

orbimed



The Biotech Growth Trust

February 2025

Portfolio Managers: Geoffrey Hsu & Josh Golomb

Geoffrey Hsu, CFA

General Partner



Geoffrey C. Hsu, CFA, is a General Partner at OrbiMed and has been portfolio manager of The Biotech Growth Trust since May 2005.

Mr. Hsu joined OrbiMed in 2002 as a biotechnology analyst. Prior to joining OrbiMed, he worked as a financial analyst in the healthcare investment banking group at Lehman Brothers. Mr. Hsu received his A.B. degree summa cum laude from Harvard University and holds an M.B.A. from Harvard Business School. Prior to business school, he spent two years studying medicine at Harvard Medical School.

Josh Golomb

Partner

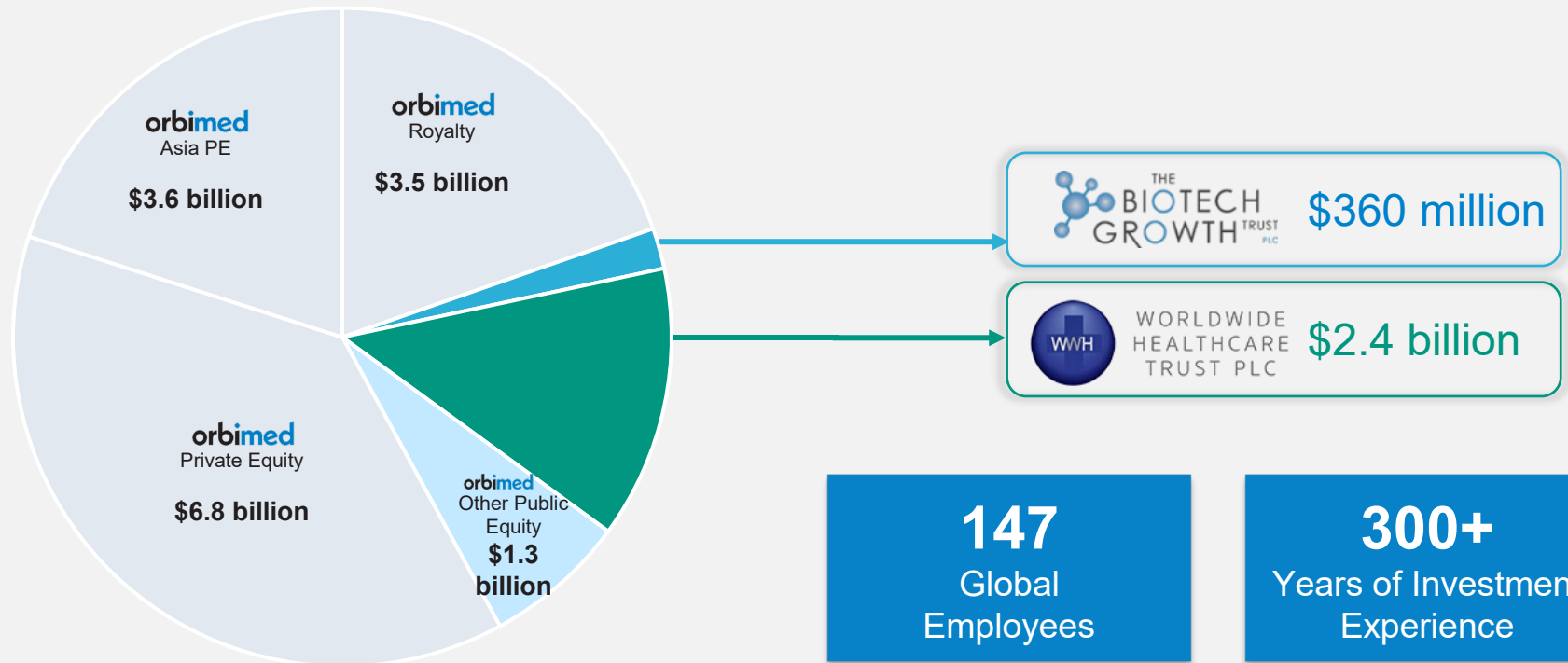


Josh Golomb is a Partner at OrbiMed focused on biotechnology. He joined the firm in 2021 and became a portfolio manager of The Biotech Growth Trust in 2023.

Mr. Golomb has covered the biotechnology and pharmaceutical sectors at investment firms since 2004. He was most recently employed at HealthCor, a healthcare-dedicated hedge fund, from 2016 to 2021 as a senior biotechnology and pharmaceutical analyst. Previously, he covered biotech at Millennium, Citadel, Diamondback and ProMed Partners. Mr. Golomb received a B.S. in Operations Research with a concentration in Engineering Management Systems from the Fu Foundation School of Engineering and Applied Science at Columbia University.

OrbiMed Corporate Update

Global Healthcare-Dedicated Investment Firm with Over 25 Years of Experience



Total AUM: \$18 billion

147
Global
Employees

300+
Years of Investment
Experience

25+
New Hires
in 2023/24

33
Colleagues with
M.D. / Ph.D.

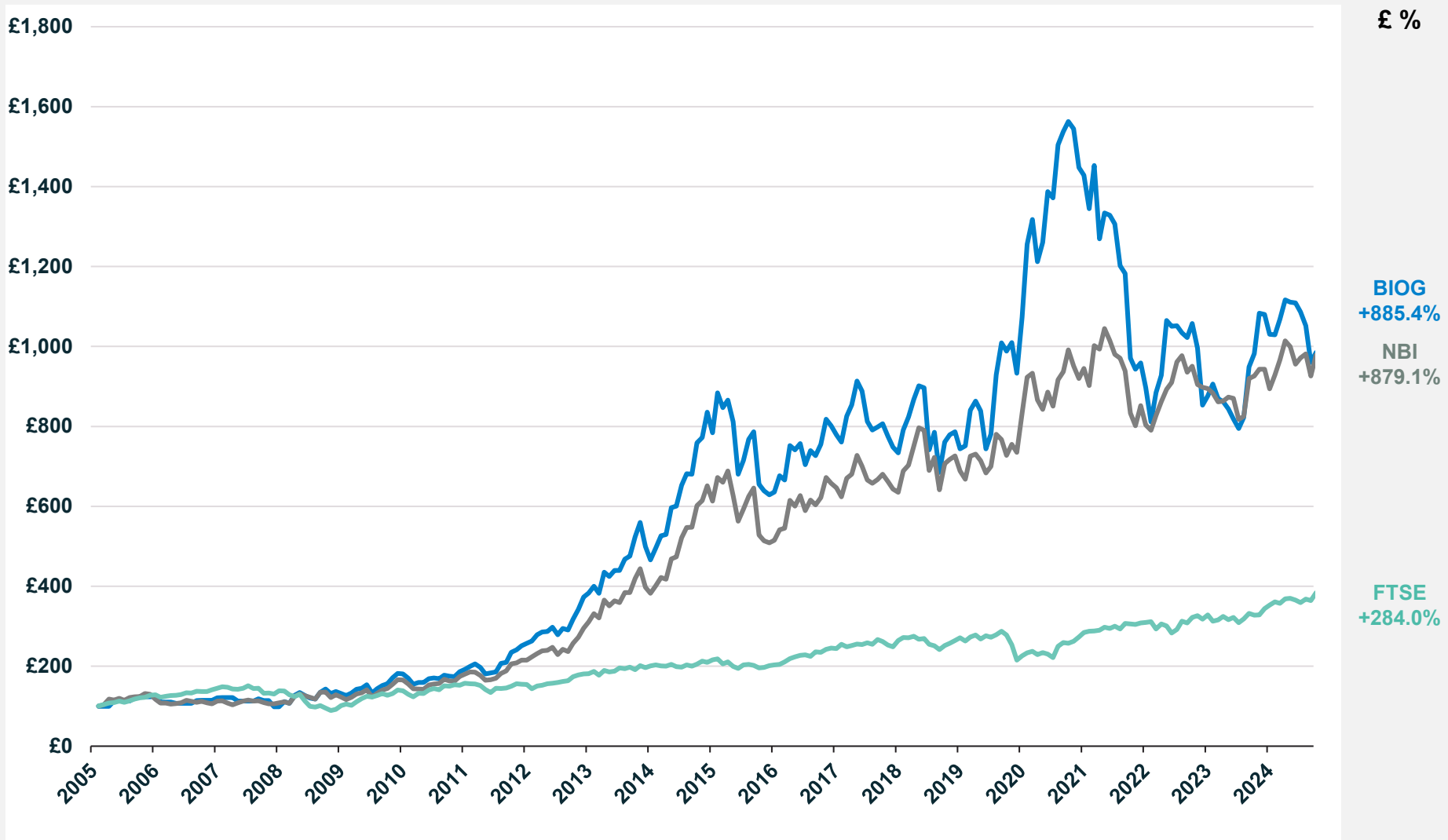
Source: OrbiMed; Data estimated as of 31 January 2025

BIOG

Performance

BIOG Performance since Inception

18 May 2005 through 31 January 2025

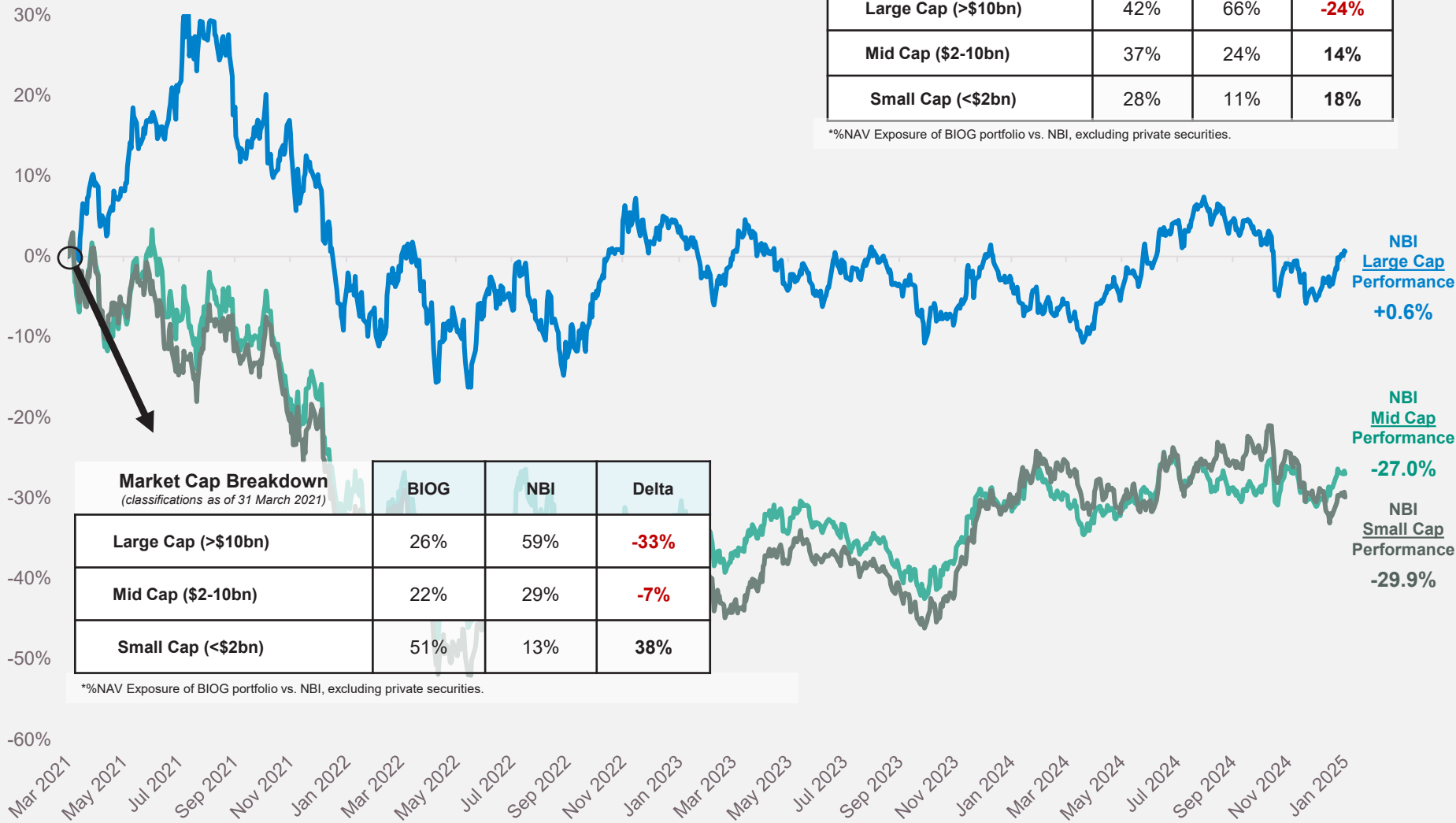


Note: See Endnotes for additional information, including with regard to the calculation of these results and the index shown above.

Source: Frostrow, Bloomberg.

Market Cap Performance Divergence in Biotech

Performance Gap Since 2021 Has Yet to Close

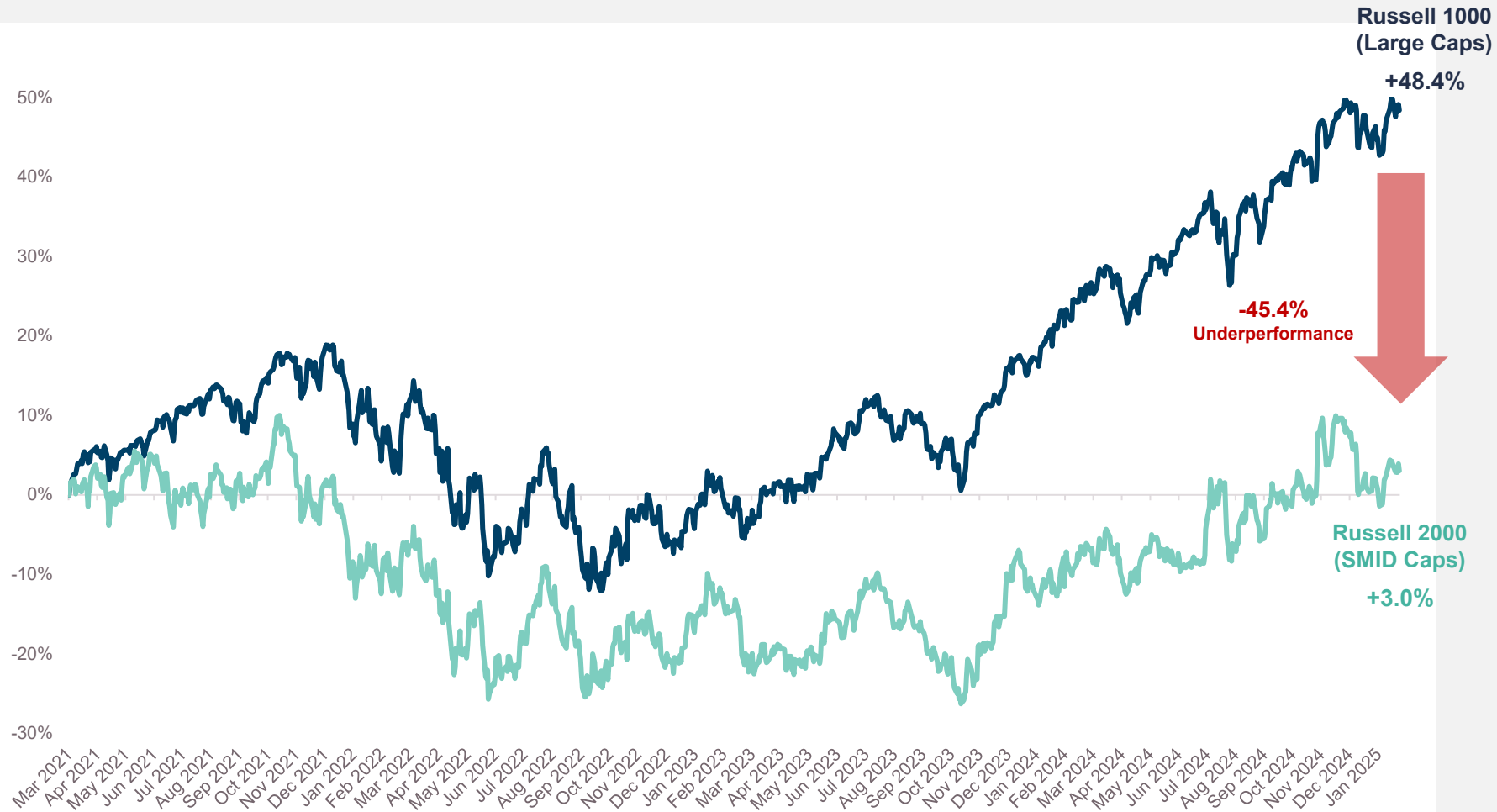


Note: Chart shows equal-weighted performance of NBI stocks in their respective market cap buckets, using market cap classifications as of 31 March 2021. Updated as of 31 January 2025, performance calculated in USD.

Size Divergence in the Broad Market

(31 March 2021 – 31 January 2025)

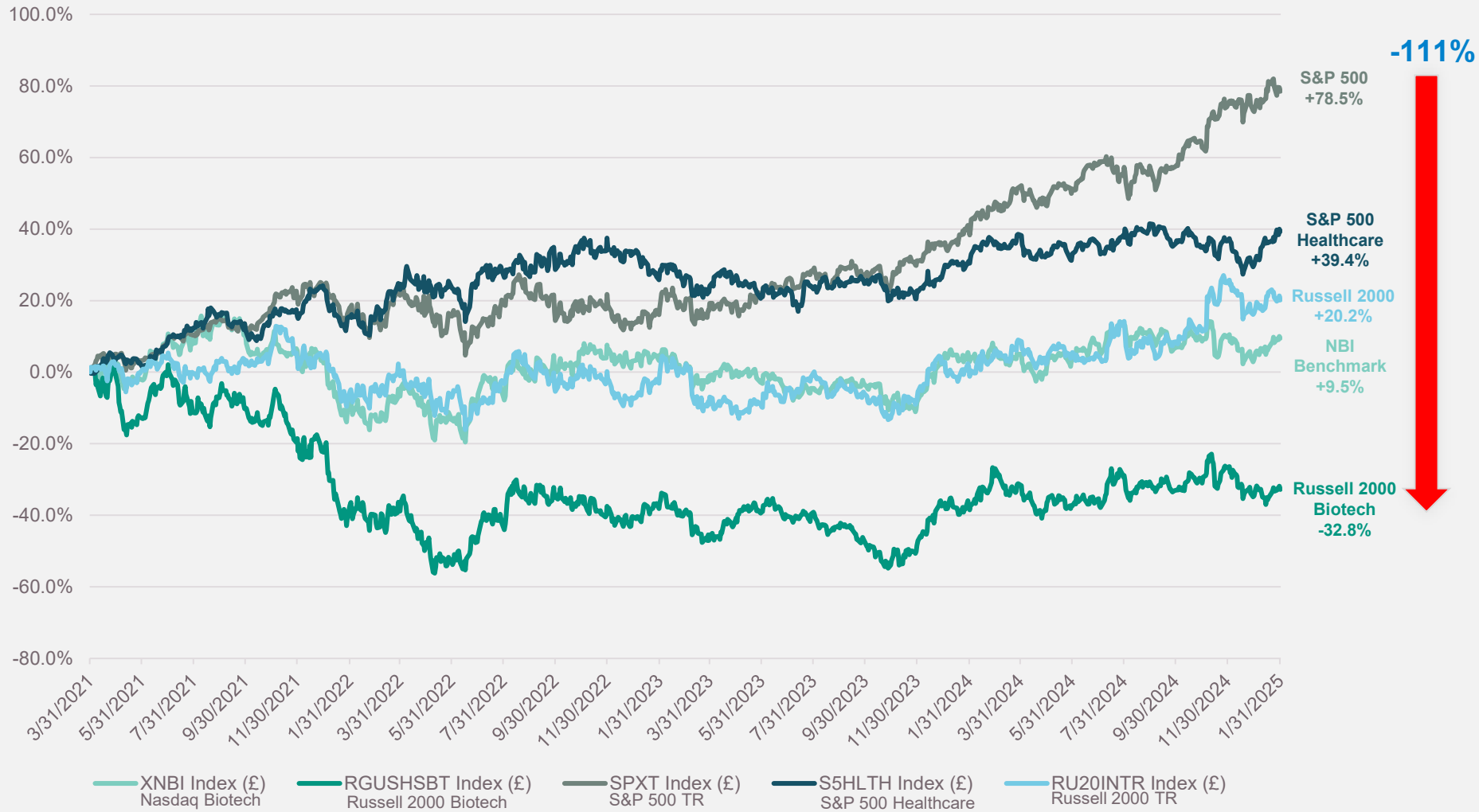
Russell 2000 (Small/Mid Cap) vs Russell 1000 (Large Cap)



Note: The Russell 2000 Index is comprised of the smallest 2000 companies in the Russell 3000 Index. The Russell 1000 Index is comprised of the largest 1000 companies in the Russell 3000 Index.

Biotech/Healthcare Underperformance vs S&P 500

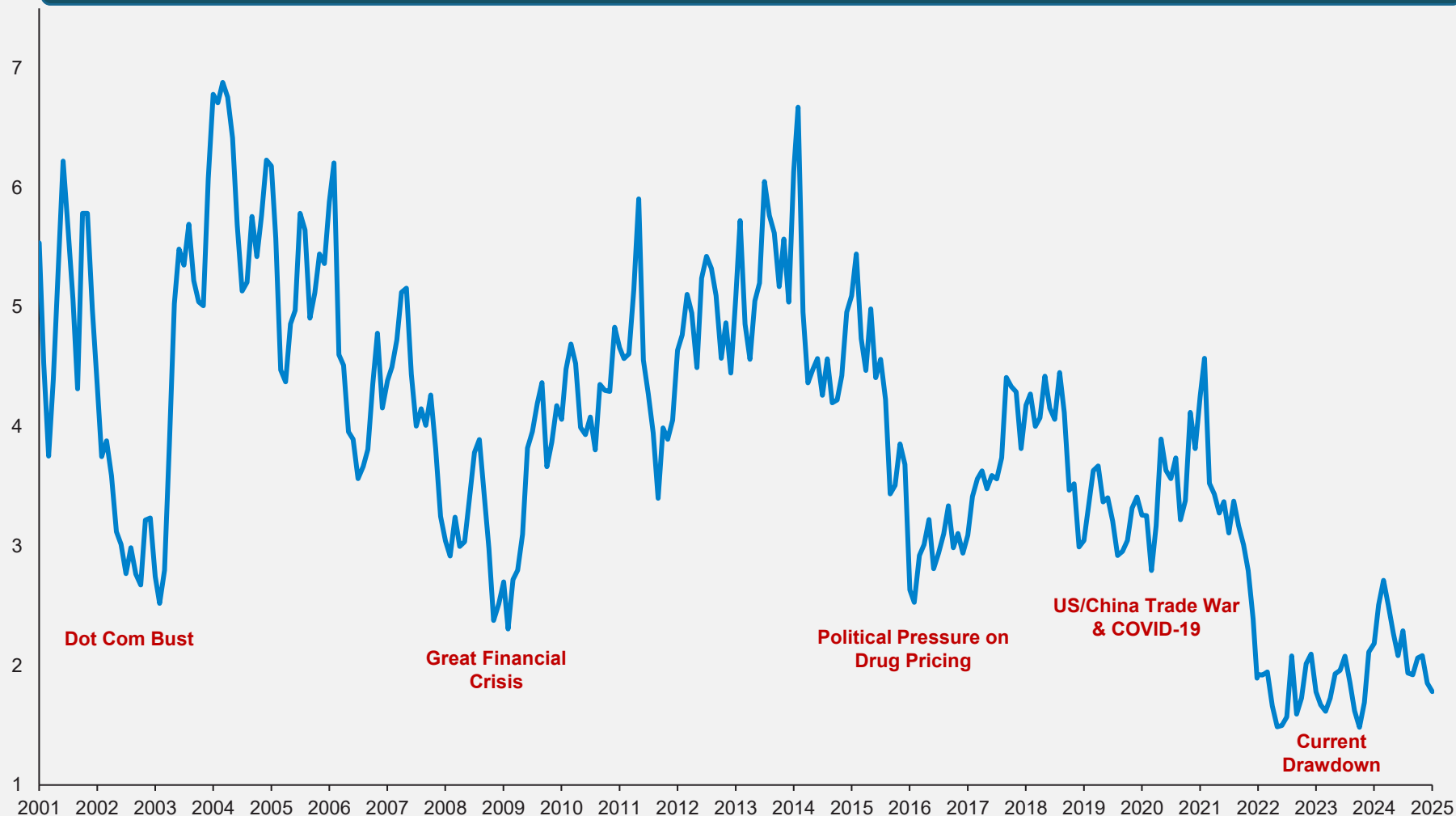
(31 March 2021 – 31 January 2025)



Note: Nasdaq Biotech Index reflects change to total return version of index as of 30 September 2024.

Biotech Valuations At Unprecedented Lows

Ratio of Market Cap to Net Cash on Balance Sheet (Median)

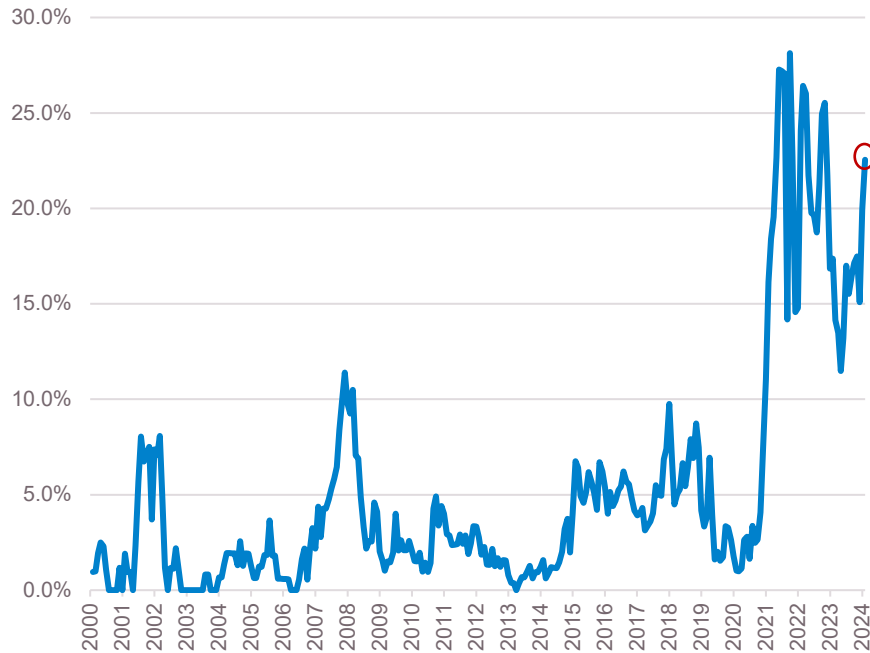


Note: Monthly chart of all GICS defined biotechnology greater than \$10mm, using historical cash and debt sourced from Bloomberg, with annual GICS biotechnology universe refreshes. Updated through 31 January 2025.

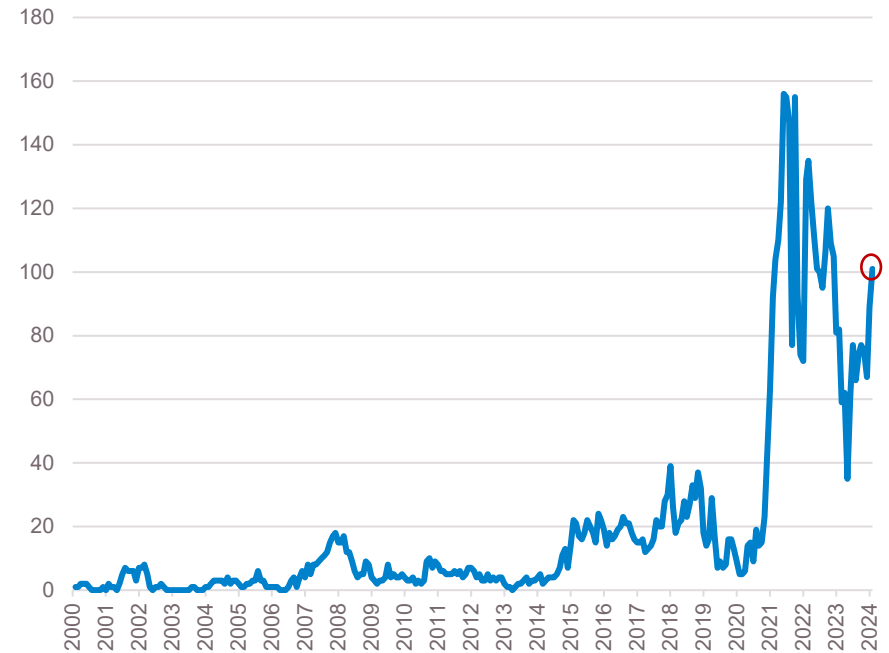
Biotech Valuations At Unprecedented Lows

Valuations have begun recovering from historical lows

Percent of Biotech Companies Trading Below Net Cash on Balance Sheet:



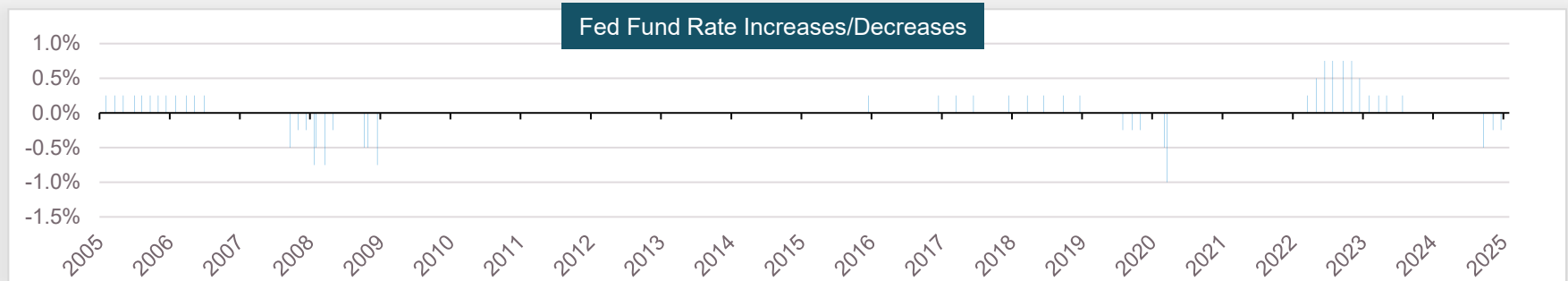
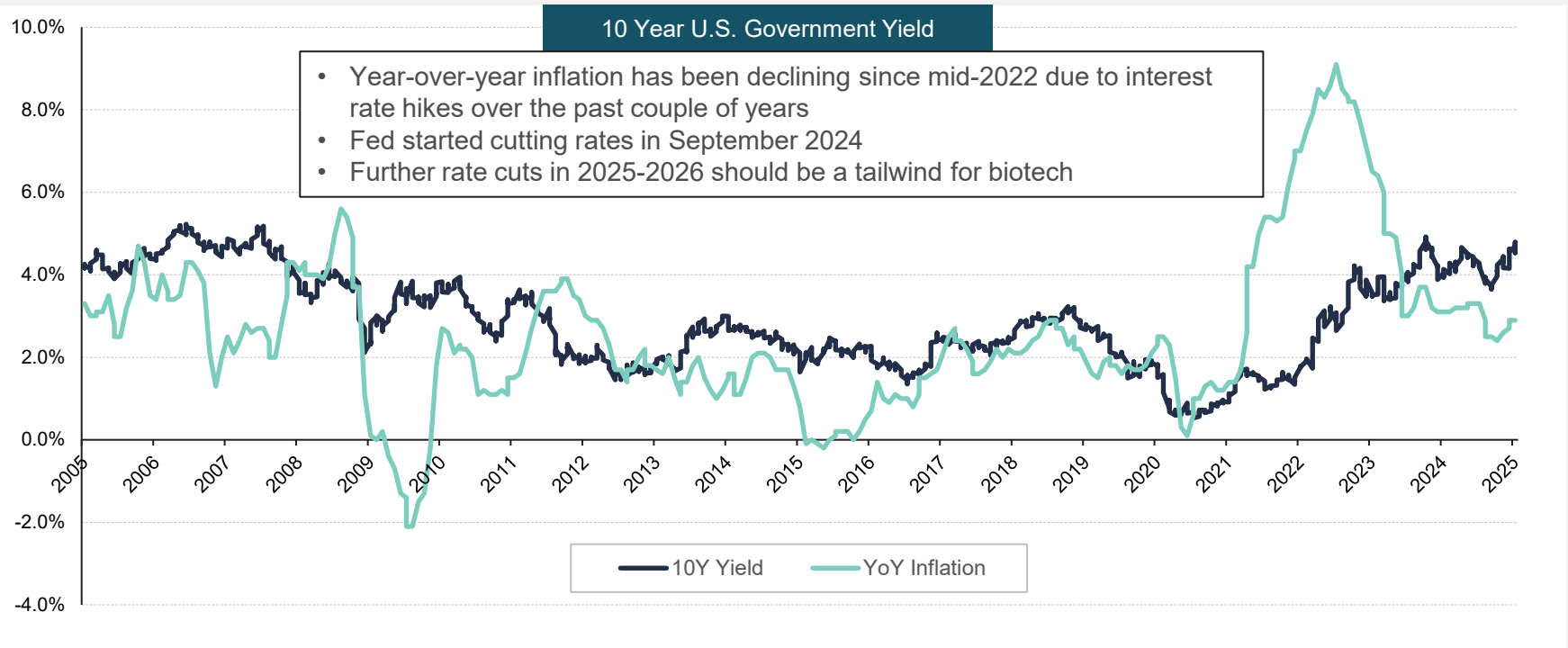
Number of Biotech Companies Trading Below Net Cash on Balance Sheet:



Note: Monthly chart of all GICS defined biotechnology greater than \$10mm, using historical cash and debt sourced from Bloomberg, with monthly GICS biotechnology universe refreshes. Updated through 31 January 2025

10-Year U.S. Government Yield Remains Elevated

(USGG10YR Index) Data as of 31 January 2025











Source: Bloomberg

BIOG










Investment Themes

Key Breakthroughs in Biotech in the last 24 Months

Company	Indication	Product (MOA)	Highlights
 agios	Non-transfusion and Transfusion Dependent Adult Thalassemia	Mitapivat (PK activator)	Reported positive Phase 3 data in two trials; first oral treatment for thalassemia
 Alnylam [®] PHARMACEUTICALS	ATTR Amyloidosis with Cardiomyopathy (ATTR-CM)	Vutrisiran (siRNA)	Reported first positive ATTR-CM outcomes study with a silencer of ATTR
 insmed	Bronchiectasis	Brensocaticb (DPP1 inhibitor)	Positive Phase 3 data with 20% reduction in exacerbations over 52 weeks. First ever successful bronchiectasis study.
 Dyne [™] THERAPEUTICS	Myotonic Dystrophy Type 1 (DM1)	DYNE-101 (antisense oligonucleotide conjugated to a fragment antibody)	Showed best in class knockdown of DMPK resulting in splicing correction and improved function relative to placebo in a Phase 1/2 trial
 AVIDITY [®] BIOSCIENCES	Facioscapulohumeral Muscular Dystrophy (FSHD)	Del-brax (siRNA bound to a monoclonal antibody)	First drug to ever demonstrate DUX4 knockdown and muscle function improvement in a Phase 1/2 trial
 kyverna [™]	Autoimmune Diseases	Auto CAR-T (CD19 targeting)	Demonstrated disease modifying activity of a one-time cellular therapy in refractory autoimmune disease
 CRISPR [®] THERAPEUTICS VERTEX	Sickle Cell Disease and Beta Thalassemia	Casgevy (CRISPR Cas9 gene-editing therapy)	First ever CRISPR therapy approved in the world
 Crinetics [®] Pharmaceuticals	Acromegaly	Paltusotine (somatostatin receptor type 2 agonist)	Positive Phase 3 trials for first once-daily oral medication for the treatment of acromegaly

Note: Public companies shown here are not necessarily representative of portfolio holdings

Significant FDA Biotech Approvals in 2024

Company	Indication	Product (MOA)	Highlights
	Metastatic Melanoma	Amtagvi	First cellular therapy approved for the treatment of a solid tumor
	Chronic Obstructive Pulmonary Disease (COPD)	Ohtuvayre	First novel mechanism approved to treat COPD in over a decade
	Low to Intermediate Risk Myelodysplastic Syndromes	Rytelo	First and only oligonucleotide telomerase inhibitor
	Small Cell Lung Cancer	Imdelltra	First bispecific T-cell engager approved to treat a solid tumor
	Pediatric Low-Grade Glioma	Ojemda	First therapy in its class approved for a type of pediatric brain tumor
	Paroxysmal Nocturnal Hemoglobinuria (PNH)	Voydeya	First oral add on therapy for the treatment of PNH
	Pulmonary Arterial Hypertension (PAH)	Winrevair	First new mechanism for the treatment of PAH in over a decade
	Non-Alcoholic Steatohepatitis (NASH)	Rezdiffra	First drug approved for the treatment of fatty liver disease
	Metachromatic Leukodystrophy (MLD)	Lenmeldy	First gene therapy for the treatment of MLD

Note: companies are not necessarily representative of portfolio holdings.

Oncology

Cancer remains #1 therapeutic area for biotech drug development given unmet need

Cellular Therapies

CD19

↓

BCMA

↓

Other

↓

Antibody-Drug Conjugates

Antibodies with chemo attached

Bispecific Antibodies

Antibodies that bind to 2 different targets

Targeted Therapies

Targeting specific genetic mutations

Radiopharmaceuticals

Using targeted radiation to kill tumor cells

Cancer Vaccines

Harnessing the immune system to attack cancer

Note: companies are not necessarily representative of portfolio holdings.

Multiple innovative approaches generating clinical benefit across tumor types, giving physicians more treatment options to extend the lives of cancer patients.

Central Nervous System (CNS) Disease Treatments

Both neurology and psychiatric disorders offer large chronic market opportunities

Anti-Psychotic Therapies



Depressive Disorders



Epilepsy / Pain



Neurocognitive Disorders



Neuromuscular Disorders



Movement Disorders

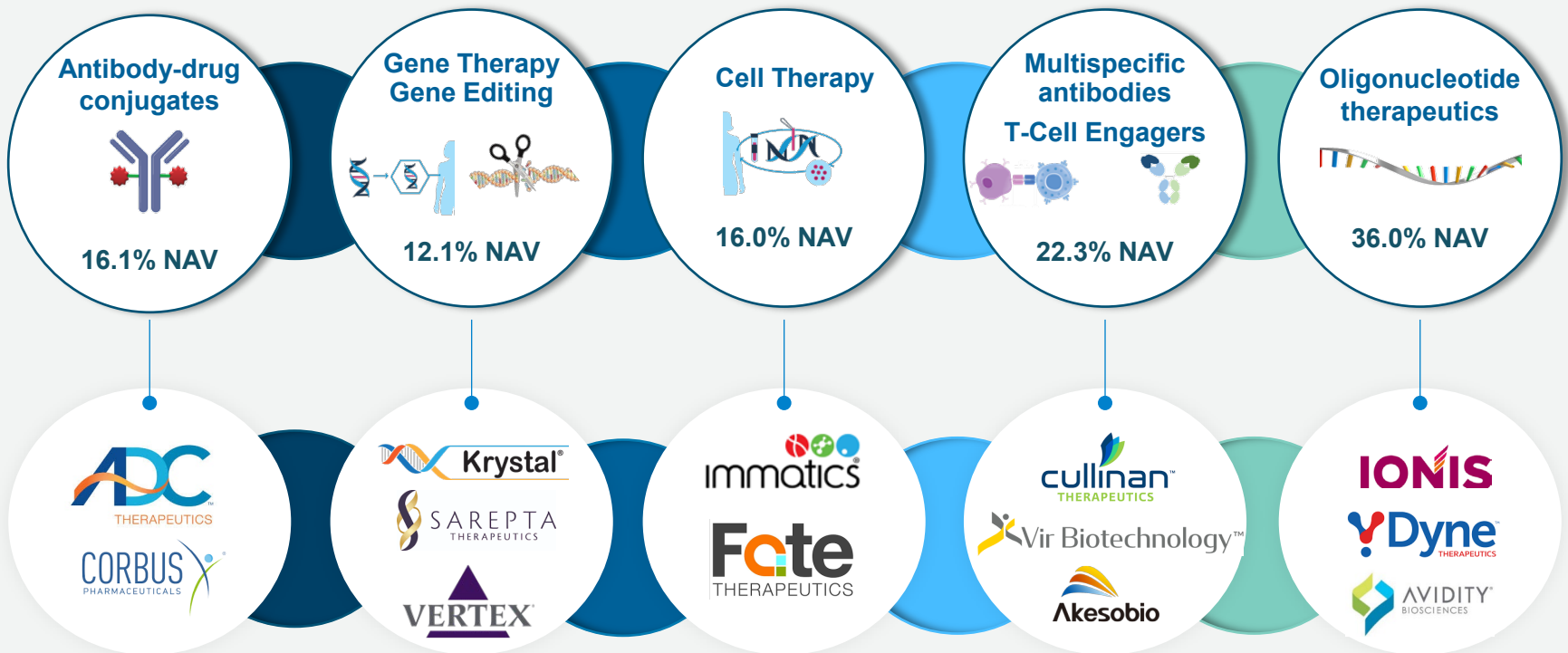


Note: companies are not necessarily representative of portfolio holdings.

Large Pharmaceutical Companies have shown interest in the CNS space, with recent multi billion dollar acquisitions of biotech players – Intra-Cellular Therapies, Karuna Therapeutics, Cerevel Therapeutics and Longboard Pharmaceuticals

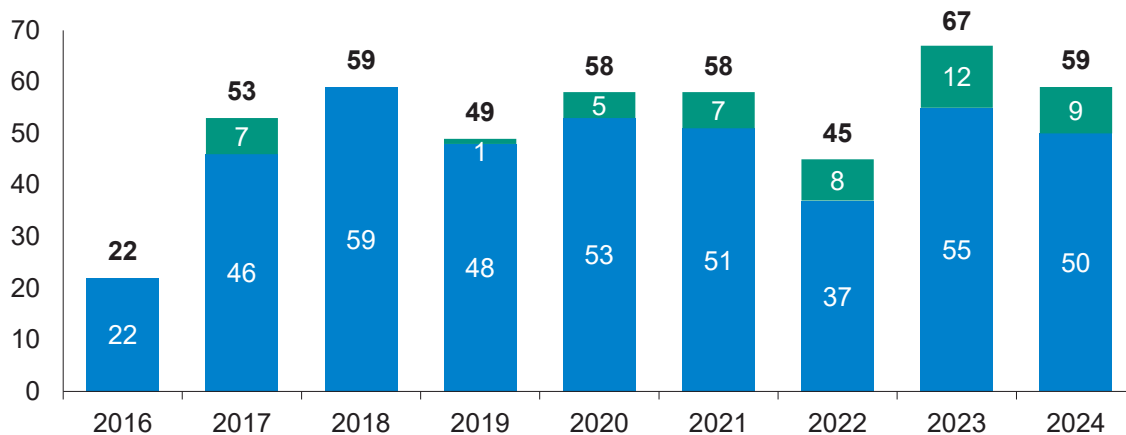
Innovation Well Reflected in BIOG

Portfolio has exposure to a wide swath of novel technologies, as shown below:



Source: OrbiMed, % of BIOG NAV as of 31 January 2025. Some positions are double-counted because they use more than one technology.

FDA New Molecular Entity Approvals



Source: FDA CDER and CBER as of 31 December 2024

CDER CBER

Dip in approvals in 2022 likely due to COVID; approval volume remains high

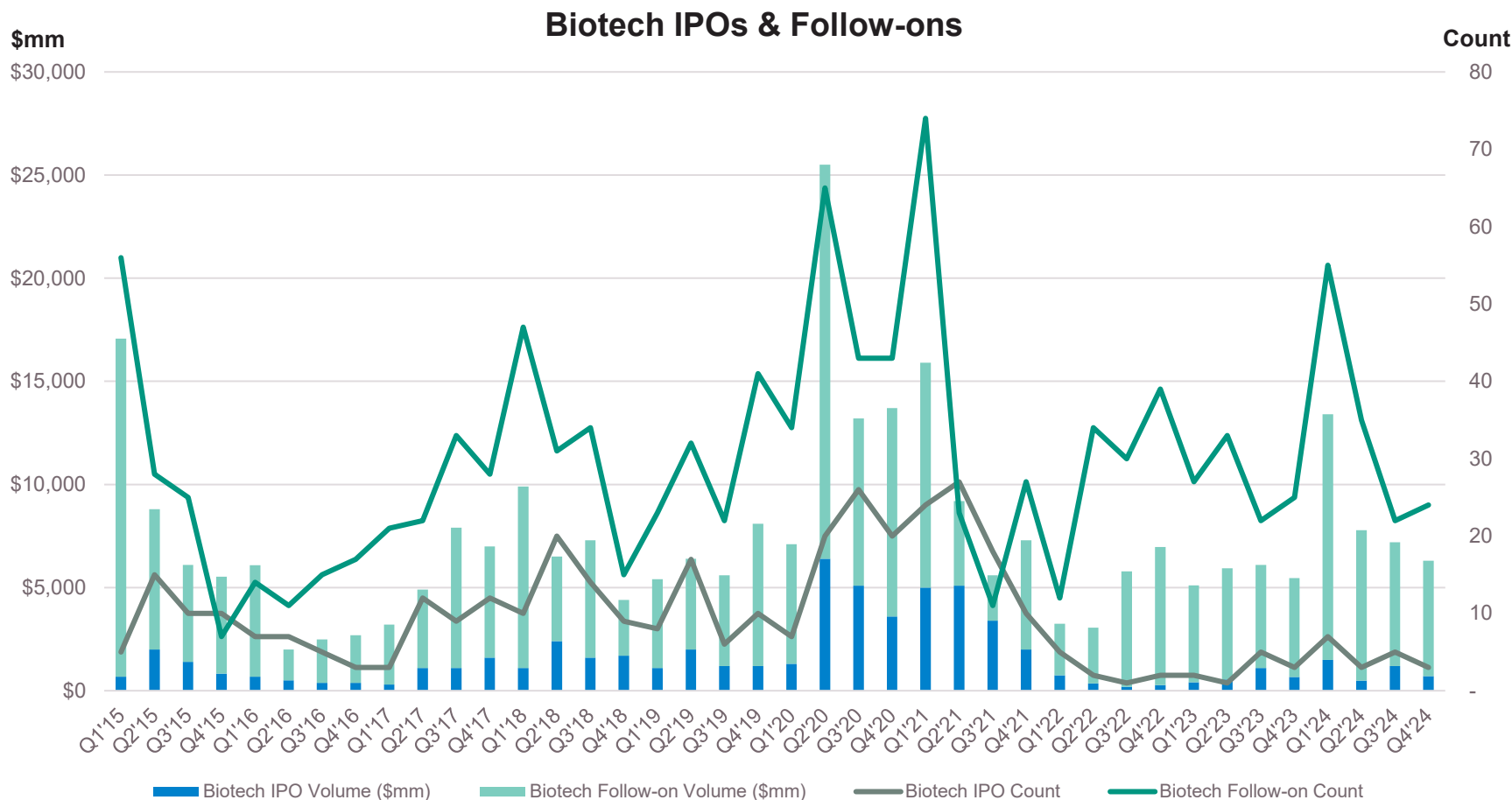


FDA approvals remain consistently high



Nearly **450** new drugs approved over the past 8 years

Financing Environment Improving



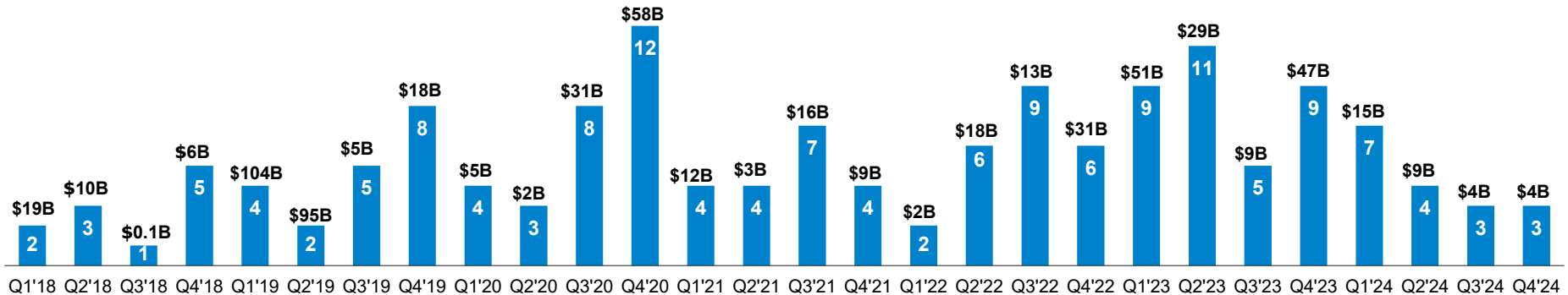
- Biotech financing volume picked up in 2024, though the number of IPOs has remained muted
- Investor demand for follow-on financings in good companies has been strong; weaker companies still face challenges getting financed
- BIOG has been participating selectively in IPOs and confidentially marketed follow-on offerings

Source: BofA "Biotech ECM Activity" report as of 31 December 2024

M&A Activity in Biotechnology

Announced Public Biotech M&A Transactions

Public biotech M&A



Source: Factset

Large Cap Pharma Supportive of Continued M&A



CEO Rob Davis

"You're going to continue to see (deals), I think both some of the smaller deals but then up to that \$15 billion range"



CEO Thomas Schinecker

"We are constantly looking at opportunities, both for partnering and acquisitions and yes, we are open to do more deals"



CEO Rick Gonzalez

"(Our) industry leadership position...affords us the ability then to really invest for growth in the next decade, which is ultimately how we're thinking about business development"



CEO Joaquin Duato

"Our capital allocation strategy will continue to be disciplined and M&A is going to remain a critical component of that, that's our M&A strategy and it's been a cornerstone of our ability to create value"

Recent M&A in BIOG

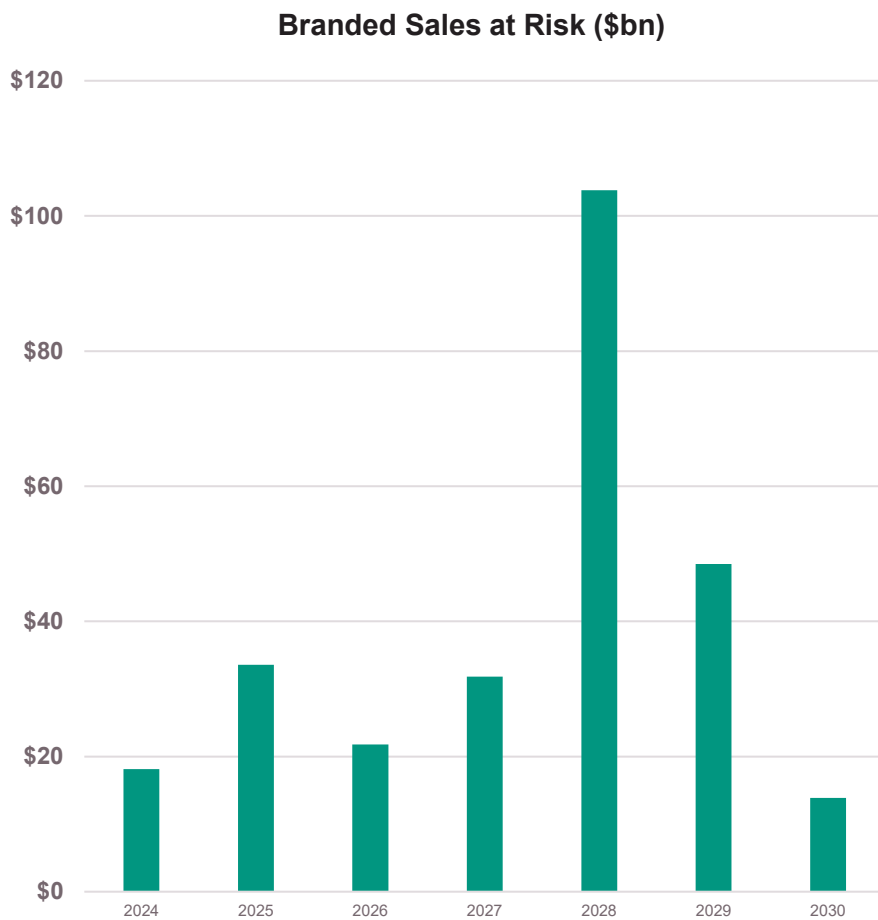


Source: Bloomberg Transcripts, quotes from Goldman Sachs Healthcare Conference May 2024 and 2Q24 Earnings Calls

Note: Recent M&A transactions announced in 2023-2025

Big Pharma Patent Cliff Drives Biotech M&A

Over **\$270 billion** in branded sales are at risk (2024-2030)



Note: Data from Wolfe Research, OrbiMed, Visible Alpha
(sales at risk represents consensus projected sales for year prior to year of expected loss of exclusivity)

Company	Drug	US Loss of Exclusivity (Projected)	'24 Global Sales (\$bn)
MERCK	KEYTRUDA <small>(pembrolizumab) injection 100mg</small>	2028	\$29.4
Bristol Myers Squibb Pfizer	Eliquis <small>(apixaban) tablets 25mg</small>	2026	\$14.1
Johnson & Johnson	Stelara <small>(ustekinumab)</small>	2025	\$10.3
Johnson & Johnson	DARZALEX	2029	\$11.6
Bristol Myers Squibb	OPDIVO <small>(nivolumab)</small>	2028	\$9.3
abbvie	HUMIRA <small>adalimumab</small>	2023	\$8.9
abbvie Johnson & Johnson	imbruvica	2027	\$4.4
Pfizer	IBRANCE <small>palbociclib</small>	2027	\$4.3

Source: S&P Global report, Company Reports

Political Environment Overall Positive

What can we expect from President Trump's second term?

POSITIVES

INFLATION REDUCTION ACT

Drug price reform could be amended or repealed and pricing exclusivity for small molecule drugs could be extended

M&A

Removal of Lina Khan as FTC Commissioner should pave the way for more biotech M&A

INNOVATION

Trump's administration should be pro-innovation, consistent with his broader domestic pro-business agenda

POLITICAL PRIORITIES

Trump administration appears focused on immigration, taxes, and curbing inflation. Drug pricing was not a focus of his campaign.

TAX CUTS

The industry clearly benefited from Trump's previous corporate tax policy initiatives

OVERHANG REMOVED

With Democratic power now severely minimized, passage of extremely negative drug pricing reform unlikely

UNCERTAINTIES

RFK Jr.

Noted vaccine skeptic nominated for head of HHS, though he has toned down his rhetoric significantly recently; FDA Commissioner nominee Martin Makary seems science-based and reasonable

BUDGET CUTS

Trump needs to cut government spending in order to pay for his tax cuts; Medicaid payments could be reduced; FDA staffing could be cut, though FDA drug reviewers paid by PDUFA fees less likely to be impacted

INTEREST RATES

Trump policies on tariffs and tax cuts could exacerbate inflation, causing the Fed to leave interest rates higher for longer; Trump likely to pressure the Fed to reduce rates; he wants 10-year yields to go down

Positives outweigh the uncertainties for Trump's second term

2025 Strategy and Outlook



Strategy to emphasize emerging biotech over large cap biotech will continue in order to fully capture eventual sector rebound

- Will capitalize on compelling investment opportunities in companies that need to finance at low share prices
- Gearing level will generally stay between 5-10%



Unprecedented low valuations in emerging biotech suggest significant upside from current levels

- Performance drawdown of small/mid cap biotech versus the S&P 500 has been the longest and most severe we have ever seen
- Percent of biotech companies with market caps below the net cash on their balance sheets well above historical norms
- Valuation levels are lower than the Great Financial Crisis and the bursting of the Dot Com bubble
- Interest rate pressure should abate with eventual Fed rate cuts; biotech has historically outperformed during recessions



Valuation contraction is disconnected from the fundamental innovation in the sector, which remains robust



M&A activity expected to accelerate given lower valuations of biotech targets and urgent need for new products by Big Pharma

OrbiMed believes this is an excellent time to invest in biotech innovation at unprecedented low valuations.

BIOG

Appendix

BIOG Holdings

As of 31 January 2025

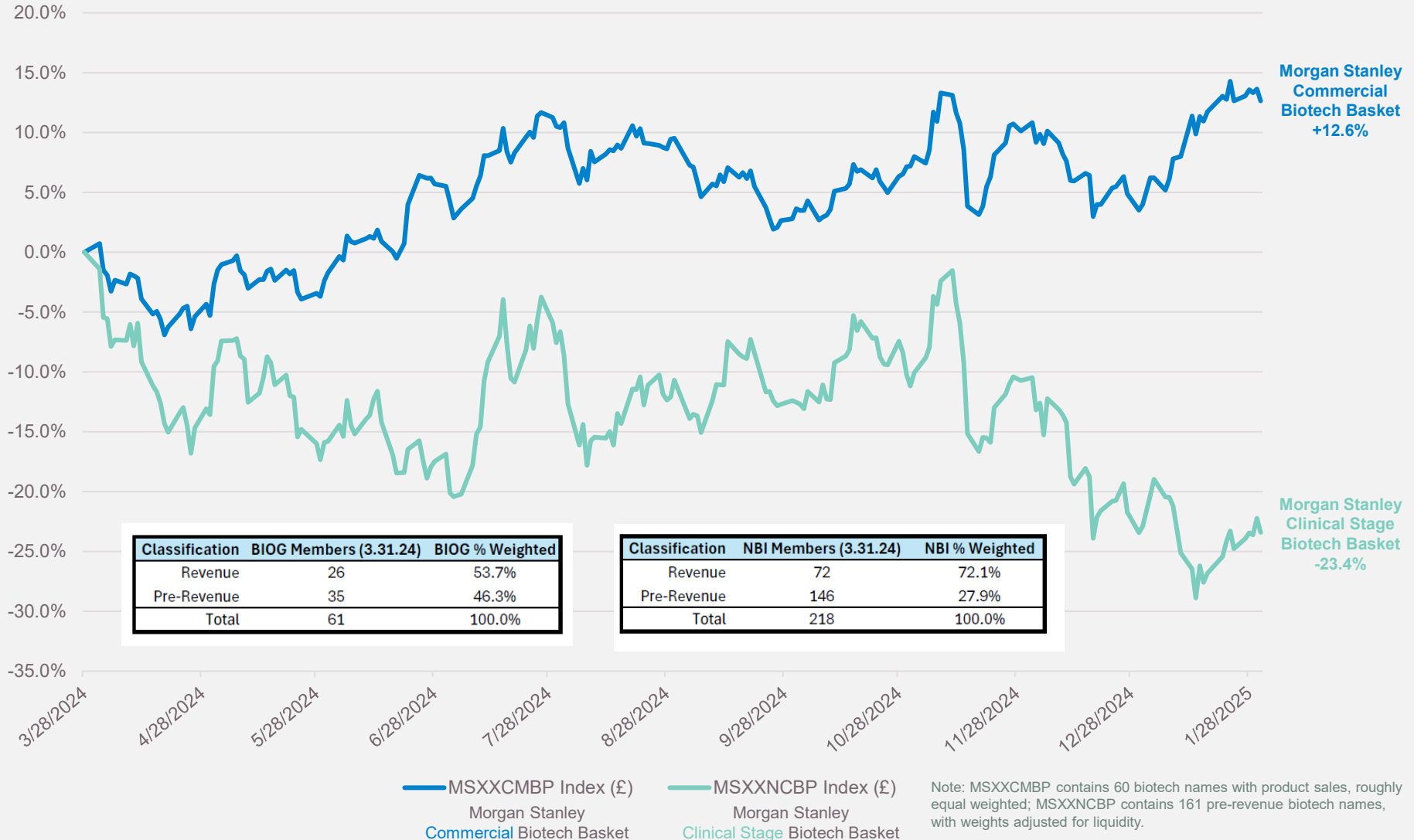
	Market Price \$ Millions	Pct. Value		Market Price \$ Millions	Pct. Value		Market Price \$ Millions	Pct. Value
UNITED STATES			UNITED STATES			INTERNATIONAL		
Emerging Biotechnology			Emerging Biotechnology (cont.)			Europe		
Agiros Pharmaceuticals Inc	0.9	0.3	Neurocrine Biosciences Inc	20.7	5.8	Emerging Biotechnology		
Akero Therapeutics Inc	1.0	0.3	Nkarta Inc	1.9	0.5	ADC Therapeutics SA	3.6	1.0
Alnylam Pharmaceuticals Inc	22.3	6.2	PepGen Inc	0.5	0.1	Argenx SE	20.4	5.7
Alto Neuroscience Inc	1.1	0.3	Prelude Therapeutics Inc	0.4	0.1	Immatics NV	3.9	1.1
Amicus Therapeutics Inc	11.0	3.1	Repare Therapeutics Inc	0.1	0.0		27.9	7.8
Amylyx Pharmaceuticals Inc	1.3	0.4	Rhythm Pharmaceuticals Inc	7.6	2.1			
Avidity Biosciences Inc	13.4	3.7	Sarepta Therapeutics Inc	21.0	5.8	Europe Subtotal	27.9	7.8
Bicara Therapeutics Inc	0.8	0.2	Scholar Rock Holding Corp	6.1	1.7			
C4 Therapeutics Inc	6.1	1.7	Structure Therapeutics Inc	5.2	1.4	Far East		
CG oncology Inc	12.0	3.3	Tyra Biosciences Inc	8.4	2.3	Emerging Biotechnology		
Compass Therapeutics Inc	11.5	3.2	Vera Therapeutics Inc	10.4	2.9	Akeso Inc	9.0	2.5
Corbus Pharmaceuticals Holdin	3.9	1.1	Vir Biotechnology Inc	5.7	1.6	Gracell Biotechnologies Inc	0.5	0.1
Cullinan Therapeutics Inc	4.4	1.2	Xenon Pharmaceuticals Inc	12.8	3.6	InventisBio Co Ltd	0.5	0.2
Cytokinetics Inc	12.1	3.4		273.8	76.2	Keymed Biosciences Inc	1.5	0.4
Dyne Therapeutics Inc	6.1	1.7	UNITED STATES			LakeShore Biopharma Co Ltd	0.4	0.1
Edgewise Therapeutics Inc	7.4	2.1	Major Biotechnology			Mabwell Shanghai Bioscience	1.5	0.4
Engene Holdings Inc	2.6	0.7	Amgen Inc	5.5	1.5	New Horizon Health Ltd	1.1	0.3
Enliven Therapeutics Inc	0.9	0.3	Gilead Sciences Inc	43.8	12.2	OrbiMed Asia Partners	1.2	0.3
Exact Sciences Corp	4.1	1.1	Regeneron Pharmaceuticals Inc	4.1	1.1	Stemirna*	0.0	0.0
Fate Therapeutics Inc	0.9	0.2	Vertex Pharmaceuticals Inc	7.5	2.1	Suzhou Basecare Medical Corp	0.8	0.2
Forte Biosciences Inc	8.6	2.4		60.9	16.9	XtalPi Holdings Ltd	9.9	2.7
Geron Corp	6.2	1.7					26.3	7.3
Immunovant Inc	0.0	0.0	United States Total	334.7	93.1			
Insmed Inc	2.2	0.6				Far East Subtotal	26.3	7.3
Instil Bio Inc	2.6	0.7						
Ionis Pharmaceuticals Inc	17.8	4.9				International Total	54.2	15.1
Kezar Life Sciences Inc	1.2	0.3						
Korro Bio Inc	1.1	0.3				Cash	-29.4	-8.2
Krystal Biotech Inc	3.8	1.0						
Milestone Pharmaceuticals Inc	1.6	0.4				Total Portfolio	359.5	100.0
Mineralys Therapeutics Inc	4.2	1.2						

Note: securities with asterisks (*) are unquoted

Commercial vs Development Stage Biotech

Pre-revenue companies have significantly underperformed their commercial peers

(31 March 2024 – 31 January 2025)



Unprofitable Tech Has Declined Meaningfully

Goldman Sachs Unprofitable Tech Basket



**GS Unprofitable
Technology Basket
-51.7%**

The GS Non-profitable tech basket (GSXUNPTC) consists of non-profitable US listed companies in innovative industries. Technology is defined broadly to include new economy companies across GICS industry groupings. Date range for chart is from 31 March 2021 to 31 January 2025

China Healthcare Near All-Time Lows

Innovation remains strong; recovery has yet to occur

Hang Seng Healthcare Index (HSHCI)



Source: Bloomberg, OrbiMed Advisors

Note: Chart updated from 30 June 2021 through 31 January 2025.

Risk Management

- Diversification across multiple parameters
 - Size and stage of company (large cap, mid cap, small cap); revenue versus pre-revenue
 - Geographical diversification (U.S., Europe, China)
 - Therapeutic area
 - Drug development technologies
- Prudent position sizing
 - Sizing depends on conviction level, liquidity of the stock, and risk/reward of the idea
 - We aim not to lose more than 100 basis points of performance on a single catalyst
 - Typical position sizes: 5-10% for large cap biotech, 1-3% for emerging biotech
 - Position sizes are actively managed to navigate the catalyst paths of emerging biotech stocks, so turnover is relatively high (~90%)
 - The fund regularly trades around positions (trimming high, adding low) to ensure position sizes appropriately reflect risk/reward, especially in advance of binary events
 - Volatility of biotech increases markedly as one descends in market cap
 - Average annual volatility of stock constituents of NASDAQ Biotech Index:

As of 31 January 2025	1 Std. Deviation
Large Cap (>\$10bn)	42.2
Mid Cap (\$2bn-10bn)	59.5
Small Cap (<\$2bn)	83.2

- Fund's emphasis on emerging biotech with stock-moving catalysts means turnover will likely remain high to manage risk appropriately

Endnotes

General Notes

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An investment in the fund is speculative and involves a high degree of risk. The fund is an investment trust listed on the London Stock Exchange. Investment trusts have the ability to borrow to invest, which is known as gearing. Companies with higher gearing are subject to higher risks, and therefore the investment value may change substantially. The value and the performance of the net asset value of the fund may not be the same as its share price. In considering an investment in the fund, prospective investors should also be aware of certain other special considerations and risk factors, including those related to: the risk of deterioration in the financial markets in general and the healthcare sector in particular; the risk that the fund could incur losses due to the failure of third parties to perform their contractual commitments to the fund or financial difficulties on the part of brokerage firms, banks or other financial institutions that hold assets of the fund; risks arising from the operation of pooled investment vehicles like the fund; and tax-related risks arising from the status and operation of the fund. See the Fund Documents for more detail on those and other risks.

No guarantee or representation is made that a fund will achieve its investment objective or that the fund's risk management strategies will be successful. The fund's performance may be volatile, and investors in the fund could lose all or a substantial amount of their investment. In addition, the fees and expenses charged in connection with an investment in the fund may be higher than those charged in connection with other investments, and in some market conditions, may offset trading profits. Accordingly, shares or interests are suitable only for sophisticated investors for whom an investment in the fund does not constitute a complete investment program and who fully understand and are willing to assume the risks involved in the fund's investment program.

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Endnotes

Indices

Indices are shown for comparison only, are unmanaged, do not charge fees or expenses and do not employ special techniques such as leveraging or short selling.

The volatility of indices may be materially different from the performance of the fund. In addition, the fund's portfolio holdings may differ significantly from the securities that comprise such indices.

The NASDAQ Biotechnology Index (the "NBI") includes securities of NASDAQ-listed companies classified according to the Industry Classification Benchmark as either Biotechnology or Pharmaceuticals, which also meet other eligibility criteria, and is calculated under a modified capitalization-weighted methodology. The Russell 2000 Index is comprised of the smallest 2000 companies in the Russell 3000 Index. The Russell 1000 Index consists of the largest 1000 companies in the Russell 3000 Index. The SPDR S&P Biotech ETF is an exchange-traded fund that seeks to replicate the performance of the S&P Biotechnology Select Industry Index, an equal-weighted index. The SPX includes 500 leading companies and captures approximately 80% coverage of available market capitalization. The FTSE 100 Index is a capitalization-weighted index of the 100 most highly capitalized companies traded on the London Stock Exchange. The Hang Seng Healthcare Index ("HSHCI") aims to reflect the overall performance of stocks listed in Hong Kong that are related to healthcare businesses.

Where stated as "Net" or "TR" (or total return), the index return numbers include reinvestment of dividends net of withholding taxes, as calculated by the index provider.