Janus Henderson INVESTORS

HORIZON BIOTECHNOLOGY FUND

At a glance

Performance*

The Fund returned 15.59%, the Index returned 12.91% and the Sector returned 13.44%.

Contributors/detractors

Cytokinetics and Ardelyx were the top positive contributors. Structure Therapeutics and Argenx detracted from results.

Outlook

With the interest rate-hike cycle ending in the US, and innovation and merger and acquisition (M&A) activity accelerating, we believe biotech could be poised for a rebound.

Portfolio management

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Investment environment

- Biotechnology stocks rallied sharply, outperforming the broader health care sector as the US Federal Reserve (Fed) signalled that its monetary policy tightening cycle may soon be over. A flurry of merger and acquisition (M&A) activity also buoyed investor sentiment.
- In keeping with the risk-on backdrop, small- and mid-cap biotechnology stocks outperformed larger stocks.

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 which 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 (e.g., 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.

Ardelyx also aided performance. In October, the US Food and Drug Administration (FDA) granted an expanded approval for tenapanor (brand name Xphozah) for the control of serum phosphate in kidney dialysis patients with an inadequate response to standard of care phosphate binders. The decision was the culmination of a two-year appeals process after regulators had surprisingly rejected the indication despite positive efficacy and safety data. The stock rose in December due to excitement over the revenue potential not only for Xphozah, but for tenapanor's original indication, Ibsrela, for irritable bowel syndrome with constipation. Ibsrela - originally approved in 2019 but not launched until 2022 - has continued to achieve strong prescription and sales growth.

Conversely, Structure Therapeutics detracted from performance. The setback was the latest example of how, despite losing some steam in the fourth quarter, the dominant GLP-1 makers continue to cast a long shadow over would-be competitors. With Eli Lilly's Zepbound and Novo Nordisk's Wegovy only available as injectables, Structure aims to be among the first to market with an oral GLP-1. Preliminary phase 1B data for its GSBR-1290 released in September looked promising. The latest (phase 2a) data was positive as well, but the weight loss and tolerability were somewhat less impressive. That was enough to send Structure's stock tumbling. Meanwhile, Structure Therapeutics said it is encouraged enough by the results to advance to the next stage of clinical trials.

Argenx was another detractor. The stock declined after autoimmune drug Vyvgart failed to reach its endpoints in a phase 3 trial for primary immune thrombocytopenia, a rare

Marketing communication
For professional investors only
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.

bleeding disorder. Shortly thereafter, Vyvgart also missed in another trial, this time for an autoimmune skin disease called pemphigus (which can cause infection-prone blisters). However, these indications represent only a few of more than a dozen autoimmune disorders being investigated for Vyvgart. In addition, the drug is already on the market for generalised myasthenia gravis, a disorder that causes weakness in the skeletal muscles, where it is already annualising at over $1.5 billion. And earlier this year, Vyvgart recorded positive phase 3 results for chronic inflammatory demyelinating polyneuropathy, a nerve condition affecting the limbs for tens of thousands of patients.

Manager outlook

Following a sharp sell-off, biotechnology stocks rebounded in the final months of 2023, benefiting from optimism that the interest rate-tightening cycle in the US was coming to an end. Positive clinical data and a surge of M&A activity also boosted investor sentiment, which in our view could continue to propel biotechnology stocks in the new year.

We believe that the current low valuations create potential. As Treasury yields climbed in 2023, markets punished biotech firms that failed to meet clinical milestones or fell short in other ways. While some industry rationalisation was arguably needed - the sector saw a surge of new biotech companies funded during the pandemic, many without proof-of-concept data - we feel many valuations were pushed too low.

At the same time, innovation has been accelerating, with the FDA approving a record 73 new therapies in 2023. Many of these drugs target large disease categories (e.g., obesity, autoimmune disease, cancer, and Alzheimer's), that could represent major new product cycles and drive revenue growth for the next decade. We expect no shortage of additional data readouts and approvals in 2024.

M&A activity has also picked up in recent months and could maintain momentum as biopharma, flush with cash, seeks to replace blockbuster products losing patent protection in the coming years. Growing market opportunities, including GLP-1s (for diabetes and obesity), gene editing, antibody drug conjugates, radiopharma, and cell therapy treatments for autoimmune diseases, could also tempt biopharma to break out their checkbooks. In short, we believe the set-up for biotech is compelling heading into 2024 and feel M&A, innovation, and attractive valuations bode well for the year ahead.

Performance (%)

Returns	Cumulative 1 Month	3 Month	YTD	1 Year	Annualised 3 Year	5 Year	10 Year	Since inception (10/12/18)
A2 USD (Net)	15.59	13.33	23.28	23.28	4.00	19.58	—	17.51
Index	12.91	10.75	4.59	4.59	-2.03	8.26	—	6.66
Sector	13.44	12.57	5.26	5.26	-6.98	5.17	—	3.61
A2 USD (Gross)	—	—	—	—	—	23.39	—	21.23
Target	—	—	—	—	—	10.43	—	8.79

Calendar year	2023	2022	2021	2020	2019	2018 from 10 Dec
A2 USD (Net)	23.28	-3.78	-5.17	61.32	34.70	-7.50
Index	4.59	-10.12	0.02	26.42	25.11	-6.85
Sector	5.26	-17.17	-7.68	27.50	25.36	-7.02

Performance is on a net of fees basis, with gross income reinvested. Source: at 31/12/23. **Past performance does not predict future returns.**
Performance/performance target related data will display only where relevant to the share class inception date and annualised target time period. **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.** Source for target returns (where applicable) - Janus Henderson Investors.

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.

Performance fees may be charged before the Fund's outperformance target is reached.

Performance fees are charged separately as a way of rewarding the investment manager for superior returns or for outperforming specified targets. A Performance Fee is accrued where the NAV outperforms the relevant Hurdle NAV (subject to a High Water Mark). For further explanation of the performance fee calculation methodology please see the relevant prospectus, available at www.janushenderson.com.

Investment objective

The Fund aims to provide capital growth over the long term. Performance target: To outperform the NASDAQ Biotechnology Total Return Index by 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	10 December 2018
Total net assets	195.93m
Asset class	Equities
Domicile	Luxembourg
Structure	SICAV
Base currency	USD
Index	NASDAQ Biotechnology Total Return Index
Morningstar sector	Sector Equity Biotechnology

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. From 31 January 2023 Agustin Mohedas 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. 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% of its assets in shares (equities) and equity-related securities of companies, which are biotechnology or biotechnology-related, of any size, including smaller capitalisation companies, in any country. The Fund may also invest in other assets including bonds (including convertible bonds), preference shares, cash and money market instruments. The investment manager may use derivatives (complex financial instruments) with the aim of making investment gains in line with the Fund's objective, to reduce risk or to manage the Fund more efficiently. The Fund is actively managed with reference to the NASDAQ Biotechnology Total Return Index, which is broadly representative of the companies in which it may invest, as this forms the basis of the Fund's performance target and the level above which performance fees may be charged (if applicable). The investment manager has discretion to choose 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 biotechnology companies addressing high unmet medical needs and trading at a significant discount to their intrinsic value. 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, prescription models and scenario simulations 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. The Fund may incur a higher level of transaction costs as a result of investing in less actively traded or less developed markets compared to a fund that invests in more active/developed markets. These transaction costs are in addition to the Fund's Ongoing Charges.

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