Global Life Sciences Fund

Investment Environment
Globally, health care stocks rebounded along with a broad recovery in equities. The sector also benefited from more than $100 billion in merger and acquisition (M&A) activity during the period, with many deals garnering premiums of 50% to more than 100%. On a sub-sector basis, health care technology and supplies were the top performers, thanks to strong demand for diagnostic tools and other related products. These firms also sit outside the drug pricing debate in the U.S. Health care services was the only sub-sector to deliver losses.

Performance Discussion
The Fund outperformed its primary benchmark, the MSCI World Health Care IndexSM, and secondary benchmark, the S&P 500® Index, for the quarter. We seek to invest in companies worldwide that are addressing high, unmet medical needs and providing efficient and cost-effective health care solutions. We believe the health care sector, with its rapid growth and high complexity, offers abundant opportunities for differentiated research. We believe understanding both the science and the business behind new therapies and having a disciplined investment process are key to driving long-term results.

During the quarter, stock selection in biotechnology and pharmaceuticals contributed positively to returns. However, the Fund’s positioning in health care supplies and a small cash allocation weighed on relative performance.

On an absolute basis, Insmed was the top contributor during the quarter. The stock continued to benefit from sales of its lead drug, Arikyza. During the fourth quarter, the antibiotic, which addresses nontuberculous mycobacterial (NTM), a serious bacterial lung infection, did roughly $10 million in sales, four times the consensus estimate. In light of strong trends so far, we believe Arikyza sales could significantly exceed street expectations for 2019. An estimated 200,000-plus people worldwide are affected by NTM, with no other approved treatment available.

Celgene also aided performance. The stock climbed after Bristol-Myers Squibb said it would acquire Celgene for $74 billion, representing a roughly 50% premium. Although not guaranteed, the deal was recently backed by two proxy advisory firms, improving the odds that Bristol-Myers shareholders will affirm the acquisition at a vote in April. Meanwhile, Celgene continues to offer growth potential. The company is a leader in hematological disease, with $15 billion in revenues in 2018. A key part of that success has been Revlimid, a treatment for multiple myeloma. Although the drug will face generic competition at some point, the U.S. Patent and Trademark Office recently dismissed an effort to challenge a key Revlimid patent. As a result, Celgene should be

Highlights
• Health care stocks rebounded during the period along with a broad recovery in equities. A wave of mergers and acquisitions also helped propel the sector.
• The Fund outperformed both its primary and secondary benchmarks.
• Despite uncertainty from potential policy changes in the U.S. and the 2020 election cycle, we believe the sector’s rapid pace of innovation will continue to drive growth.
able to fend off generic competition for a while longer. We are also excited about the firm’s late-stage pipeline, which includes five key assets, each with more than $1 billion in sales potential.

Thermo Fisher Scientific was another top contributor. Thermo is a leader in the global life sciences and diagnostics markets, with strong name-brand recognition and the widest array of product offerings compared to competitors. During the quarter, the company reported consensus-beating revenue and earnings, driven by high demand for laboratory products, analytical instruments and other research tools. We believe demand for Thermo’s products will remain strong, thanks to advances in disease testing and biopharmaceutical research and development. The company also continues to supplement its growth with bolt-on acquisitions.

While pleased by these results, other holdings weighed on returns, including AbbVie, the top detractor. The company reported declining sales for AbbVie’s blockbuster rheumatoid arthritis drug, Humira, which now faces biosimilar competition in Europe. (By definition, a blockbuster drug generates sales of $1 billion or more annually.) However, we believe this is likely a short-term headwind for the company. AbbVie has a promising pipeline, including Orlilisa, a treatment for endometrial pain, which launched in the U.S. in 2018. AbbVie also recently won approval for a second, much broader indication of Venclexta, a drug to treat severe blood cancers. Finally, AbbVie is developing upadacitinib, an oral successor to Humira, and risankizumab, an antibody for the treatment of multiple inflammatory diseases, such as psoriasis and Crohn’s disease. We believe both could have multibillion-dollar potential.

Diplomat Pharmacy also weighed on performance. The stock fell after the company announced it would postpone fourth quarter and full-year 2018 results due to an impairment charge that had to be finalized. The firm also withdrew previously released guidance for 2019, citing lower-than-expected results in January. Diplomat is a distributor of specialty pharmaceutical products and pharmacy benefit manager services. With the drug distribution industry under pressure from increased competition and drug price scrutiny, we exited the stock.

Humana was another detractor. Political uncertainty has been a headwind for managed care companies in recent months, including Humana. However, we believe the firm’s long-term growth potential is unchanged. Humana has significant exposure to Medicare Advantage, one of the few secular growth markets within health insurance. Every day, 10,000 people in the U.S. turn 65, the eligibility age for Medicare benefits. Humana does an efficient job of onboarding new members, with membership growth of 12.5% expected in 2019, twice the industry’s growth rate.

For detailed performance information, please visit janushenderson.com/performance.

Outlook

The health care sector has benefited from a wave of M&A activity in 2019, and we believe more deals could be in the offing given attractive valuations. The top 20 biopharmaceutical companies are currently generating more than $150 billion in annual free cash flow, and many are looking to supplement their aging portfolios with innovative products and platforms. We believe the qualities that we look for in small- and mid-cap biotech companies – firms developing or launching advanced medicines focused on addressing high, unmet medical needs – could appeal to large biopharma firms, as well.

In the U.S., the 2020 election cycle is already underway, and we believe drug pricing and proposals for single-payer health care plans will be a focus, potentially weighing on managed care and other related companies. However, health care often outperforms late in the business cycle. With the current economic expansion roughly a decade old, the sector could benefit if the economy shows signs of weakness.

Most importantly, we believe innovation remains robust. Last year, the U.S. Food and Drug Administration approved a record number of novel therapies. This year, we expect to see results from important clinical trials for cancer-fighting immunotherapies, Huntington’s disease and depression. We also expect to see continued advances made in endovascular valve technology, stroke protection and robotic-assisted surgery. We believe these distinct events could lead to significant growth potential for the sector.

Top Contributors and Detractors for the Quarter Ended 3/31/19

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<tr>
<th>Top Contributors</th>
<th>Ending Weight (%)</th>
<th>Contribution (%)</th>
<th>Top Detractors</th>
<th>Ending Weight (%)</th>
<th>Contribution (%)</th>
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<tr>
<td>Insmed Inc.</td>
<td>1.71</td>
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<td>Bristol-Myers Squibb Co.</td>
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<td>AC Immune SA</td>
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The holdings identified in this table, in compliance with Janus Henderson policy, do not represent all of the securities purchased, held or sold during the period. To obtain a list showing every holding as a percentage of the portfolio at the end of the most recent publicly available disclosure period, contact 800.668.0434 or visit janushenderson.com/info.
Top Contributors

**Insmed:** The biopharmaceutical firm’s lead drug, Arikayce, addresses nontuberculous mycobacterial (NTM), a serious bacterial lung infection. It’s estimated that more than 200,000 people worldwide are affected by NTM, and the number of cases is expected to grow rapidly. The drug launched in late 2018 and, so far, sales have exceeded consensus estimates. However, we continue to believe the drug has underappreciated commercial potential.

**Celgene:** Celgene is a biopharmaceutical company that develops innovative treatments for cancer and inflammatory conditions. Celgene has a leading position in the treatment of hematological disease and a late-stage pipeline consisting of five key assets, each with more than $1 billion in sales potential. In early 2019, Bristol-Myers Squibb announced plans to acquire Celgene, and we believe the deal could close later this year.

**Thermo Fisher Scientific:** The company engages in the provision of analytical instruments, equipment, software, and services for biopharmaceutical research, analysis and diagnostics. Thermo has become a market leader and, in our opinion, is on track to continue expanding revenues and profit margins. The company also recently announced that it is buying Brammer Bio for $1.7 billion, which we think will help augment Thermo’s business in the fast-growing area of gene therapy.

**Neurocrine Biosciences:** Neurocrine Biosciences’ lead drug, Ingrezza, treats tardive dyskinesia, a debilitating condition characterized by involuntary and repetitive movements. Since the drug launched, uptake of Ingrezza has exceeded estimates, and we believe the market for the therapy remains underpenetrated. In addition, Neurocrine’s partner recently launched Orilissa, an oral medicine to treat pain caused by endometriosis, and we believe the drug has blockbuster potential.

**Alexion Pharmaceuticals:** This biopharmaceutical company focuses on severe and ultra-rare disorders. Its lead drug, Soliris, treats paroxysmal nocturnal hemoglobinuria (PNH), a blood disorder characterized by anemia and the need for frequent blood transfusions. Soliris is also approved for other indications, which has helped sales to expand. In addition, Alexion recently launched a new version of Soliris – Ultomiris – that requires PNH patients to receive fewer infusions. We believe the company is successfully converting the Soliris market to Ultomiris, which could help mitigate the impact of biosimilar competition for Soliris in coming years.

Top Detractors

**AbbVie:** AbbVie is a biopharmaceutical company whose lead drug, Humira, treats rheumatoid arthritis, chronic plaque psoriasis, Crohn’s disease and other common autoimmune conditions. Although Humira faces future competition from biosimilars, AbbVie has promising therapies in its pipeline that could offset this headwind. These medicines include recently launched Mavyret for hepatitis C, rsankizumab, a treatment for psoriasis, and upadacitinib, an oral therapy for a wide range of inflammatory diseases.

**Diplomat Pharmacy:** Diplomat is a distributor of specialty pharmaceutical products and pharmacy benefit manager services. During the quarter, we exited the stock.

**Humana:** Relative to other managed care companies, Humana has attractive growth potential, in our opinion. The firm benefits from significant exposure to Medicare Advantage, one of the few secular growth markets within health insurance, and is growing membership at a double-digit rate.

**Bristol-Myers Squibb:** Bristol-Myers Squibb’s immunotherapies, Opdivo and Yervoy, are being developed as a combination medicine to fight cancer, including lung and kidney cancer. In addition, the company is helping fund studies for a combined drug involving Opdivo and NKTR-214, an immuno-stimulatory drug by Nektar Therapeutics. Finally, Bristol-Myers recently announced that it plans to acquire Celgene, a deal that we believe would help expand Bristol-Myers’ pipeline and create cost synergies.

**AC Immune:** The biopharmaceutical company is focused on developing treatments for Alzheimer’s and other neurodegenerative diseases. During the quarter, phase 3 trials for crenezumab, a treatment for early Alzheimer’s disease that AC Immune was developing with Roche, were stopped because of futility. Consequently, we exited the stock.
For more information, please visit janushenderson.com.

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Discussion is based on the performance of Class I Shares. As of 3/31/19 the top ten portfolio holdings of Janus Henderson Global Life Sciences Fund are: Merck & Co Inc (4.38%), Novartis AG (ADR) (3.51%), Takeda Pharmaceutical Co Ltd (3.21%), Abbott Laboratories (3.04%), AstraZeneca PLC (2.79%), UnitedHealth Group Inc. (2.70%), Thermo Fisher Scientific Inc (2.69%), Anthem Inc (2.68%), AbbVie Inc. (2.59%) and Humana Inc (2.45%). There are no assurances that any portfolio currently holds these securities or other securities mentioned.

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