COMMENTARY

Janus Henderson Horizon Biotechnology Fund

Q2 2023

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

Fund Managers Names

Andy Acker, CFA, Daniel Lyons, Ph.D., CFA, Agustin Mohedas, Ph.D.

Investment environment

Biotechnology stocks declined during the period, trailing a technology-driven rally in the broader equity market. A slowdown in sales of Covid-19 products was one headwind, as was an antitrust suit brought by the US Federal Trade Commission (FTC) against Amgen's $28 billion bid for Horizon Therapeutics. The chilling effect this had on possible large merger and acquisition (M&A) candidates overshadowed the ongoing momentum behind smaller deals, clinical trial results and drug approvals. By quarter end, the Food and Drug Administration (FDA) had issued 33 approvals for the year, with more than 50 applications pending. At this rate, the agency seems likely to break its previous record of 59 approvals in 2018.

Portfolio review

The fund (A2 US dollar share class) outperformed its benchmark, the NASDAQ Biotechnology Total Return Index, for the quarter.

Looking at individual holdings, ImmunoGen was the top performer. During the quarter, the company delivered impressive confirmatory data for ovarian cancer drug, Elahere. Elahere is an antibody-drug conjugate (ADC), which acts 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. In the ovarian cancer trial, patients saw a 33% reduction in the risk of death compared to conventional chemotherapy, the first time an overall survival benefit was ever achieved in chemo-resistant patients.

Biohaven was another top contributor. Spun out from its parent company during an acquisition in 2022, Biohaven has since delivered a string of positive trial results, suggesting the firm - still run by the original management team - has several promising drug candidates in development. The most advanced is troriluzole, a modulator of glutamate, a neurotransmitter involved in a wide range of neurological and psychiatric conditions. During the month, Biohaven applied for approval after demonstrating a significant benefit in patients with spinocerebellar ataxia, an inherited condition that causes problems with movement, speech and swallowing. Elsewhere, the firm is focused on a newly licensed treatment for immune-modulated neurological disorders such as Parkinson's, Multiple Sclerosis and Alzheimer's, and has other programs for epilepsy, bipolar disorder and spinal muscular atrophy.

Bellerophon Therapeutics weighed on performance. This biotech is focused on developing innovative drug-device therapies for cardiopulmonary conditions. However, during the period, Bellerophon reported that its lead product candidate, INOpulse, failed to meet the primary endpoint in a phase 3 study for fibrotic interstitial lung disease. Despite positive data from earlier trials, its management determined the phase 3 results were conclusive enough to abandon further development. Therefore, we exited the stock.

Ardelyx was another detractor, as investors grew impatient waiting for an expanded label approval for its lead drug, Tenapanor. The FDA first approved the medication in 2019 for irritable bowel syndrome. In 2021, the company sought an expanded label for controlling serum phosphate in patients on kidney dialysis. Despite three positive phase 3 trials and good safety, the FDA surprisingly rejected the indication, questioning the clinical significance of the data. Since then, Ardelyx undertook a lengthy appeals process, which the firm effectively won in late 2022. In the latest twist, the agency has formally accepted the company's resubmission of its application, setting a goal of October for a final decision. The market's impatience notwithstanding, we see it as the most conclusive step yet toward entry in a large addressable market with little viable competition.

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Manager outlook

Although declining Covid-19 sales and antitrust concerns have dominated investor attention lately, behind these headlines many biotech companies have been reaching significant milestones - and delivering sizable returns. This year for example, companies have achieved approvals in large disease categories, including obesity, Alzheimer's and age-related macular degeneration (a leading cause of blindness in the elderly). Many of these advances are setting a new standard of care for patients, from delivering record levels of weight loss, to (for the first time) slowing the progression of cognitive decline in patients with Alzheimer's Disease. These therapies could mark the start of major new product cycles, driving revenue growth for a decade or more. M&A is also ramping up, particularly among small- and mid-cap biotech. As of the end of June, a dozen deals of $1 billion or more had been announced, putting 2023 on track to surpass any other year in the past decade (a high of 14 deals was reached in both 2019 and 2021). We believe acquisitions of this size could accelerate given FTC challenges to larger deals and looming patent expirations for large-cap biopharma - potentially favouring our overweight to small- and mid-cap biotech firms.

Source: Janus Henderson Investors, as at 30 June 2023

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Fund information (Investment policy is on the next page)

Index	NASDAQ Biotechnology Total Return Index
Morningstar sector	Europe OE Equity Biotechnology
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.

Performance in (USD)

Performance %	A2 (Net)	Index	Sector	A2 (Gross)	Target (Gross)
1 month	0.9	0.2	0.3	-	-
YTD	10.6	-2.8	-1.0	-	-
1 year	50.7	9.6	6.1	-	-
3 years (annualised)	11.2	-1.0	-5.2	-	-
5 years (annualised)	-	-	-	-	-
Since inception 10 Dec 2018 (annualised)	16.8	5.7	2.6	-	-

Source: at 30 Jun 2023. © 2023 Morningstar. All rights reserved, performance is with gross income reinvested. 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	10.6	-2.8	-1.0
2022	-3.8	-10.1	-17.2
2021	-5.2	0.0	-7.7
2020	61.3	26.4	27.5
2019	34.7	25.1	25.4
2018 from 10 Dec 2018	-7.5	-6.9	-7.0
2017	-	-	-
2016	-	-	-
2015	-	-	-
2014	-	-	-
2013	-	-	-

Source: at 30 Jun 2023. © 2023 Morningstar. All rights reserved, performance is with gross income reinvested. 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.

From 31 January 2023 Agustin Mohedas also manages this fund.

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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.

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 http://www.janushenderson.com.

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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.
- 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.

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% 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.

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

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