

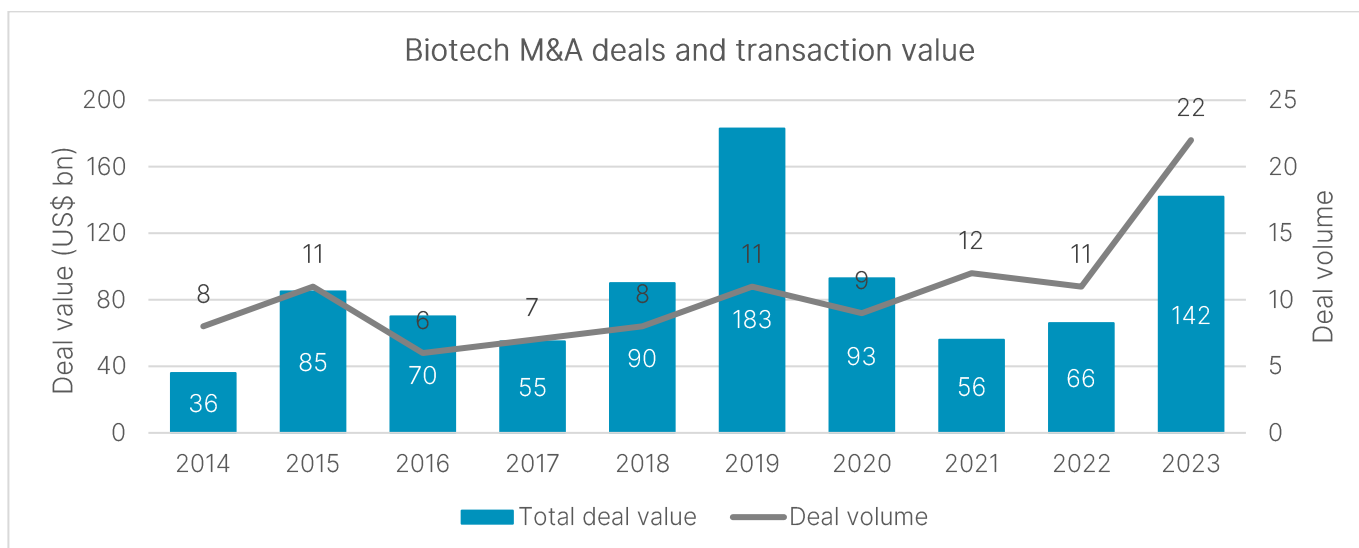
Unveiling the Promising Road to Recovery for the Biotech Sector

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After three years of underperformance, the biotech sector is exhibiting compelling indications of a revitalization. According to data from Jefferies, drug developers raised US\$6.2 billion in equity capital markets in January 2024, the highest since February 2021.¹ Fundraising has been encouraged by multiple factors, including a resurgence of stock prices, the anticipation of forthcoming interest rate cuts by the Federal Reserve, and an upswing in mergers and acquisitions (M&A) activity in the sector.

Outlook for M&A and fundraising activity in 2024 remains robust

Biotech M&A activity experienced a rebound last year, as the deal value more than doubled the amount in 2022. 22 deals valued at US\$1 billion or more were announced in 2023, and the aggregate transaction value of US\$142 billion marks the highest level since 2019.

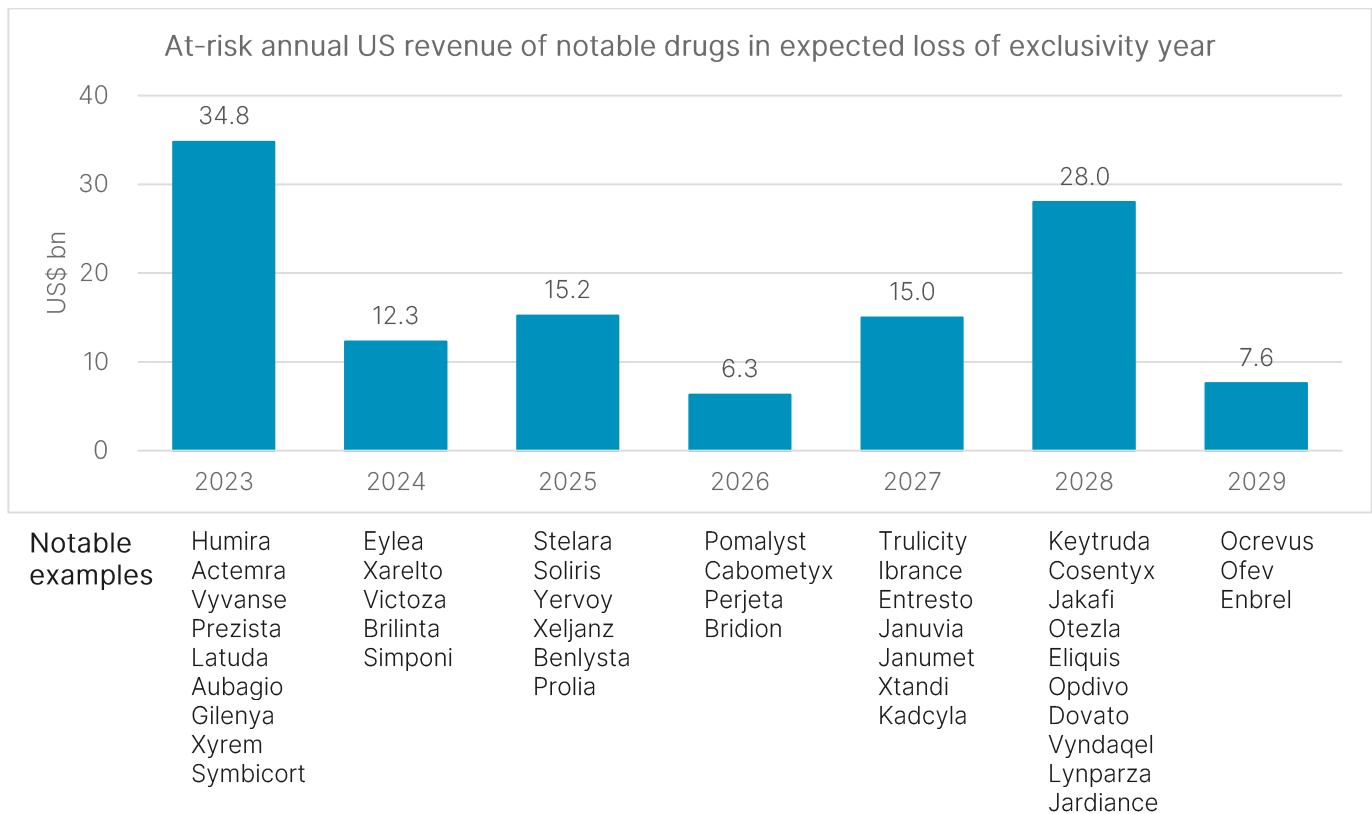


Source: TD Cowen. As of December 31, 2023. Note: Data reflect deals above US\$1 billion in transaction value in the biotechnology sector.

The industry is reaching the looming patent cliff, characterized by a sharp plunge in revenues as the patents for one or more flagship products of a firm expire. Patents will expire for nearly 200 drugs by 2030, and virtually every major biopharma firm will be impacted.² The patent cliff could intensify the need for M&A as drugmakers strive to secure sustainable long-term growth. Since some firms still have four to seven years before their patent expiration, there is a shift toward the acquisition of late-stage biotech assets, which offer the potential to emerge as approvable drugs within the forthcoming timeframe.

¹ <https://www.ft.com/content/5c45f23b-9b43-4a95-8dcc-44587317b0dd>

² <https://www.pharmavoice.com/news/pharma-patent-cliff-Merck-Keytruda-Pfizer-Seagen-Humira/652914/>



Source: RBC Capital Markets. As of September 21, 2023.

In December 2023, Bristol Myers Squibb (BMS) reported the acquisition of Karuna Therapeutics for US\$14 billion³, gaining a promising new type of antipsychotic medicine to help power growth as patents on its older therapies are set to expire later this decade. BMS saw a decrease in revenue from blood cancer treatment Revlimid as its generic versions entered the market after its patent loss in 2022. Revlimid generated only US\$6.1 billion in sales in 2023⁴, plummeting by 52% compared to US\$12.9 billion in 2021⁵ before the loss of exclusivity. Karuna's experimental schizophrenia drug, KarXT, could become a revenue driver for BMS through the late 2020s and into the next decade. This comes at a crucial juncture when BMS' leading drugs, including blood thinner Eliquis and cancer immunotherapy Opdivo, are confronting the challenges from generic competition later this decade.

As for the initial public offering market, the number of venture-capital-backed biotech companies going public experienced a substantial decline in recent years. In 2022, only 17 companies took the IPO leap, followed by an additional 18 in 2023, representing a notable decrease compared to 88 companies in 2021 and 66 in 2020. Nevertheless, six biotech firms were listed in the US in the first two months of this year. CG Oncology, which has a bladder cancer therapy in late-stage trials, raised US\$437 million during its Nasdaq-listed IPO in January 2024 and had a return of 134% since its debut.⁶ The strong start brings a sense of optimism to the industry.

³ <https://news.bms.com/news/corporate-financial/2023/Bristol-Myers-Squibb-Strengthens-Neuroscience-Portfolio-with-Acquisition-of-Karuna-Therapeutics/default.aspx>

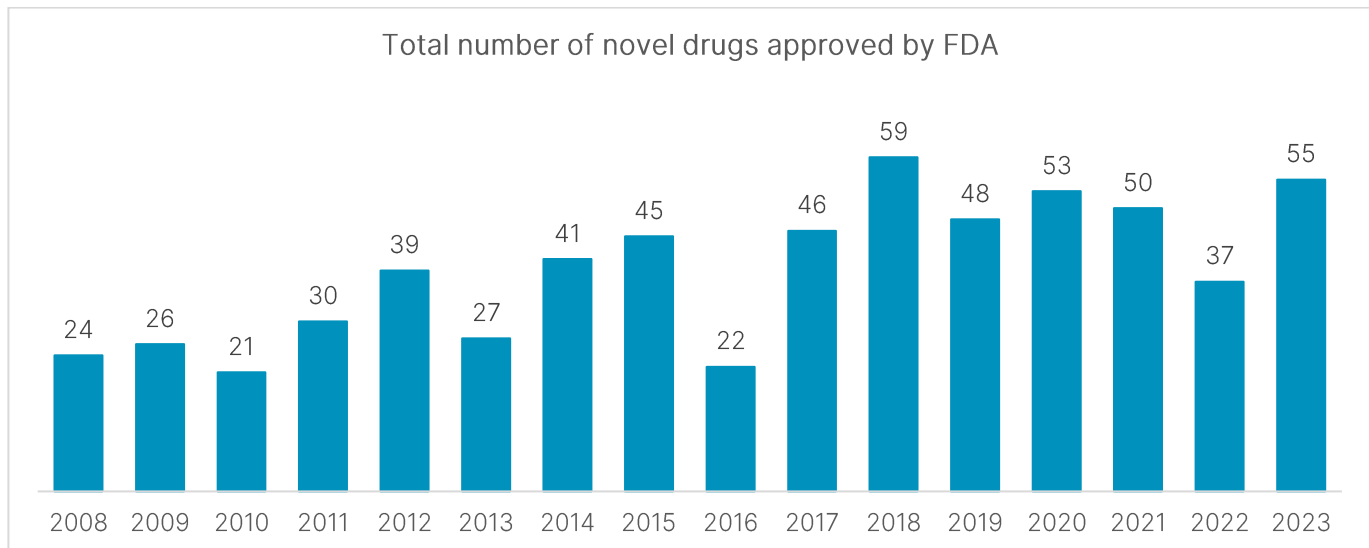
⁴ https://www.bms.com/assets/bms/us/en-us/pdf/investor-info/doc_financials/quarterly_reports/2023/BMY-Q42023-Earnings-Press-Release.pdf

⁵ https://s21.q4cdn.com/104148044/files/doc_financials/quarterly_reports/2021/BMY-Q42021-Earnings-Press-Release.pdf

⁶ Source: Bloomberg. As of February 28, 2024.

Strong innovation in the biotech sector

The Center for Drug Evaluation and Research (CDER) of the US Food and Drug Administration (FDA) approved 55 new drugs last year, marking the second-highest count in the past 30 years and a remarkable increase of nearly 50% compared to 2022. From 2008 to 2023, CDER has averaged approximately 39 novel drug approvals each year. CDER approved several high-profile therapies last year, including the Alzheimer's treatment Leqembi developed by Eisai in partnership with Biogen, and Eli Lilly's obesity drug Zepbound.



Source: Food and Drug Administration.

Cell and gene therapies have been gaining momentum in the healthcare industry as transformative treatment options that hold the potential to revolutionize the management of chronic diseases. Cell therapy and gene therapy are overlapping fields of biomedical treatment: gene therapy is the use of genetic material in the treatment or prevention of disease, while cell therapy involves the transfer of intact, live cells into a patient to help mitigate or cure a disease. According to GlobalData estimates, the global cell and gene therapy market is estimated to reach US\$80 billion by 2029, with oncology accounting for 44% of the market.⁷

In December 2023, the FDA approved two gene therapies for sickle cell disease.⁸ Developed by Vertex Pharmaceuticals and CRISPR Therapeutics, Casgevy is the first FDA-approved therapy that leverages CRISPR/Cas9, a gene-editing technology that was awarded the Nobel Prize in 2020.⁹ In January 2024, the FDA approved Casgevy as a one-time treatment for transfusion-dependent beta-thalassemia patients as well.¹⁰ The CRISPR/Cas9 genetic scissors can be used to change the DNA of animals, plants, and microorganisms with extremely high precision. Oppenheimer expects a slow and steady launch for the therapy and projects combined peak sales of approximately US\$400 million.¹¹ These groundbreaking approvals signify an important medical advance with the use of innovative cell-based gene therapies in combatting potentially devastating diseases and ultimately bolstering public health.

⁷ <https://www.globaldata.com/media/pharma/cell-gene-therapy-will-top-industry-trend-pharma-2024-finds-globaldata/>
⁸ <https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease>

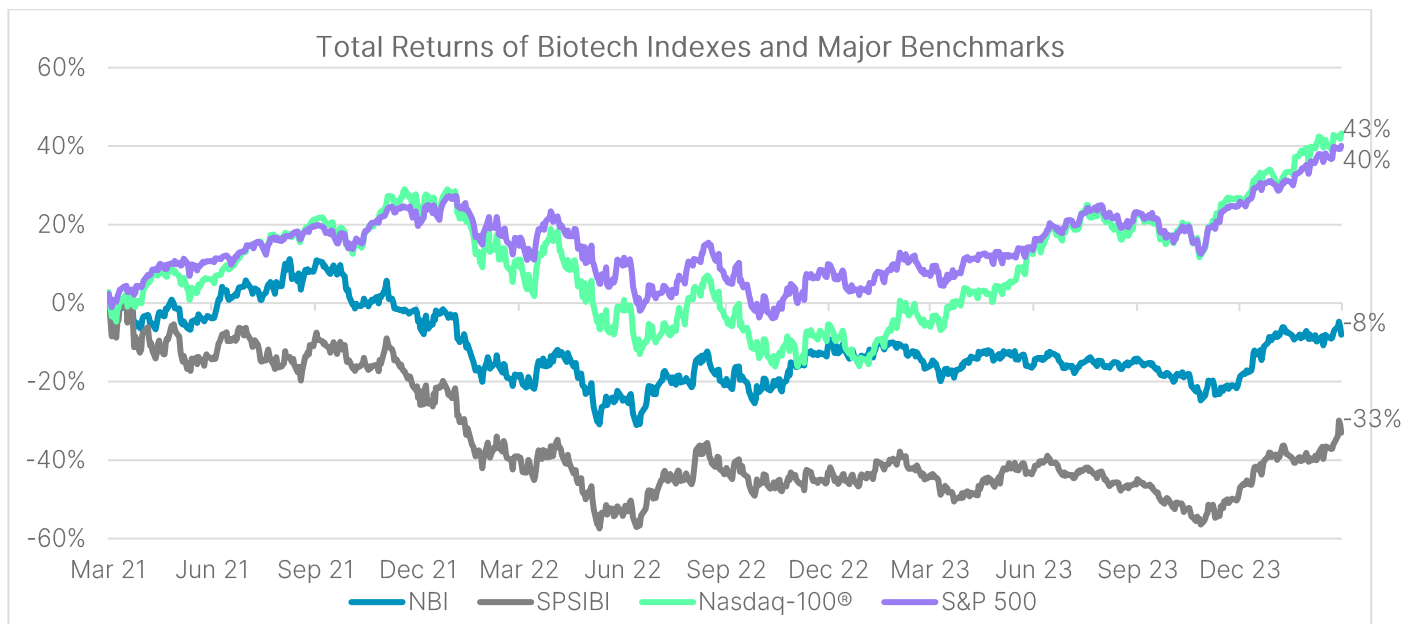
⁹ <https://www.nobelprize.org/prizes/chemistry/2020/press-release/>

¹⁰ <https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-us-fda-approval-casgevym-exagamglogene>

¹¹ <https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-approves-vertexcrispr-gene-therapy-an-inherited-blood-disorder-2024-01-16/>

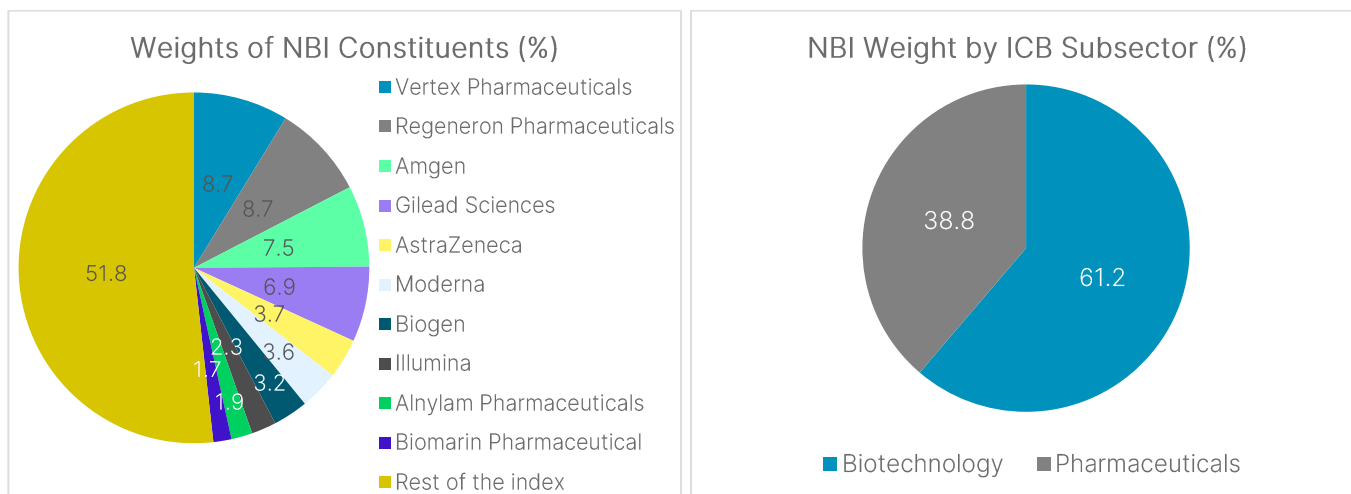
NBI – the leading benchmark for the biotech industry

The Nasdaq Biotechnology™ Index (NBI™) was launched on November 1, 1993, during the nascent stages of the biotech industry. With 221 constituents as of the end of February 2024, NBI is a modified market capitalization-weighted index that ensures its return is driven proportionally by the largest and most important biotech firms. During the three years ending on February 29, 2024, NBI experienced a modest decline of 8%, yet notably outperformed the S&P Biotechnology Select Industry Index (SPSIBI) by 25 percentage points. SPSIBI is a modified equal-weighted index with only 118 constituents. Although the biotech sector has endured challenging times in recent years, the aforementioned promising indications serve as a beacon of hope, suggesting that the worst may now be behind us. During the four months from November 2023 to February 2024, the NBI witnessed a significant rebound of 20%.



Source: Bloomberg. As of February 29, 2024

The top five constituents of NBI are capped at 8% each and the rest of the constituents are capped at 4% during quarterly rebalancing. As of the end of February 2024, the ten largest constituents accounted for 48.2% of the weight of the index. 61.2% of the constituents are classified under the Biotechnology Subsector and the rest of the constituents are in the Pharmaceuticals Subsector, according to the Industry Classification Benchmark (ICB) classification.



Source: Nasdaq Global Indexes. As of February 29, 2024

When comparing the breadth of securities covered, NBI distinguishes itself by including companies from any country of incorporation, whereas SPSIBI focuses on the US only. This inclusive approach has allowed the expansion of the non-US-based subset within NBI, comprising 42 members and accounting for 15% of the index's aggregate weight. The following are the 10 largest exclusions from SPSIBI – six of them are based outside the US.

Company Name	NBI Weight	SPSIBI Weight	Market Cap (US\$ bn)	Country
AstraZeneca (ADR)	3.66%	0.00%	195.8	UK
Illumina	2.28%	0.00%	22.2	US
Viartis	1.52%	0.00%	14.7	US
Royalty Pharma	1.39%	0.00%	13.6	US
Sanofi (ADR)	1.38%	0.00%	120.3	France
Argenx (ADR)	1.25%	0.00%	22.0	Netherlands
Medpace	1.25%	0.00%	12.3	US
BioNTech (ADR)	0.88%	0.00%	21.6	Germany
Ascendis Pharma (ADR)	0.87%	0.00%	8.5	Denmark
Jazz Pharma	0.77%	0.00%	7.4	Ireland

Source: Nasdaq Global Indexes; Bloomberg; FactSet. As of February 29, 2024. Note: The market cap shown reflects the total public market value of the listed equities of a company. NBI index weightings are based on individual security market values. In the case of an ADR, a constituent's weighting in NBI will correspond solely to the market value of its ADR shares.

Although SPSIBI covers US-based biotech companies listed on exchanges other than Nasdaq, this segment remains infinitesimal within the broader universe, exerting a minimal influence on index breadth and performance. Year after year, the overwhelming majority of biotech firms opt to list on Nasdaq, as evidenced by its remarkable IPO win rates of 98% from 2021 to 2023, cementing Nasdaq's position as the preferred choice for the industry.

As the largest constituent with an 8.7% weight in NBI, Vertex Pharmaceuticals generated a total return of 31.5% and 40.9% in 2022 and 2023, respectively. Its 2023 product revenue reached US\$9.87 billion, an 11% increase compared to 2022. The Boston-based company developed an experimental drug that alleviates moderate to severe pain, blocking pain signals before they can reach the brain. Vertex expects its new drug, named VX-548, to avoid opioids' potential to lead to addiction and plans to submit a new drug application to the FDA by mid-2024. It will represent the first new class of acute pain medicine in more than two decades if the application is successful. Defined as pain that lasts less than three months, acute pain affects more than 80 million people in the US each year.¹² Dr. Henry Kranzler, professor of psychiatry and director of the Center for Studies of Addiction at the University of Pennsylvania, described the drug as "a therapeutic breakthrough." Opioid-involved overdose deaths in the US rose from 21,089 in 2010 to 80,411 in 2021.¹³ As the US is in the midst of the opioid crisis, the need for effective, non-addictive alternatives has never been more critical.

Conclusion

The biotech sector experienced a revival in M&A last year, and biotech IPOs have been a bright spot since the start of the year. As the industry braces for an ongoing massive patent cliff projected to extend until 2030, pharmaceutical firms are proactively fortifying their positions through increased partnerships and, on occasion, pursuing bigger deals. The number of novel drugs approved by the FDA's CDER last year reached the second highest level in the past three decades, which is another encouraging sign that could lead to increased investment in biotech firms. Moreover, cell and gene therapies offer vast potential as treatments for a wide range of diseases, including cancer, genetic, and neurological diseases. The first commercially available CRISPR/Cas9 gene-editing

¹² <https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-positive-results-vx-548-phase-3-program>

¹³ <https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates>

treatment was approved by authorities in the US and UK in the fourth quarter of last year. Based on these multiple favorable factors, the biotech industry is poised for recovery in 2024.

The Nasdaq Biotechnology Index provides investors with a transparent benchmark for tracking new biotech entrants into the public markets. This well-structured index strikes a balance by maintaining appropriate weightings between the inherently volatile yet promising realm of younger, small-cap companies and the established, more stable large-cap members of the industry.

ETFs tracking NBI include the Invesco Nasdaq Biotechnology ETF (Nasdaq: IBBQ), ProShares Ultra Nasdaq Biotechnology ETF (Nasdaq: BIB), ProShares UltraShort Nasdaq Biotechnology ETF (Nasdaq: BIS), Invesco Nasdaq Biotech UCITS ETF (London: SBIO), iShares Nasdaq US Biotechnology UCITS ETF (London: BTEC), Capital Nasdaq Biotechnology Index ETF (Taiwan: 00678), Mirae Asset TIGER Nasdaq BIO ETF (Korea: 203780), and China Universal Nasdaq Biotechnology ETF (Shanghai: 513290).

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