 years (annualised)	6.8	8.5	2.6	-	-
5 years (annualised)	8.8	10.0	5.3	11.4	12.2
10 years (annualised)	11.8	10.3	8.0	14.5	12.5

 Performance/performance target related data will display only where relevant to the share class inception date and annualised target time period.

Calendar year returns %	A2 (Net)	Index	Sector
2023 to 30 Jun 2023	2.5	0.8	1.6
2022	-4.3	-5.4	-13.9
2021	4.7	19.8	7.1
2020	23.4	13.5	20.5
2019	27.1	23.2	21.8
2018	2.0	2.5	-3.4
2017	20.5	19.8	21.7
2016	-13.8	-6.8	-9.4
2015	5.7	6.6	5.9
2014	32.7	18.1	18.3
2013	52.5	36.3	35.1

 Discrete performance data may change due to final dividend information being received after quarter end.

Investment into the fund will acquire units/shares of the fund itself and not the underlying assets owned by the 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.

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 http://www.janushenderson.com.

Source for target returns (where applicable) – Janus Henderson. 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 if you have any further queries.

Past performance does not predict future returns. The value of an investment and the income from it can fall as well as rise and you may not get back the amount originally invested.

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Janus Henderson Global Life Sciences Fund

What are the risks specific to this fund?

- 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.

General risks

- Past performance does not predict future returns.
- The value of an investment and the income from it can fall as well as rise and you may not get back the amount originally invested.
- Tax assumptions and reliefs depend upon an investor's particular circumstances and may be subject to change.

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.

Janus Henderson Global Life Sciences Fund

For further information on the Janus Henderson fund range please contact your local sales office or visit our website: www.janushenderson.com.

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Important information

ESG integration is the practice of incorporating material environmental, social and governance (ESG) information or insights in a non-binding manner alongside traditional measures into the investment decision process to improve long term financial outcomes of portfolios. This product does not pursue a sustainable investment strategy or have a sustainable investment objective or otherwise take ESG factors into account in a binding manner. ESG related research is one of many factors considered within the investment process and in this material we seek to show why it is financially relevant.

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