Biopharmaceutical Sector

Weekly Update – April 1, 2024

STIFEL | Healthcare

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March 25, 2024 (Women's Health)
March 18, 2024 (Inflammasome)
March 11, 2024 (IRA, Immunology)
March 4, 2024 (Biotech Employment)
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July 1, 2023 (Obesity drugs)
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May 22, 2023 (FTC case on Amgen/Horizon)

Stifel Continues To Lead in Biopharma Financings

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Stifel Biopharma Financings - 2024 YTD

$240,100,310 nkarta Registered Direct Joint Bookrunning Manager *March 2024*	$150,000,000 geron Registered Direct Joint Bookrunning Manager *March 2024*	$180,000,000 SPYRE THERAPEUTICS PIPE Joint Placement Agent *March 2024*	$95,000,000 LEXEO therapeutics PIPE Joint Placement Agent *March 2024*	$50,000,000 evolus Registered Direct Joint Bookrunning Manager *March 2024*	$420,000,000 APOGEE THERAPEUTICS Follow-on Offering Joint Bookrunning Manager *March 2024*
$140,000,000 REGENXBIO Follow-on Offering Joint Bookrunning Manager *March 2024*	$632,540,250 VIKING THERAPEUTICS Follow-on Offering Joint Bookrunning Manager *February 2024*	$160,125,000 KalVista Pharmaceuticals Confidentially Marketed Follow-on Offering Joint Bookrunning Manager *February 2024*	$147,936,000 ALTO NEUROSCIENCE Initial Public Offering Joint Bookrunning Manager *February 2024*	€50,500,000 Sensorion PIPE Lead Placement Agent *February 2024*	$230,000,000 DIANTHUS THERAPEUTICS PIPE Joint Placement Agent *January 2024*	$345,144,000 Dyne THERAPEUTICS Follow-on Offering Joint Bookrunning Manager *January 2024*

Stifel Has completed 635 Healthcare Financing Transactions since Q4 2010 raising over $120bn

Source: Dealogic and Stifel Capital Markets as of March 22, 2024.
Note: Deal values and dates represented are as of the announcement that the definitive agreement was signed. Stifel transactions include deals completed by Stifel, Nicolaus & Company, Incorporated and its affiliated entities and Torreya Capital LLC and its affiliated entities. Any pending IPO transaction tombstones on this page are neither an offer to sell nor a solicitation of an offer to buy any of these securities. An offer may only be made by the prospectus for the offering.

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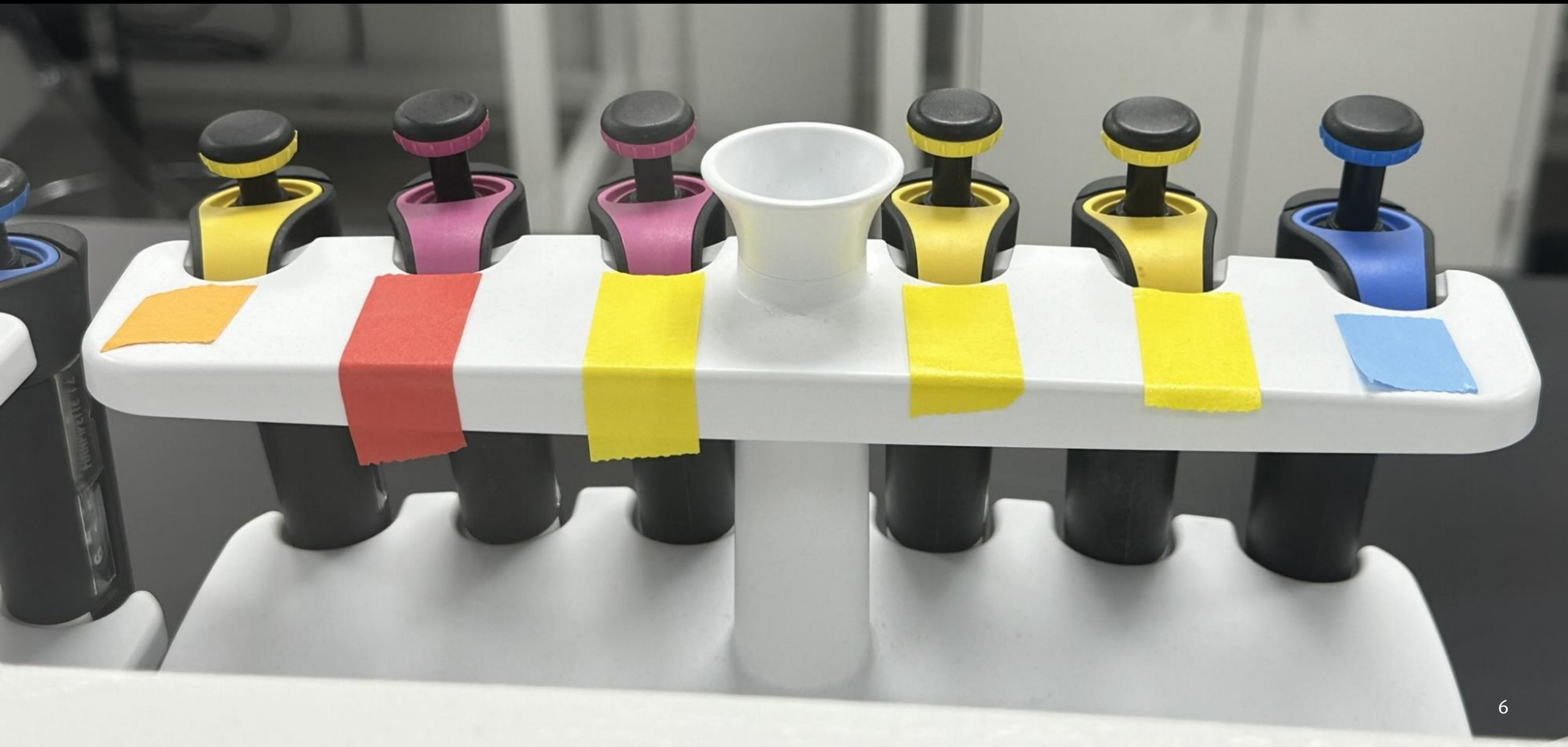
Macro Update



Why Treasury Yields Are Rising Despite Rate-Cut Expectations

Sam Goldfarb, *Wall Street Journal*, March 26, 2024 (excerpt)

The Federal Reserve keeps promising interest-rate cuts. Treasury yields, a key driver of mortgage rates and other borrowing costs, keep rising anyway.

As of Tuesday, the yield on the benchmark 10-year U.S. Treasury note was 4.233%, according to Tradeweb, up from 3.860% at the end of last year. As a result, the average rate on a 30-year fixed mortgage has also ticked higher, as has the cost of borrowing in the corporate-bond market.

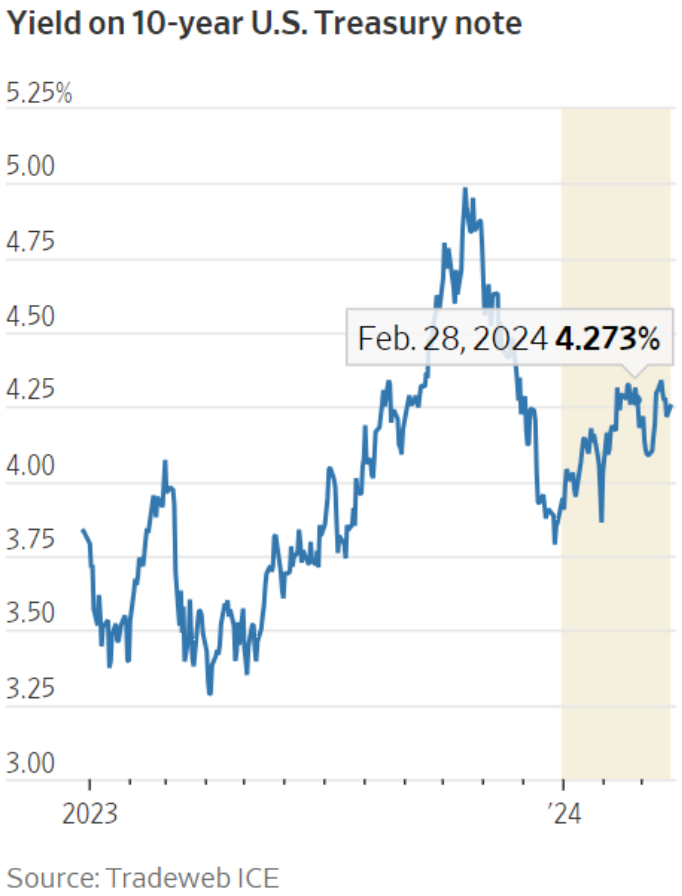
Yields on Treasurys, which rise when bond prices fall, largely reflect what investors think the Fed's benchmark short-term rate will average over the life of a bond. They in turn set a floor on mortgage rates and other types of fixed-rate debt.

Right now, the Fed's short-term rate sits in a range between 5.25% and 5.5%, a 23-year high. Coming into 2024, investors expected the Fed to cut that rate six times this year, bringing it down to 3.75%—4%.

Then came a reality check.

Inflation readings for January and February came in firmer than expected, and economic growth has proved resilient, forcing investors to dial back their rate-cut bets. Now, traders expect rates to end the year between 4.5% and 4.75%.

The central bank itself is still signaling cuts. A survey of Fed officials last week showed that their median forecast is for three cuts this year, unchanged from December.



Source: https://www.wsj.com/finance/investing/treasury-yields-rising-fed-interest-rate-expectations-4a157a85

Fed's Favored Inflation Gauge Rose to 2.5% in February

Charley Grant and Nick Timiraos, *Wall Street Journal,* March 29, 2024 (excerpt)

A key measure of U.S. inflation rose as expected in February, putting a spotlight on whether price growth will be cool enough this spring to justify an interest-rate cut by midyear.

The overall personal-consumption expenditures price index rose 2.5% over the 12 months through February, the Commerce Department said Friday. That was in line with forecasts from economists polled by The Wall Street Journal. Core prices excluding volatile food and energy prices rose 2.8%, also in line with forecasts.

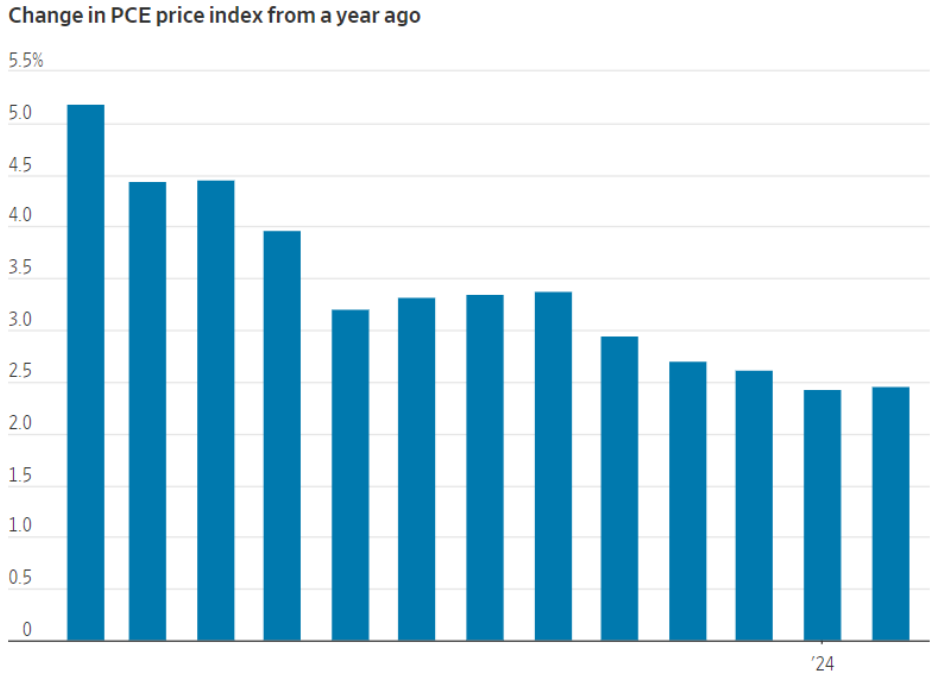
"It's good to see something coming in in line with expectations," Federal Reserve Chair Jerome Powell said Friday during a question-and-answer session at the San Francisco Fed.

In January, the overall PCE index climbed 2.4% from a year ago.

Fed officials last week reaffirmed their projections for three interest-rate cuts this year, though the timing of such cuts remains uncertain. Powell repeated his view Friday that officials need to see more inflation data before they could be confident that price growth was on track to return to the central bank's 2% goal.

From January to February, the PCE price index increased 0.3%, less than the 0.4% increase economists expected. The core index rose 0.3%.

Stock and bond markets were closed in observance of Good Friday, but a belief that the Fed can cool inflation without provoking a recession has helped push the S&P 500 to record highs. The benchmark 10-year Treasury note settled Thursday afternoon at 4.192%, down from 4.195% Wednesday.



Note: Seasonally adjusted.
Source: Commerce Department via St. Louis Fed

Source: https://www.wsj.com/economy/central-banking/fed-inflation-gauge-february-pce-f664d187

Biopharma Market Update

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

The XBI Closed at 94.89 Last Thursday (Mar 28), Up 1.4% for the Week

The XBI is up 6.5% since the year began. The biotech market picked up a bit last week as the macro picture weighed less on the sector. Positive inflation news hit on Friday when the market was closed. This presages a good start to this week.

Biotech Stocks Up Last Week

Return: Mar 23 to Mar 28, 2024

Nasdaq Biotech Index: 1.05%
Arca XBI ETF: +1.4%
Stifel Global Biotech EV (adjusted): +2.3%*
S&P 500: 0.4%

Return: Jan 1 to Mar 28, 2024

Nasdaq Biotech Index: 1.4%
Arca XBI ETF: +6.3%
Stifel Global Biotech EV (adjusted): +30%*
S&P 500: +10.2%

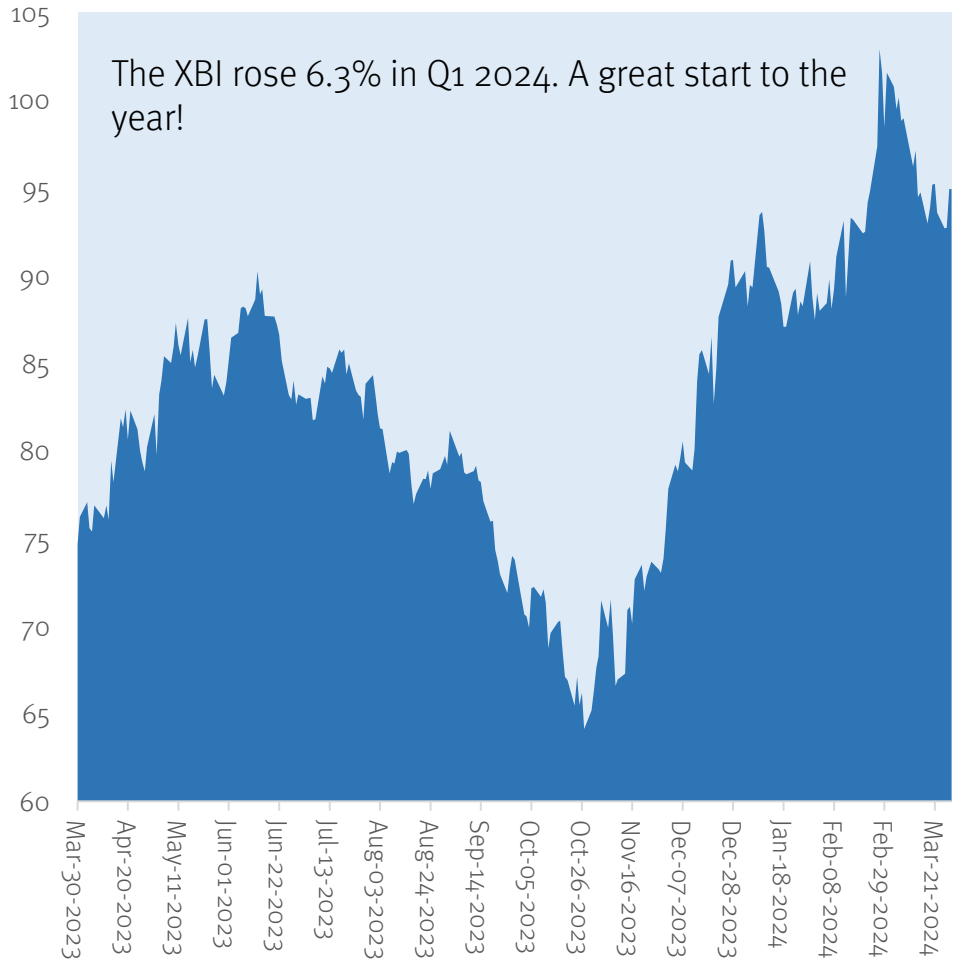
VIX Flat

Jan 20, 2023: 19.9%
July 21, 2023: 13.6%
Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Jan 26, 2024: 13.26%
Feb 23, 2024: 13.5%
Mar 22, 2024: 12.9%
Mar 29, 2024: 13.0%

10-Year Treasury Yield Down

Jan 20, 2023: 3.48%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Jan 26, 2024: 4.15%
Feb 23, 2024: 4.26%
Mar 22, 2024: 4.27%
Mar 29, 2024: 4.20%

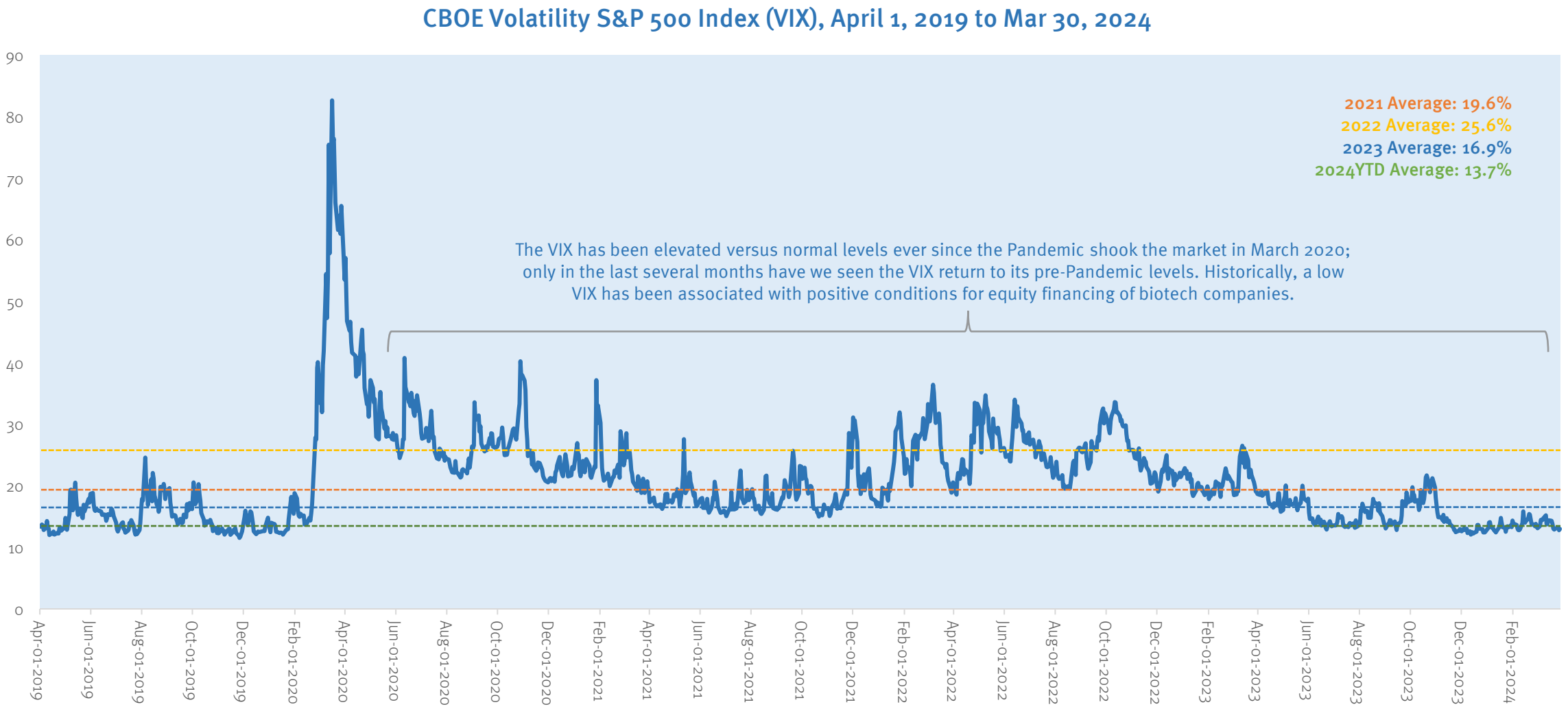
XBI, March 30, 2023 to March 28, 2024



Source: S&P Capital IQ and Stifel analysis

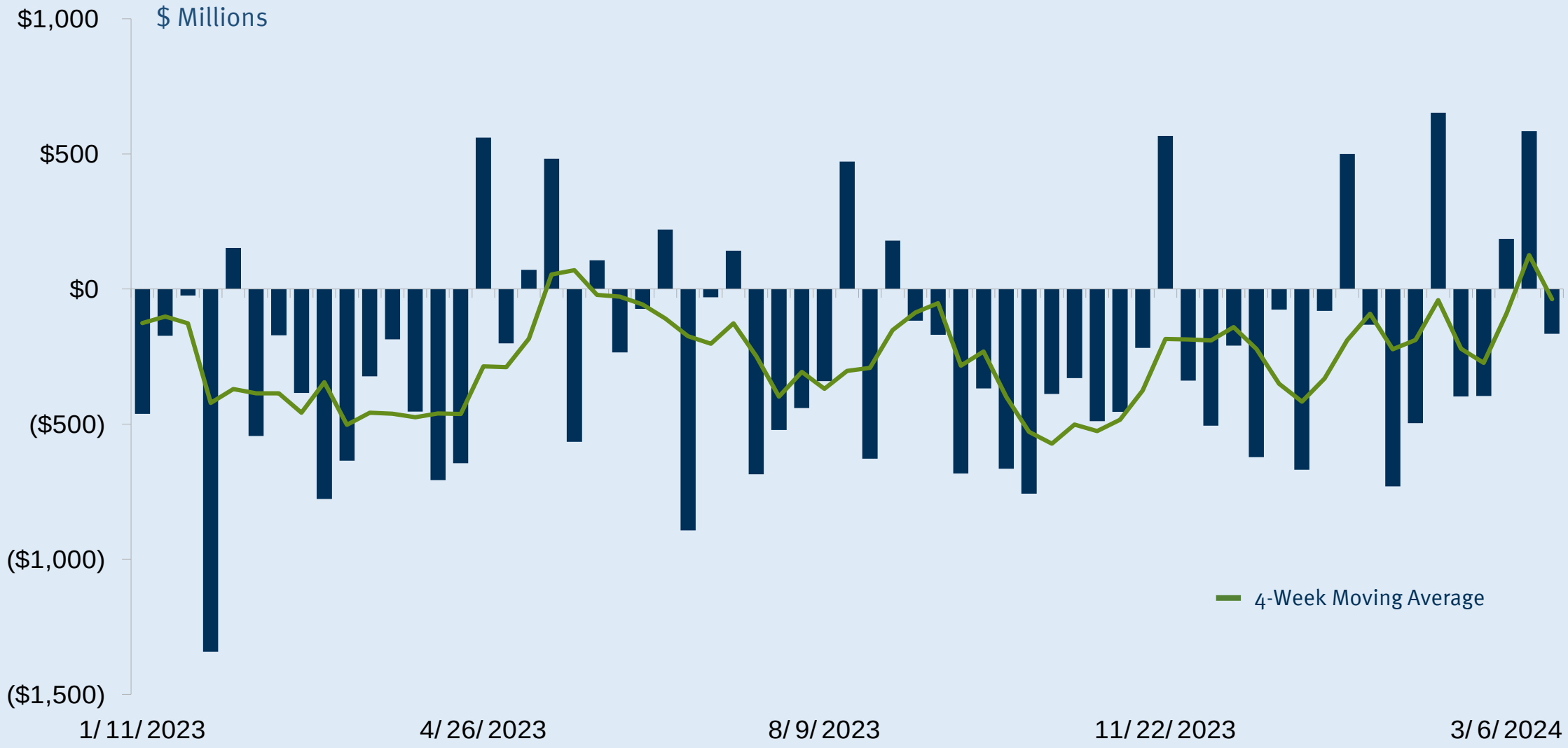
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

VIX at Lowest Level Since 2019



Source: S&P Capital IQ and Stifel analysis

Healthcare / Biotech Weekly Fund Flows Turned Positive in 2024



Source: FactSet

Total Global Biotech Sector Value Rose 2.3% Last Week*

The total enterprise value of the global biotech sector is up 30% year-to-date on an addition/exit corrected basis.

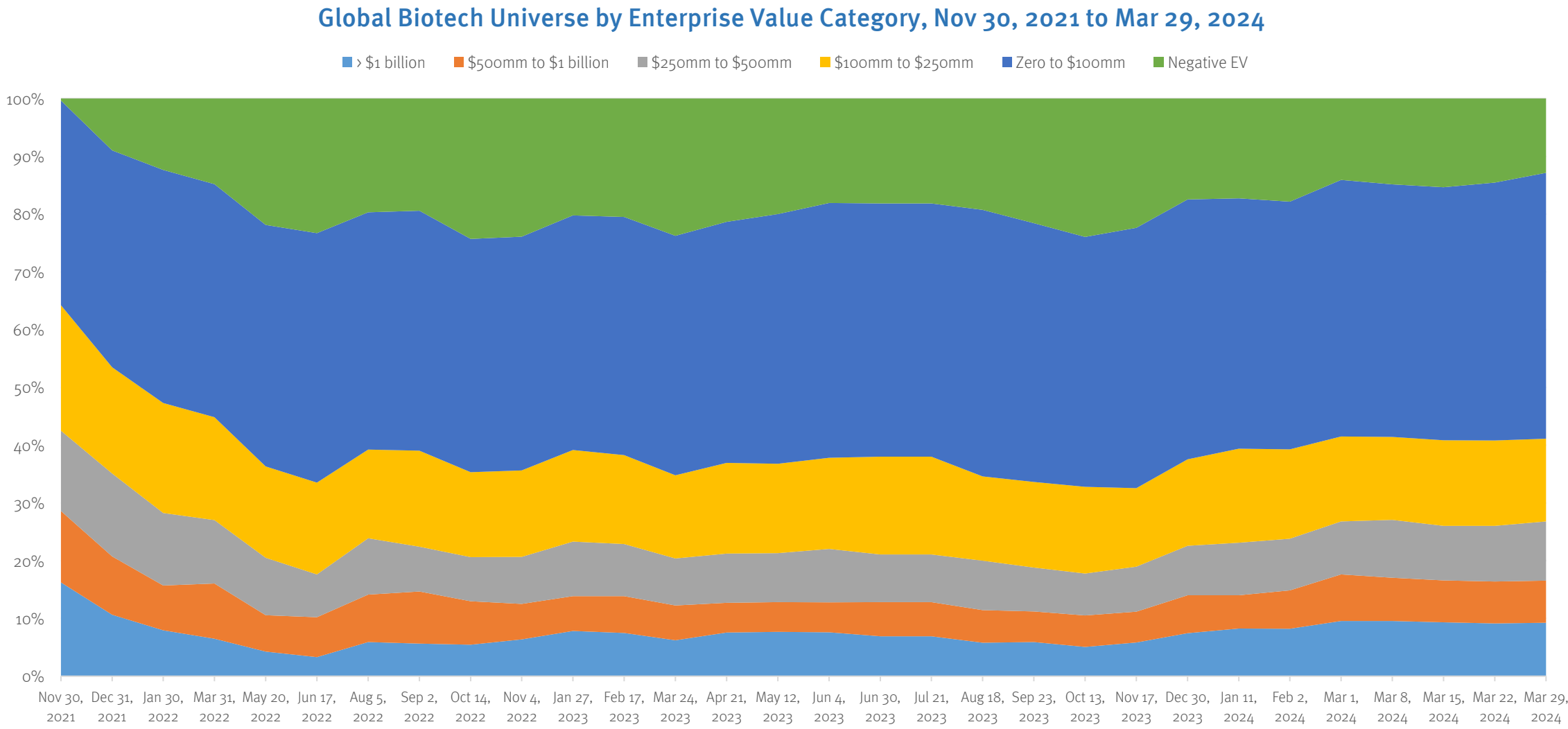
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Mar 29, 2024 ($ Billions)

Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

* Exit/addition corrected

Global Biotech Neighborhood Analysis

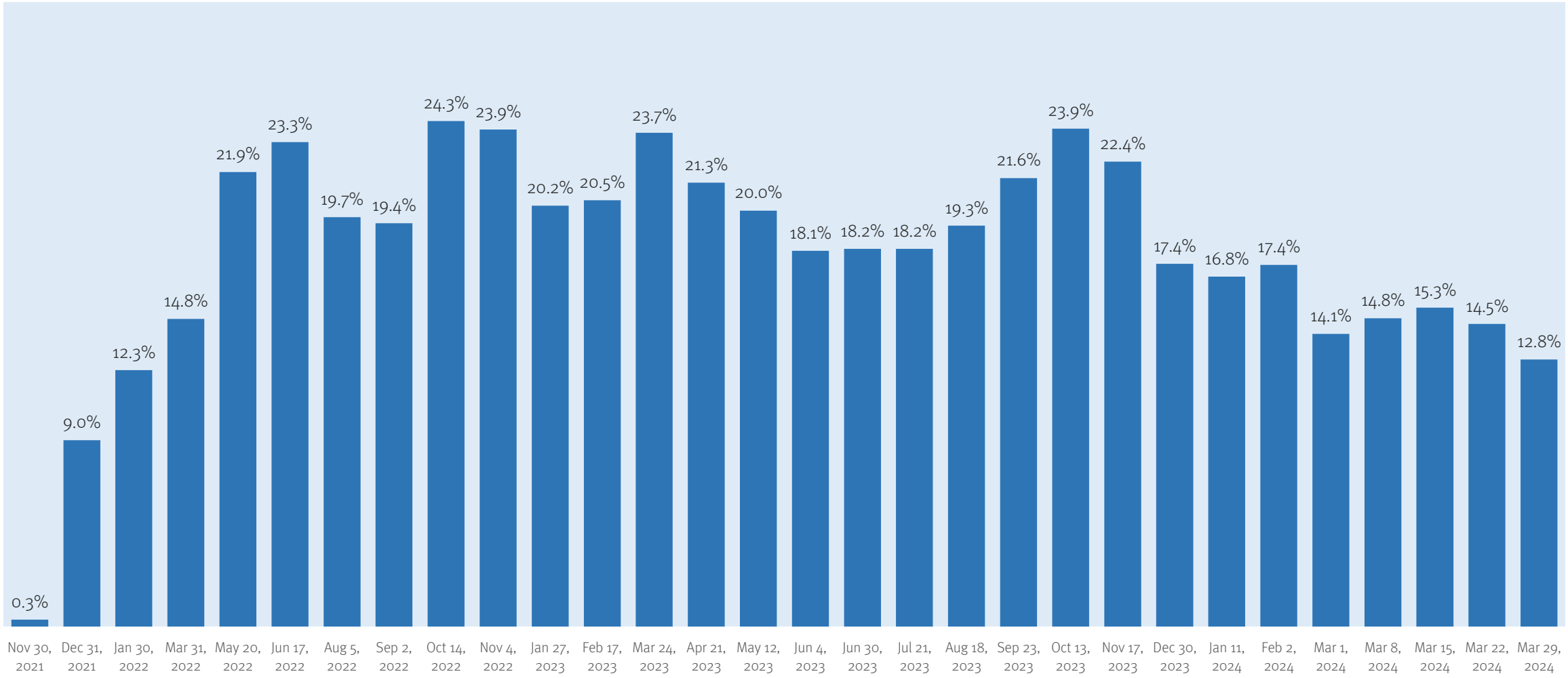
The population of negative EV companies continues to shrink. The population of $1bn+ companies was steady as CymaBay came out last week.



Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Number of Negative EV Biotechs Worldwide Shrinking Fast

Percent of Global Biotechs with Negative Enterprise Value, Nov 2021 to Mar 2024

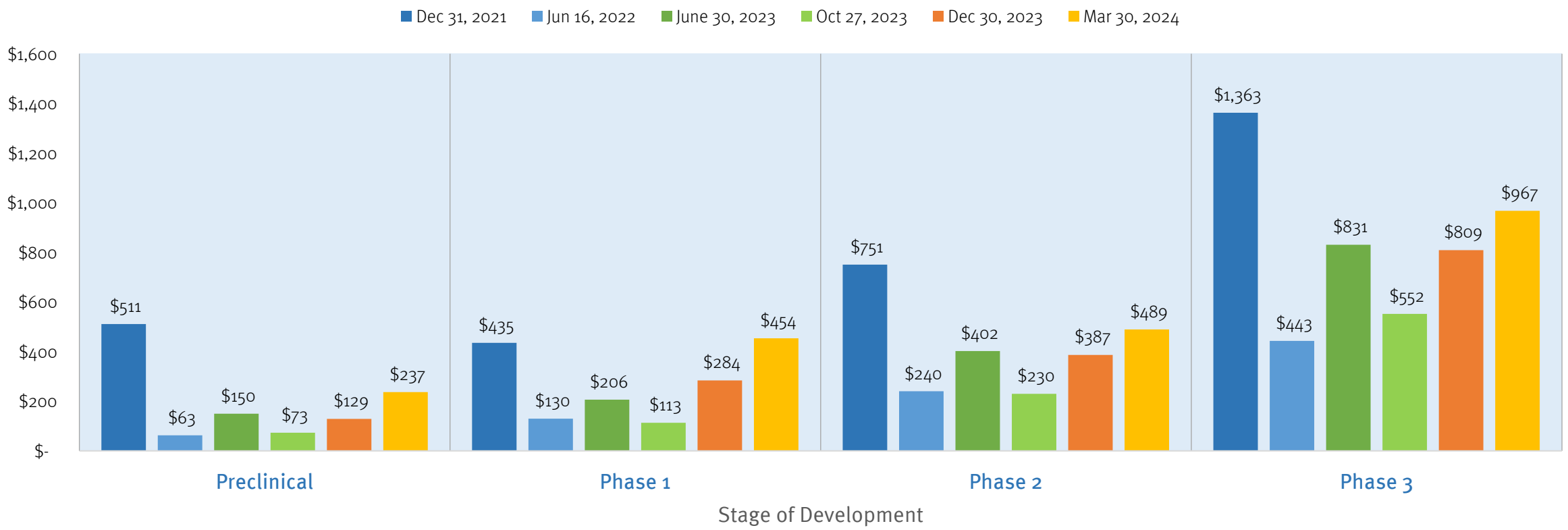


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Early-Stage Biotech Values Have Recovered the Most in 2024

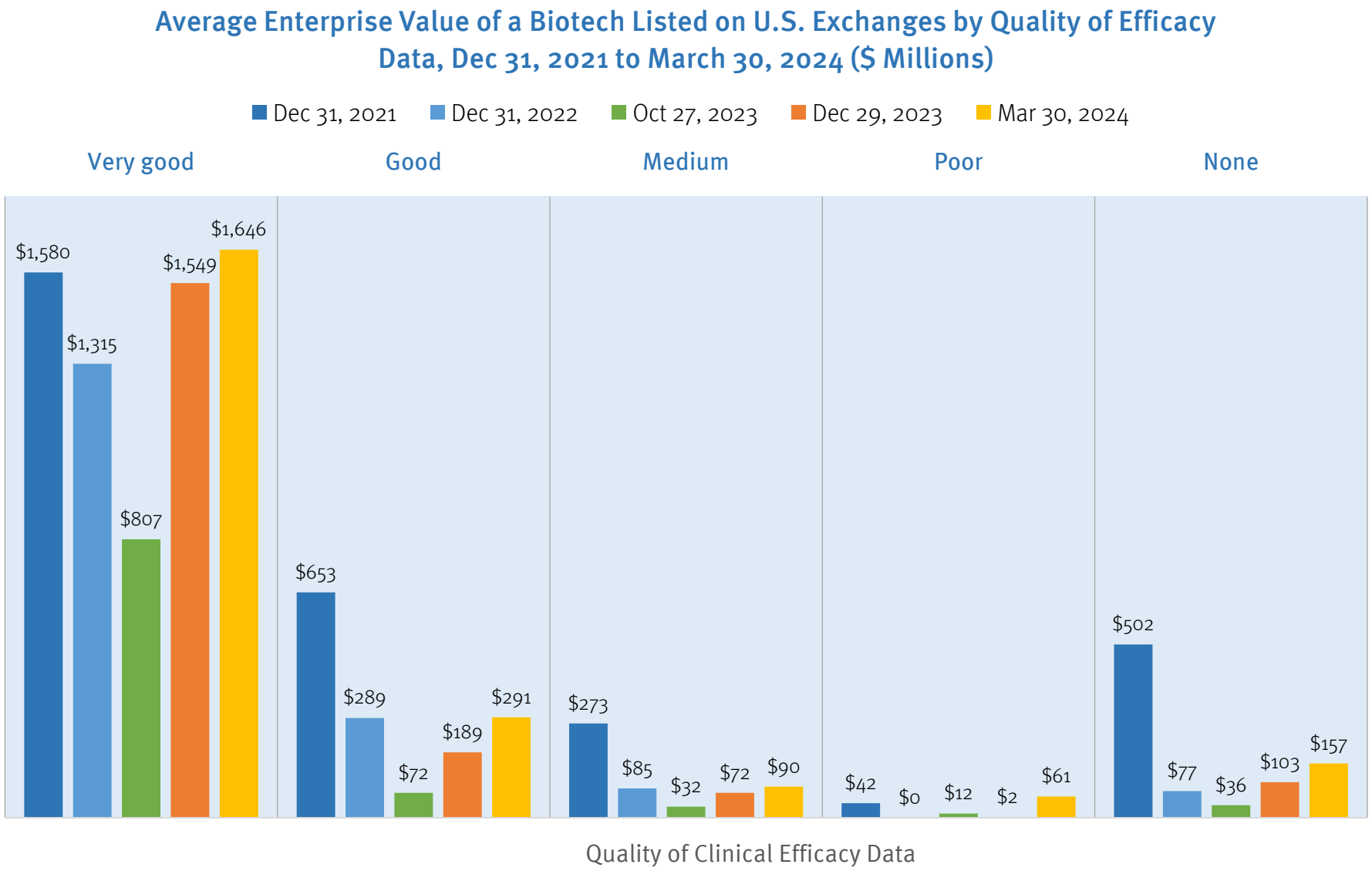
The average value of a Phase 3 biotech today is $967 million. This compares to $1.36 billion 27 months ago. In contrast, the average preclinical company value today of $237 million is less than of its value of $511 million two years ago. The downturn has tilted the market towards later stage stories. On the other hand, this year's market recovery has been strongest for preclinical and Phase 1 biotech companies.

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development, Dec 31, 2021 to March 30, 2024 ($ Millions)



Source: CapitalIQ and Stifel analysis. Phase of development is defined by release of at least some efficacy data from a given stage of clinical development.

Biotech Quality Premium in the Market is Shrinking

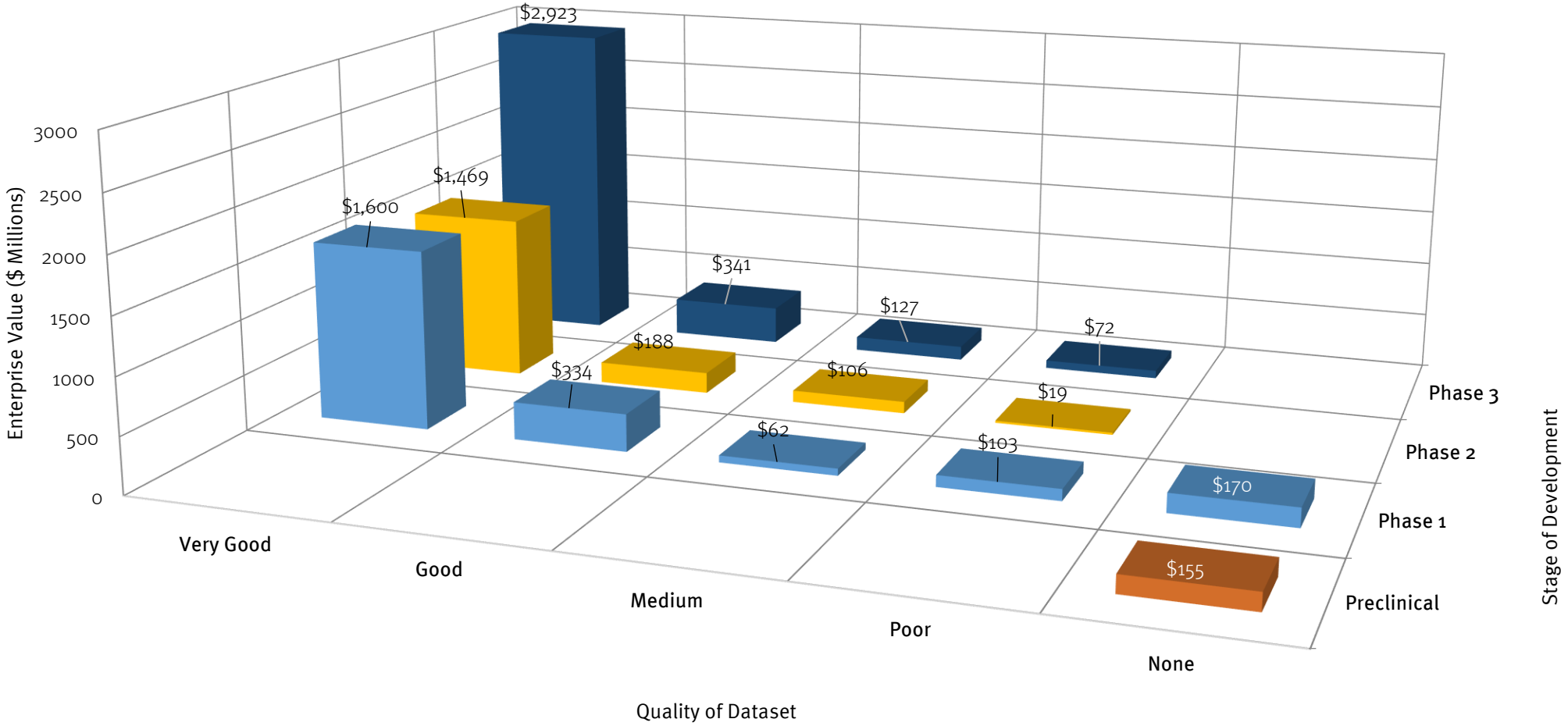


Companies with "very good" data have traded at eight to ten times the value of companies with a "good" dataset throughout the Pandemic recovery period. In 2024 we have seen a strong recovery in value of companies with "good", "medium" and "poor" data. While companies with "very good" data trade at values that are massively higher than those with "good" or "medium" data, the ratio of the average value of a very good to good data companies has shrunk from 11x last October to 5.6x at the close of Q1 2024. We view this as an important sign of market normalization as it indicates that portfolio managers are increasingly willing to take longer-term bets, playing the actuarial odds of drug success in the clinic as opposed to simply betting on the next M&A deal to hit.

Source: CapitalIQ and Stifel analysis.

Biotechs With Very Good Phase 3 Data Trade at Nearly $3 Billion in Value – 15 Times Those with No Data

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data
March 28, 2024 ($ millions)



Source: CapitalIQ and Stifel analysis.

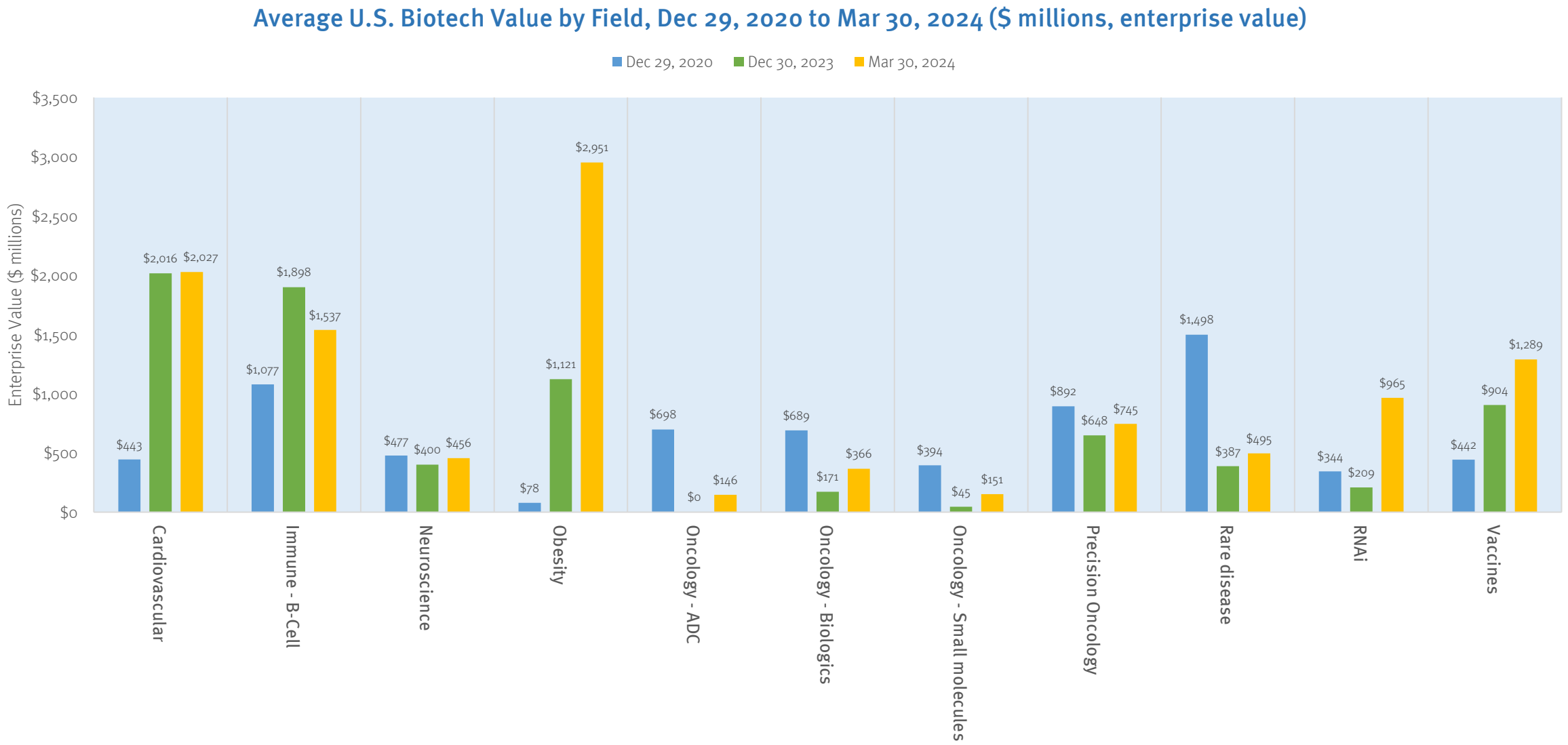
Biggest Value Accretion in 2024 in ADC's, Innate Immunology, RNAi and Virology

Average Enterprise Value by Field of Biotech, U.S. Domiciled Companies, 2020 to 2024, $mm

Field	Count	Dec 29, 2020	Dec 31, 2021	Dec 31, 2022	Jun 30, 2023	Dec 30, 2023	Mar 28, 2024	Change (Dec 30, '23 to Mar 28, '24)	Change (Dec 30, '22 to Mar 28, '24)	Change (Dec 30, '21 to Mar 28, '24)
Obesity	4	$78	$72	$284	$1,417	$1,121	$2,951	163.2%	940.0%	4002.6%
Cardiovascular	8	$443	$911	$1,643	$1,366	$2,016	$2,027	0.5%	23.4%	122.4%
Immune - B-Cell	4	$1,077	$198	$741	$830	$1,898	$1,537	-19.0%	107.3%	677.6%
Vaccines	6	$442	$541	$609	$671	$904	$1,289	42.6%	111.8%	138.3%
Artificial Intelligence	3	$0	$1,632	$377	$412	$823	$948	15.1%	151.4%	-41.9%
Nephrology	7	$49	$157	$297	$508	$407	$867	112.9%	191.7%	452.7%
Protein Degradation	4	$1,179	$1,326	$263	$260	$388	$770	98.5%	192.3%	-41.9%
RNAi	4	$344	$235	$362	$168	$209	$965	362.7%	166.3%	311.1%
Precision Oncology	27	$892	$689	$394	$476	$648	$745	15.0%	89.1%	8.1%
Allergy	4	$1,950	$423	$675	$566	$617	$708	14.7%	4.9%	67.2%
Neuro	38	$477	$417	$338	$395	$400	$456	14.0%	34.9%	9.4%
Hematology	5	$764	$325	$448	$310	$376	$584	55.3%	30.5%	79.7%
Alzheimer's	7	$1,409	$1,280	$1,010	$1,020	$528	$655	24.1%	-35.1%	-48.8%
Rare disease	35	$1,498	$1,269	$497	$497	$387	$495	27.9%	-0.4%	-61.0%
Fibrosis	5	$671	$452	$281	$592	$504	$538	6.7%	91.3%	19.1%
Hepatology	10	$481	$291	$458	$466	$175	$250	42.9%	-45.4%	-14.0%
Oncology - ADC	4	$698	$319	$121	$22	-$9	$146	› 100%	20.5%	-54.3%
Oncology - Biologics	72	$689	$501	$180	$165	$171	$366	114.0%	103.3%	-27.0%
Gene Editing	4	$107	$572	$200	$131	$309	$312	1.0%	55.6%	-45.4%
Ophthalmology	14	$995	$503	$138	$208	$152	$373	145.4%	169.7%	-25.8%
Immune - Innate	7	$111	$507	$468	$397	$37	$209	464.9%	-55.4%	-58.8%
Endocrinology	11	$143	$191	$83	$62	$171	$293	71.0%	253.3%	53.4%
Dermatology	5	$362	$141	$52	$101	$146	$281	92.5%	437.5%	99.3%
Immune - T-Cell	7	$716	$140	$59	$314	$188	$288	53.2%	391.0%	106.2%
Gene therapy	2	$249	$473	$147	$213	$235	$174	-26.0%	18.7%	-63.2%
Radiopharma	4	$30	$35	$61	$50	$185	$621	235.7%	912.4%	1650.5%
Oncology - Small molecules	43	$394	$279	$57	$122	$101	$151	41%	163.2%	-45.8%
Immune - Other	6	$143	$169	$20	$36	$38	$157	313.2%	697.2%	-7.2%
Virology	12	$1,020	$582	$90	$99	$17	$76	340.1%	-15.4%	-86.9%
Infection	7	$165	$145	$35	$29	$40	$56	40.0%	61.0%	-61.3%

Source: CapitalIQ and Stifel analysis.

Evolution of Value Structure by Field, U.S. Public Biotechs



Source: CapitalIQ and Stifel analysis.

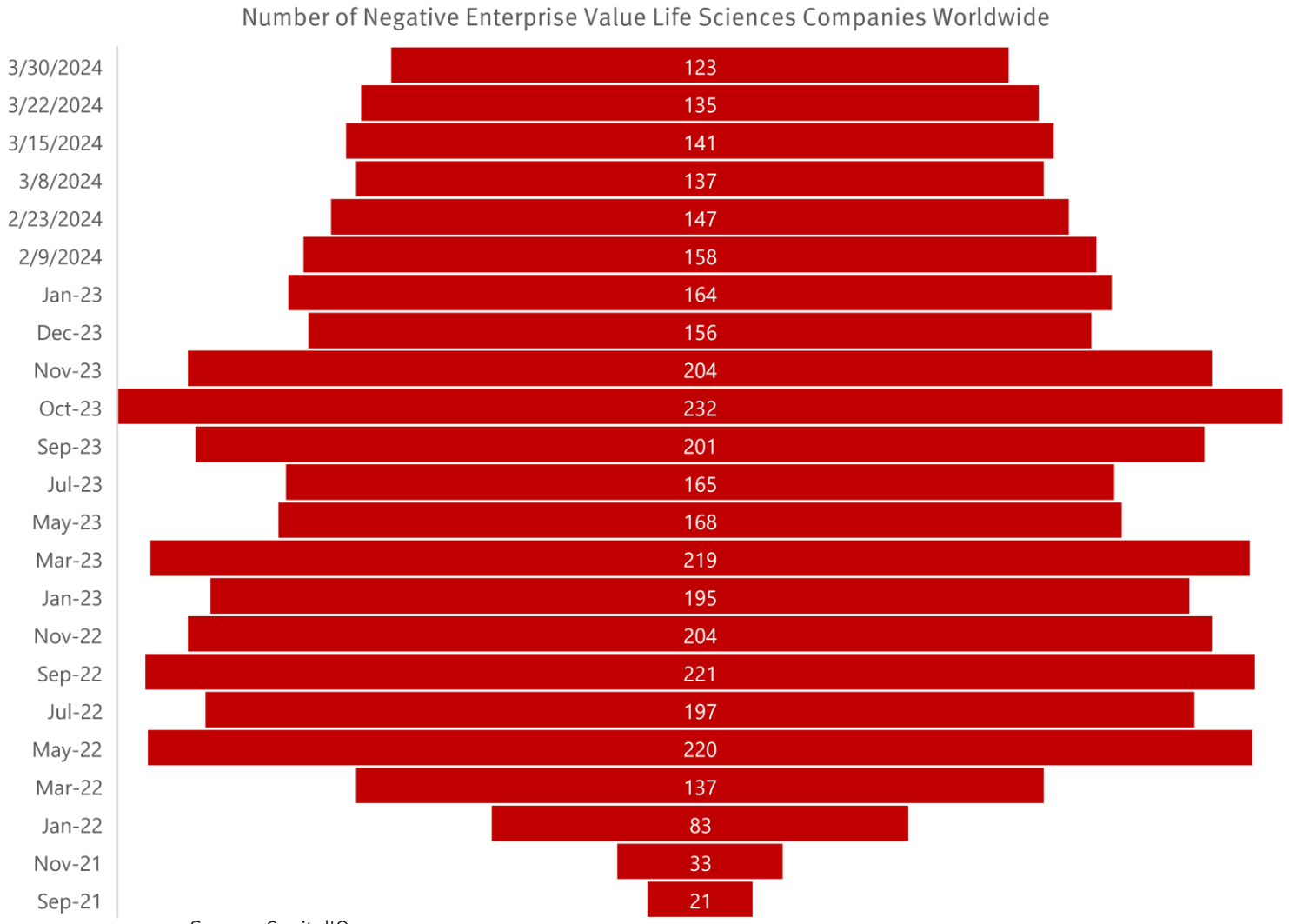
Life Sciences Sector Total Value Rose 0.9% Last Week

Last week saw the life sciences sector gain $86 billion in value. The best performing sectors were biotech, diagnostics and medical devices. The API sector, OTC and life science tools all loss 1% or more in aggregate value.

Sector	Firm Count	Enterprise Value (Mar 28, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$76,854	-2.5%	-5.2%	-3.9%
Biotech	799	$282,169	2.3%	0.1%	-5.1%
CDMO	40	$154,655	0.7%	4.6%	-17.2%
Diagnostics	81	$280,360	1.7%	3.1%	2.9%
OTC	30	$27,965	-1.1%	3.1%	-4.4%
Commercial Pharma	719	$6,290,240	1.0%	1.6%	11.3%
Pharma Services	39	$199,094	0.1%	0.5%	-2.8%
Life Science Tools	51	$726,561	-1.1%	1.2%	-2.9%
Devices	181	$1,713,530	1.4%	0.4%	5.2%
HCIT	10	$19,727	-0.7%	-6.0%	-23.6%
Total	**2031**	**$9,760,155**	**0.9%**	**1.3%**	**8.5%**

Source: CapitalIQ

Number of Negative Enterprise Value Life Sciences Companies Continued to Decline Last Week



Source: CapitalIQ

Despite the flattish market, investors are continuing to buy up companies with negative enterprise values.

The count of negative EV life sciences companies worldwide fell from 135 from 123 last week.

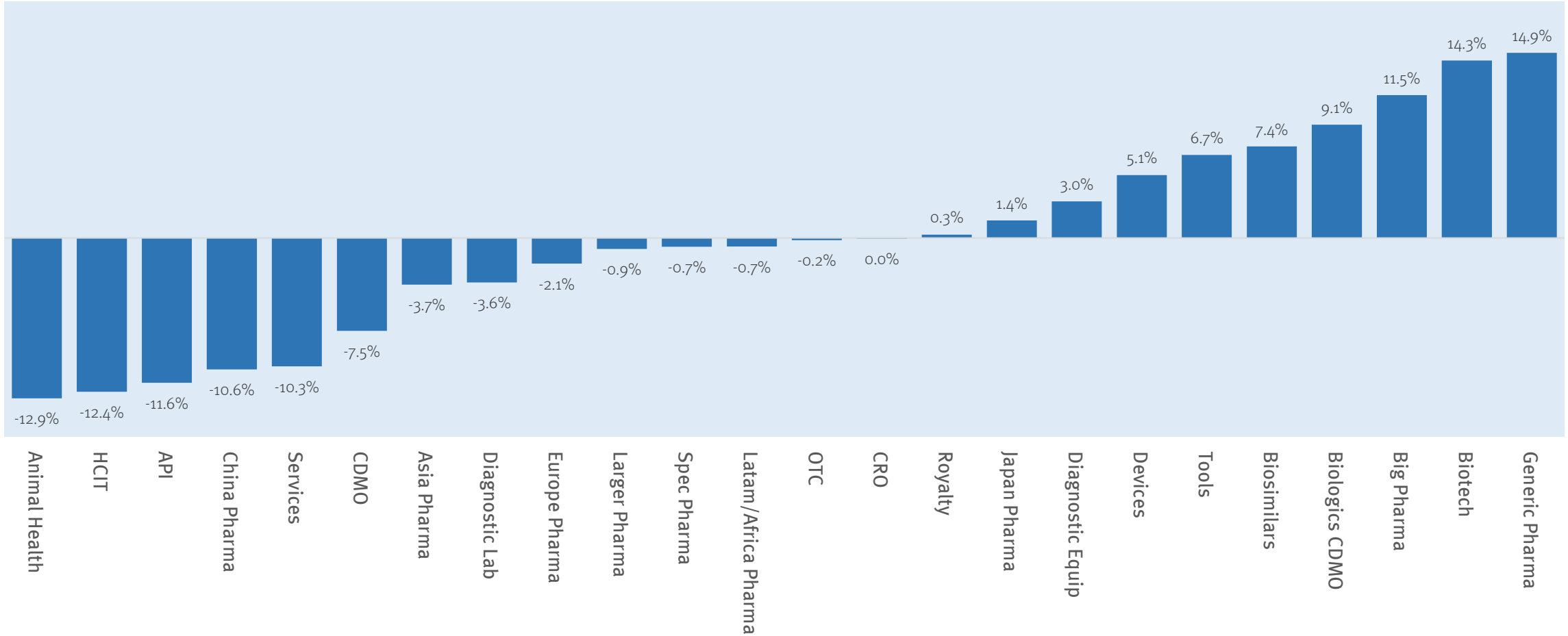
This is the lowest level since January 2022.

This is an important sign of a normalizing market.

Life Sciences Subsector Performance in Q1 2024

Generic pharma, biotech and big pharma have performed best so far in 2024 while animal health, HCIT, China, pharma services and API have all underperformed. The pressures on Wuxi have impacted the pharma services segment.

Percent Change in Aggregate Global Market Cap of Subsector of Life Sciences Industry, Dec 30, 2023 to Mar 30, 2024

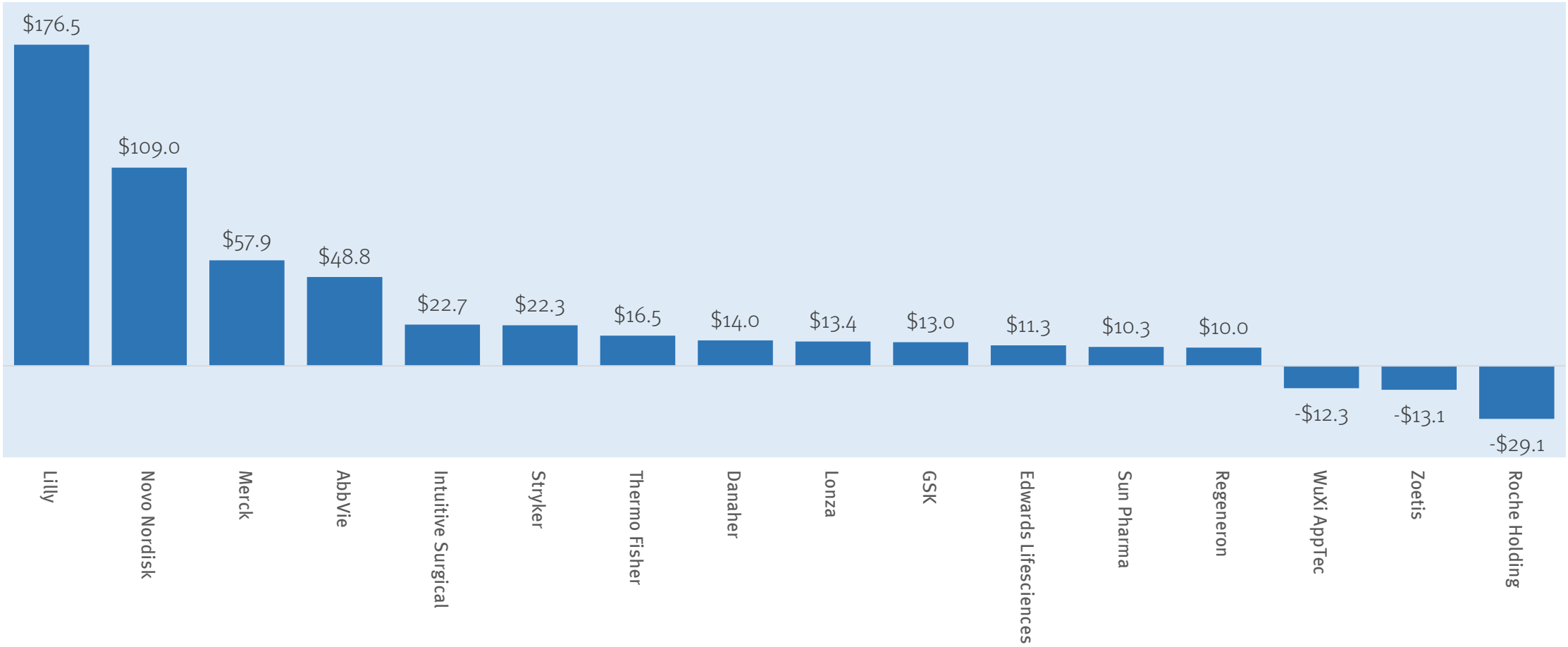


Source: S&P CapitalIQ and Stifel analysis. Note: the Asia pharma category does not include China and Japan but does include countries like Indonesia, S. Korea and Thailand.

Lilly and Novo Led the Market Up in Q1 2024

Merck did well on sotatercept approval and pipeline progress. AbbVie performed well on excellent earnings and progress in its immunology portfolio. Roche lost value on a disappointing outlook. In general, the major players in medical devices performed well based on strong 2023 earnings and excellent outlooks. Wuxi was negatively impacted by pressure from U.S. Congress and China geopolitics.

Biggest Absolute Changes in Market Cap in Public Life Sciences Sector, Q1 2024 ($ Billions)

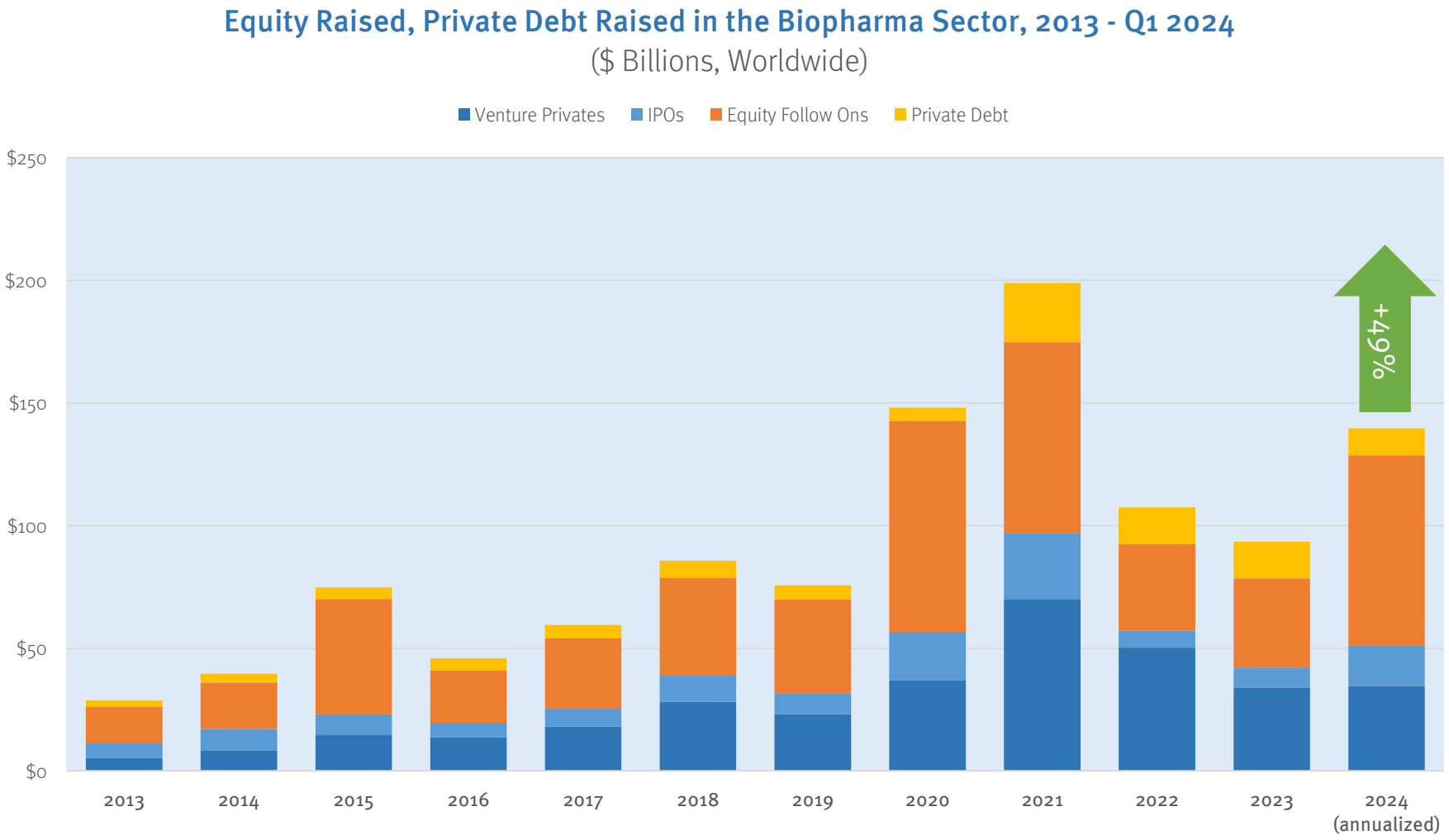


Note: This chart includes all public life science companies worldwide that gained or lost more than $10 billion in market cap in the first quarter of 2024.

Source: S&P CapitalIQ and Stifel analysis.

Biotech Balance Sheet Condition and Capital Inflows

Overall Biopharma Capital Raised To Date In 2024 is Up 49% On an Annualized Basis Versus 2023



Venture private volumes in Q1 2024 were flat versus 2023.

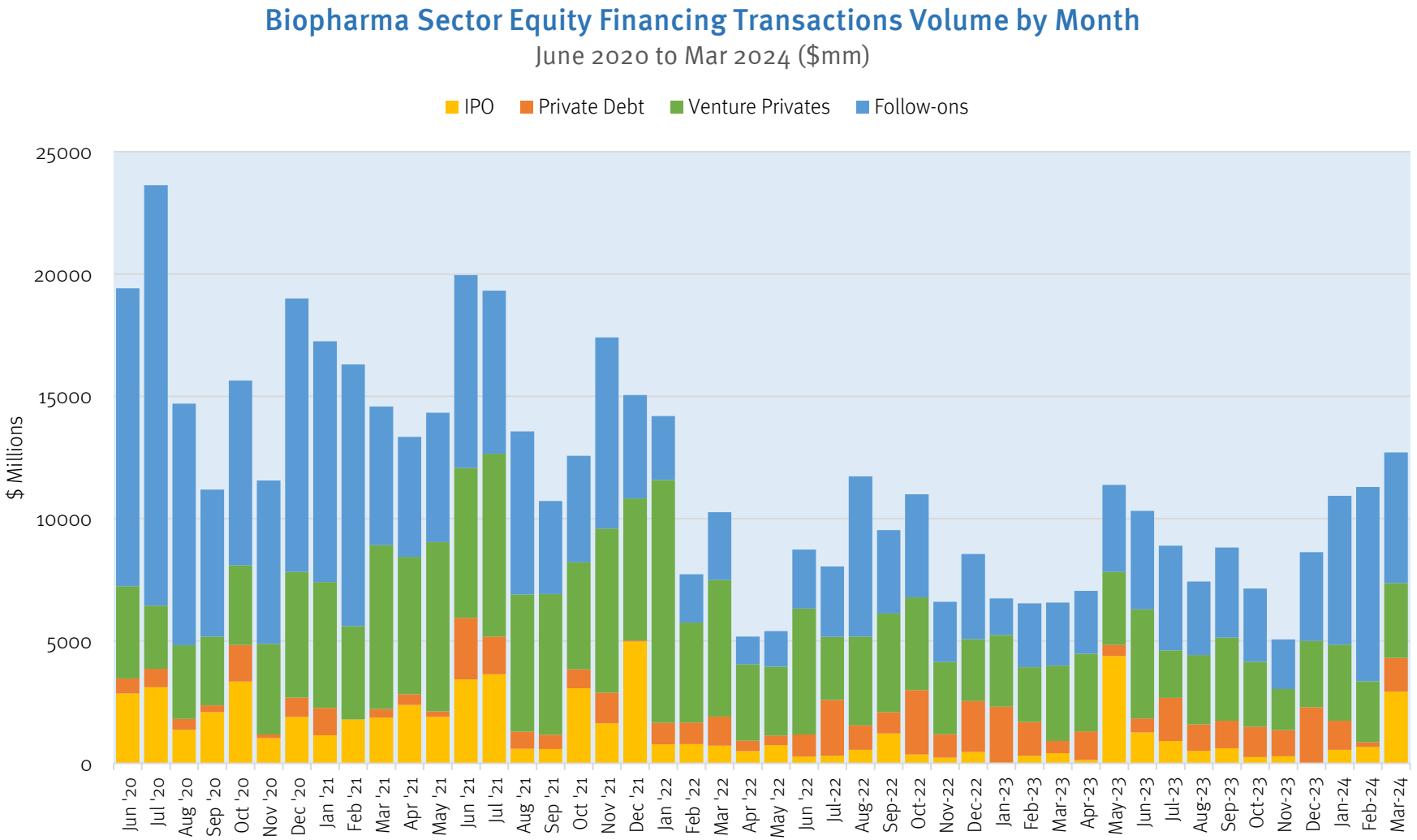
Follow-on activity was up 116% relative to 2023 and IPO activity was up 122%.

Private debt volume was down 26%.

The markets were materially stronger in 2024 than in 2023.

Source: CapitalIQ and Stifel research

Monthly Biopharma Market Capital Raise Data Show Market Picked up Substantially in Q1 2024 vs. Previous Quarter



Financing markets were much stronger in the first three months of 2024 as opposed to 2023.

Current issuance volumes remain below those from levels seen during the Pandemic.

We expect to see a substantial ongoing recovery in public capital markets throughout 2024.

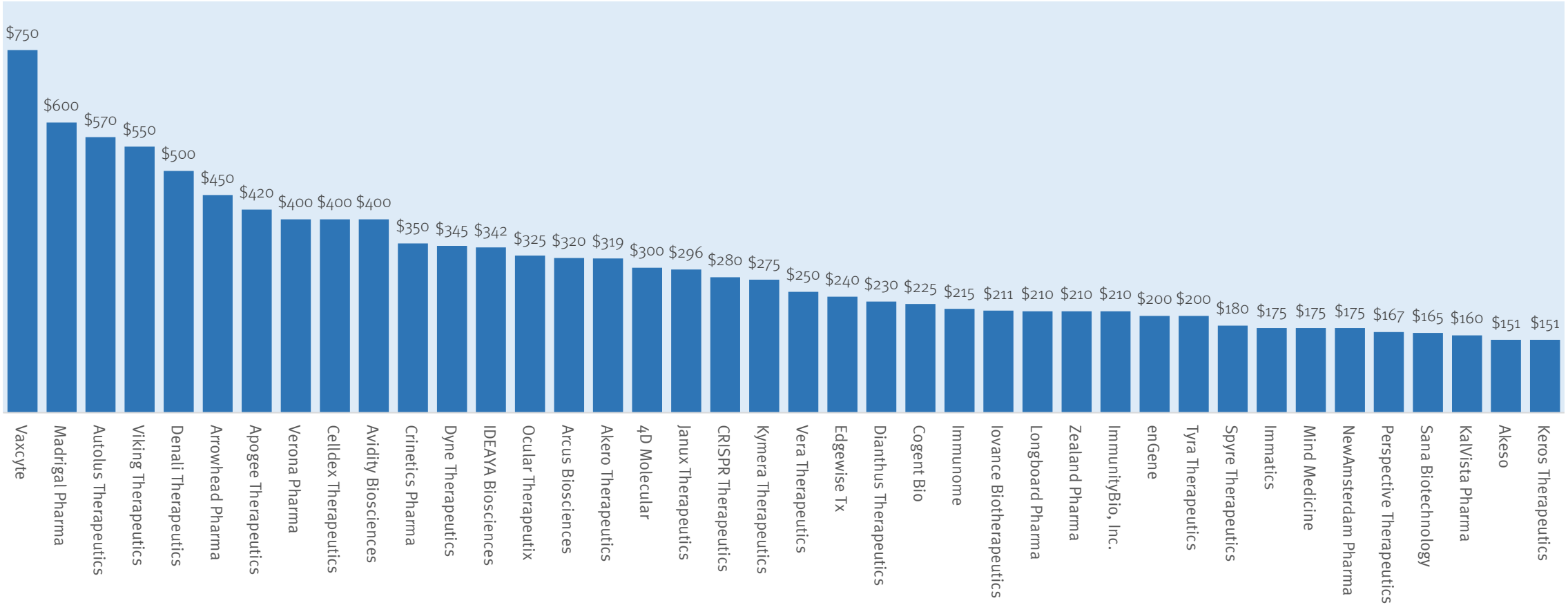
Source: CapitalIQ and Stifel research

Top 40 Q1 Capital Raises Brought in $12 Billion to Biotech

Forty companies of the top 500 raised $12.1 billion in Q1. Seventy-five companies raised another $4.9 billion. The remainder did not bring in fresh capital during the quarter. The effect of the capital market reopening has, obviously, been quite concentrated in its effect.

Amount of Capital Raised in Q1 2024 ($mm)

(Top 40 Biotech Raises out of all global biotech)



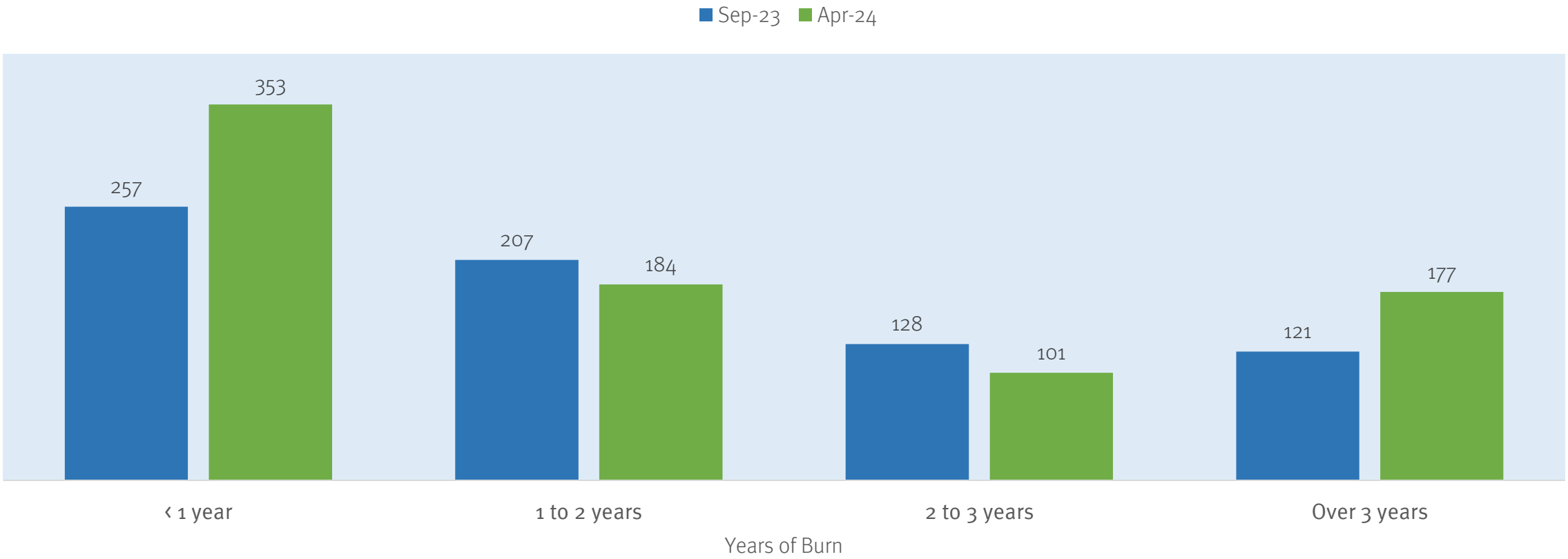
Source: CapitalIQ and Stifel research.

Over 40% of Global Biotech Has Less Than a Year of Cash

If one looks at all 815 public biotech companies worldwide, there is a substantial fraction that have less than a year of cash. On the other hand, there are far more today with three years or more cash than six months ago. The biotech world is very much divided into those with stories that have been getting financed well and those that have not.

Biotech Company Count by Years of Remaining Burn

(Global Publicly Traded Biotech Population, Sep 23, 2023 and April 1, 2024)

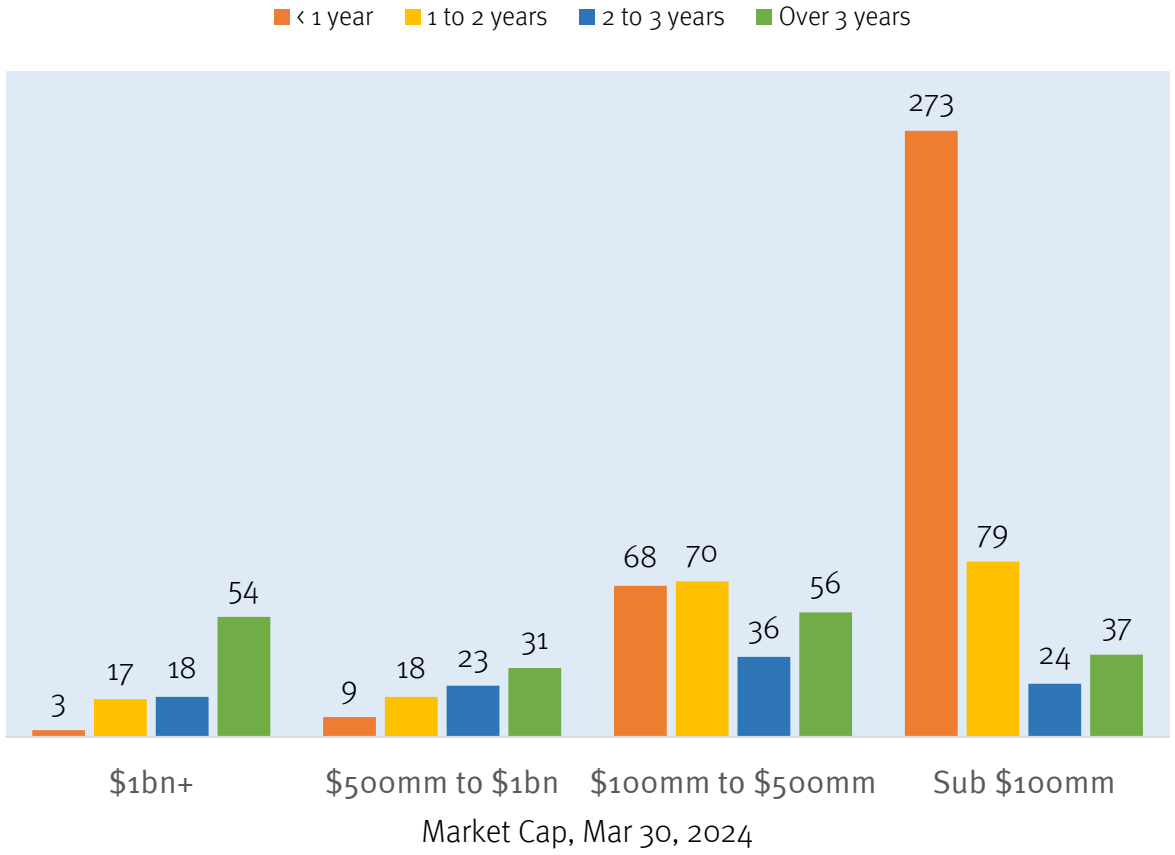


Notes: Data from CapitalIQ and Stifel Analysis. Data on burn and cash not available for all companies in dataset. Biotechs were defined as companies in the biopharma sector that do not yet have a commercial product.

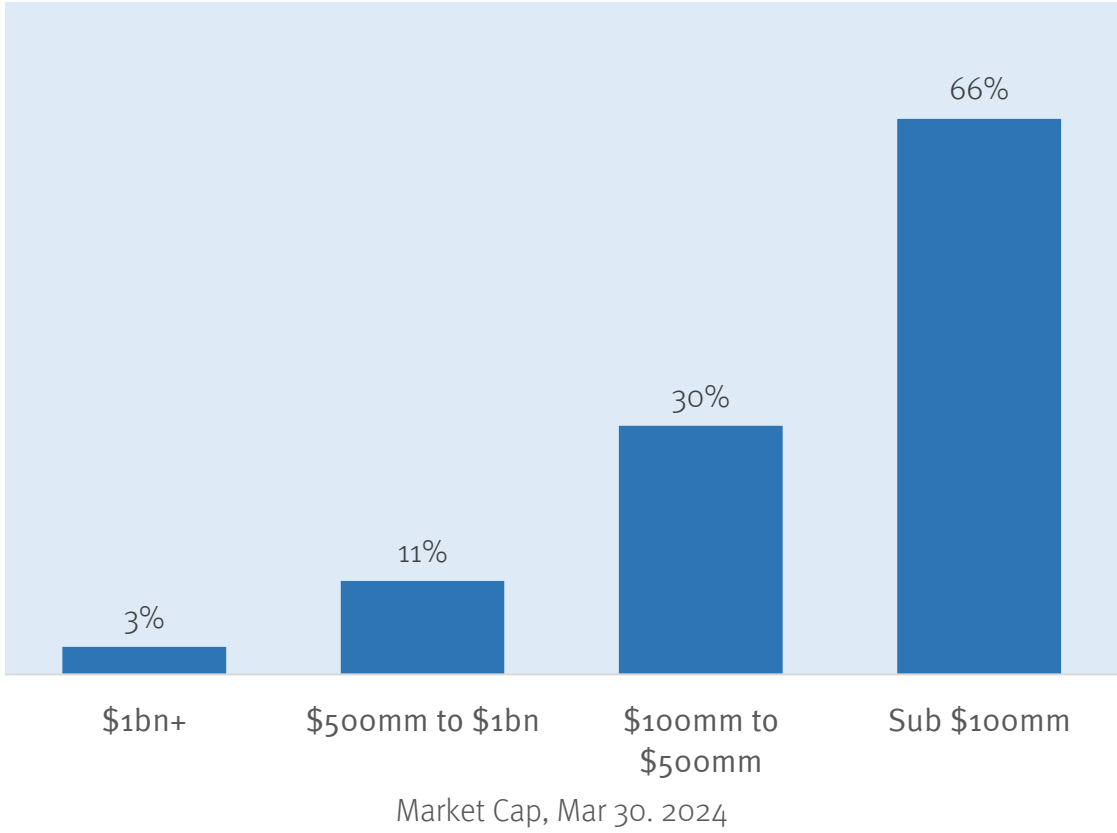
Few Biotechs with Market Caps Over $500mm are Tight on Cash

Two thirds of companies with market caps under $100mm have less than a year of remaining burn. In contrast, only three percent of companies with more than a billion in market cap have less than a year of remaining burn on the balance sheet. We know that market caps are linked to quality of data and scientific story. By and large, the market is directing cash to companies that have the most tangible promise to get drugs approved.

Years of Burn of Global Publicly Traded Biotech Population



Percent Global Biotechs with Less Than One Year of Remaining Burn (Mar 28, 2024, N=815)



Source: CapitalIQ and Stifel Analysis. Biotechs were defined as companies in the biopharma sector that do not yet have a commercial product.

Median Years of Burn of Top 500 Public Biotechs Reverses its Sharp Decline that Ran Into Mid-2023

Median Years of Burn Among Top 500 Global Biotechs
(only including companies that burn cash)

This page looks at the top 500 biotechs by market cap.*

Cash positions for quarter ended Dec 30, 2023 have now been fully reported.

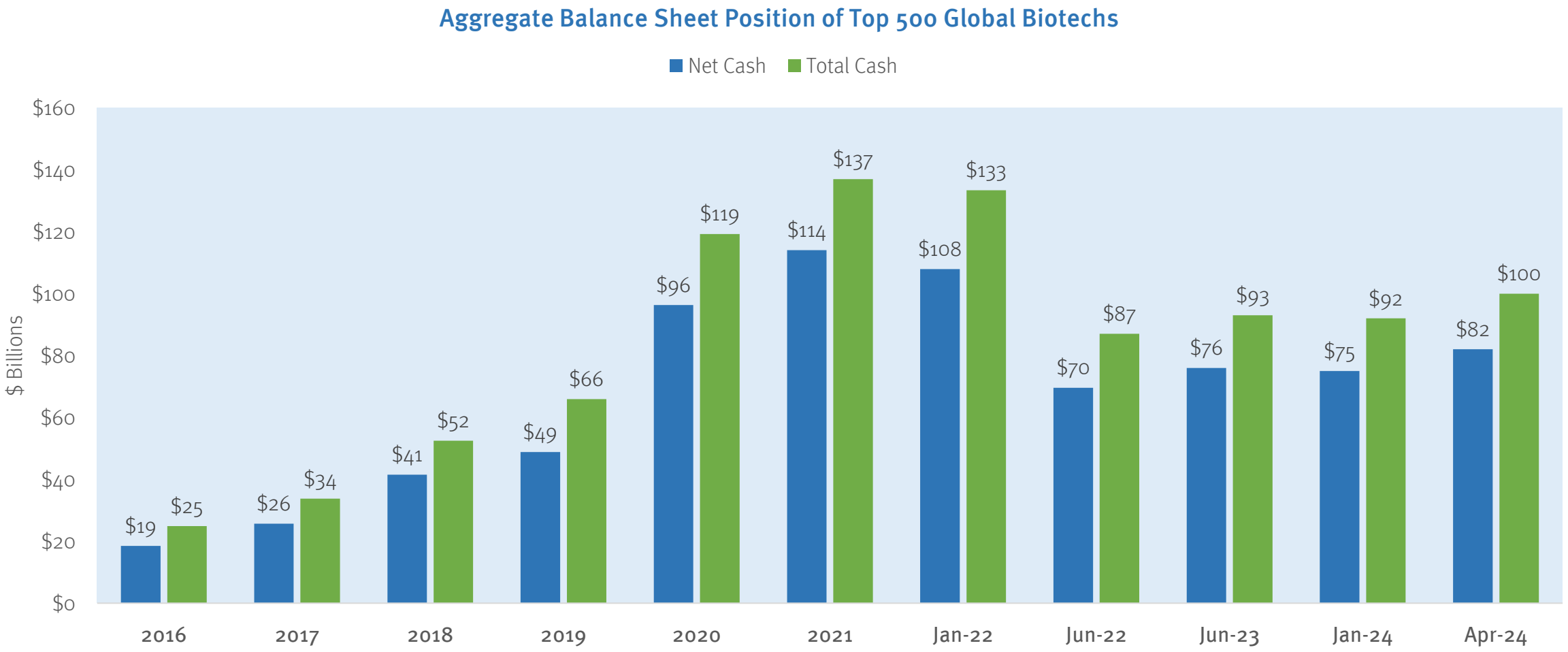
The median Top 500 biotech company at 2023 year-end had 1.9 years of burn on its balance sheet.

By the end of the first quarter of 2024 the median years of burn at risen to 2.0 years.

* Data from CapitalIQ. We took all public biotech companies in Sep 2021 and chose the largest 500 by enterprise value at the time for this analysis. This chart tracks the balance sheets of this cohort to June 2023 (and back to 2016 for historic reference). Years of burn is defined as net cash at last quarter end dividend by trailing 12-month EBITDA. After that we looked at the top 500 companies by market cap at quarter end 2024. For April 2024 estimated burn we added funds raised via disclosed ATM use, follow-ons, royalty deals and debt deals. We then deducted 25% of trailing annual EBITDA.

Top 500 Public Biotech Aggregate Balance Sheet Status

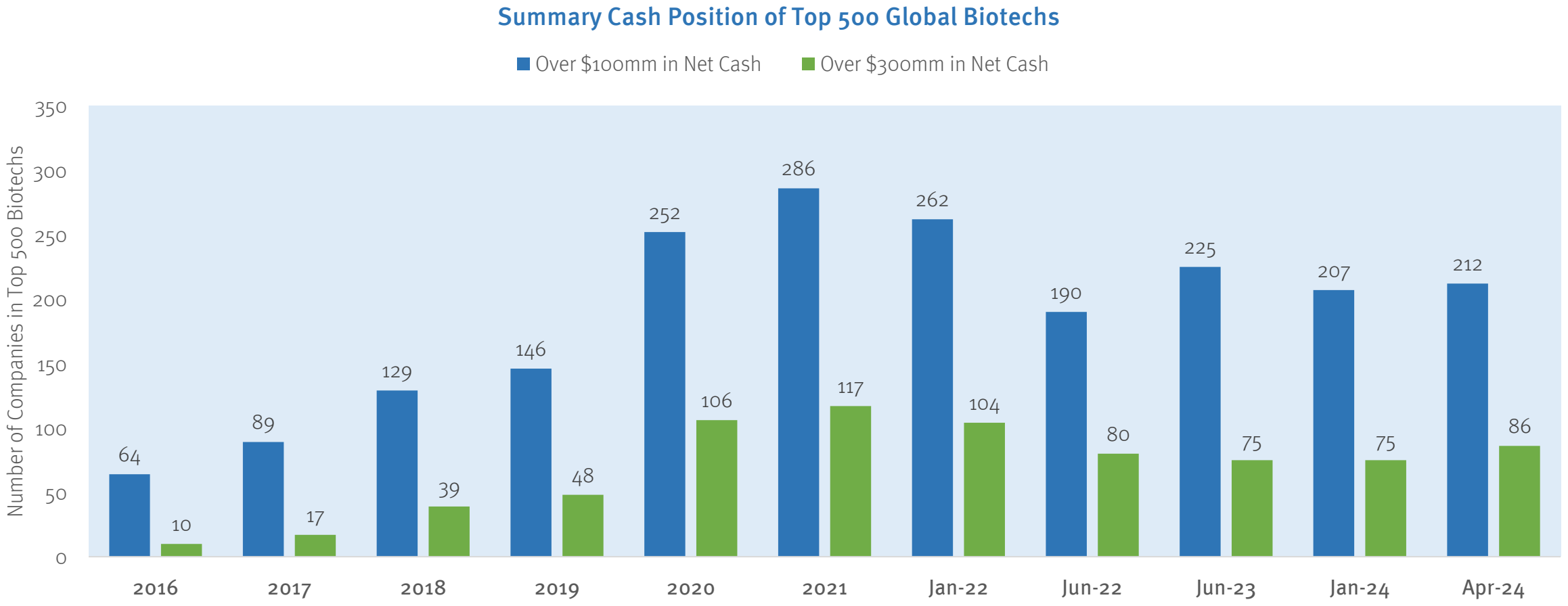
The total net cash held by the top 500 biotechs has recovered from $70 billion as of June 30, 2022 to $82 billion as of April 1, 2024. The reopening of the capital markets has obviously helped but biotech balance sheet condition is still nowhere near where it was at the peak of the Pandemic.



Source: CapitalIQ, Biotechs were defined as companies in the biopharma sector that do not yet have a commercial product. We took all public biotech companies in Sep 2021 and chose the largest 500 by enterprise value at the time for this analysis. This chart tracks the balance sheets of this cohort to June 2023 (and back to 2016 for historic reference). After that we looked at the top 500 companies by market cap at quarter end 2024. For April 2024 estimated burn we added funds raised via disclosed ATM use, follow-ons, royalty deals and debt deals. We then deducted 25% of trailing annual EBITDA.

Top 500 Public Biotech Aggregate Balance Sheet Status

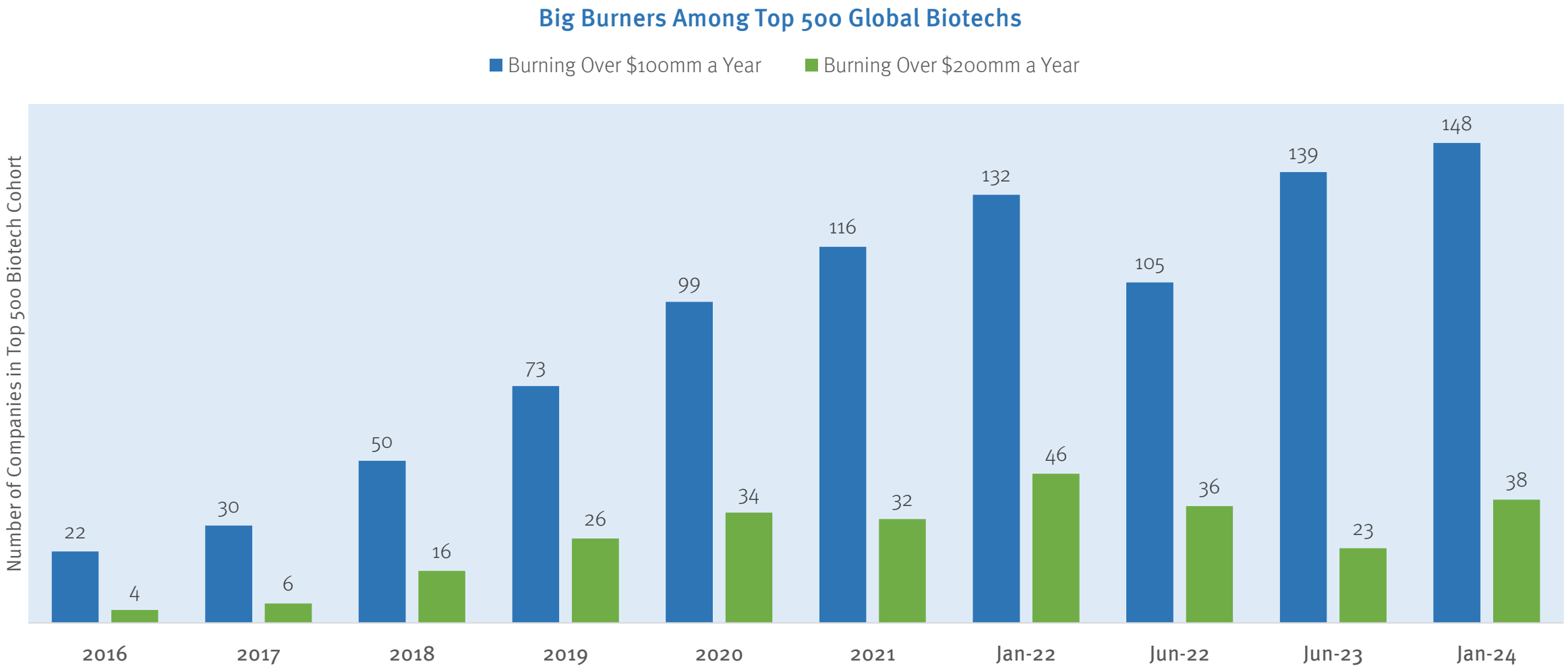
The number of biotechs with more than $100mm in net cash has shrunk since June 2023. But the number with more than $300mm in net cash has risen. The reopening of the capital markets has resulted in relatively large raises for companies with the strongest stories.



Source: CapitalIQ, Biotechs were defined as companies in the biopharma sector that do not yet have a commercial product. We took all public biotech companies in Sep 2021 and chose the largest 500 by enterprise value at the time for this analysis. This chart tracks the balance sheets of this cohort to June 2023 (and back to 2016 for historic reference). After that we looked at the top 500 companies by market cap at quarter end 2024. For April 2024 estimated burn we added funds raised via disclosed ATM use, follow-ons, royalty deals and debt deals. We then deducted 25% of trailing annual EBITDA.

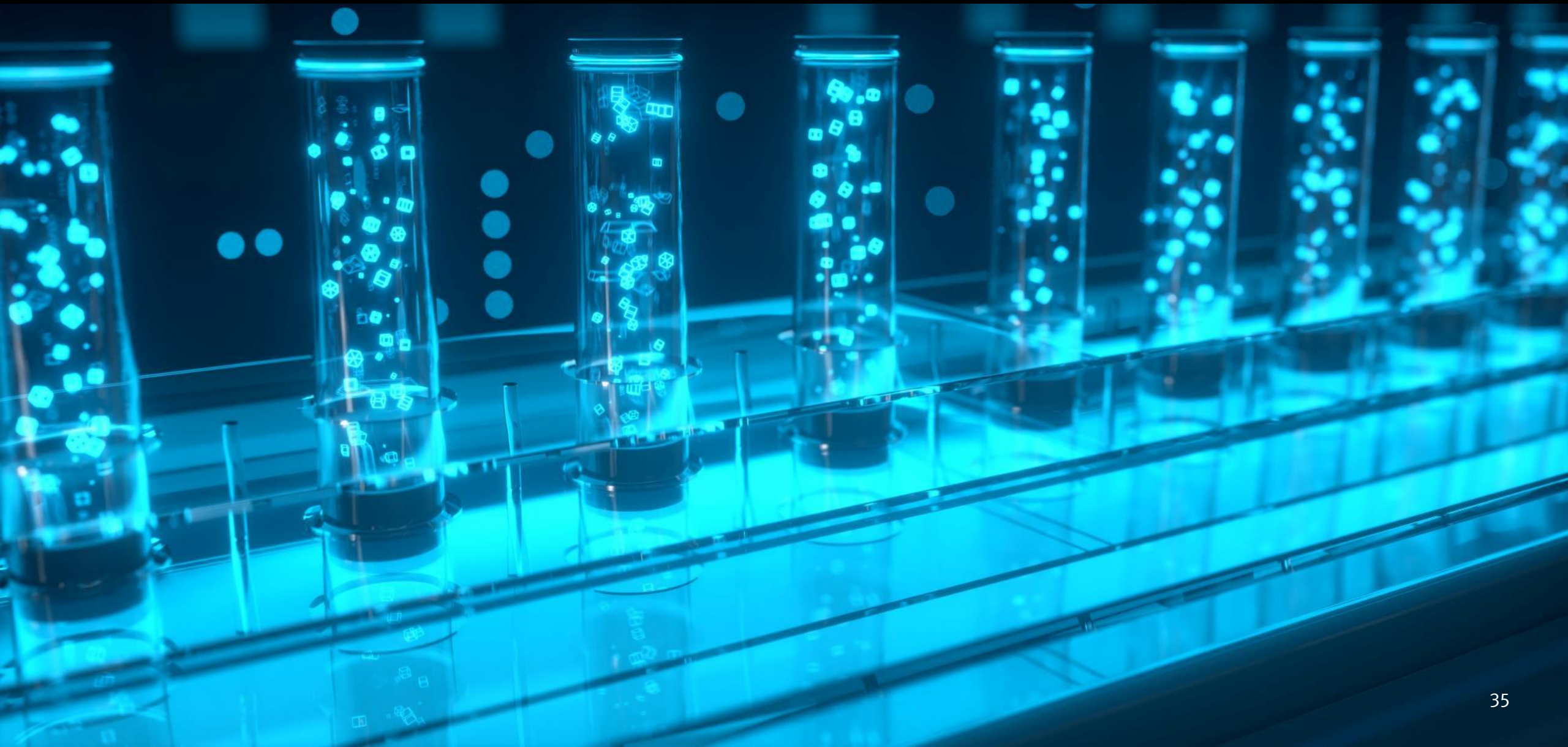
Top 500 Public Biotech Spend Behavior

Biotechs have not restrained spend, on average, in recent years. The number of companies burning over $100mm a year is at an all-time high.

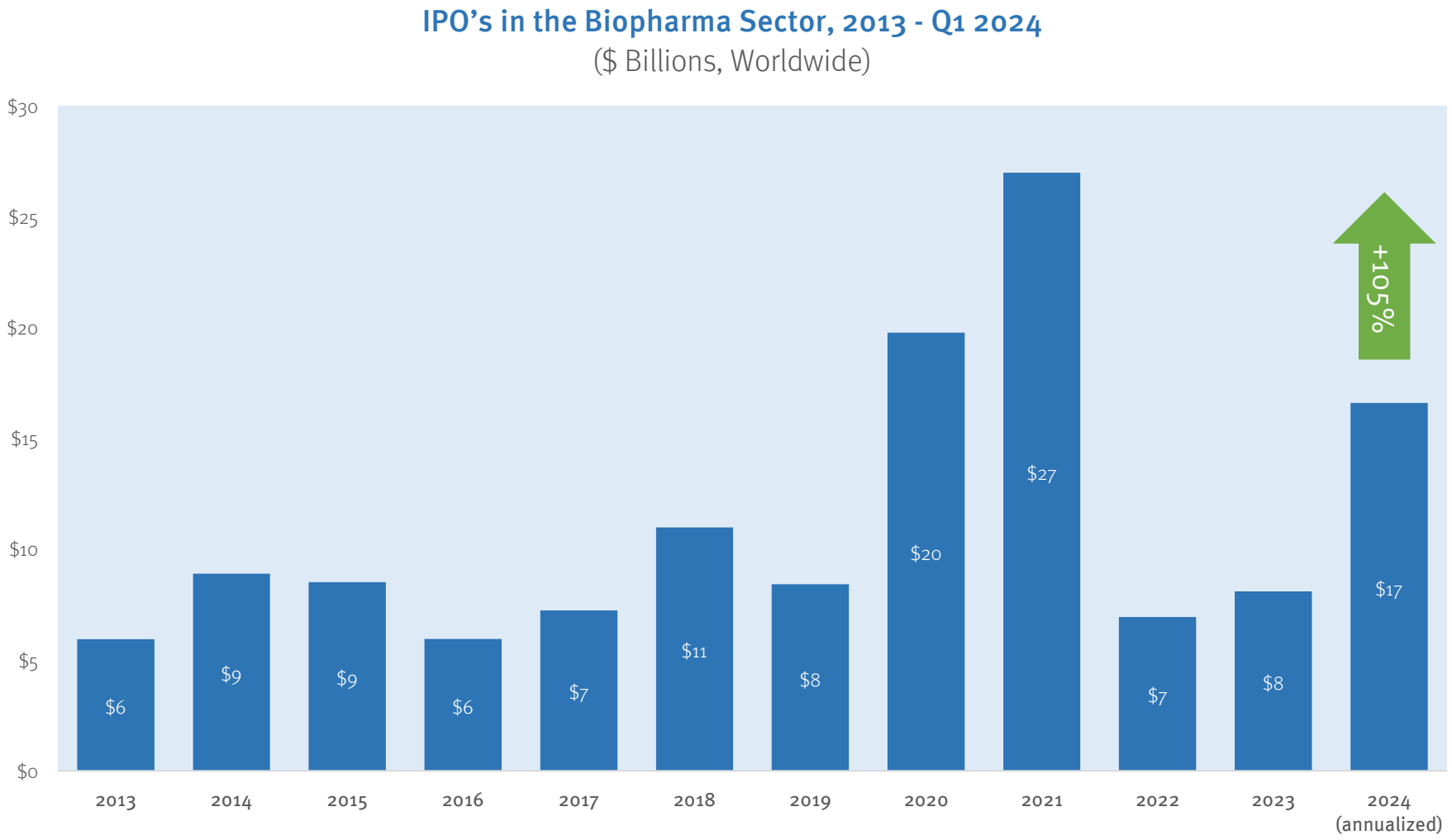


Source: CapitalIQ, Biotechs were defined as companies in the biopharma sector that do not yet have a commercial product.

Capital Markets Update



Biopharma IPO Volume Level Up 105% in 2024 versus 2023



IPO activity has picked up rather substantially in 2024 compared to the "drought years" of 2022 and 2023.

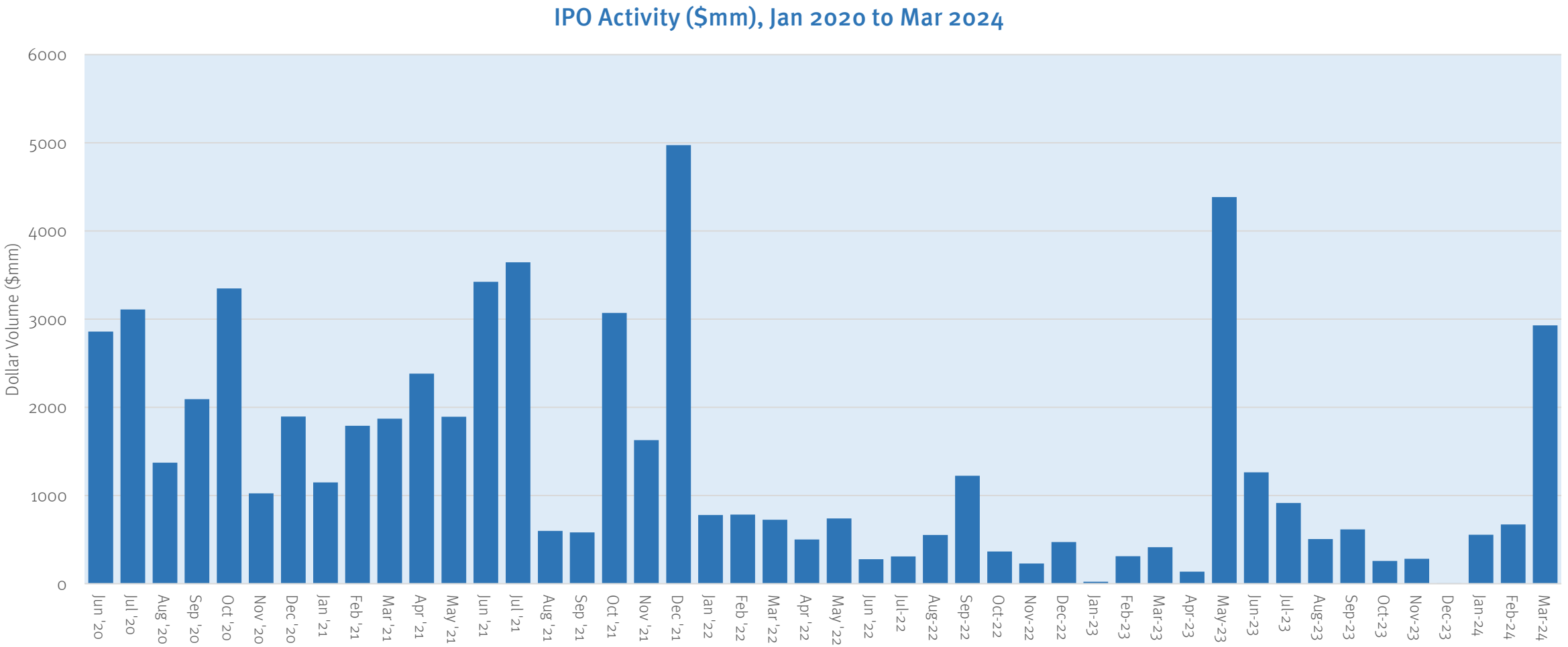
This mirrors the pickup in market conditions.

The buyside remains fairly selective at this point so, while reopened, the IPO market is not operating with the same vigor seen in 2020 and 2021.

Source: CapitalIQ and Stifel research

Monthly IPO Activity in the Biopharma Sector

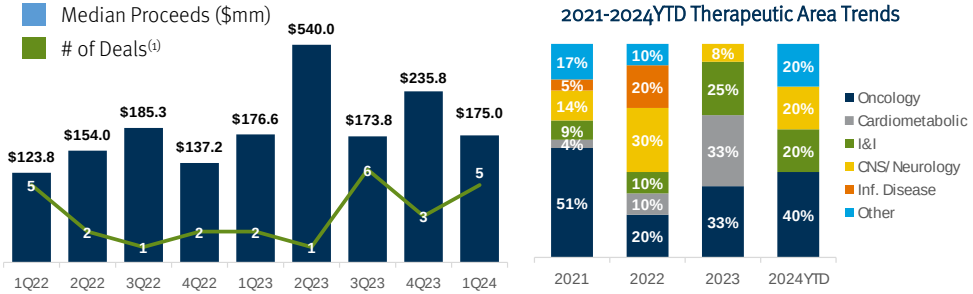
The month of March saw a pickup in global IPO volume in biopharma. Last week saw Boundless Bio go public on the Nasdaq and raise $100 million.



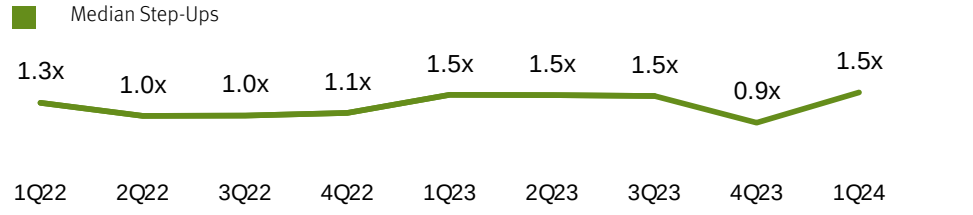
Source: Data from CapitalIQ and Stifel research.

IPO Market in Early Stages of a Rebound

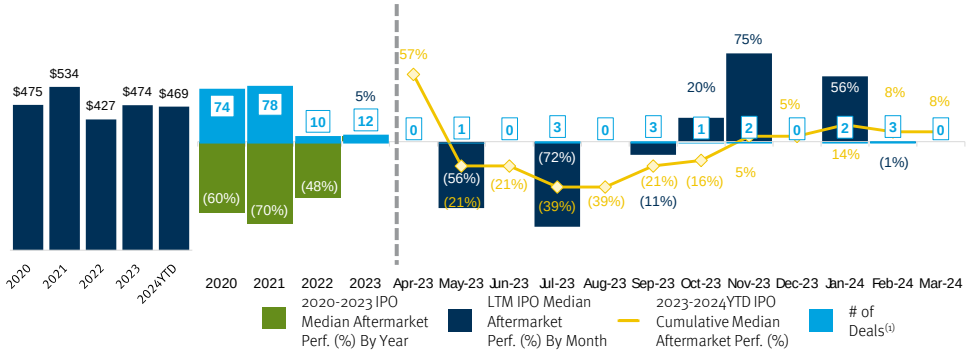
Biopharma IPO Market Remains Highly Selective



IPO Step-Ups Remain Deal Dependent



Pre-Money Valuations Have Rebounded And Performance Has Been Improving(2)



Biotech IPOs, November 2021 to Mar 22 2024

Issuer	Offer Date	Issuance Amount	Pre-Money Valuation	Pricing vs. Range	Step-Up	Price Change Offer to Day 1	Price Change Offer to Current
Metagenomi Technologies, LLC	02/08/24	$93.8	$469.2	Low End	0.6x	(31.3%)	(32.4%)
Kyverna Therapeutics, Inc.	02/07/24	319.0	652.3	$3.00 Above	2.6x	36.4%	16.9%
Alto Neuroscience, Inc.	02/01/24	128.6	321.7	High End	1.5x	29.4%	(0.2%)
ArriVent BioPharma, Inc.	01/25/24	175.0	435.1	Midpoint	1.1x	11.1%	8.3%
CG Oncology, Inc.	01/24/24	380.0	911.7	$1.00 Above	1.5x	95.6%	113.2%
CARGO Therapeutics, Inc.	11/09/23	281.3	329.4	Low End	1.1x	(3.1%)	108.5%
Lexeo Therapeutics, Inc.	11/02/23	100.0	187.0	Below	0.6x	(8.6%)	41.5%
Abivax SA(3)	10/20/23	235.8	495.0	Low End	NA	(28.4%)	20.3%
Adlai Nortye Ltd.(4)	09/29/23	97.5	769.3	In Range	1.2x	(34.8%)	(60.9%)
RayzeBio, Inc.	09/14/23	311.0	800.6	High End	1.4x	33.3%	247.2%
Neumora Therapeutics Inc.	09/14/23	250.1	2,509.6	Midpoint	1.5x	(4.4%)	(11.2%)
Turnstone Biologics Corp.	07/20/23	80.0	194.1	Low End	0.5x	(8.3%)	(72.3%)
Sagimet Biosciences Inc.	07/13/23	85.0	301.4	Midpoint	1.5x	(0.3%)	(74.8%)
Apogee Therapeutics, Inc.	07/13/23	300.1	505.8	High End	2.0x	24.9%	301.8%
ACELYRIN, Inc.	05/04/23	540.0	1,221.5	High End	1.5x	30.6%	(56.4%)
Mineralys Therapeutics, Inc.	02/09/23	192.0	452.8	High End	1.7x	15.3%	(20.7%)
Structure Therapeutics, Inc.	02/02/23	161.1	414.3	High End	1.2x	73.3%	135.0%
Acrivon Therapeutics, Inc.(5)	11/14/22	99.4	183.0	Below	0.9x	33.1%	(50.5%)
Prime Medicine, Inc.	10/20/22	175.0	1,501.9	Midpoint	1.2x	(9.6%)	(57.9%)
Third Harmonic Bio, Inc.	09/14/22	185.3	496.0	Midpoint	1.0x	15.8%	(45.0%)
PepGen, Inc.	05/05/22	108.0	169.1	Below	0.8x	7.4%	28.7%
HilleVax, Inc.	04/28/22	200.0	449.8	Midpoint	1.3x	12.3%	5.9%
AN2 Therapeutics, Inc.	03/25/22	69.0	230.7	Midpoint	1.0x	2.7%	(80.0%)
Arcellx, Inc.	02/04/22	123.8	436.7	Low End	1.3x	12.0%	370.8%
Vigil Neuroscience, Inc.	01/07/22	98.0	329.0	Below	1.4x	(9.6%)	(76.1%)
Amylyx Pharmaceuticals, Inc.	01/07/22	190.0	955.8	Midpoint	1.9x	(4.9%)	(82.9%)
CinCor Pharma, Inc.(6)	01/07/22	193.6	417.9	Midpoint	1.2x	0.0%	62.5%
Vaxxinity Inc	11/11/21	78.0	1,720.2	Below	1.0x	27.3%	(94.2%)
IO Biotech, Inc.(7)	11/04/21	100.1	300.6	Low End	1.0x	11.8%	(88.2%)
Evotec SE	11/03/21	435.0	3,411.2	Below	NA	1.1%	(68.3%)
Last 30 IPO Summary Statistics:							
Mean		**$192.8**	**$719.1**		**1.3x**	**11.0%**	**16.5%**
Median		**$175.0**	**$451.3**		**1.2x**	**9.3%**	**(16.0%)**

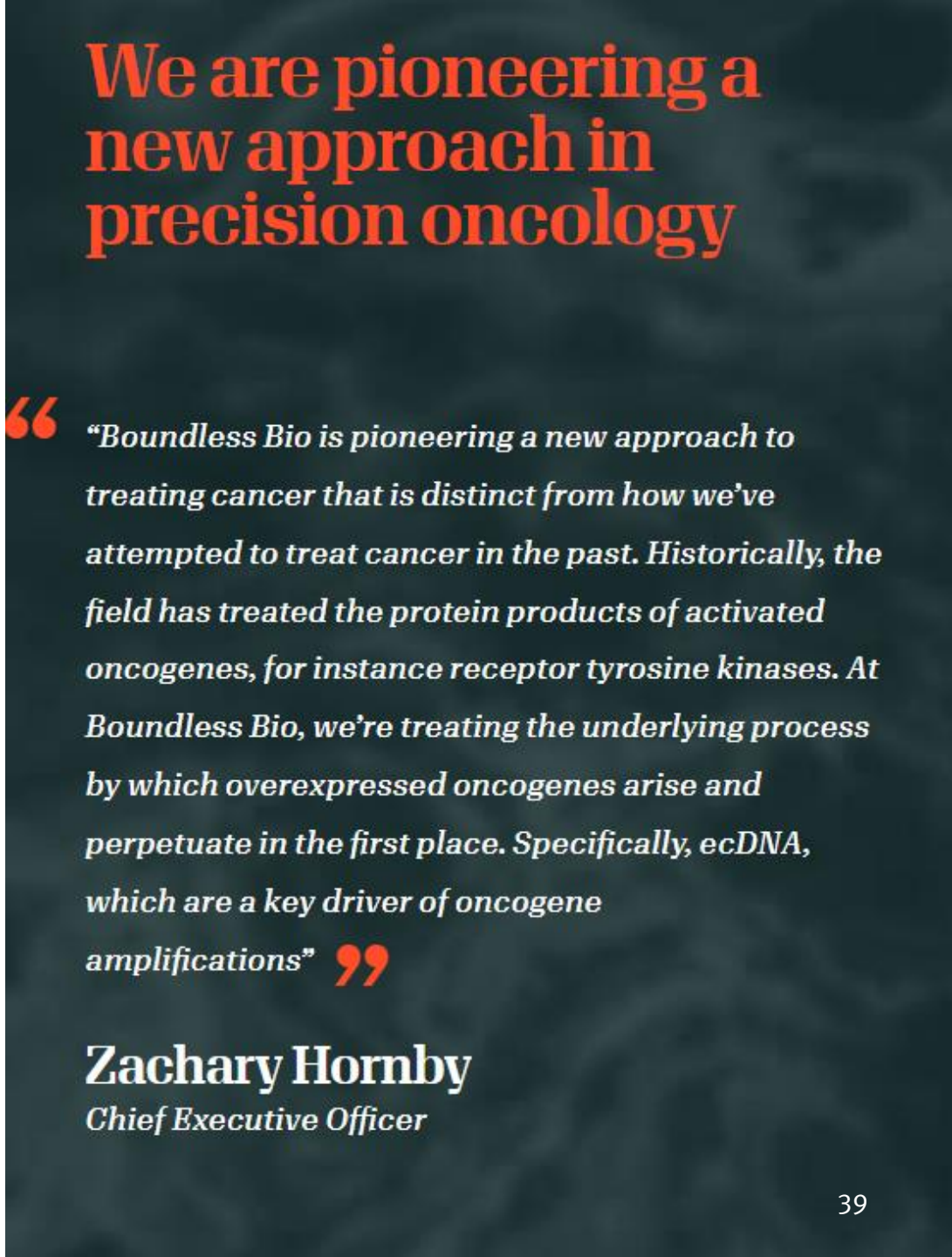
Source: Stifel Capital Markets as of March 22, 2024. Amounts raised in concurrent private placements are included as part of the IPO issuance amount. Pre-money equity values at pricing are fully diluted, accounting for options and warrants using the Treasury Stock Method. Excludes IPOs with total proceeds of less than $50.0mm or greater than $1.0bn. Note: Highlighted IPOs represent Stifel bookrun offerings.

(1) Number of deals includes re-IPOs (companies with a previous foreign listing that list on a U.S. exchange). (2) Median aftermarket performance represents current performance. (3) Includes concurrent European private placement of 1,626,040 shares of common stock. (4) Includes concurrent private placement of 5,217,371 shares of common stock. (5) Includes concurrent private placement of 400,000 shares of common stock to Chione Limited. (6) Price change offer to current utilizes $26.00, AstraZeneca's acquisition price per share to acquire CinCor, as current price. (7) Step-up is calculated based on the implied conversion ratio of the preferred stock to reflect the corporate reorganization which occurred on October 2021.

Boundless Bio Raises $100 Million in IPO Last Week

SAN DIEGO--(BUSINESS WIRE)--Mar. 27, 2024-- Boundless Bio, Inc. (Nasdaq: BOLD), a clinical stage oncology company interrogating extrachromosomal DNA (ecDNA) biology to deliver transformative therapies to patients with previously intractable oncogene amplified cancers, today announced the pricing of its initial public offering of 6,250,000 shares of its common stock at an initial public offering price of $16.00 per share. All of the shares are being offered by Boundless Bio. The gross proceeds from the offering, before deducting underwriting discounts and commissions and other offering expenses, are expected to be $100.0 million. Boundless Bio's common stock is expected to begin trading on the Nasdaq Global Select Market on March 28, 2024 under the ticker symbol "BOLD." The offering is expected to close on April 2, 2024, subject to the satisfaction of customary closing conditions. In addition, Boundless Bio has granted the underwriters a 30-day option to purchase up to an additional 937,500 shares of common stock at the initial public offering price, less underwriting discounts and commissions.

Source: https://investors.boundlessbio.com/news-releases/news-release-details/boundless-bio-announces-pricing-initial-public-offering



TALES OF A STARTUP

BOUNDLESS BIO™

Unbound By Convention, Bound To Save Lives With Boundless Bio

February 11, 2021

Developing medicines to combat the role of ecDNA in aggressive cancers, the San Diego based therapeutics company Boundless Bio has worked with UC San Diego to advance the first ecDNA-targeting therapeutics in development.

Charting a new DNA map to transform the world of cancer care, the team at Boundless Bio is out to make them cancer's weakest link, led by CEO and biotech veteran Zachary Hornby (ZH). Offering novel, life-improving options for patients with cancer, UC San Diego's and Ludwig Institute for Cancer Research's Paul Mischel, M.D. (PM), is committed to developing more effective, less toxic therapies.

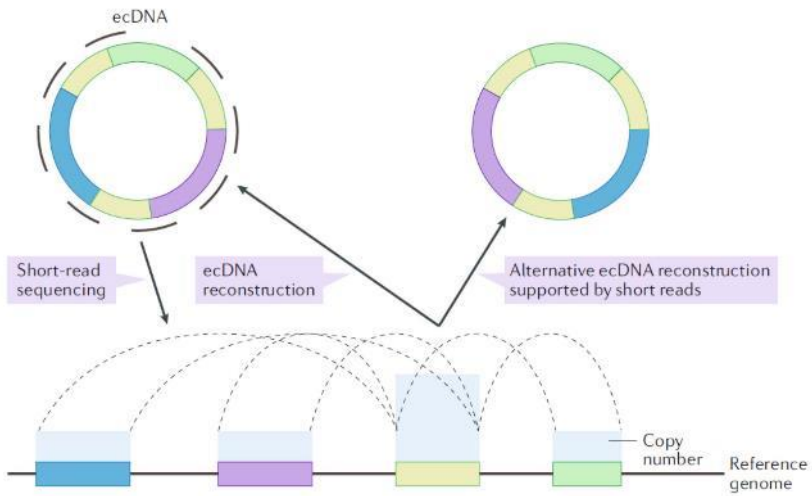
What excites you about your work?

ZH: I work with fantastic people. People who are mission driven and want to make a difference in people's lives. I love working with people so dedicated. It is not only purpose driven but intellectually stimulating. I am constantly learning and having fun strategizing about science, all with a great cause.

How do you define innovation in the 21st Century?

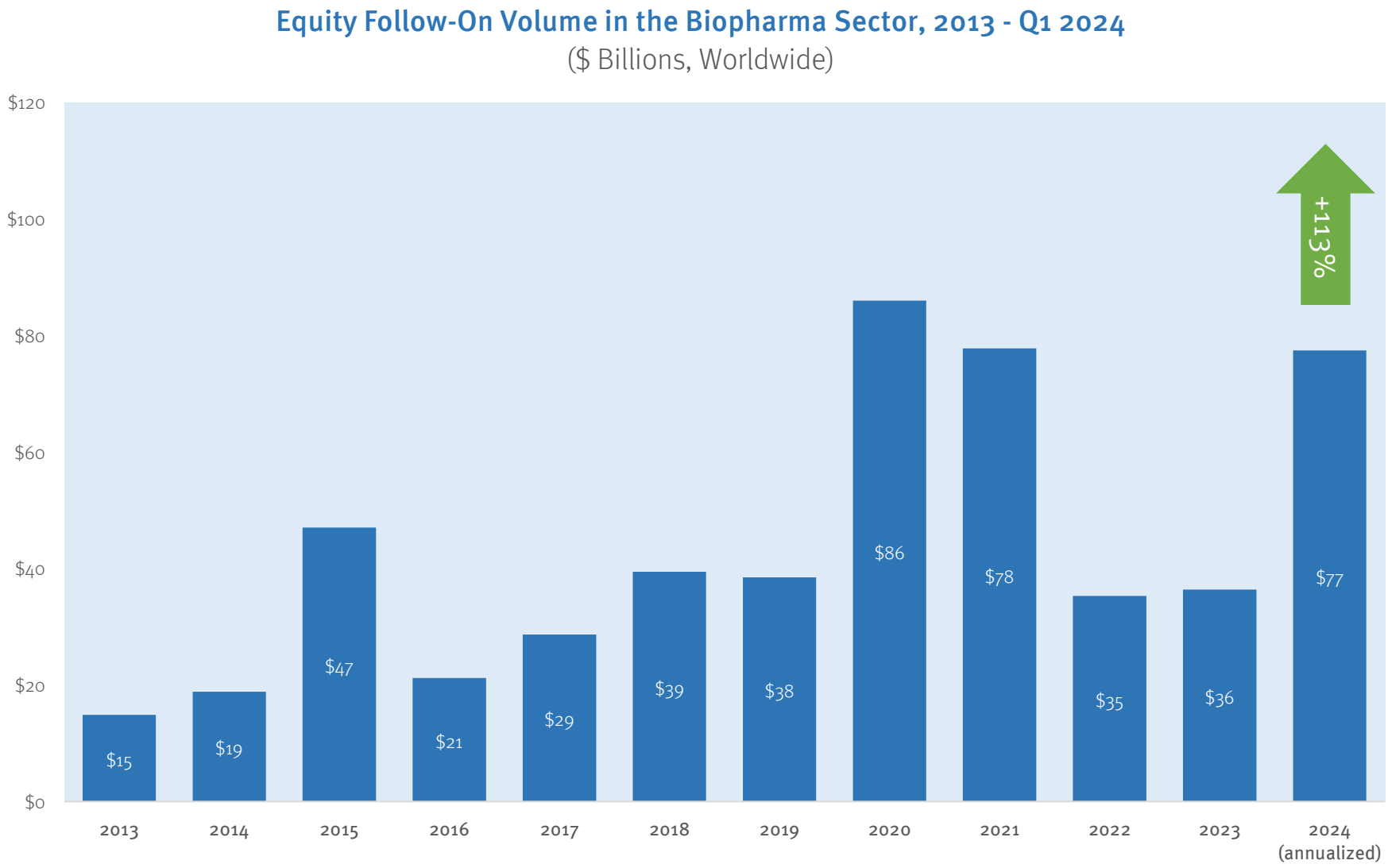
PM: Real innovation requires crossing disciplines that have existed in separate bins, that we can break apart and bridge via new knowledge spanning from scientific discovery, through drug development and precision oncology to make a difference for patients.

ZH: It is about looking at old problems in new ways, such as the observation of ecDNA. ecDNA has been known about for 50/60 years, but today's technologies are so different and evolved, allowing us an entirely new understanding of ecDNA. The field of precision medicine is vast and interdisciplinary, involving an intricate understanding of underlying cancer biology, targeted therapeutic modalities to intercept biology, and patient selection methods to optimize that intersection. The epitome of precision medicine in ensuring you have the right drug for the right patient. That's the true hallmark of innovation.



Source: https://innovation.ucsd.edu/stories/news-archives/2021/tales-of-a-startup-boundless-bio.html

Follow-on Market Pace in 2024 Up 113% Over 2023 Levels



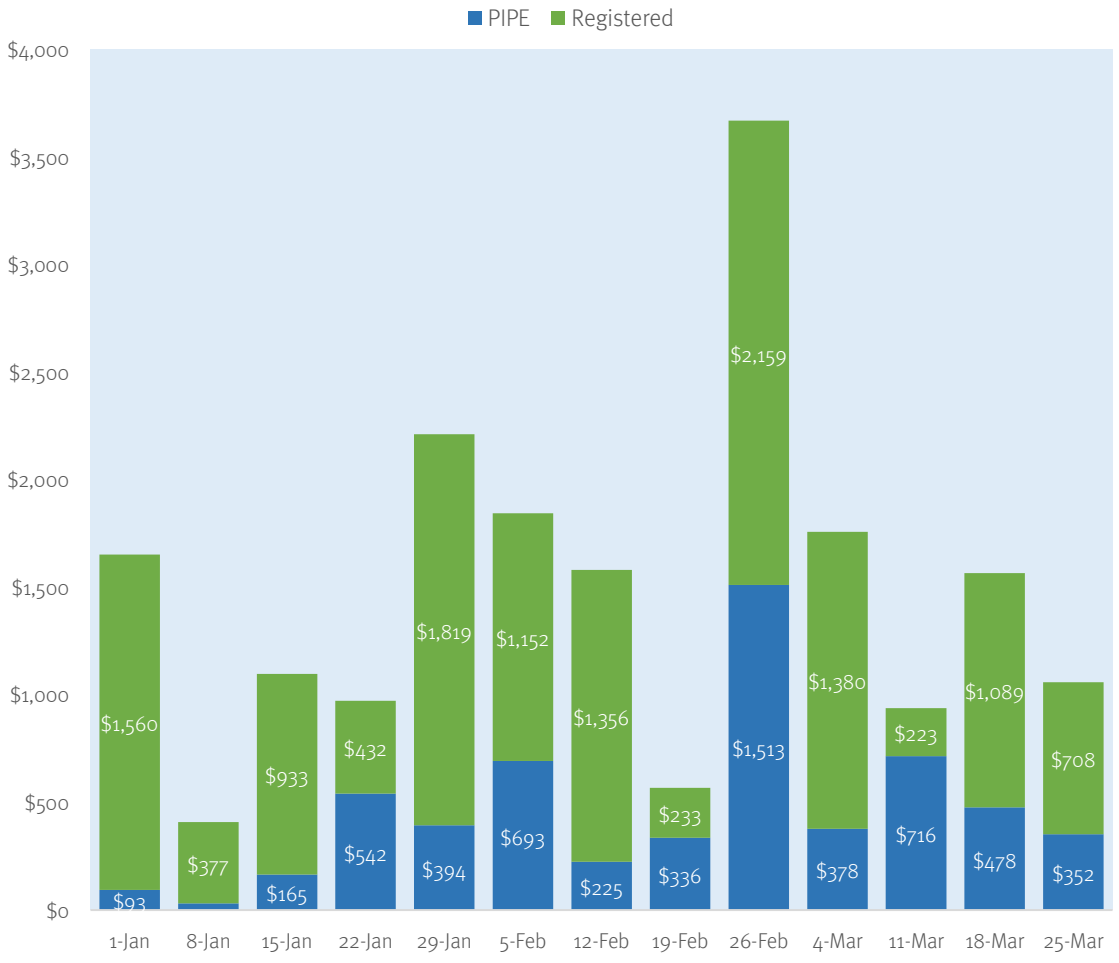
The pace of equity follow-ons in 2024 has been the same as we saw in 2021 and is close to the all-time record set at the peak of the Pandemic in 2020.

This year is shaping up to be the third strongest for equity follow-on offerings in the history of the biopharmaceutical sector.

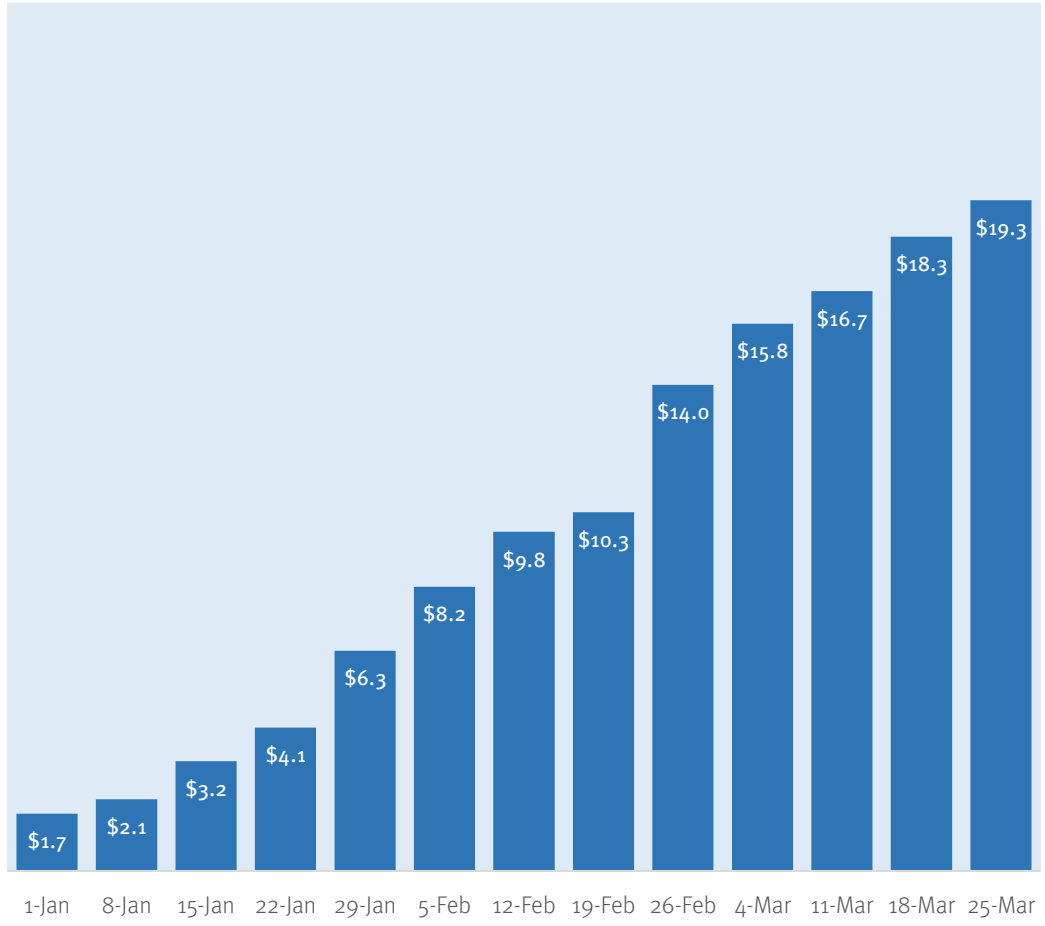
Source: CapitalIQ and Stifel research

Last Week Saw $1bn in Biopharma Equity Follow-On Activity

Weekly Biopharma Follow-On Issuance Volume, Dec 31, 2023 to Mar 28, 2024 ($ millions)



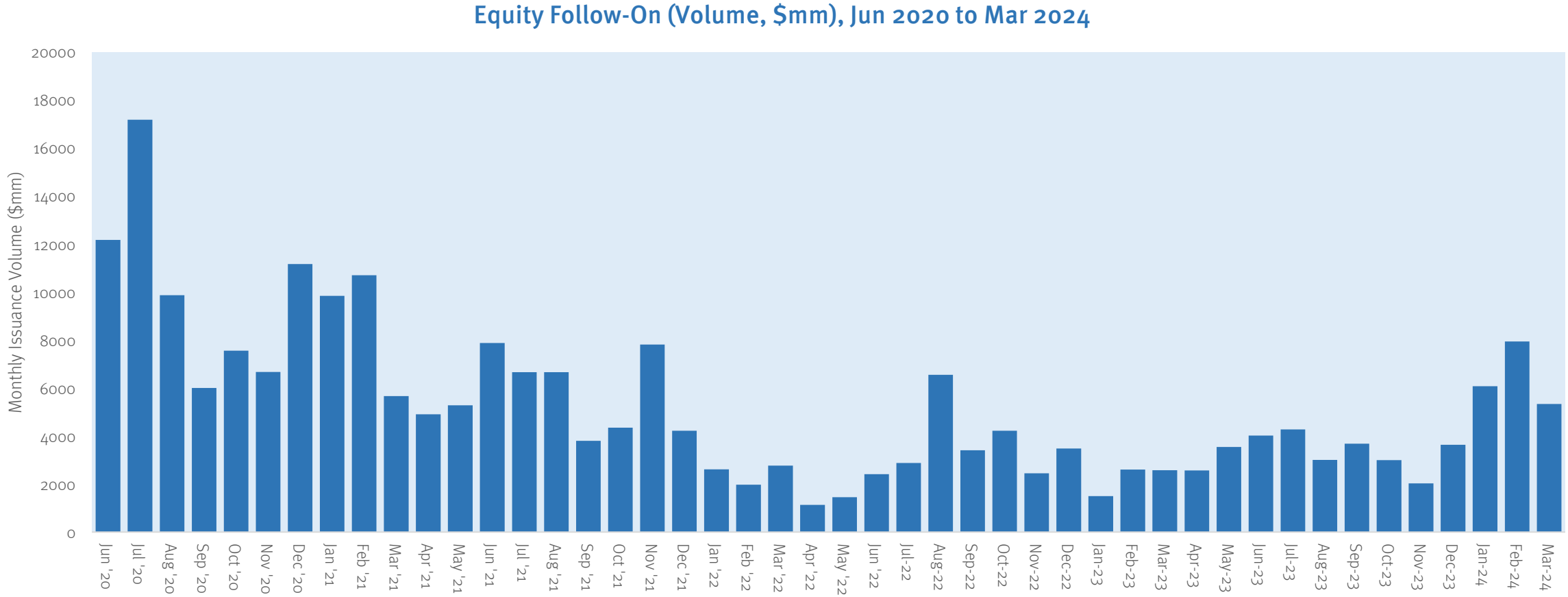
Cumulative Weekly Biopharma Follow-On Issuance Volume, Dec 31, 2023 to Mar 28, 2024 ($ billions)



Source: Data from CapitalIQ and Stifel research.

February 2024 Follow-On Volume the Highest Since February 2021

March saw the biotech market flatten out. This was accompanied by a reduction in total follow-on issuance volume. In contrast, the market was rising vigorously in February. February was one of the strongest months in the history of the follow-on market, not matched since February of 2021.

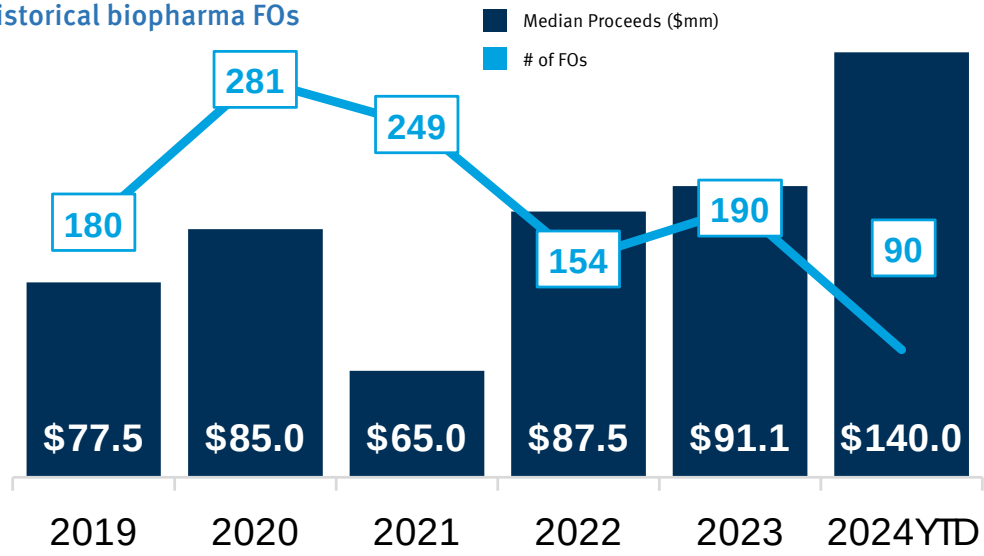


Follow-On Market Stats: Proceeds Much Higher in 2024

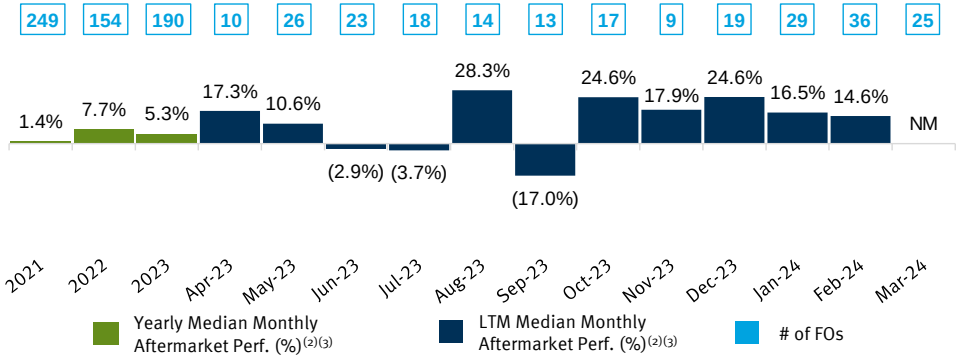
Format, Deal Sizes and Discounts in 2021 (through Mar 22, 2024)

Deal Type	# of Deals	Market Cap (mm)	Deal Size (mm)	Deal Size/ Market Cap	File to Offer	% of Deals w/ Warrants	"All-In" Discount
Marketed	11	$1,749	$300	16.7%	(7.8%)	0.0%	(7.8%)
Bought	2	$629	$86	13.7%	(12.2%)	NA	(4.4%)
CMO	28	$700	$145	18.8%	(8.9%)	3.6%	(8.9%)
RD	17	$615	$124	20.2%	0.0%	23.5%	(5.1%)
PIPE	32	$518	$114	28.2%	0.1%	6.3%	0.0%

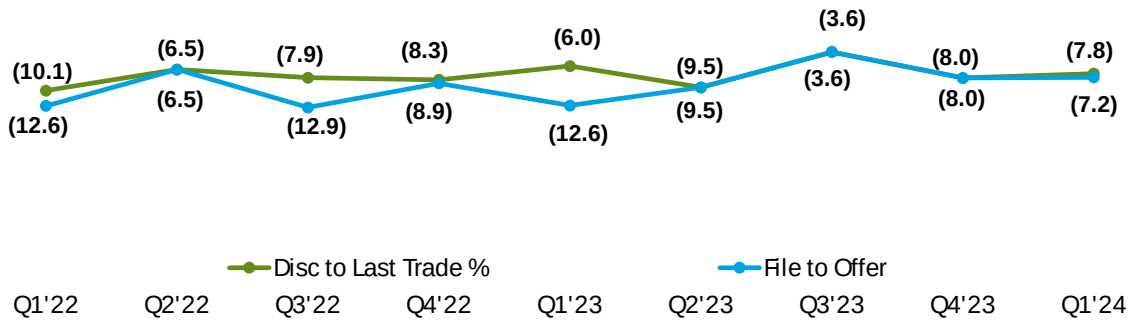
Historical biopharma FOs



Strong Aftermarket Performance in the Oct 2023 to Mar 2024 Period[1]



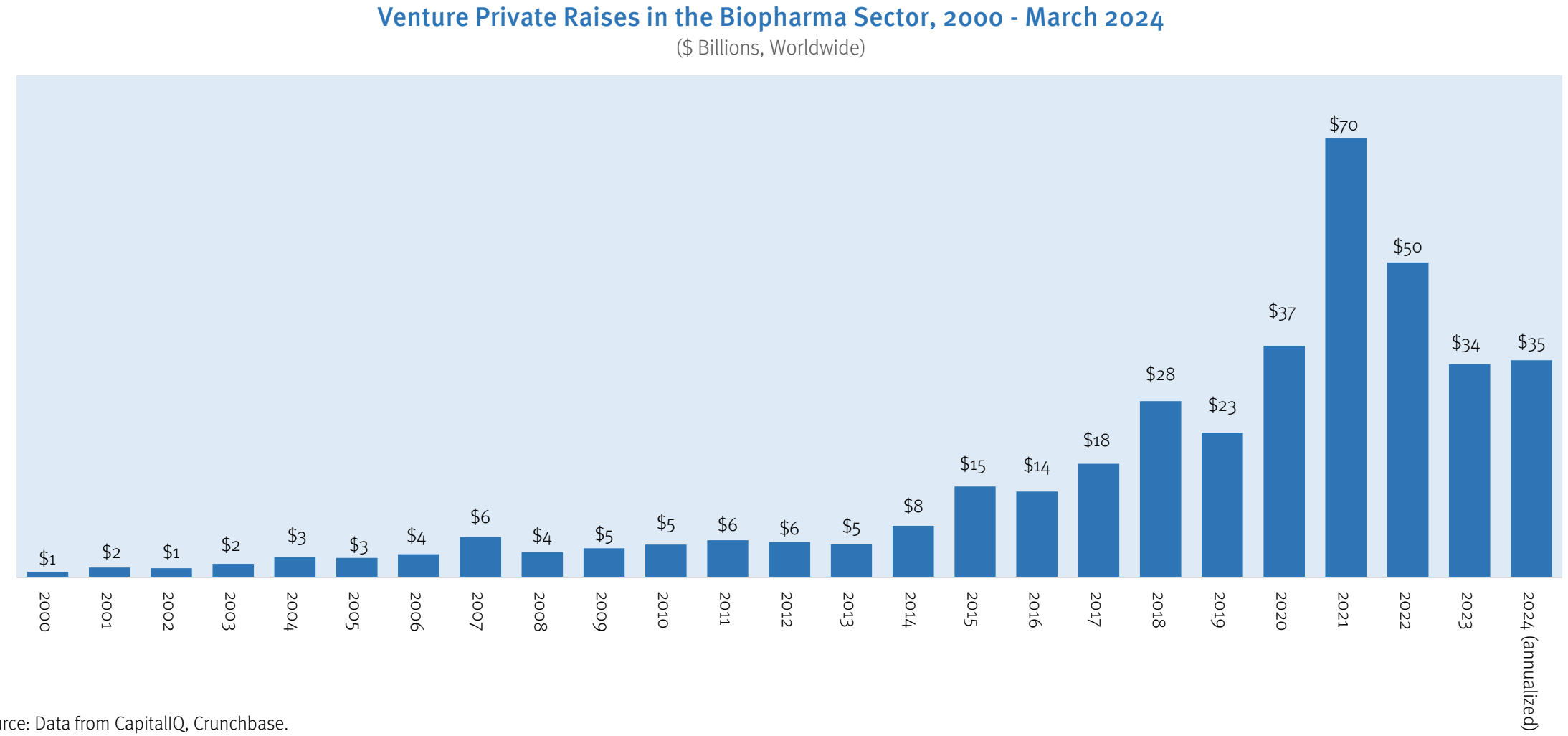
Discounts Have Remained in Line[2]



Source: FactSet and Dealogic as of March 22, 2024. Note: File to offer represents “all-in” discount for offerings with warrants. Includes marketed, bought, confidentially marketed, registered direct and PIPE offerings with proceeds of $20.0 million and greater. Only includes marketed, confidentially marketed and registered direct offerings with proceeds of $20.0 million and greater, excludes bought and PIPE offerings. Median monthly aftermarket performance represents +30 day performance.

Private Venture Equity Investments Flat in 2024 vs. 2023

Despite the strong public markets for equities, the pace of venture raises in 2024 has not increased from 2023. Venture investors remain quite restrained in their outlays this year. This is, in part, a reflection of a worsened environment for raising LP capital into venture funds.

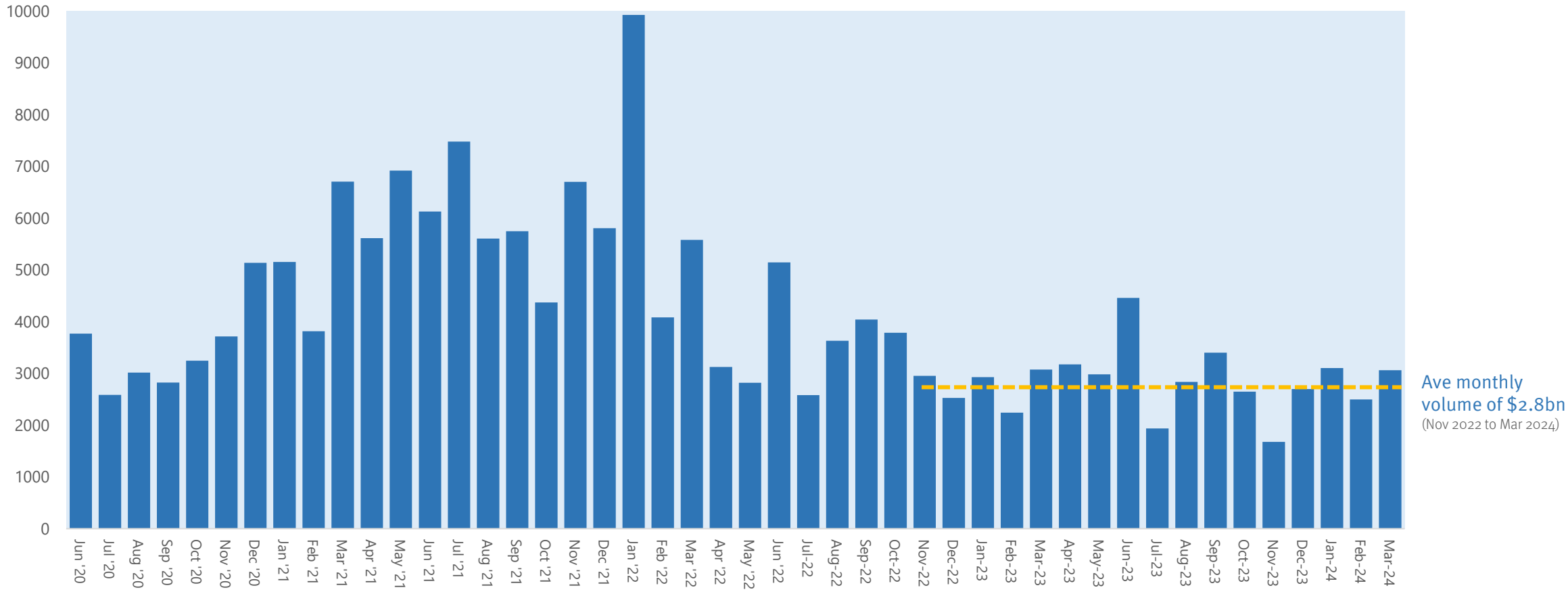


Source: Data from CapitalIQ, Crunchbase.

March 2024 Venture Privates Activity Stable from Previous Months

We saw $3 billion in venture private raises last month. This was slightly above the average issuance level of $2.8bn that has been seen for the last 17 months.

Monthly Private Equity Placement Volume ($mm), Jun 2020 to Mar 2024



Source: Data from CapitalIQ, Crunchbase.

Avenzo Therapeutics Announces $150 Million Financing To Advance Emerging Oncology Pipeline

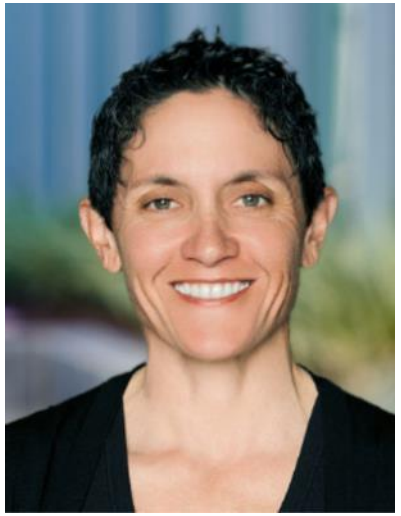
SAN DIEGO, Calif., March 26, 2024-- Avenzo Therapeutics, Inc., a clinical-stage biotechnology company developing next generation oncology therapeutics, today announced the closing of an oversubscribed $150 million Series A-1 financing. The total capital raised since the company's founding in August 2022 is $347 million. The financing round includes nine new investors and was led by New Enterprise Associates (NEA), Deep Track Capital, Sofinnova Investments, and Sands Capital, with participation from additional new investors, including INCE Capital, TF Capital, Delos Capital, and Quan Capital. In conjunction with the announcement, Jakob Dupont, M.D., Executive Partner, Private Equity, Sofinnova Investments, will join the Avenzo Board of Directors.

Proceeds from the financing will be used to advance Avenzo's emerging oncology pipeline which is led by AVZO-021, a potentially best-in-class cyclin-dependent kinase 2 (CDK2) selective inhibitor being studied in an ongoing U.S.-based Phase 1 clinical study for the treatment of HR+/HER2- metastatic breast cancer and other advanced solid tumors.

"We see significant opportunity with AVZO-021 and this team to advance potential best-in-class therapies for some of the most pressing needs in oncology today," said Jakob Dupont, M.D., Executive Partner, Private Equity, Sofinnova Investments. "I have been impressed by the progress Avenzo has made to date and look forward to supporting Athena and the Board as they advance their emerging oncology pipeline and grow their promising company."

Dr. Dupont brings more than two decades of experience in the field of oncology and other therapeutic areas, in developing therapies and programs dedicated to addressing high unmet medical needs. Prior to joining Sofinnova Investments, Dr. Dupont served in key leadership roles at Atara Biotherapeutics, Gossamer Bio, Genentech/Roche and OncoMed Pharmaceuticals, Inc.

Source: https://avenzotx.com/press-releases/avenzo-therapeutics-announces-150-million-oversubscribed-financing-to-advance-emerging-oncology-pipeline/

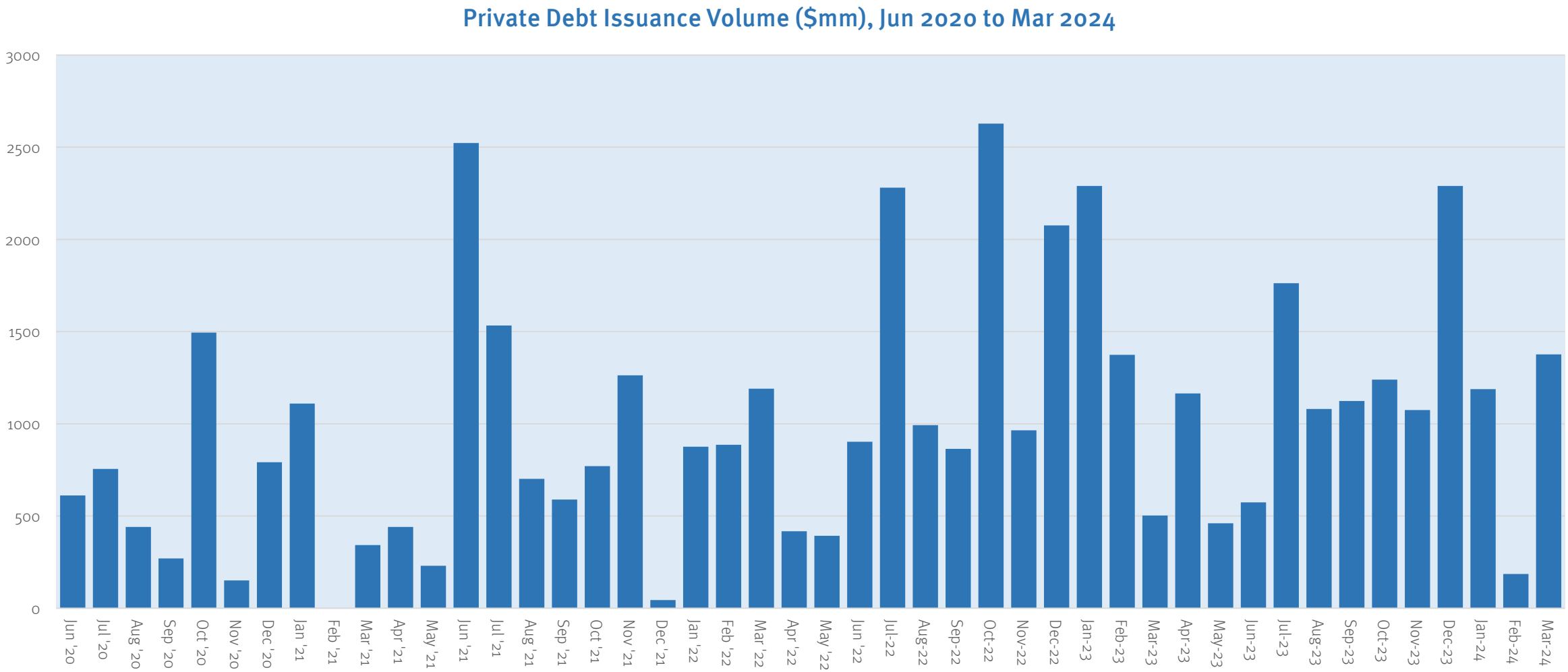


"The team at Avenzo has made great progress over the past 18 months since formation on our mission to advance the next generation of oncology therapies for patients. With the support of our new and existing investors, including OrbiMed, Foresite Capital, SR One, Lilly Asia Ventures and Surveyor Capital (a Citadel company), we are in a strong position to advance our potentially best-in-class CDK2 inhibitor, AVZO-021, expand our pipeline with additional assets, and continue to grow our team."

Athena Countouriotis
Chief Executive Officer
Avenzo Therapeutics

Biopharma Private Debt Placement Steady in March 2024

The debt privates market saw a $750 million project financing completed by Moderna with Blackstone last week.



Source: Data from CapitalIQ, Crunchbase, Stifel research.

Moderna Raises Up to $750 Million from Blackstone to Support its Influenza Vaccine Program

NEW YORK – Blackstone (NYSE:BX) announced today a new collaboration with Moderna, Inc. (NASDAQ: MRNA, "Moderna") through a development and commercialization funding agreement where funds managed by Blackstone Life Sciences ("Blackstone") will provide up to $750 million to fund Moderna's influenza ("flu") program.

"Moderna has demonstrated a remarkable ability to impact human health through mRNA vaccines targeting respiratory illnesses. This landmark collaboration is another example of our long-standing strategy to partner with the world's leading life science companies to advance their critical path vaccines, medicines and medical technologies to patients," said Nicholas Galakatos, Ph.D., Global Head of Blackstone Life Sciences.

This new collaboration continues Blackstone Life Sciences' work and support for many of the world's leading and most innovative biopharmaceutical and medical technology companies. Blackstone seeks to provide customized financing solutions for companies across therapeutic areas to support mission critical scientific innovation and advance important products to patients.

About the Transaction

Under the terms of the agreement, funds managed by Blackstone Life Sciences will provide up to $750 million to fund Moderna's flu program. If successful, BXLS will be eligible to receive milestones and royalties on resultant flu products. Moderna will recognize the funding as a reduction in research and development expenses and will retain full rights and control of the Company's influenza program.

Source: https://www.blackstone.com/news/press/blackstone-life-sciences-announces-collaboration-to-support-modernas-influenza-program/

moderna

"Moderna is advancing a broad and diverse pipeline at a pace not seen before in our industry. Our goal is to launch multiple vaccine products in the next few years and deliver the greatest possible impact to people through mRNA medicines. Achieving this ambition requires substantial investment in late-stage studies and we are excited to welcome Blackstone and their innovative financing model."

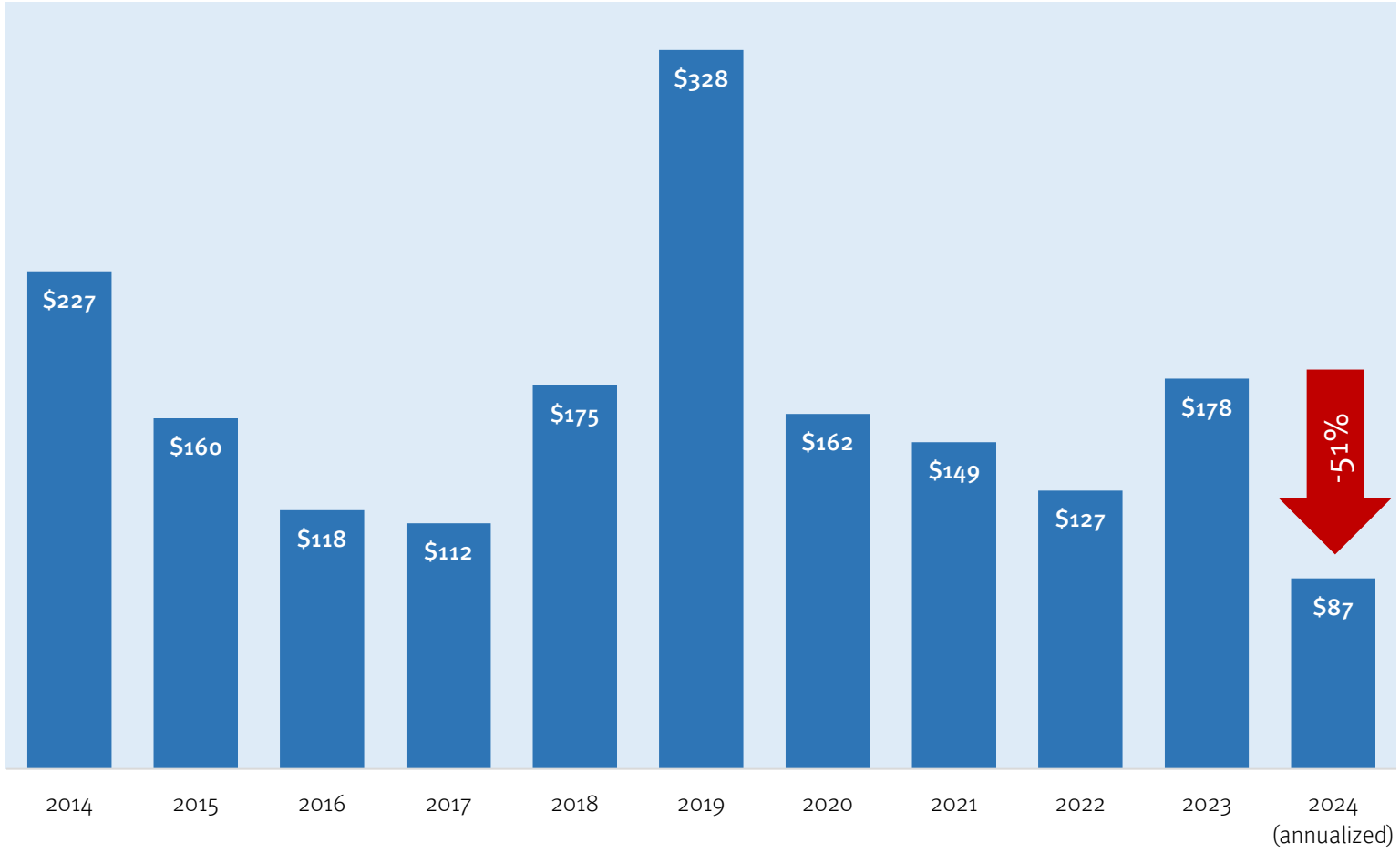
Stéphane Bancel
Chief Executive Officer
Moderna

Deals Update

Q1 M&A Volume Down Substantially from 2023 Level

M&A Volume in the Biopharma Sector, 2014 - Q1 2024

($ Billions, Worldwide)



Source: CapitalIQ and Stifel research

With $21.8 billion in deals in Q1 2024, we are on track for the lightest M&A volume year in a decade. There simply have not been transactions of the scale seen in 2023.

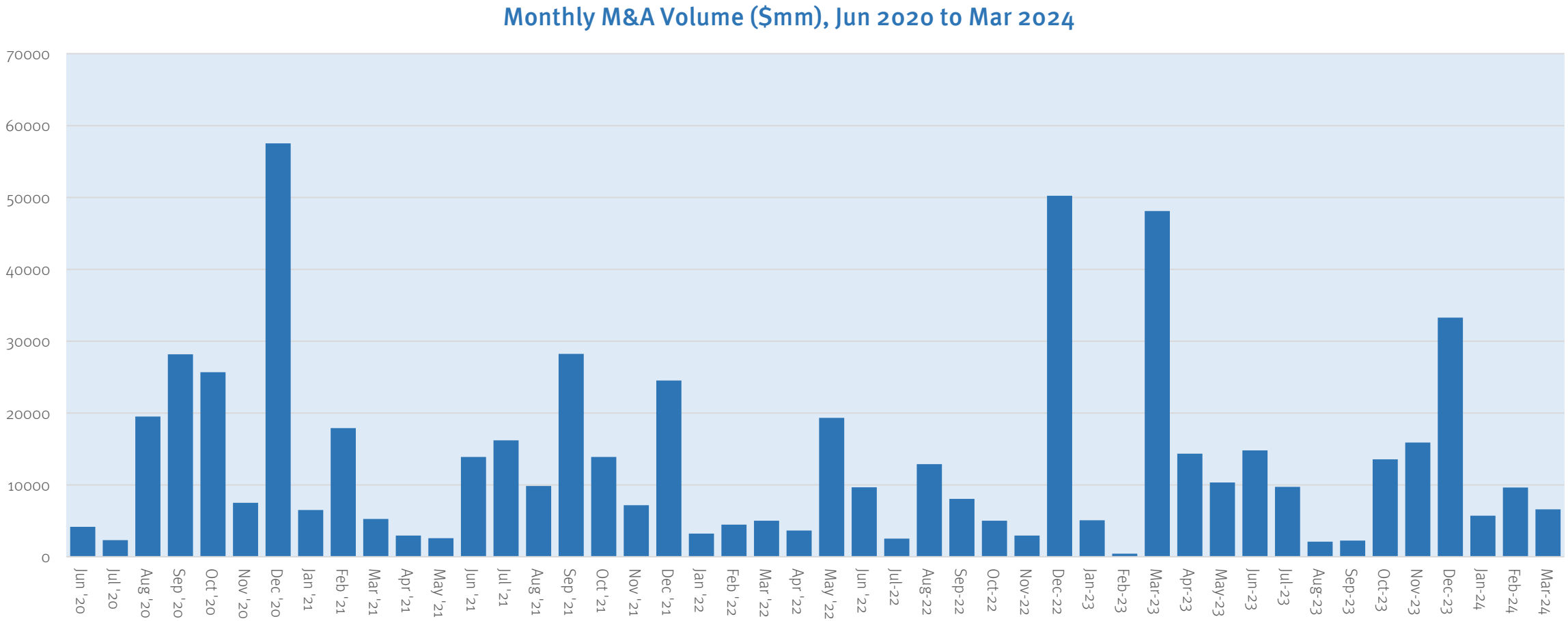
The largest M&A transaction announced in Q1 2024 was Gilead's $4.2 billion purchase of CymaBay. The next largest was Novartis' $2.8 billion purchase of Morphosys. By contrast, March of last year saw Pfizer announce its acquisition of Seagen for $43 billion.

Recent history would suggest that Q1 2024 was anomalous, and we expect to see higher volumes emerge this year.

On the cautionary front, it's an election year in the U.S. and large pharma most likely think this is not the time to give the FTC anti-pharma ammo going into November. Further, pharmas we talk to indicate that biotechs have not adjusted down premia asks despite the market recovery.

Last Month Saw $6.4 Billion in M&A Volume

The largest deals last month was AZ's acquisition of Fusion for $2 billion upfront. The largest deals last week were Novo Nordisk's acquisition of Cardior and AbbVie's acquisition of Landos Biopharma.



Source: S&P, CapitalIQ

Novo Nordisk To Acquire Cardior

Bagsværd, Denmark, and Hannover, Germany, 25 March, 2024

Novo Nordisk and Cardior Pharmaceuticals today announced that Novo Nordisk has agreed to acquire Cardior for up to 1.025 billion Euros, including an upfront payment and additional payments if certain development and commercial milestones are achieved.

Cardior is a leader in the discovery and development of therapies that target RNA as a means to prevent, repair and reverse diseases of the heart. The company's therapeutic approach targets distinctive non-coding RNAs as a platform for addressing root causes of cardiac dysfunctions with an aim to achieve lasting patient impact. The agreement includes Cardior's lead compound CDR132L, currently in phase 2 clinical development for the treatment of heart failure.

The acquisition is an important step forward in Novo Nordisk's strategy to establish a presence in cardiovascular disease. Novo Nordisk aims to build a focused, impactful portfolio of therapies through internal and external innovation to address the significant unmet needs that still exist within cardiovascular disease, the most common cause of death globally.

"By welcoming Cardior as a part of Novo Nordisk, we will strengthen our pipeline of projects in cardiovascular disease where we already have ongoing programmes across all phases of clinical development," said Martin Holst Lange, executive vice president for Development at Novo Nordisk. "We have been impressed by the scientific work carried out by the Cardior team, especially on CDR132L, which has a distinctive mode of action and potential to become a first-in-class therapy designed to halt or partially reverse the course of disease for people living with heart failure."

CDR132L is designed to halt and partially reverse cellular pathology by selectively blocking abnormal levels of the microRNA molecule miR-132, potentially leading to long-lasting improvement in heart function. In a phase 1b trial published in the European Heart Journal1, CDR132L was reported to be safe and well tolerated and the results suggested cardiac functional improvements in people with heart failure compared to placebo. CDR132L is currently being investigated in the phase 2 trial HF-REVERT in 280 people with heart failure with reduced ejection fraction (HFrEF) who have previously suffered a heart attack (myocardial infarction). The first patient was dosed in the HF-REVERT trial in July 2022.

Novo Nordisk plans to initiate a second phase 2 trial that will investigate CDR132L in a chronic heart failure population with cardiac hypertrophy – a condition that causes the walls of the heart muscle to become thick and stiff, affecting the heart's ability to pump blood.

The transaction will not impact Novo Nordisk's previously communicated operating profit outlook for 2024 or the ongoing share buy-back programme. Novo Nordisk will fund the acquisition from financial reserves.

Source: https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=167038

‘The Heart is Back,’ Says Cardior CEO — Novo’s $1B+ Deal Rejuvenates a Stale Field

Michael Gibney, *PharmaVoice*, Mar 28, 2024 (excerpt)

When the FDA this month approved Novo Nordisk’s weight loss drug Wegovy to also reduce the risk of cardiovascular death, the Danish biotech giant had already made a pipeline commitment to developing drugs in the space.

The approval, paired with the news this week that the company would purchase German cardiovascular specialist Cardior Pharmaceuticals for north of $1 billion, made the signal clear: “The heart is back,” Cardior CEO and co-founder Claudia Ulbrich told PharmaVoice. “It’s back for venture capital, and it’s back for the pharma industry.”

As revenue from Ozempic and Wegovy sales pour in — with no end in sight — Novo Nordisk is in the position to bolster its pipeline further, and the deal to buy Cardior, whose lead candidate CDR132L is a phase 2 RNA-based treatment that cuts to the core of heart failure, serves that purpose.

Cardior is a 2016 spinout from Germany’s Hannover Medical School, building on the work of Professor Thomas Thum, now the company’s co-founder and chief scientific and medical officer. Different from the mRNA technology used in vaccines, Cardior’s approach makes use of non-coding RNAs that aren’t translated into proteins, but regulate processes like cardiovascular function, Ulbrich said. Specifically, CDR132L is an antisense oligonucleotide that binds to genetic material to alter behavior.

Claudia Ulbrich, CEO, Cardior

Source: https://www.pharmavoice.com/news/novo-nordisk-cardior-cardiovascular-deal-acquisition-billion-weight-loss-wegovy/711572/

AbbVie to Acquire Landos Biopharma for $137.5 Million in Cash Plus a CVR

NORTH CHICAGO, Ill. and NEW YORK, March 25, 2024

AbbVie Inc. and Landos Biopharma, Inc. today announced a definitive agreement under which AbbVie will acquire Landos, a clinical stage biopharmaceutical company focused on the development of novel, oral therapeutics for patients with autoimmune diseases. Landos' lead investigational asset is NX-13, a first-in-class, oral NLRX1 agonist (a member of the NOD-like receptor family) with a bimodal mechanism of action (MOA), which is anti-inflammatory and facilitates epithelial repair.

"With this acquisition, we aim to advance the clinical development of NX-13, a differentiated, first-in-class, oral asset with the potential to make a difference in the lives of people living with ulcerative colitis and Crohn's disease," said Roopal Thakkar, M.D., senior vice president, chief medical officer, global therapeutics, AbbVie.

"This announcement is a testament to Landos' talented team and their commitment to our mission of creating oral treatments that can address a therapeutic gap," said Gregory Oakes, president and chief executive officer, Landos. "NX-13 and its bimodal MOA have the potential to provide a novel approach to the treatment of ulcerative colitis and Crohn's disease. With AbbVie's therapeutic area leadership and expertise in global development, they are the right company to further advance NX-13."

NLRX1 regulates immunometabolism and inflammation, and its activation impacts multiple mechanisms of inflammatory bowel disease (IBD) pathogenesis. The randomized controlled Phase 2 NEXUS clinical trial evaluating NX-13 in UC is currently enrolling patients in the United States and Europe (NCT05785715).

Under the terms of the agreement, AbbVie will acquire Landos at a price of $20.42 per share in cash upon closing, or approximately $137.5 million in the aggregate, plus one non-tradable contingent value right per share with a value of up to $11.14 per share, or approximately an additional $75 million in the aggregate, subject to the achievement of a clinical development milestone. The proposed transaction is expected to close in the second calendar quarter of 2024, subject to customary closing conditions, including approval by Landos' stockholders.

About the NEXUS Study

NEXUS is a Phase 2 proof-of-concept clinical trial evaluating NX-13 in patients with moderate to severe UC. NEXUS is a randomized, multicenter, double-blind, placebo-controlled, multiple dose, 12-week induction study evaluating 80 patients with moderate to severe UC with a long-term extension (LTE) period. All subjects will be randomized to receive either 250 mg or 750 mg immediate release NX-13, or placebo. The primary objective of the trial will be to evaluate the clinical efficacy, safety and pharmacokinetics of oral NX-13 versus placebo (NCT05785715 ClinicalTrials.gov).

Source: https://news.abbvie.com/2024-03-25-AbbVie-to-Acquire-Landos-Biopharma,-Further-Strengthening-its-Portfolio-in-Inflammatory-and-Autoimmune-Diseases

Nuvation Bio to Acquire AnHeart Therapeutics for $107 Million in Stock

March 25, 2024

NEW YORK--(BUSINESS WIRE)-- Nuvation Bio Inc. (NYSE: NUVB), a biopharmaceutical company tackling some of the greatest unmet needs in oncology by developing differentiated and novel therapeutic candidates, and AnHeart Therapeutics Ltd. (AnHeart), a global clinical-stage biopharmaceutical company developing novel precision therapies for people with cancer, today announced that the companies have entered into a definitive agreement for Nuvation Bio to acquire AnHeart in an all-stock transaction (the Acquisition). Immediately following the closing of the Acquisition, the former shareholders of AnHeart will own approximately 33% and the current stockholders of Nuvation Bio will own approximately 67% of Nuvation Bio on a fully diluted basis. The Acquisition, which has been approved by the board of directors of each company and is subject to approval by AnHeart's shareholders and other customary closing conditions, will position Nuvation Bio as a late-stage global oncology company with multiple programs in clinical development. The Acquisition is expected to close in the second quarter of 2024.

"This transaction represents a significant milestone for our company and reflects Nuvation Bio's continued commitment to developing therapies for patients with the most difficult-to-treat cancers," said David Hung, M.D., Founder, President, and Chief Executive Officer of Nuvation Bio. "AnHeart's lead asset, taletrectinib, which will become our lead asset as it completes two pivotal studies, is a differentiated, next-generation ROS1 inhibitor with a potentially best-in-class profile that may overcome the significant limitations of existing therapies. We are impressed by what the AnHeart team has done to develop this asset and intend to build on the progress made to date."

Dr. Hung added, "Nuvation Bio is well capitalized, and this all-stock transaction maintains our robust cash balance and removes any need for near-term financing to develop both new assets and our current pipeline. With our combined talented teams and resources, we will continue to focus on executing the development strategy for our differentiated pipeline. We expect this deal will bring Nuvation Bio much closer to realizing our goal of delivering novel cancer therapies to patients, and we look forward to this exciting next chapter together with the AnHeart team."

"AnHeart, named for our deep sense of service to patients, has worked tirelessly over the past five years to advance our pipeline of next-generation precision oncology medicines. We are excited to continue our mission as part of Nuvation Bio given their shared vision to improve the lives of people with cancer," said Junyuan Jerry Wang, Ph.D., Co-Founder and Chief Executive Officer of AnHeart. "We believe the pipeline and financial strength of the combined company have the potential to create a market leader, and we look forward to working with David and the Nuvation Bio team to bring new cancer therapies to patients in need of better options."

Source: https://www.businesswire.com/news/home/20240325982081/en/Nuvation-Bio-to-Acquire-AnHeart-Therapeutics-in-All-Stock-Transaction

Other M&A and Licensing Deals Last Week

March 28, 2024

Avalo Therapeutics acquired AlmataBio, which has an anti-IL-1β mAb candidate for treatment of hidradenitis suppurativa. Avalo is planning a Phase II trial for the Almata candidate, now known as AVTX-009 in hidradenitis suppurativa. Concurrent with the acquisition, Avalo announced a private placement $185 million structured with an upfront investment of $115.6 million and an additional $69.4 million warrant. Shares of Avalo surged on the announcement giving Avalo an implied market cap of over $750 million at market close on Thursday (assuming exercise of the warrant).

Stifel was pleased to advise Avalo on its restart transaction with Almata.

March 26, 2024

Gilead Sciences is licensing Xilio Therapeutics' XTX301, a tumor-activated IL-12, and XTX101, a tumor-activated, Fc-enhanced CTLA-4 inhibitor, for $43.5 million upfront, including $30 million in cash and a $13.5 million equity investment in Xilio. Future contingent payments worth as much as $604 million include milestone payments, additional equity investments and the option for Gilead to buy the XTX301 development and commercialization program outright for $75 million.

March 26, 2024

Juvisé Pharmaceuticals has purchased the global commercial rights outside the U.S. and Canada to Ponvory (ponesimod) from Johnson & Johnson's Actelion Pharmaceuticals. The multiple sclerosis treatment is Juvisé's first patent-protected compound. Vanda Pharmaceuticals bought the U.S. and Canadian rights to the drug in December.

Source: https://www.biospace.com/article/biospace-mergers-and-acquisitions-tracker

Gamida Taken Private by Highbridge in Restructuring Deal

Tyler Patchen, *BioSpace*, March 29, 2024 (excerpt)

Despite having an FDA-approved product, Gamida Cell is entering into a restructuring agreement in which it will become a private company under the ownership of Highbridge Capital Management amid financial struggles, the company announced Wednesday.

Under the agreement, Gamida Cell will become a private company wholly owned by Highbridge Capital Management—the biotech's principal lender. The move is designed to give the company some long-term runway and support the commercialization of Omisirge, an FDA-approved nicotinamide modified allogeneic hematopoietic progenitor cell therapy. This comes after the biotech announced in January that it was seeking "strategic alternatives" and was focused on an asset sale, merger, or other deal.

"In March 2023, Gamida Cell embarked on an extensive strategic process to address its capital structure and liquidity constraints by partnering Omisirge with a third party," Gamida Cell CEO Abbey Jenkins said in Wednesday's statement. "Unfortunately, that process did not yield any actionable alternatives. This restructuring will enable Gamida Cell to remain a going concern. It will support our ongoing efforts to make Omisirge available to more transplant centers and their patients as a potentially lifesaving donor source option."

The terms of the restructuring will see Highbridge convert $75 million of its existing unsecured convertible senior note into equity for Gamida Cell. The biotech will also get $30 million of new capital from Highbridge when the restructuring goes into effect.

The biotech will now be off the stock market and wholly owned by Highbridge, with all ordinary shares expected to be canceled. The reorganized Gamida Cell will also issue contingent value rights with a maximum value of $27.5 million to shareholders.

Gamida Cell's main product, Omisirge, was approved by the FDA in April 2023 after a lengthy regulatory road and is indicated for patients who are scheduled to undergo umbilical cord blood transplantation after chemotherapy or radiotherapy. However, the therapy does come with a boxed warning for potentially fatal conditions such as infusion reactions, graft failure, engraftment syndrome, and graft-versus-host disease.

Source: https://www.biospace.com/article/gamida-restructures-under-ownership-of-highbridge-capital-management/

M&A Gathers Steam for Biotech Startups

Brian Gormley, *Wall Street Journal*, March 26, 2024 (excerpt)

Mergers and acquisitions of venture-backed drug developers are starting to rebound following a relatively slow period in 2023, brightening the outlook for venture capitalists seeking to cash out of biotechnology investments.

On Monday, venture-backed biotech startup Cardior Pharmaceuticals agreed to be acquired by drugmaker Novo Nordisk in a deal worth more than €1.02 billion ($1.11 billion) in upfront and success-based payments. The companies expect the transaction to close in the second quarter.

AnHeart Therapeutics also disclosed merger plans Monday. The venture-backed biotech said it would merge with publicly traded drugmaker Nuvation Bio. The all-stock deal is expected to close next quarter.

From the start of the year through March 18, four private venture-backed biotech companies globally closed merger deals in which at least $75 million was paid up front, according to Silicon Valley Bank. That compares with two during the same period of 2023.

Dealmaking had been tepid the previous two years, with 12 biotech startups acquired in 2023 and nine in 2022, down from 15 in 2021 and 20 in 2020, according to SVB.

Earlier this month drugmaker AstraZeneca agreed to buy venture-backed Amolyt Pharma, which moved a drug for a rare disease into Phase 3 clinical studies, for a total consideration of up to $1.05 billion.

Top drugmakers need new medicines to replace ones losing patent protections in coming years, and much of their innovation is coming from the biotech industry, said Sofia Ioannidou, a partner with Amolyt investor Andera Partners.

Large drugmakers aren't just acquiring biotechs with drugs in late-stage clinical trials, said Antoine Papiernik, chairman and managing partner of venture investor Sofinnova Partners, which also backed Amolyt.

Drugmaker Eli Lilly in October struck a deal to acquire Mablink Bioscience, a preclinical-stage biotech startup in Sofinnova's portfolio.

Pharmaceutical companies are buying at the bookends, acquiring later-stage products that could help them in the near term and earlier-stage drugs to build for the future, Papiernik said.

Source: https://www.wsj.com/articles/m-a-gathers-steam-for-biotech-startups-32a71d59

Industry News

FDA Approves Merck Lung Disease Drug Acquired in $11B Deal

Jonathan Gardner, *Biopharma Dive*, Mar 26, 2024 (excerpt)

The Food and Drug Administration on Tuesday approved a new Merck & Co. drug to treat pulmonary arterial hypertension. Called Winrevair, the drug is the first treatment that targets the underlying cause of the lung condition, which typically leads to death within a decade of diagnosis.

The FDA's approval was based on clinical trial data showing Winrevair improved exercise duration and quality of life, as well as delayed death or worsening of the disease.

The shot, known scientifically as sotatercept, blocks proteins that contribute to the thickening of blood vessel walls in the lung and lead to rising blood pressure, an overworked heart and symptoms like shortness of breath, fatigue and chest pain. It's administered every three weeks.

"Sotatercept is a paradigm shift and a huge step forward in the treatment of PAH," said Ioana Preston, a study investigator and director of the pulmonary hypertension center at Tufts Medicine, in an interview.

"I've had some amazing stories from a few of the patients who I enrolled who went from really impaired and short of breath and very close to being on ... rescue therapy, to getting off oxygen and going back to their jobs, and maintaining the improvement for more than a year," Preston said.

Source: https://www.biopharmadive.com/news/merck-winrevair-fda-approval-pah-pulmonary-arterial-hypertension/711149/

Merck's $11.5 Billion Bet on Its Next Big Drug Finally Arrives

Peter Loftus, *Wall Street Journal*, Mar 26, 2024 (excerpt)

Merck is making a big bet that its new drug, approved Tuesday in the U.S. for a potentially fatal lung disease, will take the company a long way toward heading off a massive revenue decline later this decade.

The drug, which will sell under the name Winrevair, treats a condition called pulmonary arterial hypertension that affects nearly 40,000 people in the U.S. In 2021, Merck paid $11.5 billion for the company developing the medicine. Some analysts estimate sales as high as $7.5 billion a year.

We see this as a multibillion-dollar potential opportunity for the company," Merck Chief Executive Rob Davis said in an interview. "Over time we think we can move into earlier lines of therapy and potentially into much broader patient populations."

Davis said progress in Merck's research pipeline would help make the Keytruda loss of exclusivity "more of a hill than a cliff. And our confidence that we will be able to grow beyond that is high."

In a Phase 3 study, a sotatercept injection every three weeks significantly improved volunteers' exercise capacity—measured by distance walked in six minutes—and extended the time until either death or disease progression, compared with a placebo.

"It's a big breakthrough," said Dr. Jessica Huston, a cardiologist at Ascension Saint Thomas Heart in Nashville, Tenn., who enrolled patients in the Merck-funded study. "It feels like this drug is finally something different than we've been doing all along, and is actually disease modifying."

The drug was associated with side effects including bleeding and the formation of small blood vessels on the skin in some patients.

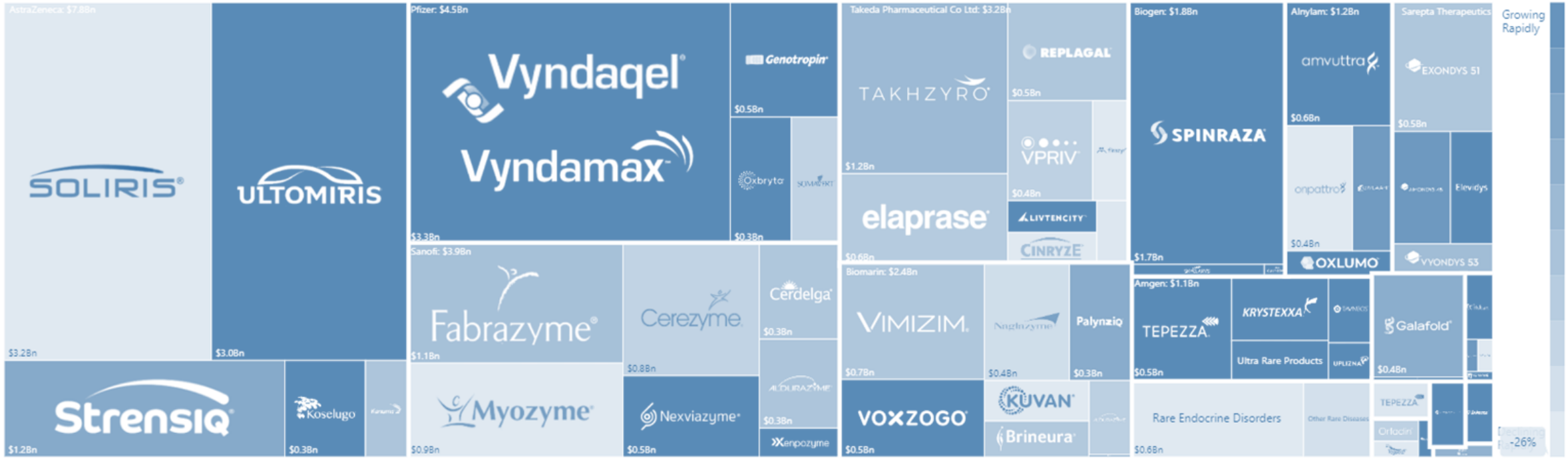
Rob Davis
Chief Executive Officer, Merck

Source: https://www.wsj.com/health/pharma/merck-new-drug-winrevair-pulmonary-hypertension-db2c19a3

Rare Disease Drugs Sold $28 Billion in 2023

Rare Diseases Market Map, 2023

Includes Branded Rx Drugs Only by Revenue



Source: PharmaSights (https://www.pharmasights.com/)

FDA Approves Akebia's Vafseo® – HIF Inhibitor for Anemia

Jonathan Gardner, *Biopharma Dive*, Mar 28, 2024 (excerpt)

Drug developers have studied pills like Jesduvroq and Vafseo as alternatives to injectable biologic drugs like Amgen's Epogen in the hopes they would be safer and more convenient. Rather than mimicking a natural blood-boosting protein called erythropoietin as the biologics do, Jesduvroq and Vafseo trick the body into responding as if it were in a high-altitude environment by blocking a protein called HIF-PH. That, in turn, stimulates red blood cell production.

But the FDA has viewed the pills as no safer than biologics, stating in the black box warning that targeting a hemoglobin level above 11 grams per deciliter with Vafseo adds similar risk as with the biologics. Normal hemoglobin levels are 12 to 16 for women and 14 to 18 for men.

Doctors using Vafseo should use a low dose that can reduce the need for blood transfusions, the FDA said.

The FDA's initial rejection of Vafseo prompted Akebia to lay off 42% of its workers in a restructuring that reoriented the company around marketing its approved drug Auryxia, an iron replacement and phosphorus control agent for people with anemia from chronic kidney disease.

Akebia got a lifeline when the FDA approved Jesduvroq and then accepted a resubmission for Vafseo, known scientifically as vadadustat. With the Jesduvroq approval and the Vafseo resubmission, the agency only considered use for patients on dialysis, as recommended by FDA's outside experts, and not those patients whose disease hadn't progressed enough to need dialysis.

The outlook for these drugs in only dialysis patients is unclear. GSK reported sales of only 26 million pounds, or about $33 million, for Jesduvroq in its annual report for 2023.

Source: https://www.biopharmadive.com/news/akebia-vadadustat-vafseo-fda-approval-anemia-pill/711631/

Big Pharma CEOs Gather in Beijing to Show Continued Interest in China, Offer Advice

Angus Liu, *FiercePharma*, Mar 26, 2024 (excerpt)

The CEOs of AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Novartis, Pfizer and Takeda came together in Beijing to show the companies' continued interest in China and to offer their advice for the country's healthcare industry.

Pfizer CEO Albert Bourla, while complimenting China's large market opportunity, urged the Chinese government to further improve its protection of intellectual property, according to a Pfizer social media post (Chinese).

Bourla made the comment Sunday during a one-on-one dialogue with Li Daokui, an economist at Tsinghua University who is known as a key adviser to China's core leadership, at the annual China Development Forum (CDF). Back in 2019, Li had stated that Beijing could block exports of medicines as a countermeasure to the U.S.'s trade war.

The 2024 CDF conference marked perhaps the largest gathering of multinational pharma CEOs in China since the pandemic. The CEOs' attendance comes as several U.S. lawmakers, through the draft BIOSECURE Act, aim to ban certain Chinese firms labeled as "foreign adversary biotech companies of U.S. national security concern" from getting federal contracts.

Pfizer remains committed to improving the health of the Chinese people, the company said in the release. The New York pharma previously devised a goal to include China in its initial round of drug filings by including the country in all its pivotal phase 3 trials by 2027.

"I'm encouraged by opportunities to continue to expand the biopharmaceutical industry in China," Bourla said Wednesday in a separate meeting organized by the Chinese Ministry of Commerce to attract foreign investment, as quoted by Bloomberg. "I'm particularly inspired by the prospect of holistic, innovative drug development here."

Source: https://www.fiercepharma.com/pharma/big-pharma-ceos-gather-beijing-continued-interest-china-policy-advice-local-drug-industry

Phil Needleman, a Pharma Giant, Passed Away Last Week

***STL Jewish Light*, March 28, 2024 (excerpt)**

Phil Needleman died when a 100-foot tree came crashing down on him while he was walking in the woods with his dog. This freak accident was a mythical end to an Epic life. He leaves behind his beloved wife, Sima, his daughter Nina, Son Larry (Lisa), Grandsons William and Joshua, brother Paul Needleman, sister Arlene Robbins, brother Alvin Needleman, many nieces and nephews, and hundreds of admiring friends and colleagues.

Starting out as a cross-eyed troublemaker in Brooklyn, he rose to international prominence for his world-class research in the academic world, in industry and in shaping future scientific innovation. His research at Washington University and later in industry had a major impact on four important areas of scientific knowledge and patient care, improving the daily health and quality of life of millions of patients. He cherished relationships, took great interest in people, was kind, generous, encouraging, challenging and mentoring. He was advisor to anyone asking for guidance from disadvantaged students to Nobel laureates. He delighted in others' achievement and growth.

Scientifically, he was best known for Celebrex—both discovering the mechanism in his laboratory at Washington University and developing the drug Celebrex as Chief Scientist at Pharmacia, a drug that is used daily by millions of patients. However, he was even more proud of other scientific achievements, especially discovering and elucidating an endocrine system that is characterized by the heart communicating with the kidneys, influencing blood pressure. He received award after award for his major contributions, and even a couple weeks before his passing at 85, he delivered the major address at a national meeting of pharmaceutical industry leaders.

Phil was always grateful to his own mentors and for his opportunities, and he was extremely generous. During the last several years, he focused on combining his immense expertise in biological sciences and vision, with funding. It was his wish to create research centers that have the most promise for having high impact. His goal was to fashion these centers in novel ways to avoid institutional obstacles and to make profound and rapid progress …`in my lifetime, and I'm old.' As a result, he was the architect and funder of 3 such centers at Washington University and worked extremely closely with colleagues at the university until he was satisfied that they would achieve this lofty vision.

Those who knew him well and loved him will miss his personal qualities the most. Phil Needleman found life to be an alluring puzzle to solve, a quest. His curiosity, enthusiasm, optimism and lack of self-imposed internal limits plus his enormous intellectual brilliance allowed him to have a lifetime of profound achievements. But most importantly he was a mensch. People knew him as a kind, thoughtful, generous person with great integrity.

Source: https://stljewishlight.org/obituaries/phil-needleman/

Phil Needleman: The Ultimate Drug Developer

Lessons Learned in Industry

Philip Needleman, M.D.
Former Head R&D, Pharmacia

From Bruce Booth's Blog Post on Needleman's Ten Commandments:

"Phenomenology is very different than pharmacology". Phil's admonition is to only take drugs into patients where you know the mechanism of action and can therefore optimize the drug's SAR rationally.

"Define and do the killer experiments". "you need ice in your veins – if a killer experiment doesn't work then kill the program".

"Find the shortest route to heaven". In discovery, don't spend years doing every preclinical pharmacology model – do a few, not half-a-dozen or more – and then with confidence sprint quickly to the drug's PoC in patients. In the clinic, if you need to focus on a limited-use first, go for it and get approved with a narrow label fast, even over the cries of your commercial colleagues.

"I'm from Missouri… show me data". As he says, "the coinage of the realm is data" so spare the hand-waving talk, wordy powerpoints, and show the data, "gleamed both at the bench but also occasionally in hard-nosed reviews with experts". Needleman loved the great Edwards Deming quote: *"In god we trust, all others must bring data".*

Source: https://lifescivc.com/2013/03/phil-needlemans-ten-commandments-of-drug-rd/

Needleman Remained Active and Engaged in 2024

We had the pleasure of spending a few hours with Phil Needleman in January 2024 at the opening ceremony for the new neuroscience building at Wash U St. Louis.

As you might note from the pictures at right, Phil could go from being serious to impish in seconds. He spoke to us on many scientific topics including his new center at WashU to fund scientists who wished to conduct “killer experiments” related to disease hypotheses. He was an active, curious and engaged 85-year-old man.

One topic that came up included his view of the importance of ApoE variants in Alzheimer’s disease. Dr. Needleman’s thought was that the ApoE theory of AD is the best developed one from the perspective of genetic evidence and warrants a real “killer experiment”. He was aware that Lexeo is conducting clinical trials in the area and was looking forward to seeing the results.

Another topic of lifelong interest was the arachidonic acid pathway. As a key inventor of celecoxib, Phil took his Celebrex® every day and felt that the pharmacologic potential of this area of biology has yet to be fully interrogated. He discussed overlooked opportunities in our most recent meeting. We, ourselves, are looking forward to seeing progress from drugs under development in the AA area from companies like Amgen.

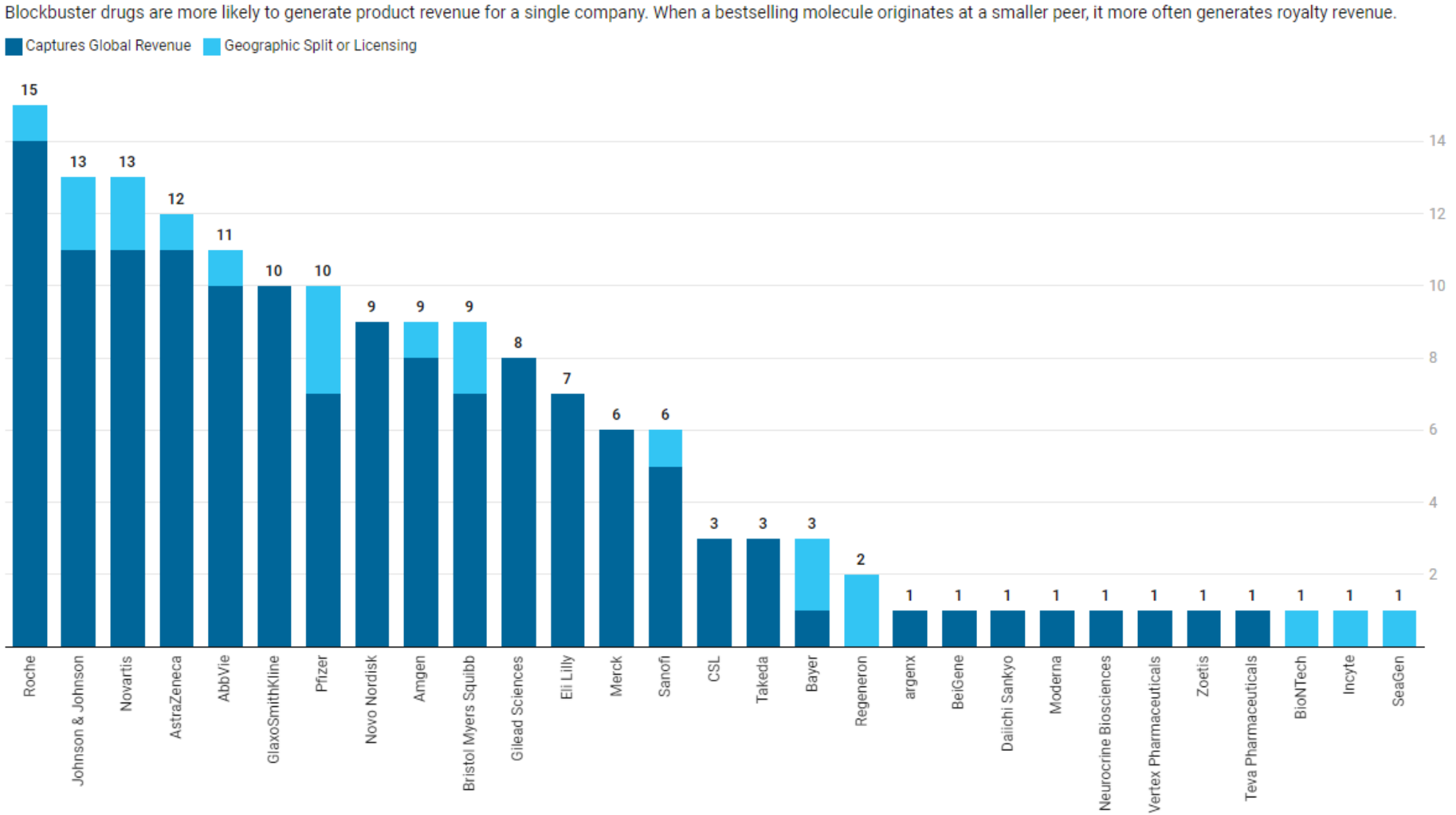
Another topic that came up was the need for efficiency in industry and academic research. He noted that far too much money was being spent on science that would not necessarily yield cures for important diseases and joked that if he were a bit younger, he would be thrilled to come in and help fix the waste.*

Needleman trained generations of scientists and clinicians in academia and industry on the principles of pharmacology and was quick to share lessons on life and on how to make the biggest impact from the bench. His impact on our industry was profound and wide. He will be missed by many.

Needleman listening to a talk on neuroscience and then soon after joking about scientific waste, Wash U, Jan 18, 2024

* This remains a highly relevant topic – particularly in an issue that highlights burn rates in biotech. After Pfizer’s acquisition of Pharmacia in 2002, Needleman volunteered to help sort out Pfizer’s lumbering R&D operation, the largest in the industry at the time, and whip it into shape based on his principles of R&D management. His services were not retained. Looking back, it’s not obvious that Pfizer made the right decision. Phil went on to help many other pharma companies optimize their R&D operations in a consulting capacity.

Number of Drugs with $1bn+ in Revenue by Pharma

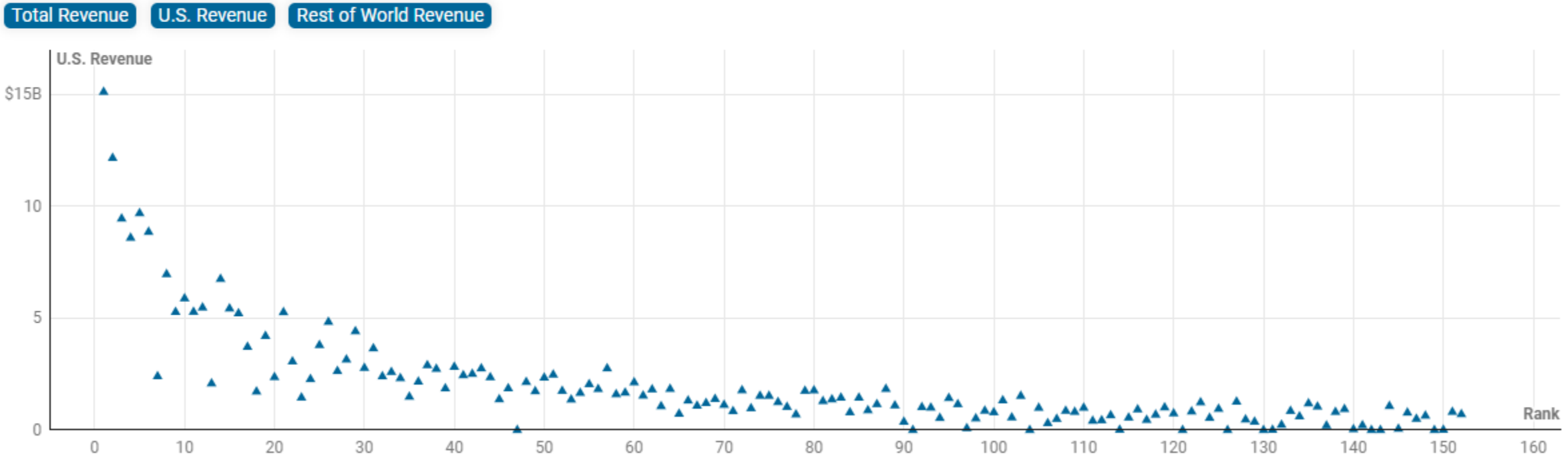


Source: https://www.living.tech/articles/worlds-bestselling-drugs-addicted-broken-us-healthcare

U.S. Market Driving Pharma Sector

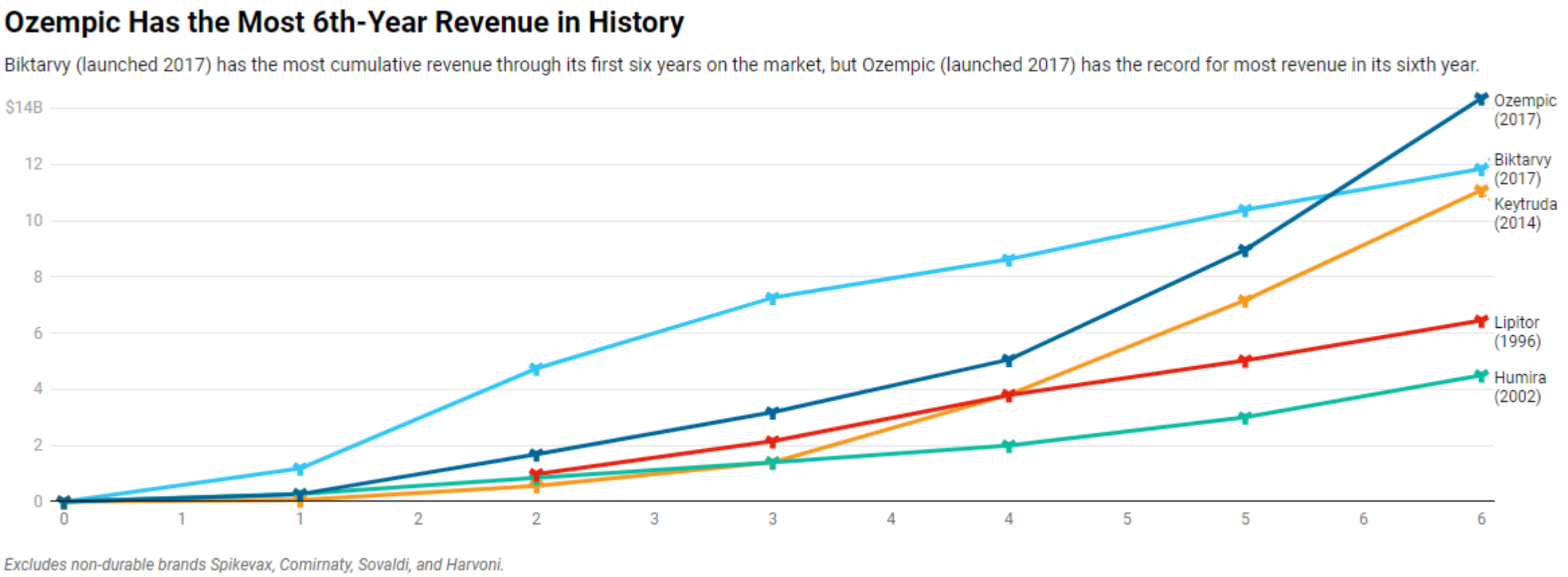
U.S. Patients Generated 60% of Blockbuster Drug Sales in 2023

Whereas three (3) blockbusters generated >$5 billion in international revenue alone, 15 crossed that level in the United States alone.



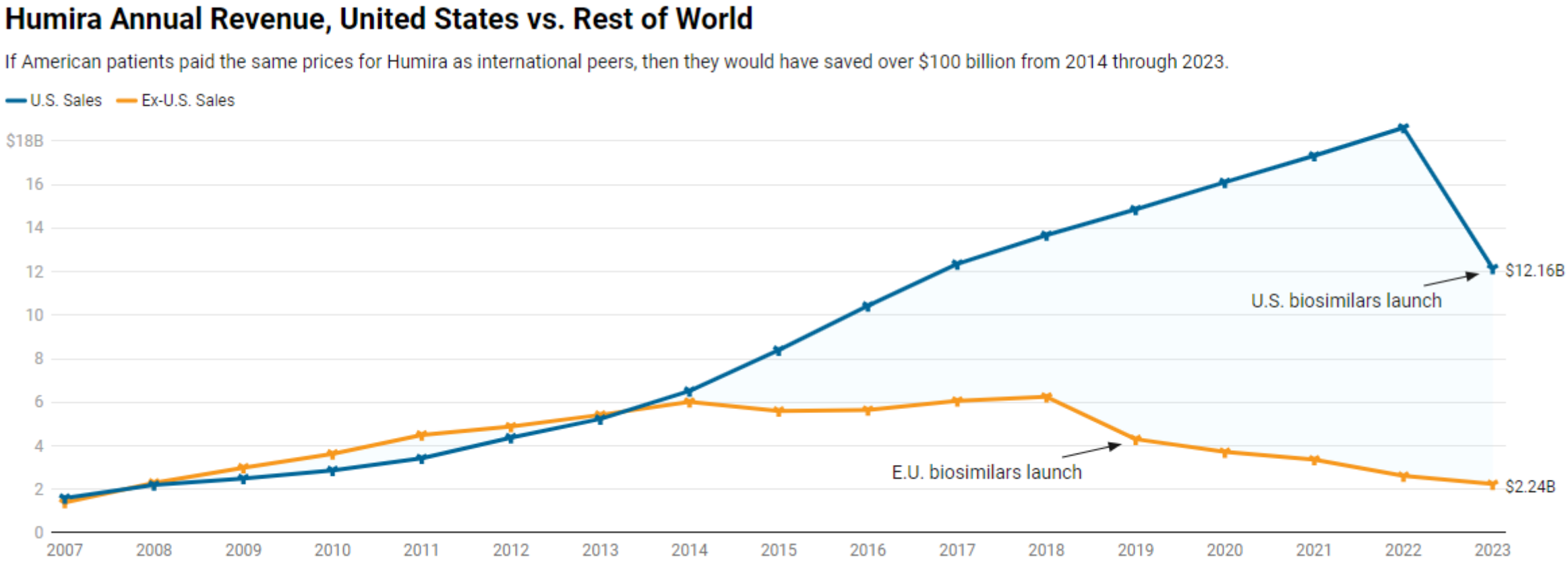
Source: https://www.living.tech/articles/worlds-bestselling-drugs-addicted-broken-us-healthcare

Ozempic the Fastest Revenue Gainer at Year 6 in History



Source: https://www.living.tech/articles/worlds-bestselling-drugs-addicted-broken-us-healthcare

Biosimilars Impact on Humira Sales



Source: https://www.living.tech/articles/worlds-bestselling-drugs-addicted-broken-us-healthcare

Healthcare Services: Greater Integration Across Value Chain

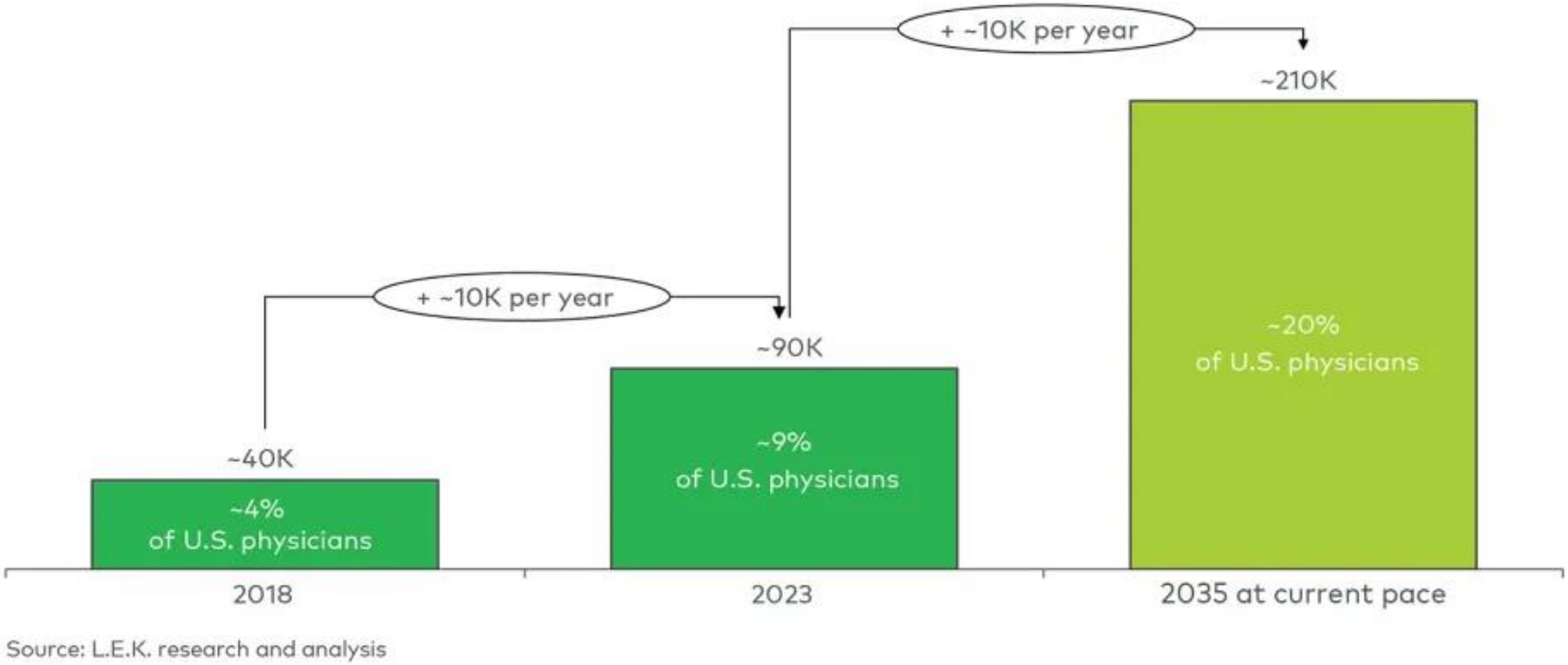
LEK Report, Feb 29, 2024

Note: PBM=pharmacy benefit manager; HCIT=healthcare information technology
Source: L.E.K. research and analysis

https://www.lek.com/insights/hea/us/ei/looking-ahead-us-healthcare-provider-landscape-2035-part-2

Optum On Track to Employ a Fifth of U.S. Physicians by 2035

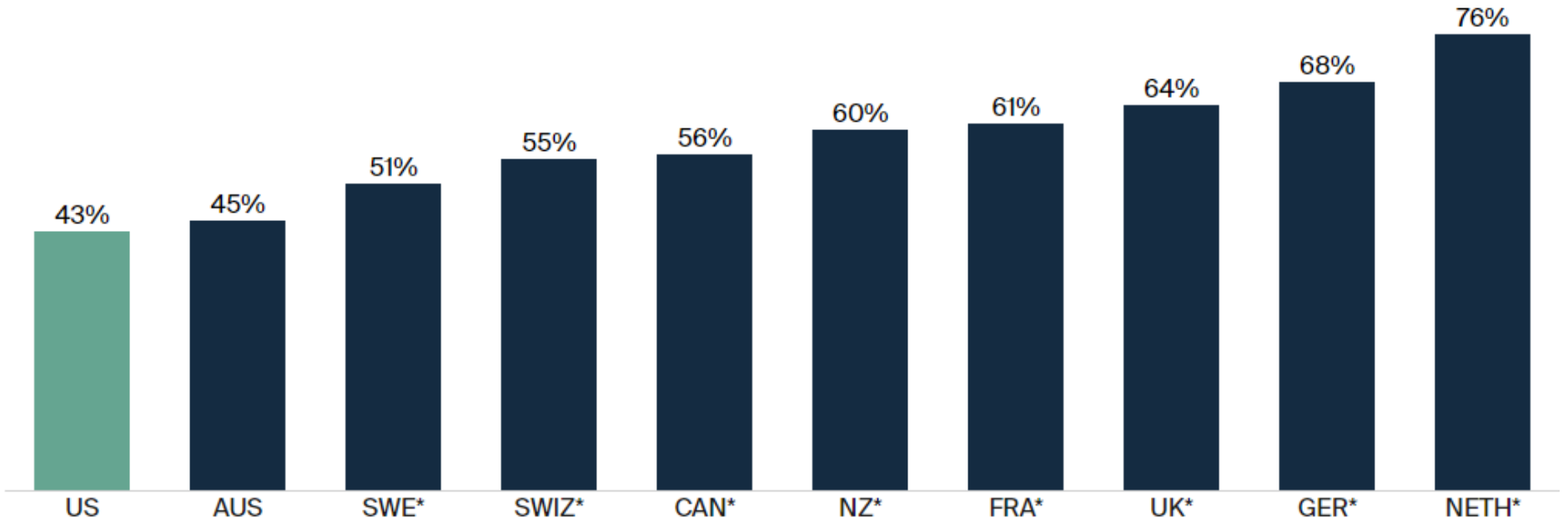
LEK Report, Feb 29, 2024



https://www.lek.com/insights/hea/us/ei/looking-ahead-us-healthcare-provider-landscape-2035-part-2

Less than half of adults in the U.S. and Australia reported having a longstanding relationship with a primary care provider.

Percentage of adults who have a regular doctor or place of care and have been with them for five years or more



Download data

* Statistically significant difference from US at p<.05 level; statistically significant difference to bar in comparison for within-country stratification analyses at p<.05 level.

Data: Commonwealth Fund International Health Policy Survey (2023).

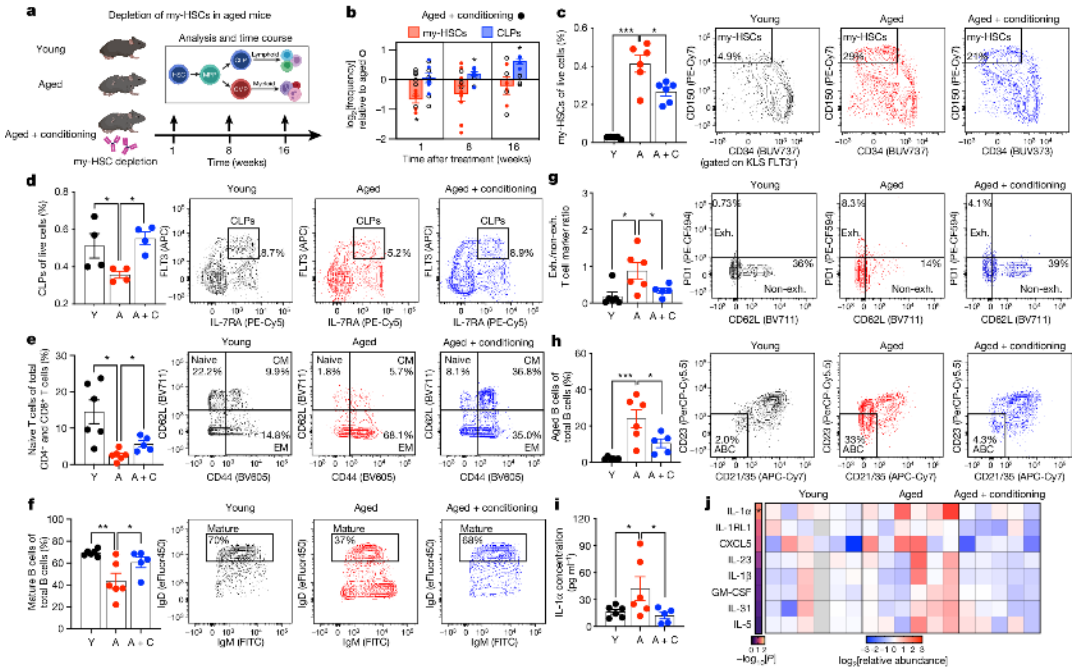
Source: Evan D. Gumas et al., *Finger on the Pulse: The State of Primary Care in the U.S. and Nine Other Countries* (Commonwealth Fund, Mar. 2024). https://doi.org/10.26099/p3y4-5g38

Source: https://www.commonwealthfund.org/publications/issue-briefs/2024/mar/finger-on-pulse-primary-care-us-nine-countries

Depleting Myeloid-Biased Hematopoietic Stem Cells Rejuvenates Aged Immunity

Ross, Weissman et.al., *Nature,* March 27, 2024 (excerpt)

Ageing of the immune system is characterized by decreased lymphopoiesis and adaptive immunity, and increased inflammation and myeloid pathologies. Age-related changes in populations of self-renewing haematopoietic stem cells (HSCs) are thought to underlie these phenomena. During youth, HSCs with balanced output of lymphoid and myeloid cells (bal-HSCs) predominate over HSCs with myeloid-biased output (my-HSCs), thereby promoting the lymphopoiesis required for initiating adaptive immune responses, while limiting the production of myeloid cells, which can be pro-inflammatory4. Ageing is associated with increased proportions of my-HSCs, resulting in decreased lymphopoiesis and increased myelopoiesis. Transfer of bal-HSCs results in abundant lymphoid and myeloid cells, a stable phenotype that is retained after secondary transfer; my-HSCs also retain their patterns of production after secondary transfer. The origin and potential interconversion of these two subsets is still unclear. If they are separate subsets postnatally, it might be possible to reverse the ageing phenotype by eliminating my-HSCs in aged mice. Here we demonstrate that antibody-mediated depletion of my-HSCs in aged mice restores characteristic features of a more youthful immune system, including increasing common lymphocyte progenitors, naive T cells and B cells, while decreasing age-related markers of immune decline. Depletion of my-HSCs in aged mice improves primary and secondary adaptive immune responses to viral infection. These findings may have relevance to the understanding and intervention of diseases exacerbated or caused by dominance of the haematopoietic system by my-HSCs.



Depletion of my-HSCs in aged mice restores youthful immune features

Source: https://www.nature.com/articles/s41586-024-07238-x

How to Make an Old Immune System Young Again

Heidi Ledford, *Nature*, March 27, 2024 (excerpt)

For decades, researchers in Irv Weissman's group at Stanford University in California have painstakingly tracked the fate of blood stem cells. These replenish the body's stores of red blood cells (which carry oxygen from the lungs to all parts of the body) and white blood cells (which are key components of the immune system).

In 2005, Weissman and his colleagues found that populations of blood stem cells shift as mice age. In young mice, there is a balance between two types of blood stem cell, each of which feeds into a different arm of the immune system. The 'adaptive' arm produces antibodies and T cells targeted to specific pathogens; the 'innate' arm produces broadbrush responses, such as inflammation, to infection.

In older mice, however, this balance becomes skewed towards the pro-inflammatory innate immune cells. Similar changes have been reported in the blood stem cells of older humans, and researchers speculate that this could lead to a diminished ability to mount new antibody and T-cell responses. That might explain why older people are more prone to serious infections from pathogens such as influenza viruses and SARS-CoV-2, and why they have weaker responses to vaccination than younger people do.

Restoring the balance

If that were the case, then restoring balance to the populations of blood stem cells could also rejuvenate the immune system. The team tested this by generating antibodies that bind to the blood stem cells that predominantly generate innate immune cells. They then infused these antibodies into older mice, hoping that the immune system would destroy the stem cells bound by the antibodies.

The antibody treatment rejuvenated the immune systems of the treated mice. They had a stronger reaction to vaccination, and were better able to fend off viral infection, than older mice that had not received the treatment. The treated mice also produced lower levels of proteins associated with inflammation than did old, untreated mice.

Weissman says that his team is working on a similar approach to rebalance aged human blood stem cells. But even assuming ample funding and no unexpected setbacks, it will be at least three to five years before they can begin testing it in people, he says.

Irv Weissman
Stanford University

Source: https://www.nature.com/articles/d41586-024-00871-6

Anti-Aging Antibodies Revive Immunity

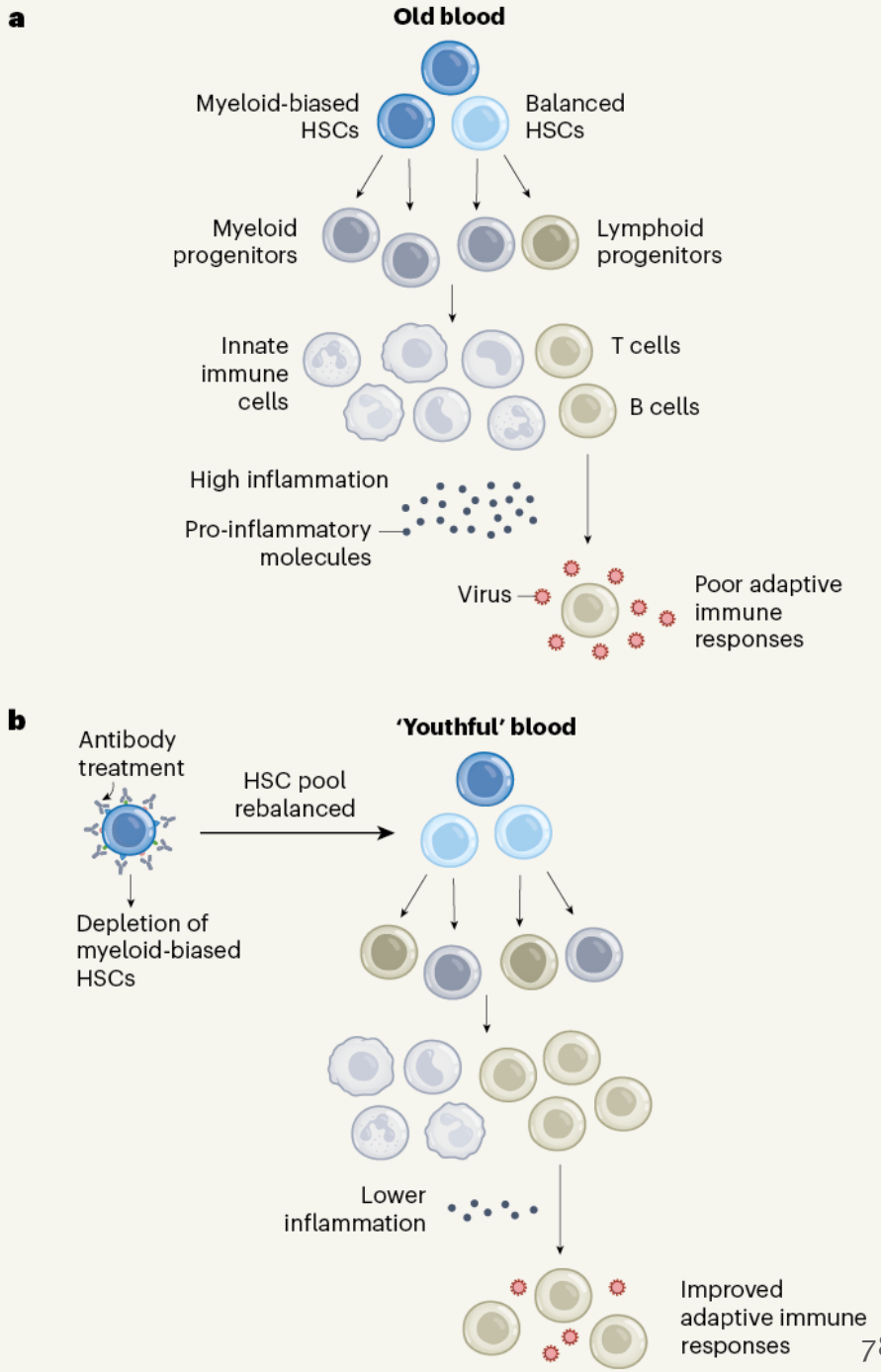
Yasar Arafat Kasu and Robert Signer, *Nature*, March 27, 2024 (excerpt)

Ageing is associated with an increased prevalence of a condition called clonal haematopoiesis, in which a subpopulation of HSCs with the same genetic mutation expands and, in some cases, dominates the pool of HSCs; this, in turn, can increase the risk of developing blood cancer and cardiovascular disease. Ross et al. contend that targeted depletion of myeloid-biased HSCs could preferentially eradicate these dominant or pre-cancerous HSC clones. However, antibody conditioning could, in fact, exacerbate the emergence of clonal haematopoiesis by narrowing the total repertoire of HSCs. Depletion of myeloid-biased HSCs could force a compensatory expansion of the remaining HSC pool and confer a selective pressure on residual HSCs harbouring advantageous mutations; ultimately, this could accelerate clonal dominance and progression to cancer.

Although a reduction in the production of lymphoid cells (lymphopoiesis) probably contributes to impaired adaptive immunity in older individuals, previous studies have shown that this reduction could come with the benefit of tumour suppression11. Lymphoid leukaemias are the most common form of cancer in children, and age-related activation of tumour-suppressor genes in lymphoid progenitors helps to prevent these cells from becoming cancerous in adulthood, but this occurs at the expense of maintaining robust lymphopoiesis11. Boosting lymphopoiesis in older adults could therefore raise the risk of their developing lymphoid cancers. However, the burden of an increased risk of lymphoid leukaemia could be offset by the greater protection from infection, and the reduced risk of other cancers, that would be afforded by enhanced immune surveillance.

Eliminating the underlying drivers of ageing is central to preventing several age-related diseases. Advances with a class of drugs called senolytics, which broadly target senescent cells in tissues, have so far been at the forefront of this effort. Ross and colleagues now demonstrate that specifically targeting aberrant, lineage-biased HSCs is an exciting approach that could revitalize the immune system and alleviate some of the detrimental effects of ageing.

Source: https://www.nature.com/articles/d41586-024-00871-6



Memories are Made by Breaking DNA — And Fixing It

Nerve cells form long-term memories with the help of an inflammatory response, study in mice finds.

Max Kozlov, *Nature*, March 27, 2024 (excerpt)

When a long-term memory forms, some brain cells experience a rush of electrical activity so strong that it snaps their DNA. Then, an inflammatory response kicks in, repairing this damage and helping to cement the memory, a study in mice shows.

The findings, published on 27 March in Nature, are “extremely exciting”, says Li-Huei Tsai, a neurobiologist at the Massachusetts Institute of Technology in Cambridge who was not involved in the work. They contribute to the picture that forming memories is a “risky business”, she says. Normally, breaks in both strands of the double helix DNA molecule are associated with diseases including cancer. But in this case, the DNA damage-and-repair cycle offers one explanation for how memories might form and last.

It also suggests a tantalizing possibility: this cycle might be faulty in people with neurodegenerative diseases such as Alzheimer’s, causing a build-up of errors in a neuron’s DNA, says study co-author Jelena Radulovic, a neuroscientist at the Albert Einstein College of Medicine in New York City.

Inflammatory response

This isn’t the first time that DNA damage has been associated with memory. In 2021, Tsai and her colleagues showed that double-stranded DNA breaks are widespread in the brain, and linked them with learning.

To better understand the part these DNA breaks play in memory formation, Radulovic and her colleagues trained mice to associate a small electrical shock with a new environment, so that when the animals were once again put into that environment, they would ‘remember’ the experience and show signs of fear, such as freezing in place. Then the researchers examined gene activity in neurons in a brain area key to memory — the hippocampus. They found that some genes responsible for inflammation were active in a set of neurons four days after training. Three weeks after training, the same genes were much less active.

The team pinpointed the cause of the inflammation: a protein called TLR9, which triggers an immune response to DNA fragments floating around the insides of cells. This inflammatory response is similar to one that immune cells use when they defend against genetic material from invading pathogens, Radulovic says. However, in this case, the nerve cells were responding not to invaders, but to their own DNA, the researchers found.

Clara Ortega de San Luis, a neuroscientist who works with Ryan at Trinity College Dublin, says that these results bring much-needed attention to mechanisms of memory formation and persistence inside cells. “We know a lot about connectivity” between neurons “and neural plasticity, but not nearly as much about what happens inside neurons”, she says.

Source: https://www.nature.com/articles/d41586-024-00930-y

Comprehensive Whole-genome Sequence Analyses Provides Insights Into the Genomic Architecture of Cerebral Palsy

Fehlings et.al., *Nature Genetics*, March 29, 2024 (excerpt)

We performed whole-genome sequencing (WGS) in 327 children with cerebral palsy (CP) and their biological parents. We classified 37 of 327 (11.3%) children as having pathogenic/likely pathogenic (P/LP) variants and 58 of 327 (17.7%) as having variants of uncertain significance. Multiple classes of P/LP variants included single-nucleotide variants (SNVs)/indels (6.7%), copy number variations (3.4%) and mitochondrial mutations (1.5%). The COL4A1 gene had the most P/LP SNVs. We also analyzed two pediatric control cohorts (n = 203 trios and n = 89 sib-pair families) to provide a baseline for de novo mutation rates and genetic burden analyses, the latter of which demonstrated associations between de novo deleterious variants and genes related to the nervous system. An enrichment analysis revealed previously undescribed plausible candidate CP genes (SMOC1, KDM5B, BCL11A and CYP51A1). A multifactorial CP risk profile and substantial presence of P/LP variants combine to support WGS in the diagnostic work-up across all CP and related phenotypes.

Table 2 | P/LP SNVs and indels identified in the CP cohort and overlap of SNVs in the clinical genomic cohorts

Case	Sex	Type	Location	Size (bp)	Genes/variant	inh/zyg	Class	SK clinical cohort[a]	SK complex care[b]	SJ clinical cohort[c]	Any[d]
264594	F	SNV	3q21.1	1	*ADCY5*:c.2088+2T>G:p.?	dn, het	LP	het, VUS (inheritance unknown)[e]			Yes
266349	M	SNV	13q34	1	*COL4A1*:c.G2317A:p.G773R	dn, het*	P	YES dn, het, P (2 instances)[e]	dn, het, P[e]	(3 instances)[e]: dn, het, LP; mat, het, LP; mat (mosaic), het, P	Yes
324623	F	SNV	13q34	1	*COL4A1*:c.G2869A:p.G957R	dn, het	LP	YES dn, het, P (2 instances)[e]	dn, het, P[e]	(3 instances)[e]: dn, het, LP; mat, het, LP; mat (mosaic), het, P	Yes
267092	F	SNV	13q34	1	*COL4A1*:c.1537-1G>A:p.?	dn, het	LP	YES dn, het, P (2 instances)[e]	dn, het, P[e]	(3 instances)[e]: dn, het, LP; mat, het, LP; mat (mosaic), het, P	Yes
20_14777	F	DEL	13q34	1	*COL4A1*:c.1509delT:p.P503fs	pat, het	P	YES dn, het, P (2 instances)[e]	dn, het, P[e]	(3 instances)[e]: dn, het, LP; mat, het, LP; mat (mosaic), het, P	Yes
324576	F	INS	8p11.23	14	*ERLIN2*:c.859_860ins AGGCCATTGCTTCC:p.K287fs	hom	LP				No
261783	F	SNV	9p13.2	1	*EXOSC3*:c.A395C:p.D132A	hom	P	hom, P[e]	3 hom P, 1 compound het, P/LP (4 instances)[e]		Yes
302991	F	SNV	1q21.3	1	*GATAD2B*:c.T1321C:p.C441R	dn, het	LP	dn, het, LP[e]		dn, het, P[e]	Yes
19_1885	M	SNV	16q12.2	1	*GNAO1*:c.A711C:p.E237D	dn, het	P			(2 instances)[e]: dn, het, P; dn, het, LP	Yes
323572	F	SNV	5q31.2	1	*KDM3B*:c.G4879A:p.E1627K	dn, het	LP	pat, het, LP[e]			Yes
285253	M	DEL	5q14.3	3	*MEF2C*:c.51_54del:p.R17fs	dn, het	P			dn, het, LP[e]	Yes
264583	M	DEL	6q27	1	*PDE10A*:c.1783delC:p.H595fs	dn, het	LP				No
278746	M	INS	6q14.1	4	*PHIP*:c.2517_2518insATGG: p.H840fs	dn, het	P				No
19_1851	M	SNV	Xp22.13	1	*PHKA2*:c.G557A:p.R186H	dn, hem	P				No
20_983	F	SNV	19p13.11	1	*PIK3R2*:c.G1117A:p.G373R	dn, het	P				No
324567	F	DEL	3q26.33	18	*SOX2*:c.59_78del:p.G20fs	dn, het	P				No
20_13820	M	DEL	2p22.3	6	*SPAST*:c.1413+3_1413+6del:p.?	dn, het	LP		dn, het, P[e]		Yes
324636	F	SNV	11p15.5	1	*TH*:c.G931A:p.G311S	hom	P		hom, P[e]	compound het (inherited), P[e]	Yes
20_19577	M	SNV	2q36.3	1	*TRIP12*:c.3624+1G>A:p.?	dn, het	P	pat, het, VUS[e]			Yes
260471	M	SNV	12q13.12	1	*TUBA1A*:c.G1000A:p.A334T	dn, het	P		dn, het, P[e]	(3 instances)[e]: dn, het, P; unknown inheritance, het, LP; unknown inheritance, het, P	Yes
317945	M	SNV	Xq26.1	1	*ZDHHC9*:c.881+1G>T:p.?	mat, hem	P	mat, hem, LP[e]			Yes
19_7945	M	DEL	3q32.3	1	*ZIC2*:c.1330delA:p.S444fs	dn, het	P	pat, het, VUS[e]			Yes

All variants were inspected using Integrative Genomics Viewer and subsequently confirmed using another method (qPCR or Sanger sequencing), except those marked with an asterisk (*) where adequate DNA was unavailable. INS, insertion; hom, homozygous; hem, hemizygous; het, heterozygous. [a]Clinical sequencing cases from the Hospital for Sick Children (SK), Toronto, Canada. [b]Children with medical complexity followed by a structured complex care program over a period >10 years (ref. 32). [c]Clinical sequencing cases from Hôpital Ste-Justine (SJ), Montréal, Québec, Canada. Six of these have been previously reported (one *COL4A1*, two *GNAO1*, one *MEF2C*)[64]; one *TUBA1A*[65]; one *GATAD2B*[66]. [d]Of 19 genes with SNV/indel variants, 13 were also found in at least 1 of the 3 clinical genomic cohorts. There was no overlap of individuals with variants in the cohorts. [e]Clinical phenotype encompasses CP/neuromotor disability.

Source: https://www.nature.com/articles/s41588-024-01686-x

Disclosure

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