



# Biopharmaceutical Sector

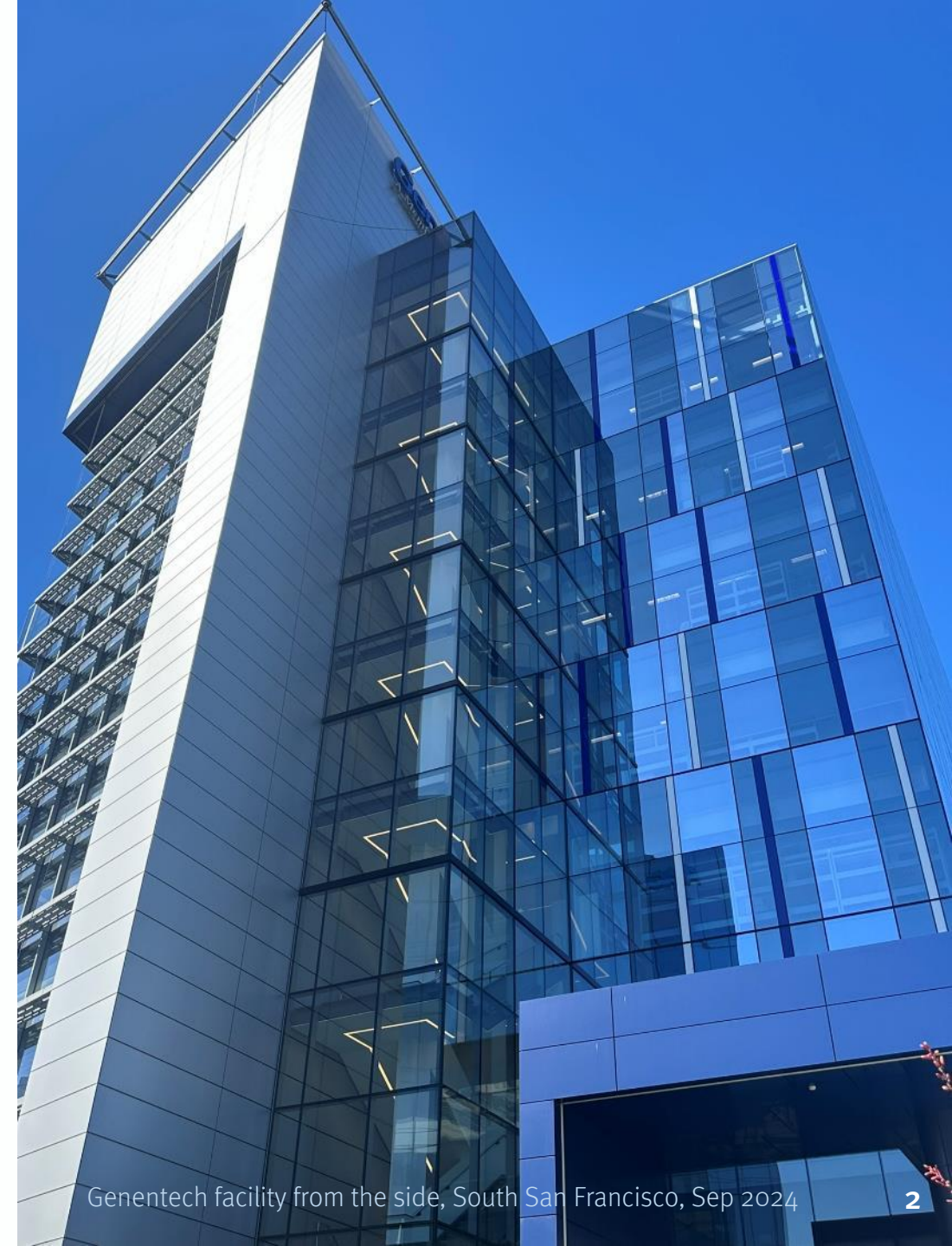
Update – Oct 7, 2024

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Genentech facility from the side, South San Francisco, Sep 2024



# Past Issues

If you wish to be added to the mailing list for this publication, please notify Natasha Yeung ([yeungn@stifel.com](mailto:yeungn@stifel.com)). Past issues:

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[May 22, 2023](#) (FTC case on Amgen/Horizon)



The Beaded Prayers Project, Museum of Arts and Design, NYC, Sep 2024



# Join Us at Biotech Hangout This Friday

And meet us at a number of upcoming conference events:



**To Learn More**

<https://www.biotechhangout.com/>



**New York City**

**@Cure**

**October 28-30, 2024**

<https://biofuture.com/>

**To meet with Stifel at BioFuture:**

[yeungn@stifel.com](mailto:yeungn@stifel.com)



The week of Nov 4 will feature over 5,000 biopharma professionals in Stockholm for Bio-Europe. We'd love to meet you there.

<https://informaconnect.com/bioeurope/>

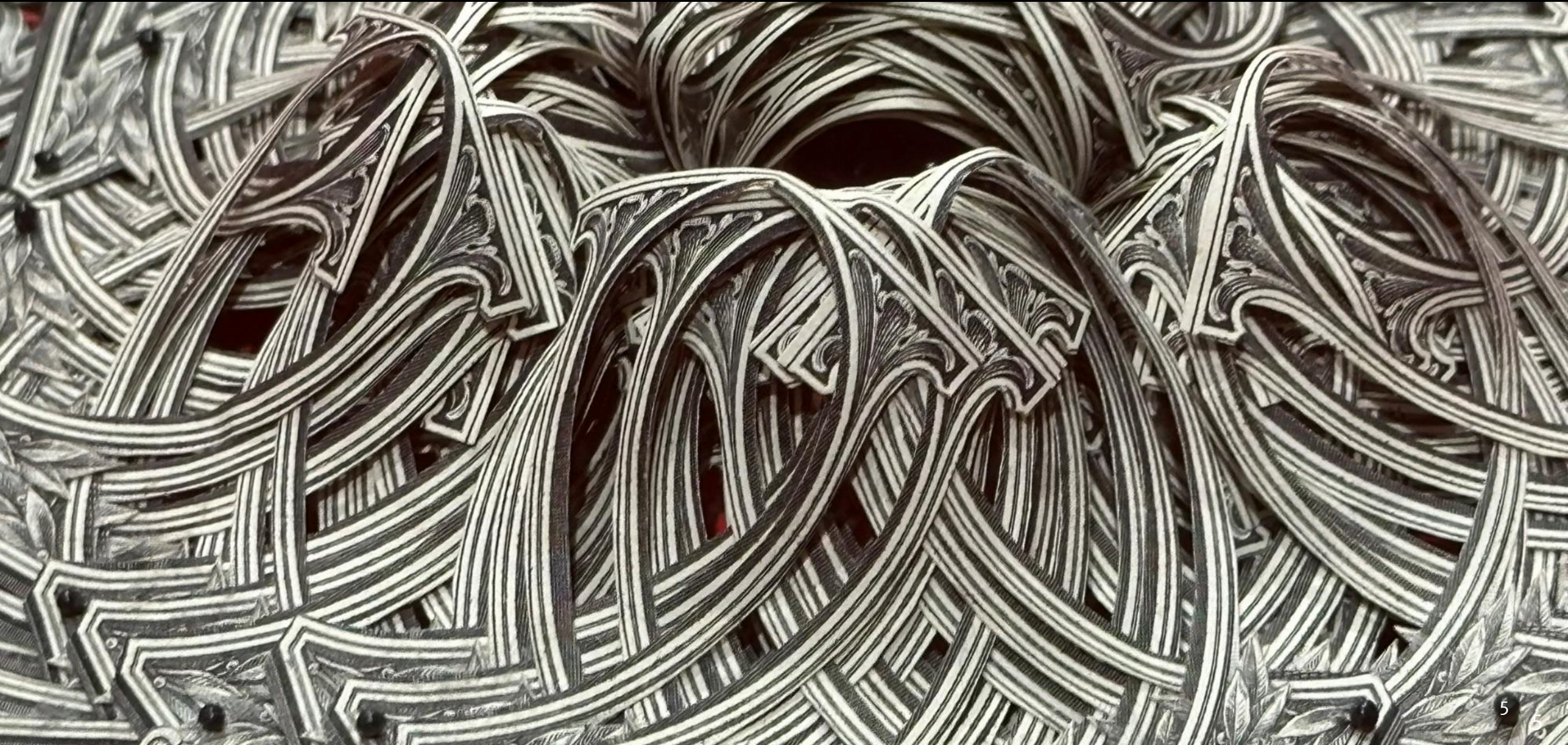
**To meet with Stifel @ Bio-Europe**

[yeungn@stifel.com](mailto:yeungn@stifel.com)



# The Macro Picture

Lauren Tickle, U.S. Dollars Currency Pendant, Museum of Arts and Design, NYC, Sep 2024





# Blowout U.S. Jobs Report Boosts Shares, Hits Bonds

*Wall Street Journal, Oct. 4, 2024 (excerpt)*

Major stock indexes rose Friday after a stronger-than-expected jobs report showed robust health in the labor market.

The climb came after Friday's payrolls report showed the U.S. added 254,000 jobs in September, topping forecasts by more than 100,000 positions. Gains in previous months were revised up, and the unemployment rate also defied expectations, moderating to 4.1%.

Bond yields jumped and the dollar strengthened. Futures traders stepped up bets that the Federal Reserve's next move, when policymakers meet in November, will be a modest quarter-point cut.

Employment is important to the Fed's deliberations about how far and how fast to bring down interest rates. Friday's jobs report also helped reassure some economists that the Fed is on track to cool inflation without a significant decline in economic activity.

"There are no big examples from today's data of why inflation would pick back up. With the Fed already starting to reduce rates, that's going to take further pressure off the economy," said Matthew Bush, U.S. economist at Guggenheim Investments. "A soft landing is our base case going forward."

Source: <https://www.wsj.com/livecoverage/jobs-report-today-stock-market-dow-sp500-nasdaq-10-04-2024>



# Market Seeing Rate Cuts as More Likely After Jobs Report

*The Times of London, Oct. 4, 2024 (excerpt)*

Jobs growth in the US economy surged and unemployment fell as the central bank cut interest rates for the first time in four years last month.

A closely watched measure of payrolls rose by 254,000 in the world's largest economy, exceeding the 150,000 expected by economists, and up from 159,000 in August. The unemployment rate fell unexpectedly from 4.2 per cent to 4.1 per cent, defying forecasts of no change.

The figures will raise hopes that the US is undergoing a “soft landing” after two years of high inflation and rising interest rates, with the jobs market and economic growth showing signs of resilience. Payroll estimates for August were also revised up by 17,000 and by 55,000 in July. “The economic expansion is motoring along,” Justin Wolfers, professor of economics at the University of Michigan, said.

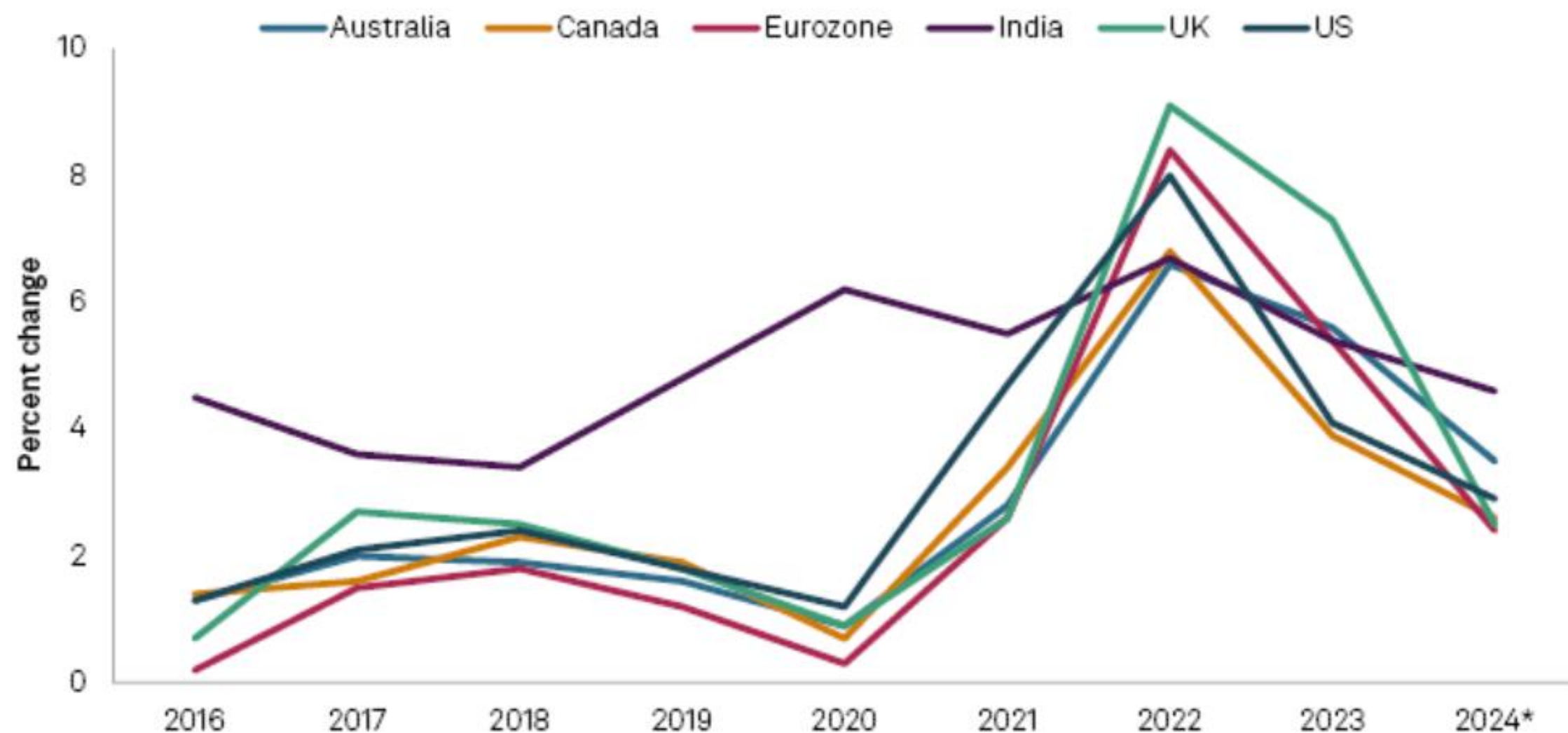
After the payrolls release, traders increased the probability of a quarter percentage point cut to interest rates at the Fed's next meeting in November, from 69 per cent to 92 per cent. The decision will take place two days after voting in the presidential election is concluded.

Source: <https://www.thetimes.com/business-money/companies/article/jobs-boom-raises-hope-of-soft-landing-for-us-economy-mbmzgfm92>





## Consumer price inflation (annual percent change)



Data compiled Sept. 26, 2024.

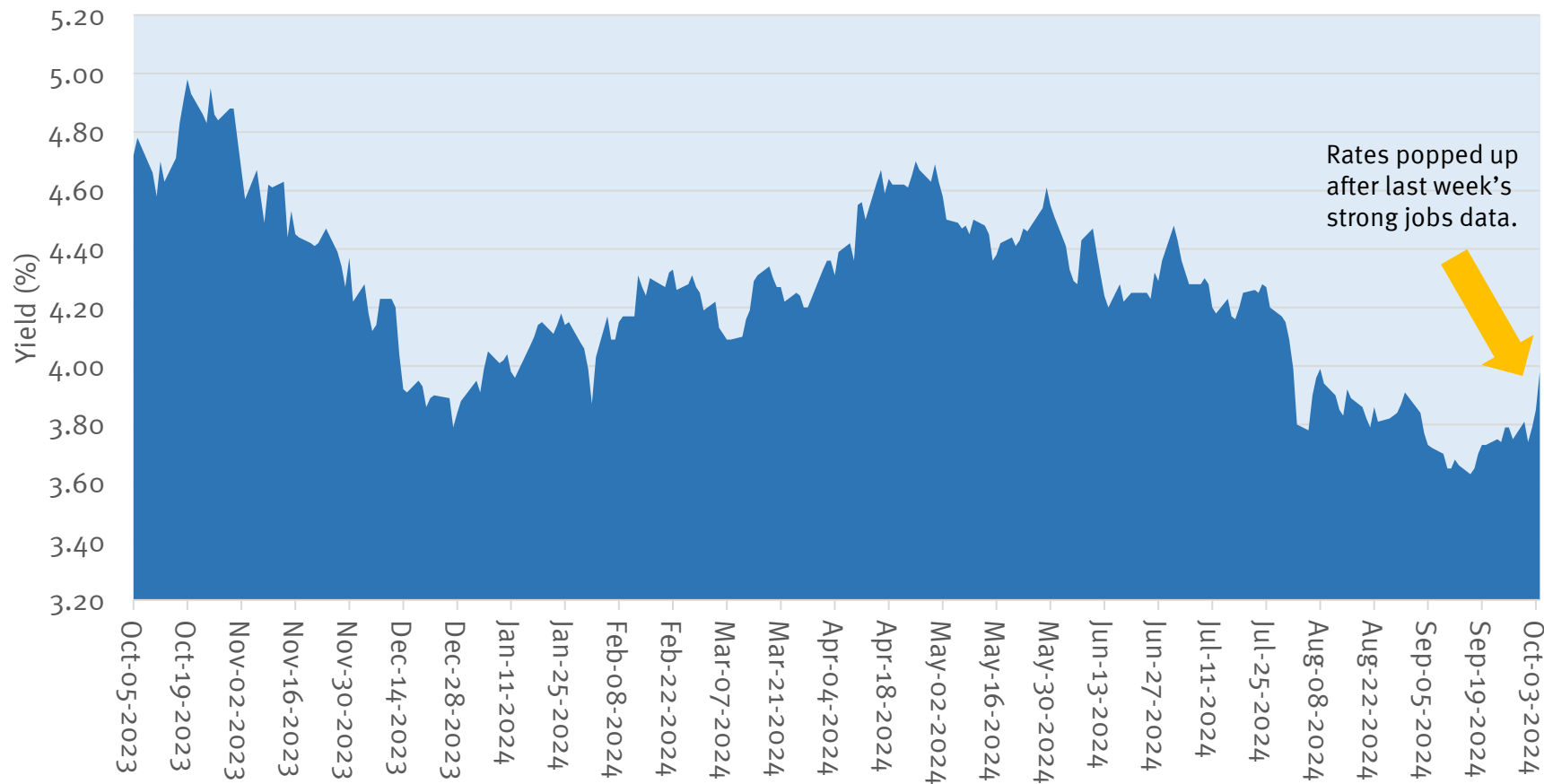
\* Projection from IMF World Economic Outlook Report (April 2024).

Source: International Monetary Fund.



# Treasury Bond Yields Going Up – Not Good for Biotech

Ten Year Treasury Bond Yield, Oct 5, 2023 to Oct 4, 2024 (%)



Treasury bond yields have risen over the past two weeks because of concerns over persistent inflation, strong jobs data and the possibility of prolonged higher interest rates.

Investors are increasingly demanding higher yields to compensate for uncertainty in monetary policy, including potential policy missteps and the rising U.S. fiscal deficit. Additionally, the term premium—the extra return investors expect for holding longer-term bonds—has increased, reflecting concerns about policy risks and economic conditions



# Xi Jinping's Belated Stimulus has Reset the Mood in Chinese Markets

*The Economist*, Oct 2, 2024 (excerpt)

If Chinese retail investors had their way they would forgo the seven-day National Day holiday that ends on October 7th. An aggressive stimulus package, announced in Beijing on September 24th, has unleashed the biggest weekly stockmarket rally the country has witnessed in more than 15 years. Major indices have soared more than 25%; the Shanghai stock exchange has suffered glitches under the volume of buying activity. The prospect of halting for a full week has made netizens anxious: “We must keep trading; we must cancel National Day,” one young investor screamed into a video widely shared on WeChat, a social-media platform.

The package, unveiled by top regulators, included a policy-rate cut, mortgage-rate cuts and 800bn yuan (\$114bn) in support of the stockmarket. Two days later a meeting of the Politburo, a group of China's 24 most senior leaders, drove the point home by using phrases such as “action comes first”, rather than the passive verbiage repeated in recent years. At another high-level meeting on September 29th Li Qiang, China's premier, pledged to speed up the implementation of easing measures.

## A W-shaped recovery

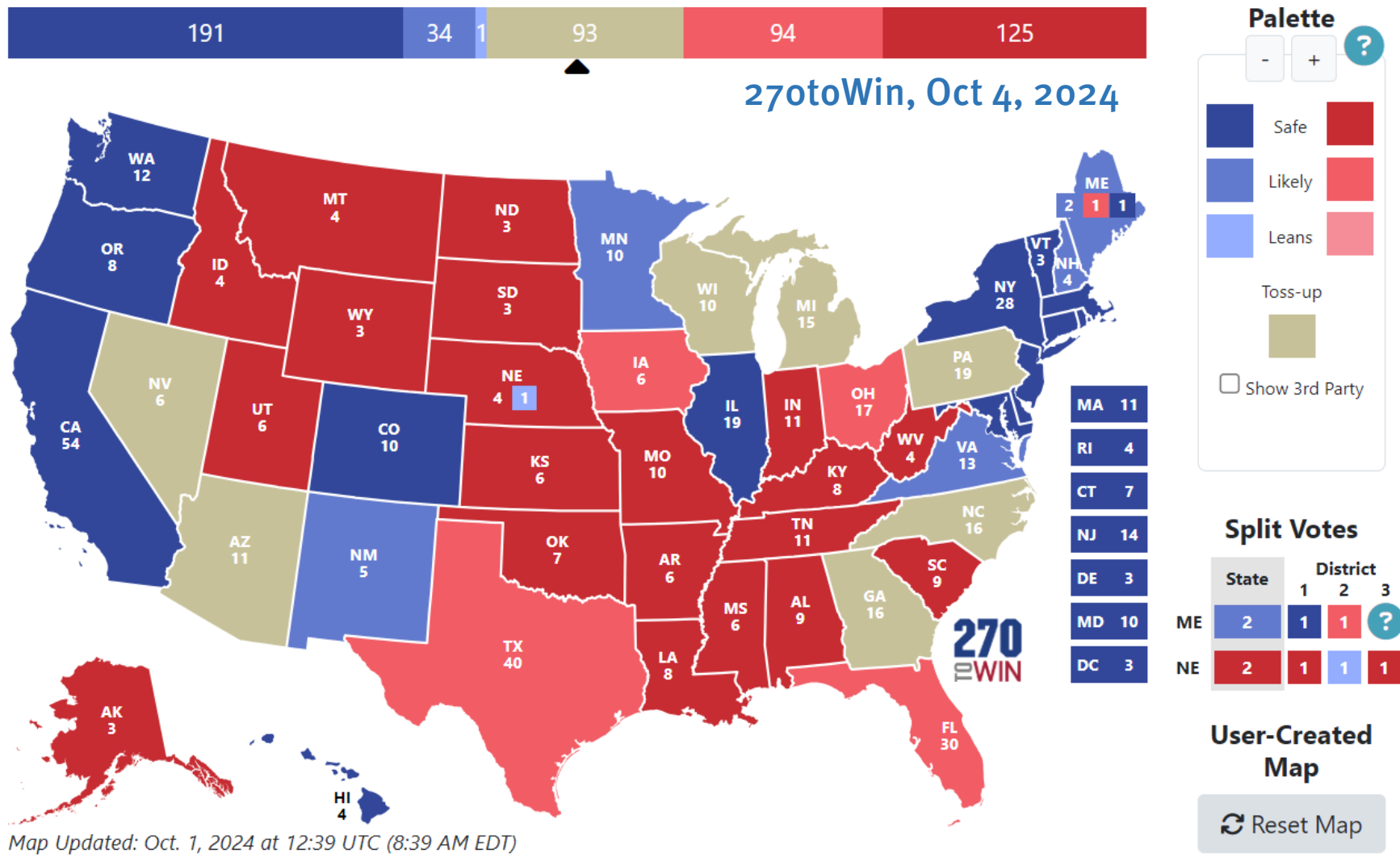
CSI 300 index, September 1st 2023=100



Source: Bloomberg



# Current Polls: U.S. Presidency a Tossup



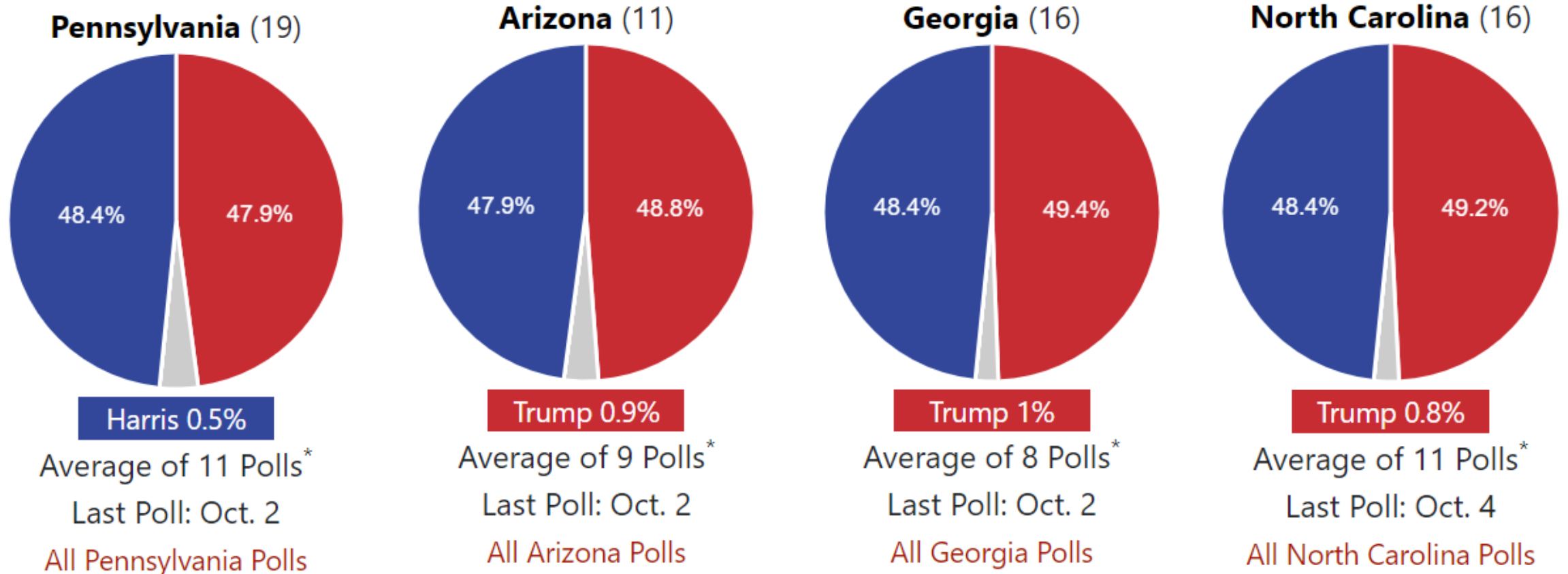
There is no clear winner emerging in the U.S. race for President.

We are now a month away from election day and the key states that will determine the race (Pennsylvania, Arizona, Wisconsin, Michigan and Georgia) remain far from decided.



# Trump Leading by a Hair in Three of Four Key Battleground States

27otoWin, Oct 4, 2024



# Betting Odds Have Harris 1% Point Ahead

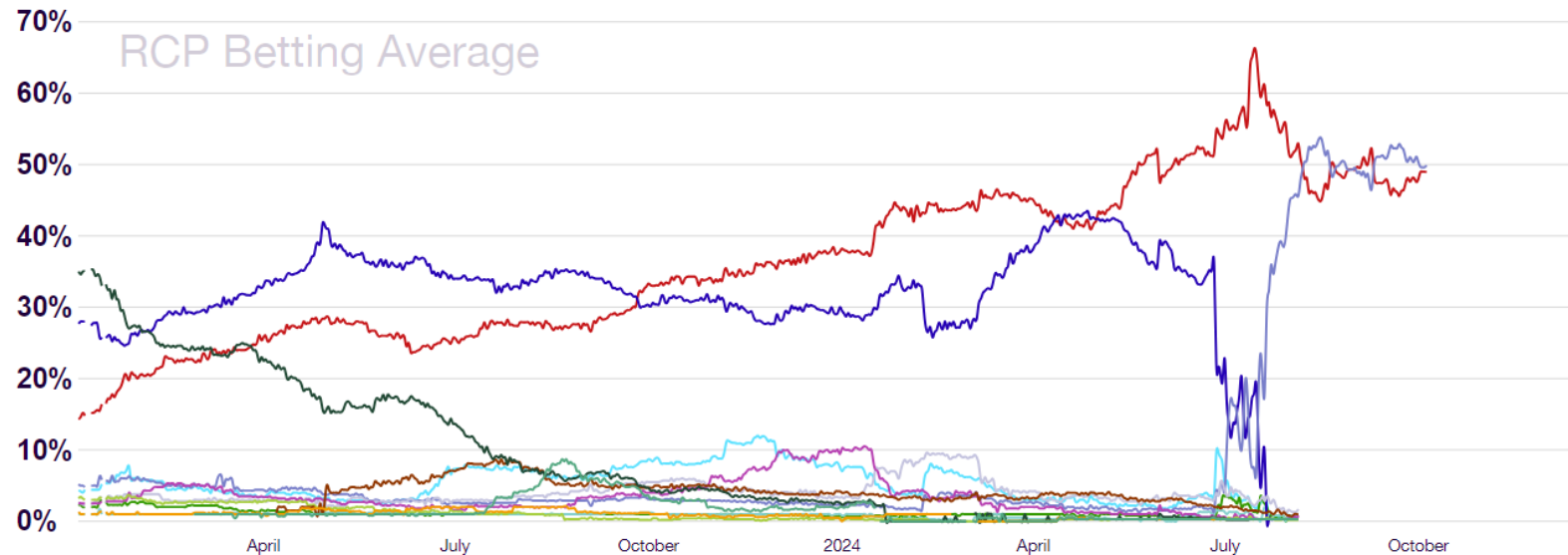


RealClearPolitics Betting Average

49.9 Harris

48.9 Trump

## 2024 U.S. President



There is some irony in a prognostication from a website called RealClearPolitics. If there is any truth in the data, it is that the outcome of the election is murky and not clear. This race appears to be a tossup.

Source: <https://www.realclearpolling.com/betting-odds/2024/president>





# Biopharma Market Update

Reflection on a Biotech building, South San Francisco, Sep 2024



# The XBI Closed at 97.5 Last Friday (Oct 4), Down 0.9% for the Week

The XBI was down slightly last week as Treasury bonds rose on news of a strong jobs market. An increase in rates is, in general, not a positive for biotech. We would note that Stifel's global biotech value tracker rose slightly last week.

## Biotech Stocks Down Last Week

### Return: Sep 27 to Oct 4, 2024

Nasdaq Biotech Index: -0.7%

Arca XBI ETF: -0.9%

Stifel Global Biotech EV (adjusted): +1.1%\*

S&P 500: +0.2%

### Return: Dec 29, 2023 to Oct 4, 2024 (YTD)

Nasdaq Biotech Index: +7.8%

Arca XBI ETF: +9.2%

Stifel Global Biotech EV (adjusted): +37.3%\*

S&P 500: +20.6%

## VIX Rose

Sep 29, 2023: 17.3%

Dec 29, 2023: 12.45%

Mar 29, 2024: 13.0%

May 17, 2024: 12.0%

Aug 2, 2024: 23.4%

Sep 6, 2024: 22.4%

Sep 20, 2024: 16.1%

Oct 4, 2024: 19.2%

## 10-Year Treasury Yield Up a Lot

Sep 29, 2023: 4.59%

Dec 29, 2023: 3.88%

Mar 29, 2024: 4.20%

May 17, 2024: 4.42%

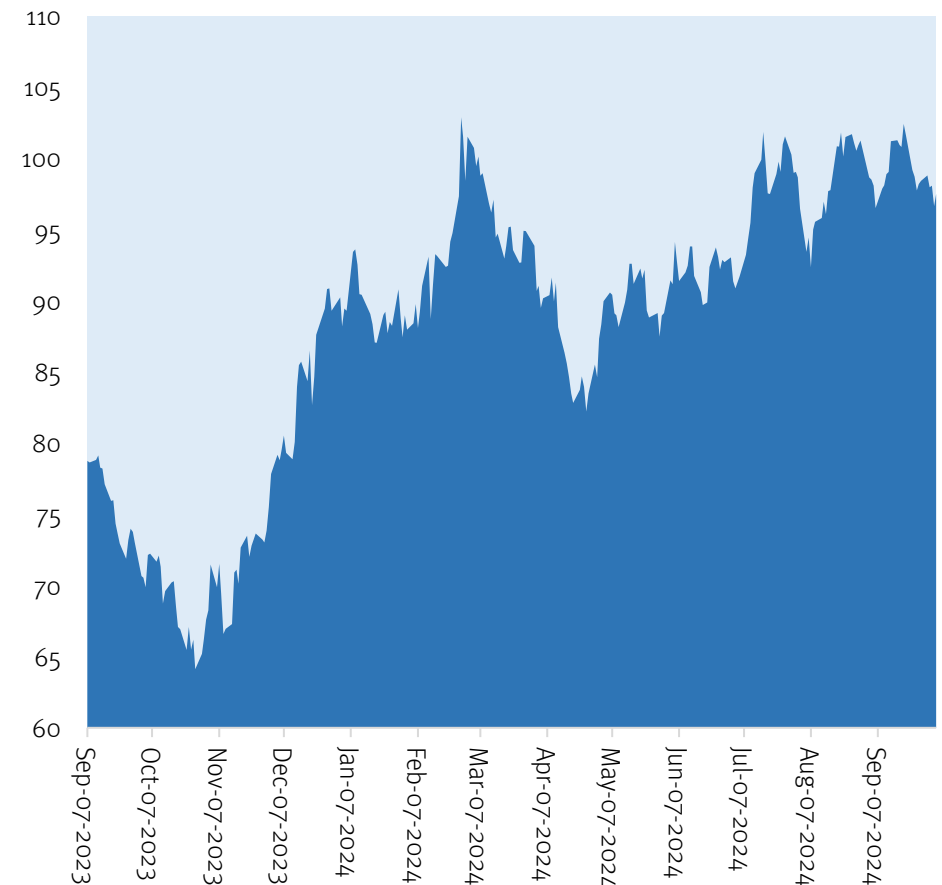
Aug 2, 2024: 3.80%

Sep 6, 2024: 3.72%

Sep 20, 2024: 3.73%

Oct 4, 2024: 3.98%

XBI, Sep 7, 2023 to Oct 4, 2024

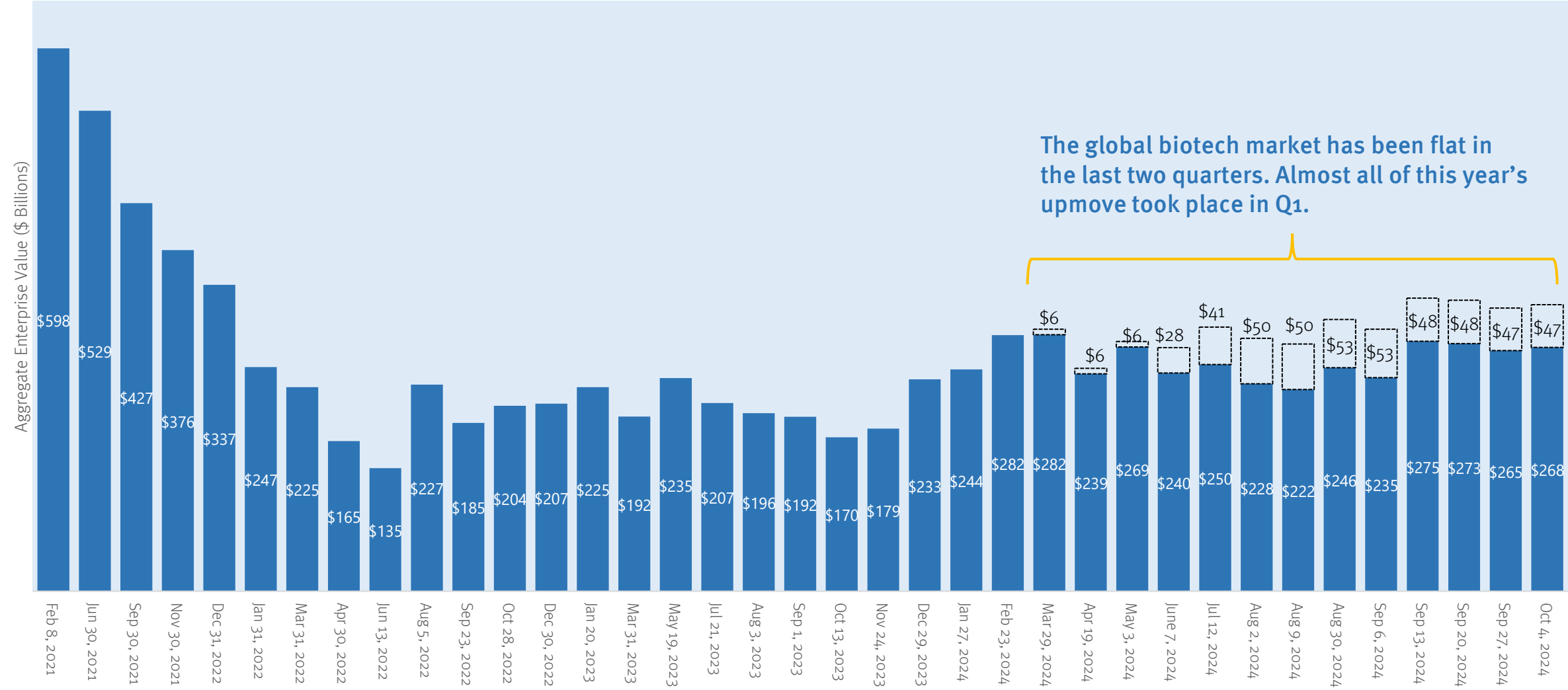




# Total Global Biotech Sector Up 1.1% Last Week

Biotech stocks were up 1.1% in the last week. On a disappearance adjusted basis, biotech is up 35.3% for the year to date (enterprise value). The market has been flat since the start of Q2 2024.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Oct 5, 2024 (\$ Billions)

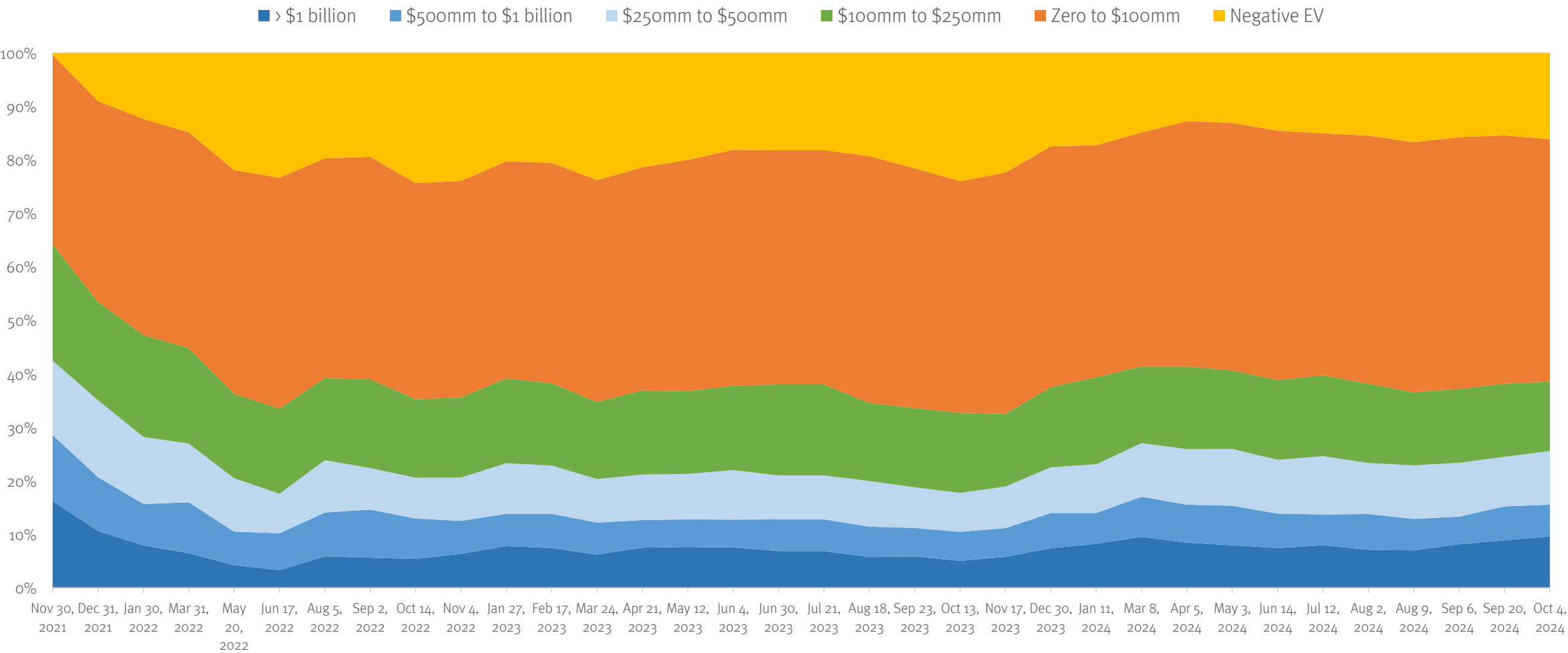


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

# Global Biotech Neighborhood Analysis

The population of high valued biotechs continues to grow. The population of companies worth \$100mm to \$250mm has shrunk meaningfully in recent weeks. The population of companies worth \$100mm or less has been more or less stable all year.

Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Oct 4, 2024



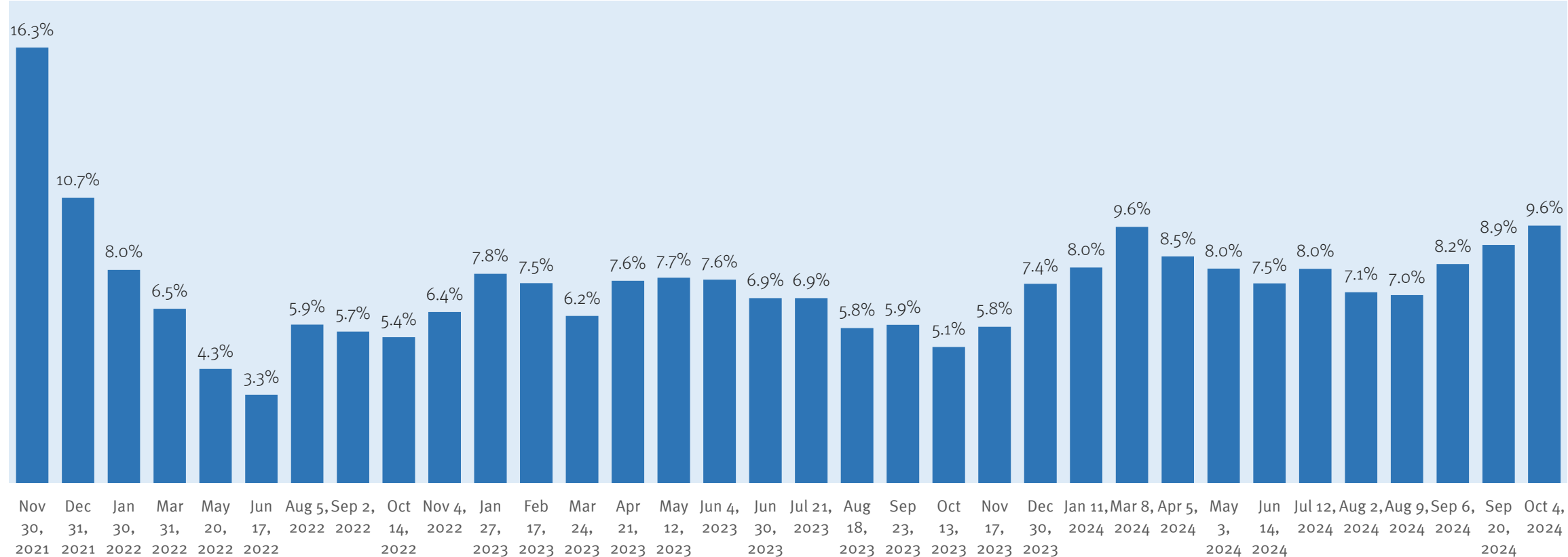
Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.



# The Percent of Biotechs Worth More than a Billion Continues to Rise

On August 9<sup>th</sup>, 2024 there were 56 biotechs with an EV > \$1 billion. As of last Friday, there were 74 such companies.

Percent of Biotechs with an Enterprise Value of \$1bn or More, Nov 2021 to Oct 2024



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

# Life Sciences Sector Total Value Down 0.9% Last Week

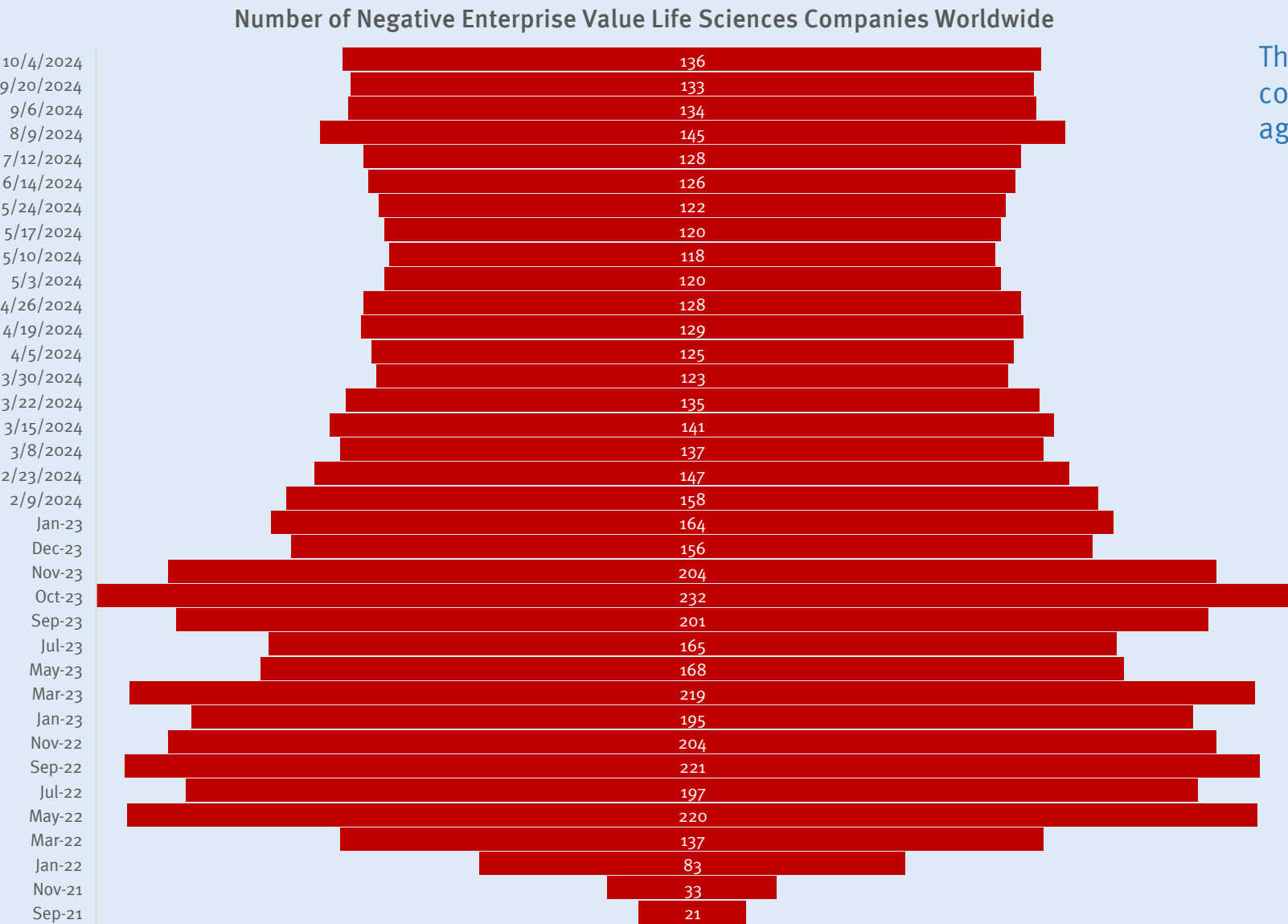
Performance was flat in the life sciences sector last week. The best performing sectors were HCIT, API and pharma services. OTC, medical devices and pharma were all down slightly.

Sector	Firm Count	Enterprise Value (Oct 4, 2024, \$millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	79	\$96,345	3.2%	7.1%	20.1%
Biotech	778	\$262,565	1.1%	9.3%	-5.1%
CDMO	39	\$172,472	1.3%	9.0%	8.7%
Diagnostics	81	\$254,998	-2.1%	2.8%	12.2%
OTC	29	\$26,673	-2.8%	-3.3%	-4.2%
Pharma	713	\$6,724,456	-0.9%	-2.0%	17.4%
Pharma Services	38	\$186,698	1.0%	3.3%	-5.8%
Tools	50	\$725,634	-1.8%	1.5%	14.3%
Devices	180	\$1,792,569	-1.0%	1.5%	20.5%
HCIT	10	\$26,609	13.3%	33.0%	33.0%
<b>Total</b>	<b>1997</b>	<b>\$10,269,020</b>	<b>-0.9%</b>	<b>-0.4%</b>	<b>17.9%</b>

Source: CapitalIQ and Stifel analysis



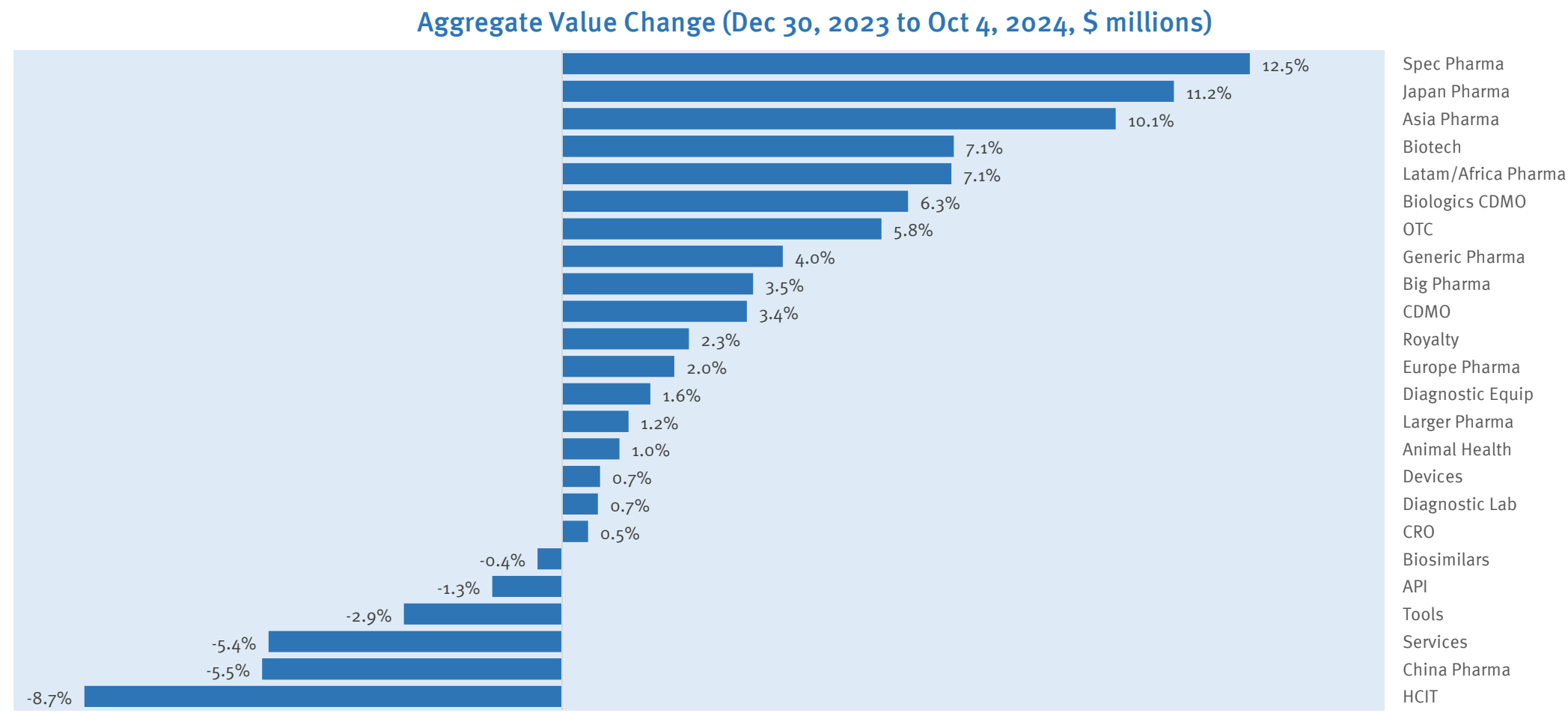
# Count of Negative Enterprise Value Life Sciences Companies Has Changed Little in Recent Weeks



The number of negative EV life sciences companies has risen to 136 from 133 two weeks ago.

# Life Sciences Subsector Performance: 2024 YTD

We are seeing a resurgence in specialty pharma as the rate environment improves. Japan pharma, LatAm pharma biotech and Asia pharma (ex-China, ex-Japan) are also doing well this year. In contrast, pharma services, HCIT and China pharma have all underperformed thus far in 2024.



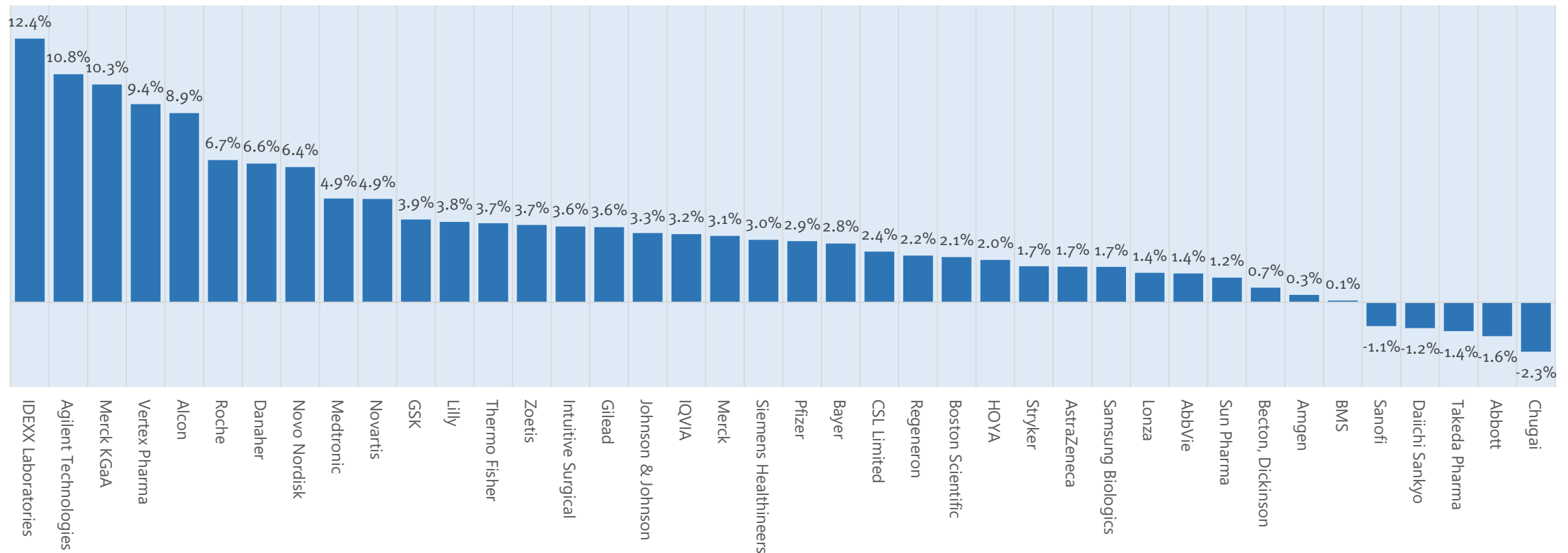
Source: CapitalIQ and Stifel analysis  
Note: This is before adjusting for disappearances and additions due to IPOs.



# Top 40 Players in Life Sciences: Share Price Returns Over Last Two Weeks

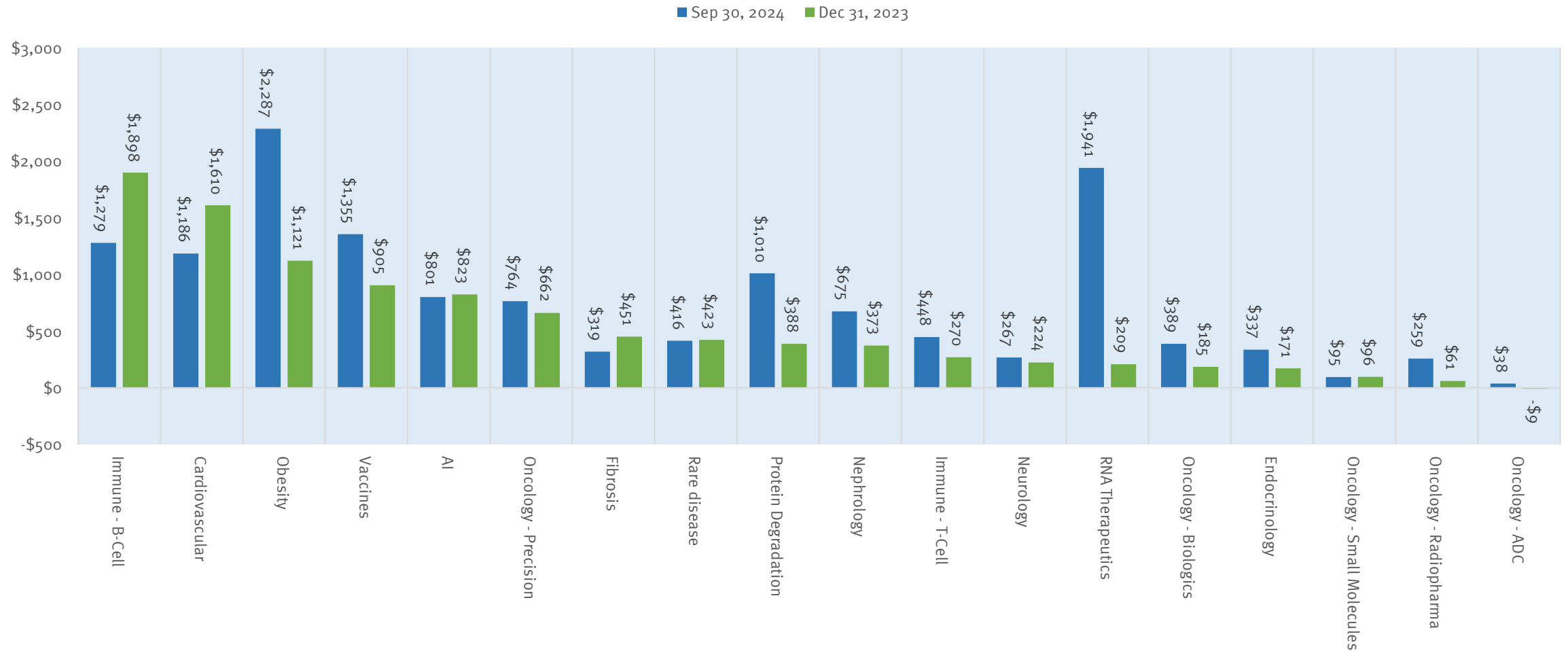
IDEXX, a diagnostics player in animal health, has been the returns leader in recent weeks, followed by Agilent and Merck KGaA. Vertex, Alcon and Roche have done quite well as have Novo Nordisk and Eli Lilly. Chugai, Abbott, Takeda and Daiichi-Sankyo have all underperformed. The Japanese Yen has dropped by 5% in the last two weeks, explaining much of the drop in the Japanese names.

Top 40 Life Science Players: Percent Change in Market Cap, Sep 20 to Oct 4, 2024



# RNA, Obesity, Degraders and Vaccines Have Done Well This Year While CV, B-Cell and Fibrosis Have Lost Ground

Average Enterprise Value of U.S. Listed Biotechs by Therapeutics Area, Sep 30, 2024 vs Dec 31, 2023 (\$ millions)

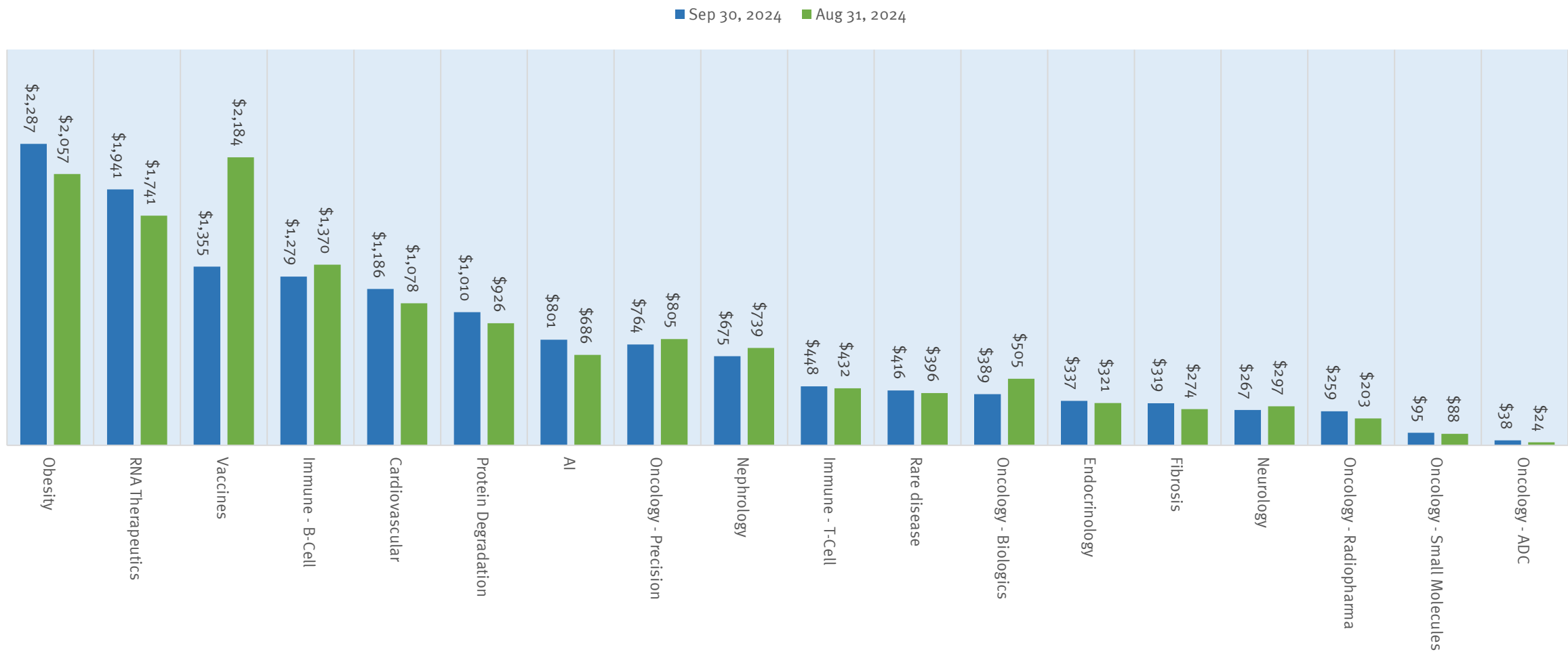


NOTES: Data from CapitalIQ. Sifted categorized companies by therapeutic area.



# Obesity Stocks Power Past Vaccines in the Last Month. RNA, B-Cell, CV and Degraders Doing Best While Oncology Stocks Languish

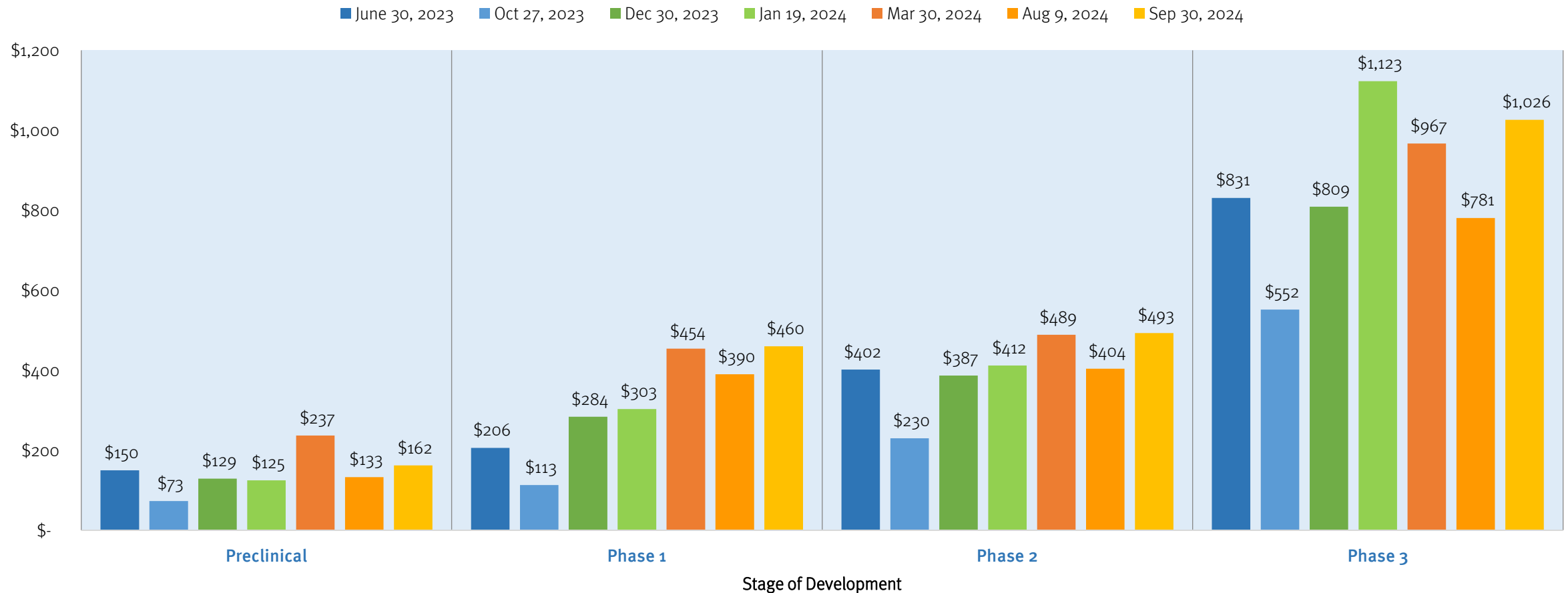
Average Enterprise Value of U.S. Listed Biotechs by Therapeutics Area, Sep 30, 2024 vs Aug 31, 2024 (\$ millions)



NOTES: Data from CapitalIQ. Sifted categorized companies by therapeutic area.

# Value of a Typical U.S. Phase 3 Biotech is up by 30% Over Last Two Months

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development, June 30 2023 to Sep 30, 2024 (\$ Millions)



Notes: Data from CapitalIQ. Stifel categorized companies by therapeutic area.



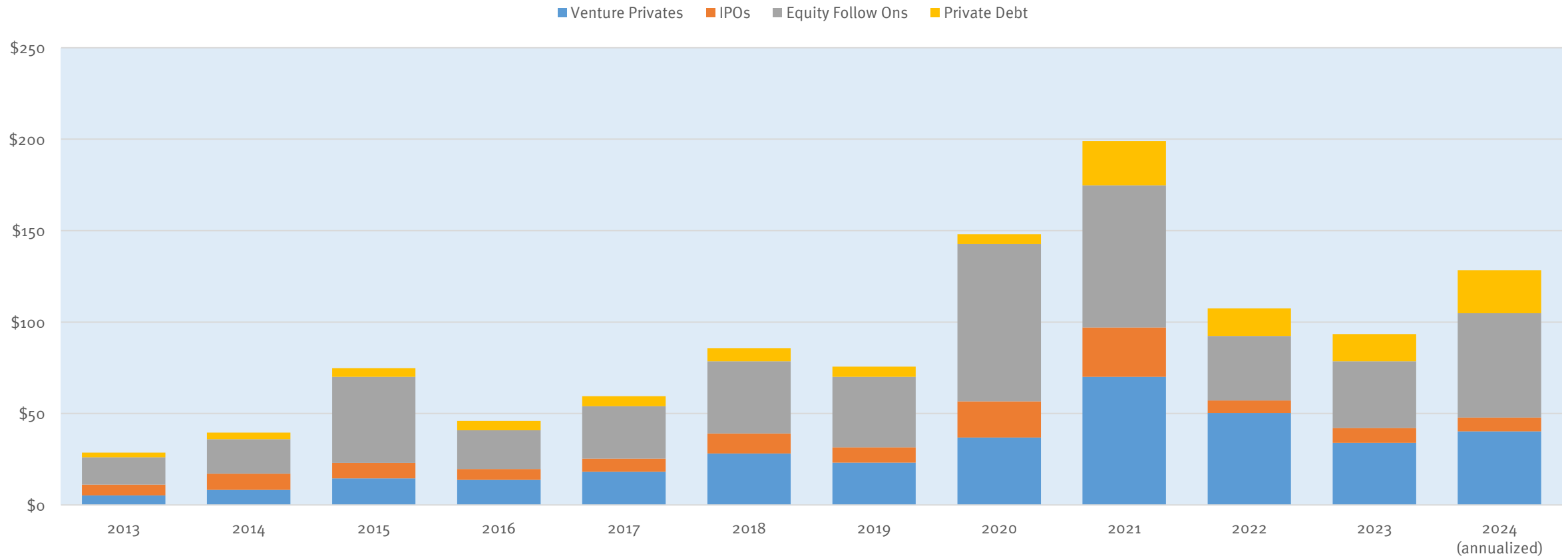
# Capital Markets Update

MIT Facility, Kendall Square, Cambridge, May 2024



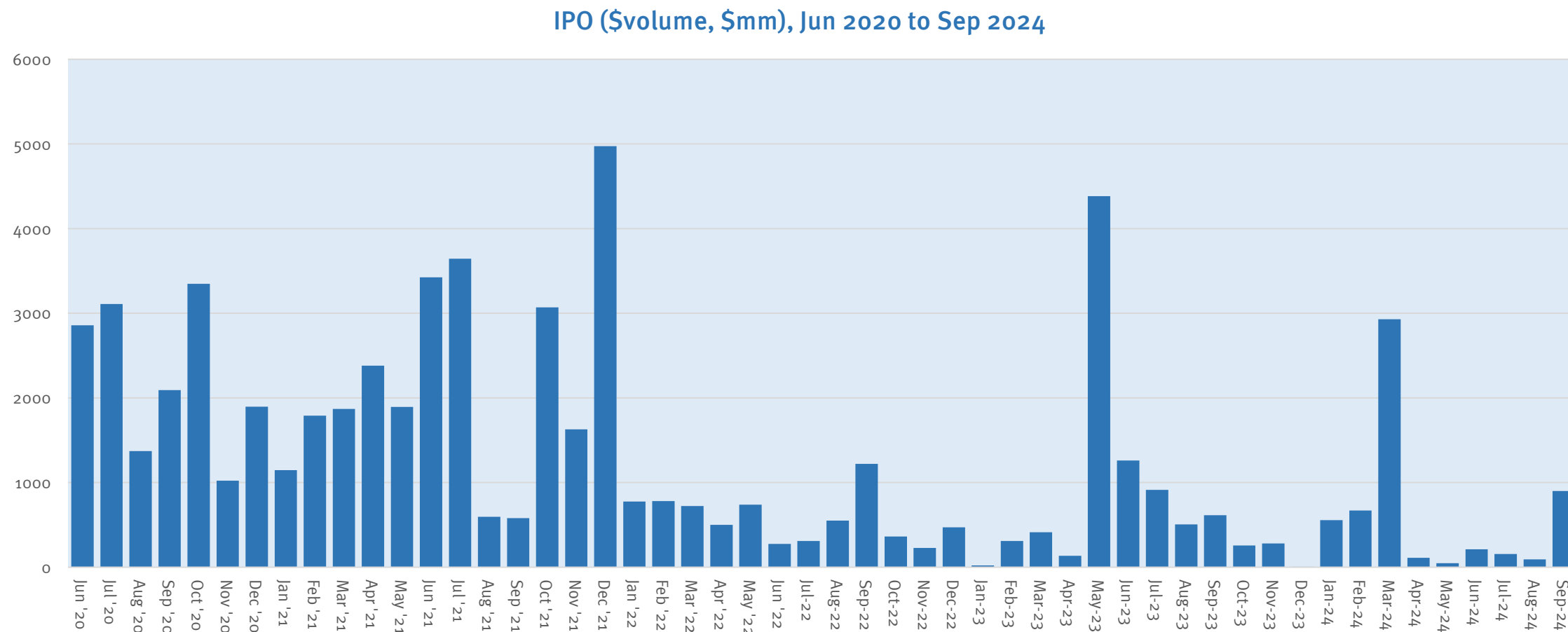
# Through End of Q3 We are on Track for an Up Year in Capital Raises in the Biopharma Sector

Equity and Private Debt Raised in the Biopharma Sector, 2013 - Sep 30, 2024  
(\$ Billions, Worldwide)



# September Saw Close to a Billion Dollars of Biopharma IPOs

After months of inactivity the U.S. IPO market priced four offerings in September (Bicara, BioAge, MBX and Zenas). All four of these companies have traded up in the aftermarket which is a great sign for the market going forward. The IPO market is perking up and is open for strong stories.

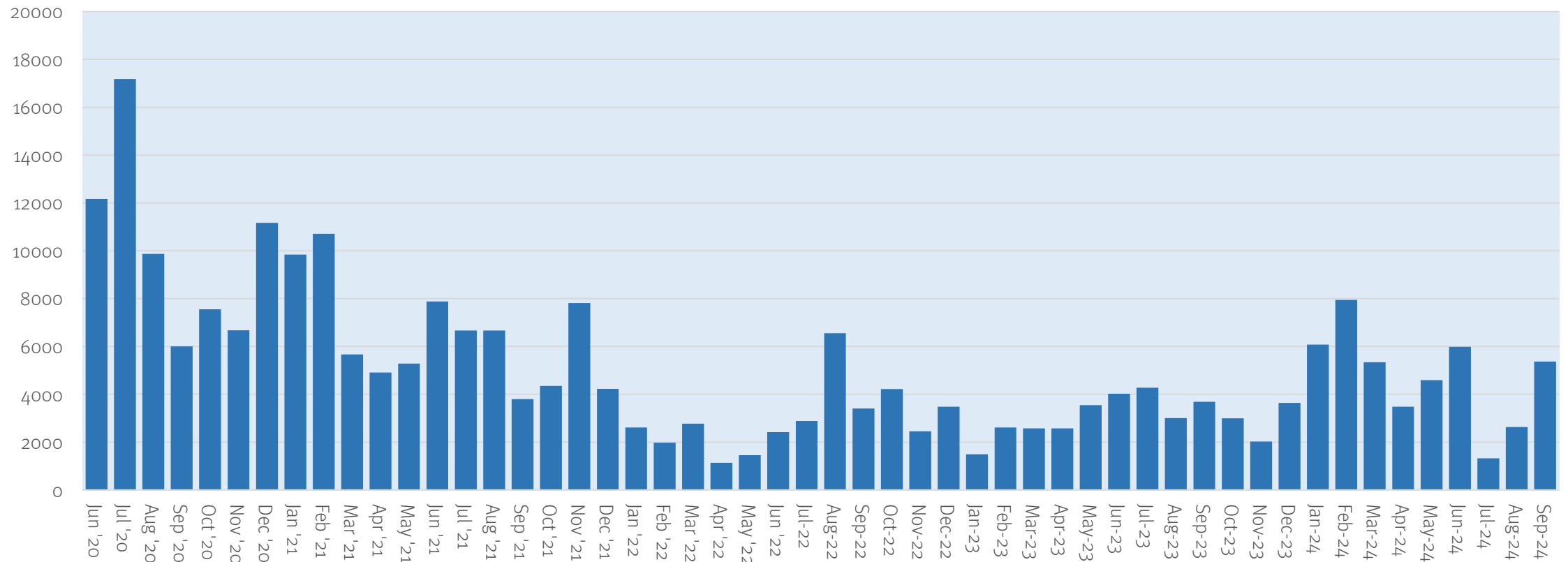




# September 2023 Started as a Strong Month for Follow-Ons

We saw the equity follow-on market open up after Labor Day with guns blazing – only to slow down in the last three weeks of September. Issuers were keen to take advantage of the window surrounding the Fed rate cut and wanted to stay well away from the election period. The biopharma equity follow-on market remains highly catalyst driven. Ten of twelve major follow-ons that took place in September were accompanied by a data event. Most issuers have had market caps over \$1 billion. The market remains challenging for smaller issuers that lack tangible data catalysts.

Equity Follow-On (\$volume, \$mm), Jun 2020 to Sep 2024

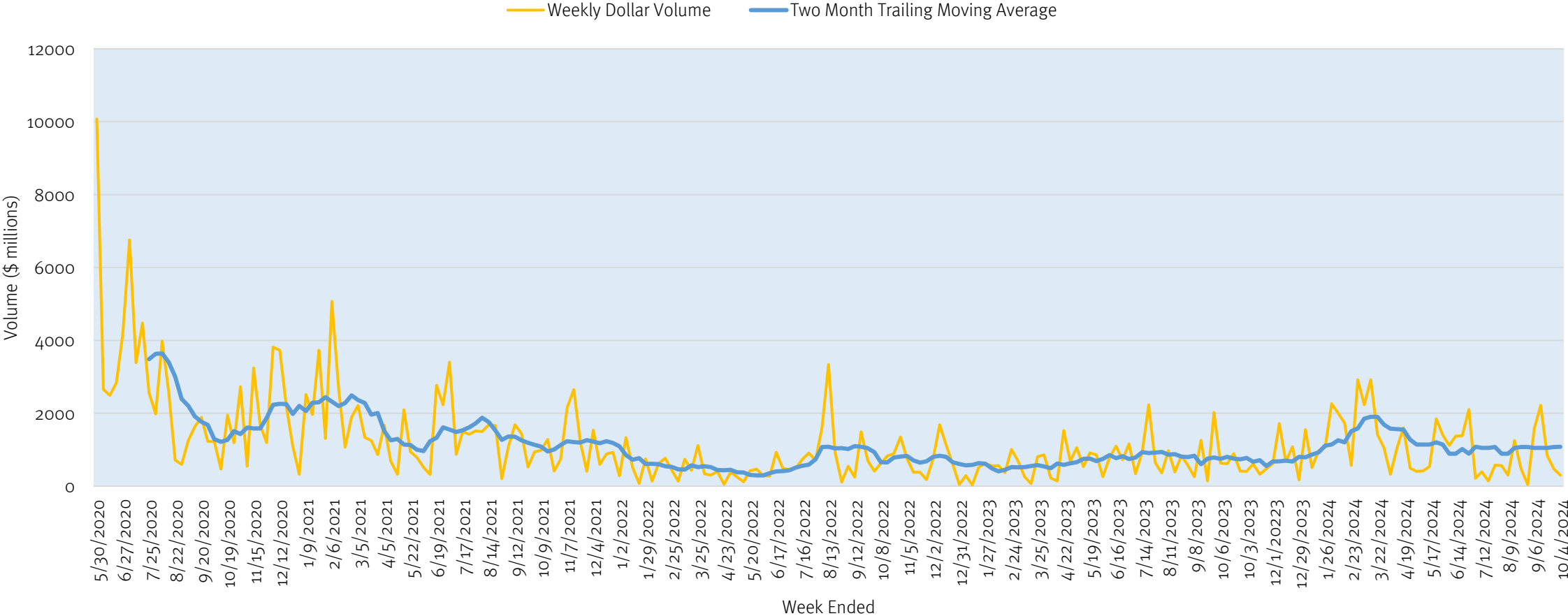


Source: Data from CapitalIQ, Stifel research.

# Equity Follow-On Market Slowed Down in Last Three Weeks

In the first two weeks after Labor Day we saw \$3.8 billion of equity offerings (an exceptional pace). In the next three weeks, however, we saw only \$1.6 billion. The market has returned to the type of pace that was seen in the 2022 and 2023 time periods.

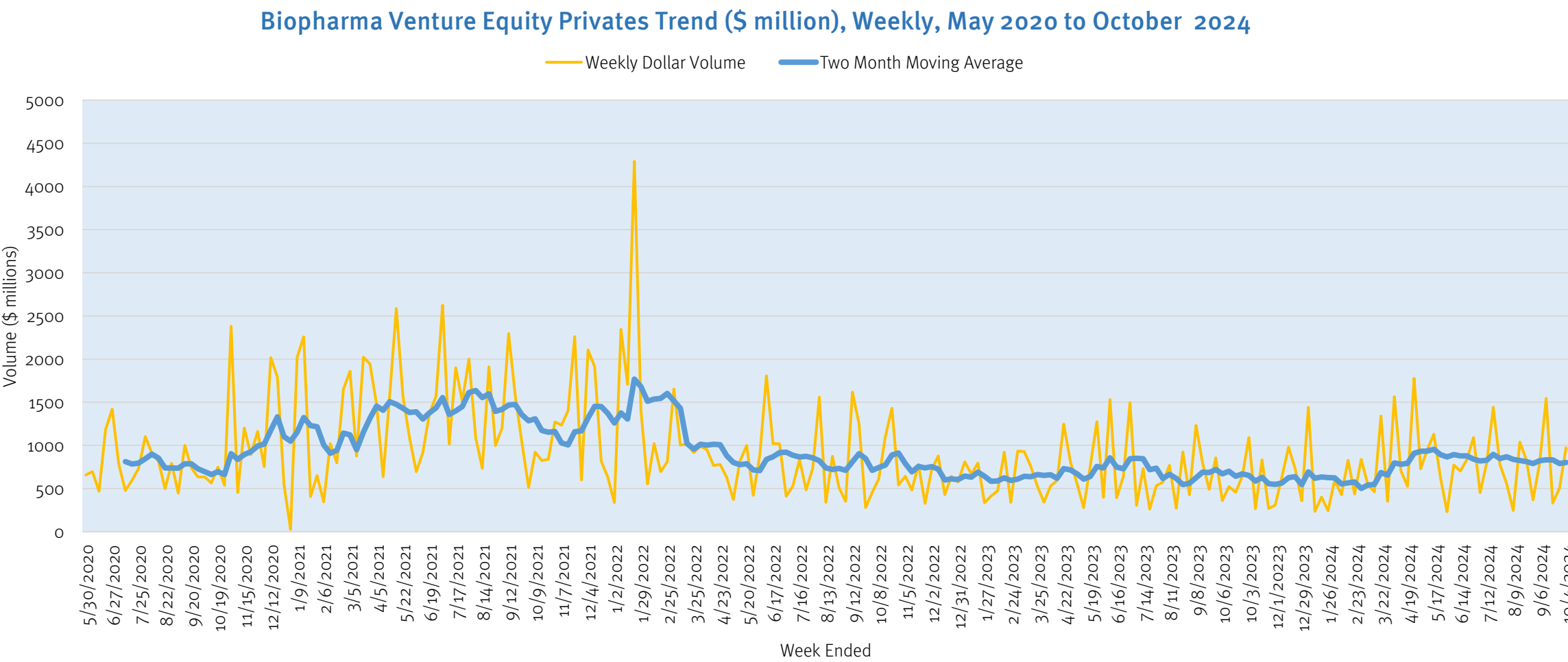
Biopharma Equity Follow-On Volume (\$ million), Weekly, May 2020 to October 2024



Source: Data from CapitalIQ.

# Private Venture Equity Market Normal in Recent Weeks

Weekly volume of venture privates this year has averaged \$750mm. The volume in recent weeks has been in line with this average.



Source: Data from CapitalIQ, Crunchbase.



# Kailera Therapeutics Launches with \$400 Million Series A to Advance Portfolio of Next-Generation Therapies for Obesity

**Press Release, Boston, MA, October 1, 2024**

Kailera Therapeutics, Inc. (“Kailera” or “the Company”), today announced its launch as a clinical-stage biopharmaceutical company focused on advancing a broad pipeline of next-generation therapies for the treatment of obesity and related conditions. Kailera launches with a \$400 million Series A financing co-led by Atlas Venture, Bain Capital Life Sciences, and RTW Investments, with participation from Lyra Capital. The Company is developing several clinical-stage injectable and oral therapies that have demonstrated potential as best-in-class treatments for chronic weight management.

Kailera acquired exclusive rights for global development and commercialization of a portfolio of four metabolic disease assets outside of greater China from Jiangsu Hengrui Pharmaceuticals Co., Ltd (Hengrui), a leading global pharmaceutical company, in May 2024.

Kailera’s most advanced program, KAI-9531 (in development as HRS9531 in China) is an injectable GLP-1/GIP (glucagon-like peptide-1, glucose-dependent insulintropic polypeptide) receptor dual agonist that demonstrated compelling results in Phase 2 trials in obesity and type 2 diabetes in China. The Company is also advancing a diversified pipeline leveraging several mechanisms and routes of delivery, including KAI-7535, a clinical-stage oral small molecule GLP-1 receptor agonist, KAI-9531 formulated as a once-daily oral tablet, and KAI-4729, an injectable GLP-1/GIP/glucagon receptor tri-agonist.

“In this period of rapid innovation in the metabolic space, I believe that Kailera is poised to make an impact beyond the current market leaders. We have an incredible opportunity to develop next-generation treatments for chronic weight management, helping people reclaim their health and live their lives to the fullest,” said Ron Renaud, Chief Executive Officer, Kailera Therapeutics. “With a clinically-advanced, differentiated pipeline, a talented and experienced team with a track record for building companies with lasting impact, and the support of a world-class investor syndicate, we are uniquely positioned to advance innovative therapies that have the potential to meaningfully impact both quality of life and overall health for many people.”



# Ron Renaud, Biotech's Serial CEO, is Ready for a New Assignment — And Maybe Another Deal?

Adam Feuerstein, Stat+, October 3, 2024 (excerpt)

When it comes to delivering shareholder value through M&A, Ron Renaud is a biotech investor's best friend. Over the last 10 years, all three of the companies he has helmed were sold to Big Pharma for a combined \$16 billion.

With that track record — and the financial windfall it brings — no one would have begrudged Renaud, 55, had he desired to spend more time with his Cape Cod fishing buddies. But he can't quit biotech. Weeks after overseeing the close of Cerevel Therapeutics's \$8.7 billion acquisition by AbbVie, Renaud is back as CEO of Kailera Therapeutics, a newly formed company with a pipeline of weight loss drug candidates.

"I like fishing, but you can't do it every day," Renaud told me. "But the older I get, the more I realize that I like doing this. You figure out what really works, what doesn't work, and you also figure out who you want to work with." At Kailera, that means coming full circle. The obesity company is backed by a fairly astounding \$400 million in new capital, co-led by Atlas Ventures, Bain Capital, and RTW Investments.

Several executives who worked with Renaud at his prior companies have also joined the management team at Kailera. The company's chairman is John Milligan, the former CEO of Gilead Sciences, who some old-timers might remember was engaged in a contentious legal fight with Idenix (and Renaud) over hepatitis C drug patents. Now, Milligan and Renaud are simpatico. "Ron is uniquely positioned because of his experience, his intelligence, and I think his EQ, as much as his IQ," said Adam Koppel, a partner at Bain Capital. "Ron has an uncanny ability — in a humble way and with real humility — to build and lead a team. I've rarely seen someone who is so well liked by people at all levels."

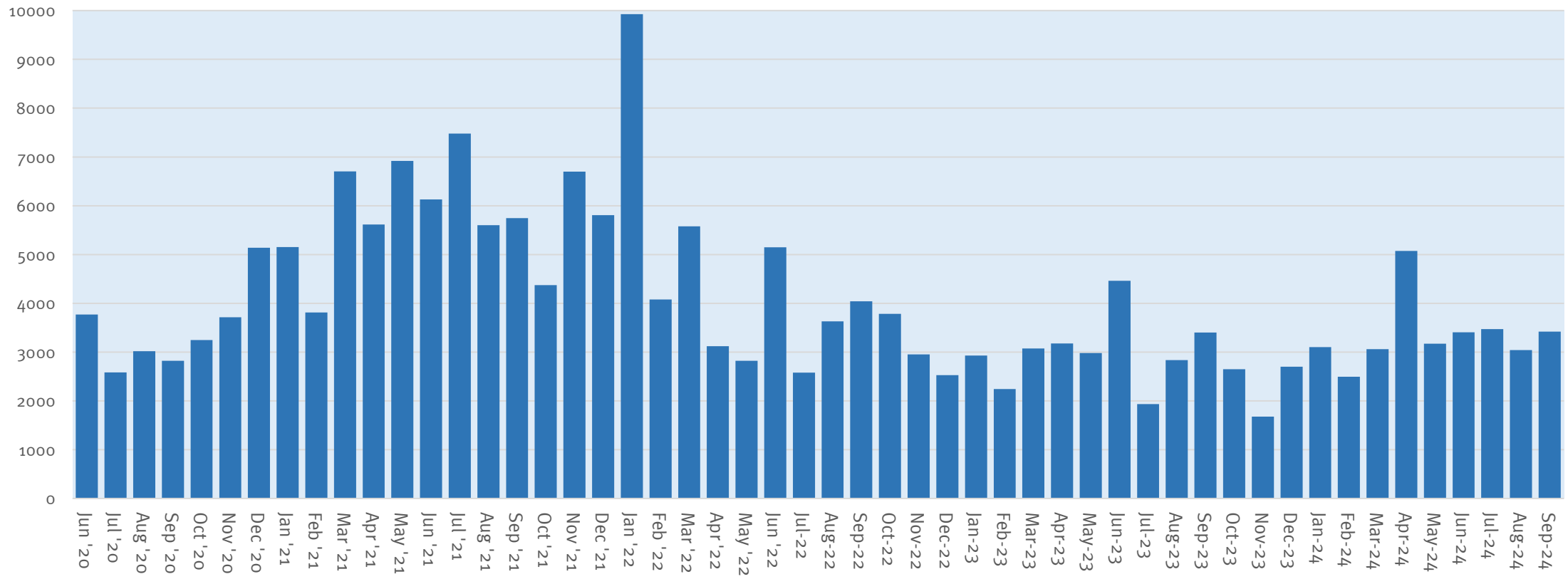
Renaud said he learned his people-centric approach to biotech management while working in Amgen's finance department in the 1990s. Asked by legendary Amgen CEO Gordon Binder to identify the company's most essential asset, Renaud replied "Epogen," at that time Amgen's biggest-selling drug. Wrong, said Binder, pointing out the window to an employee parking lot at the end of the workday. "Our most important asset is driving off the lot right now," Renaud remembers Binder telling him. "The minute we lose sight of having the best people in the business, the business is going away."



**Ron Renaud**  
*Chief Executive Officer*  
Kailera Therapeutics

# Biotech Venture Financing Volume Flat in September Versus Rest of the Year

Monthly Private Equity Placement (\$volume, \$mm), Jun 2020 to Sep, 2024



Source: Data from CapitalIQ, Stifel research.

# Crossover Financings and PIPEs Slow Down in Q3 2024

Stephen Taub, *Institutional Investor*, Oct 3 2024 (excerpt)

Hedge fund activity in the venture capital business for biopharma and life sciences companies slowed down in the third quarter. Even so, many of the hedge fund firms — most of which have dedicated VC funds — remain on pace to complete their largest number of deals for a full year since 2021 or 2022, the peak of the market.

RA Capital Management continues to lead. It made nine new investments in the third quarter — just two in September — more than other life sciences hedge fund firms traditionally involved in venture capital, according to Crunchbase. However, this was down significantly from the firm's 22 investments in the second quarter and 27 in the first quarter, according to the website.

In 2024 so far, RA Capital has completed 58 deals, already exceeding the 46 private investments it made in 2023 and the 44 in 2022. It remains short of the 82 deals completed in 2021, Crunchbase notes. Most of the private investments have been in early-stage deals, especially when RA Capital was the lead investor.

Perceptive Advisors also sharply scaled back its activity in the third quarter, when it made just five new investments, compared with 16 in the second quarter and 15 in the first, according to Crunchbase. The 36 total deals so far this year, however, exceed the 19 it made in 2023 and the 21 in 2022. It made 50 private investments at the peak in 2021, per Crunchbase.

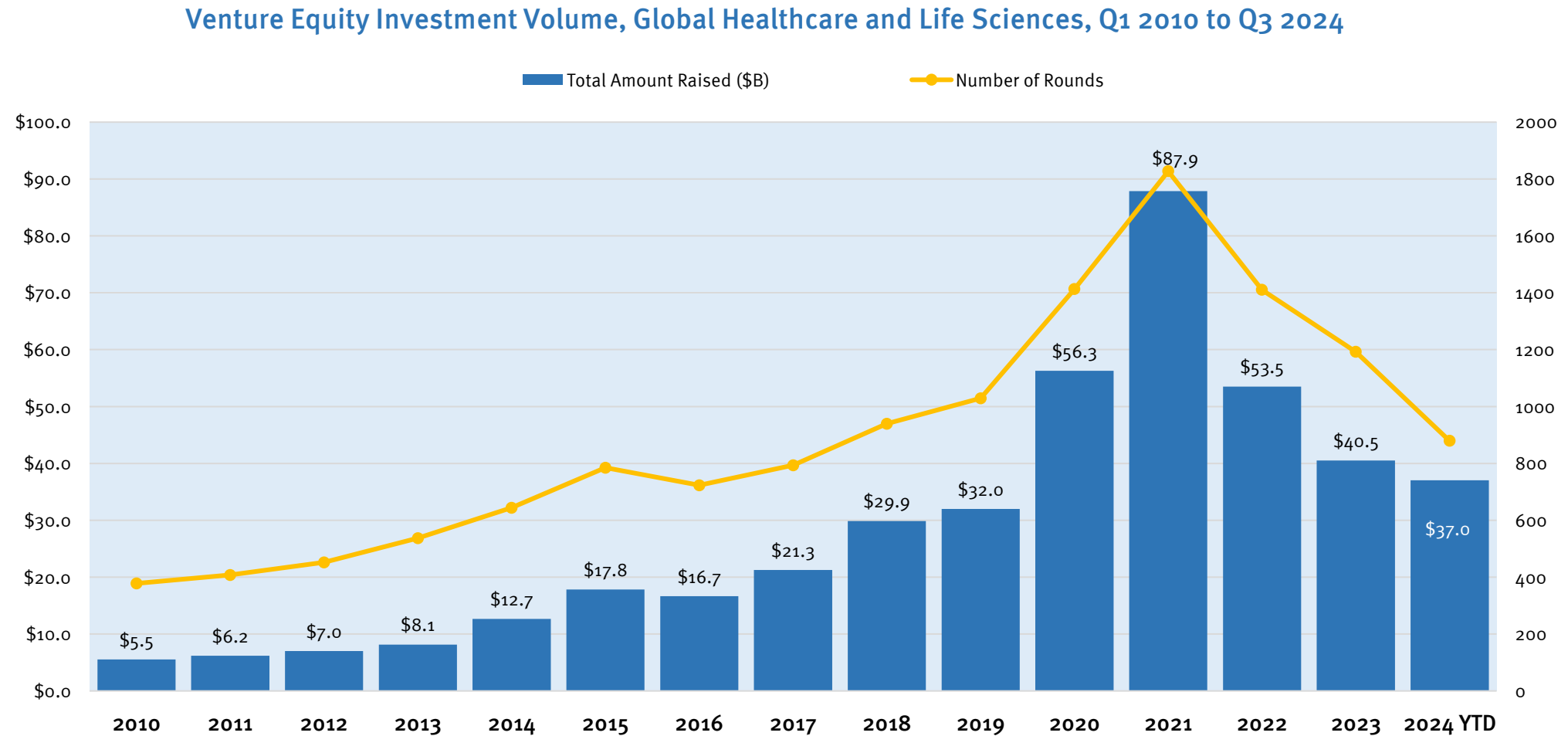
RTW Investment completed three private deals in the third quarter, down from six and ten in the second and first quarters, respectively. It made at least ten investments in 2023, 13 in 2022, and 27 in 2021, per Crunchbase.

EcoR1 Capital has made 14 investments this year, but just three in the third quarter. Even so, the full-year total already exceeds the 11 the firm made in 2023 and equals the number in 2022.

At least one firm boosted its activity in the third quarter. Cormorant Asset Management made seven new investments in the period after doing five in the second quarter. Altogether, it has made 20 new investments this year, compared with 23 in 2023 and 20 in 2022, Crunchbase says. Most recently, Cormorant led a \$65 million Series A financing of GC Therapeutics, which is working on the next generation of cell therapy medicines.

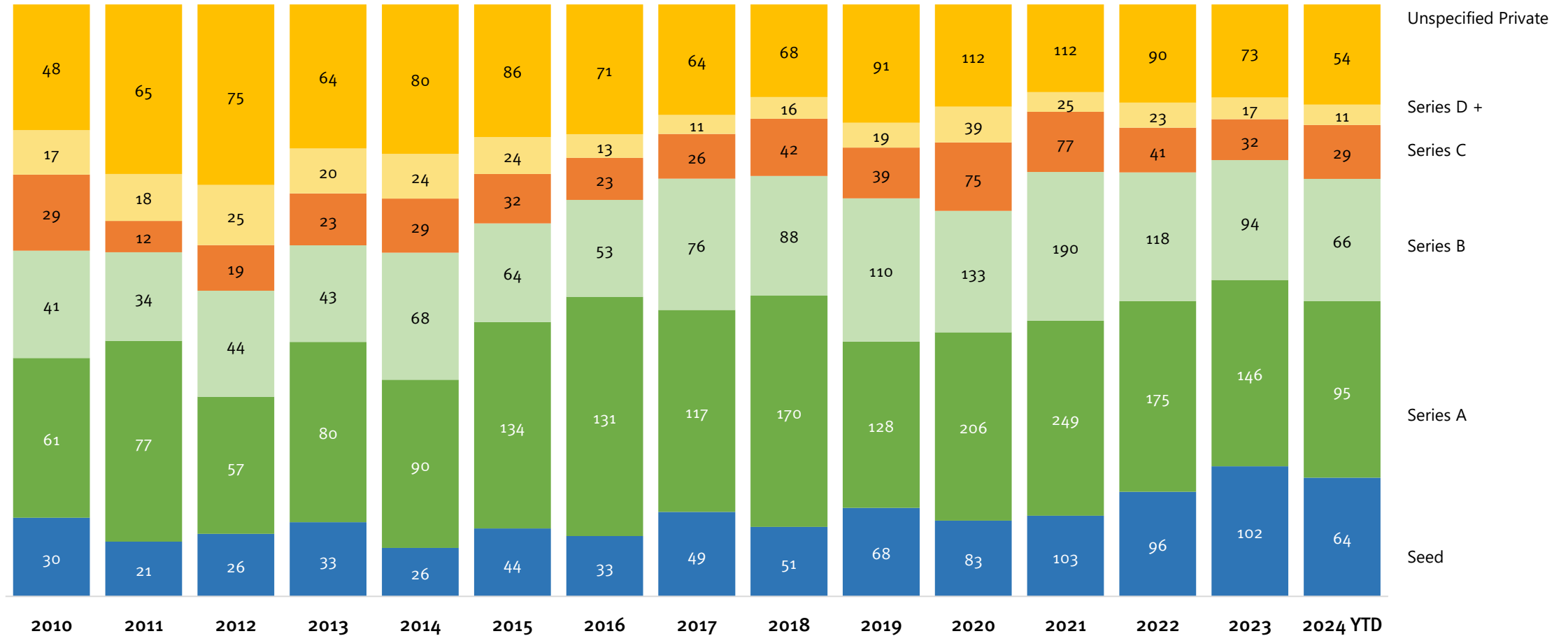


# Global Venture Investment Volume in Healthcare and the Life Sciences is Down in 2023 and 2024



# Earlier Stage Rounds More Common in 2023 to 2024 Period

Share of Number of Venture Rounds by Series - Biopharma (\$B), Q1 2010 to Q3 2024



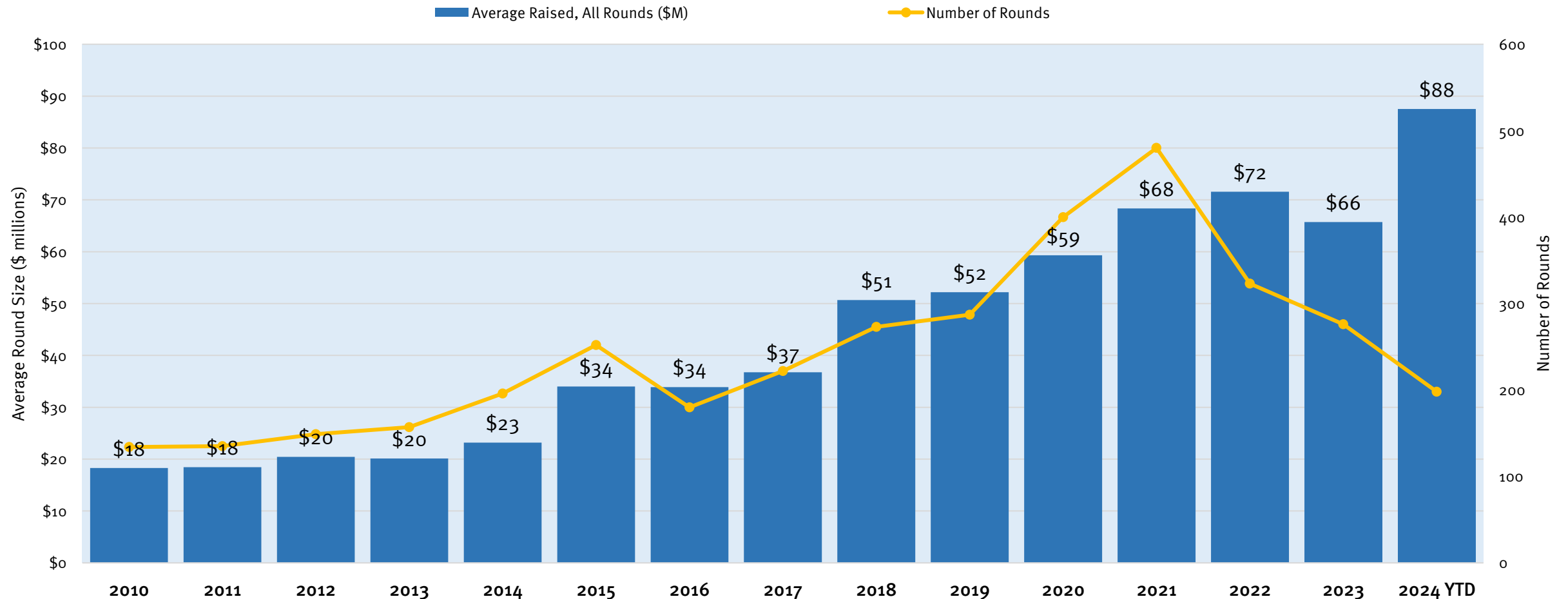
# Biotech Venture Dollars Bunching in Series A and B Rounds in 2024

Global Biopharma Venture Equity Investment Dollar Totals by Series – Q1 2010 to Q3 2024 (\$ billions)

Year	Seed	Series A	Series B	Series C	Series D and Beyond	Unspecified Private	Total
2010	\$0.1	\$0.8	\$1.0	\$0.8	\$0.4	\$0.6	\$3.6
2011	\$0.0	\$1.1	\$0.8	\$0.3	\$0.6	\$0.6	\$3.4
2012	\$0.1	\$0.8	\$0.9	\$0.6	\$0.9	\$1.0	\$4.3
2013	\$0.1	\$1.2	\$0.9	\$0.7	\$0.8	\$0.8	\$4.5
2014	\$0.1	\$1.7	\$2.0	\$0.9	\$0.9	\$0.9	\$6.4
2015	\$0.7	\$3.3	\$2.5	\$1.2	\$1.2	\$2.7	\$11.6
2016	\$0.1	\$3.2	\$2.1	\$1.0	\$0.7	\$2.0	\$9.1
2017	\$0.1	\$3.0	\$3.4	\$1.4	\$0.7	\$2.6	\$11.2
2018	\$0.3	\$7.1	\$4.5	\$3.0	\$1.8	\$1.8	\$18.5
2019	\$0.3	\$4.2	\$7.4	\$2.6	\$1.6	\$2.7	\$18.8
2020	\$0.5	\$9.2	\$9.0	\$5.9	\$3.6	\$4.2	\$32.4
2021	\$1.4	\$10.9	\$16.0	\$8.7	\$2.3	\$4.7	\$44.0
2022	\$1.1	\$7.7	\$8.7	\$3.4	\$2.0	\$5.1	\$27.9
2023	\$1.2	\$7.8	\$7.1	\$3.3	\$1.4	\$2.7	\$23.5
2024 YTD	\$0.8	\$7.0	\$5.8	\$3.1	\$1.5	\$2.6	\$20.8
<b>Total</b>	<b>\$6.7</b>	<b>\$69.0</b>	<b>\$72.1</b>	<b>\$36.8</b>	<b>\$20.4</b>	<b>\$34.9</b>	<b>\$239.9</b>

# Average U.S. Biotech VC Deal Round Size Way Up in 2024 While Number of Venture Deals is Down Substantially

Venture Averages - Biopharma Tx and Platforms - U.S., Q1 2010 to Q3 2024 (\$ millions)

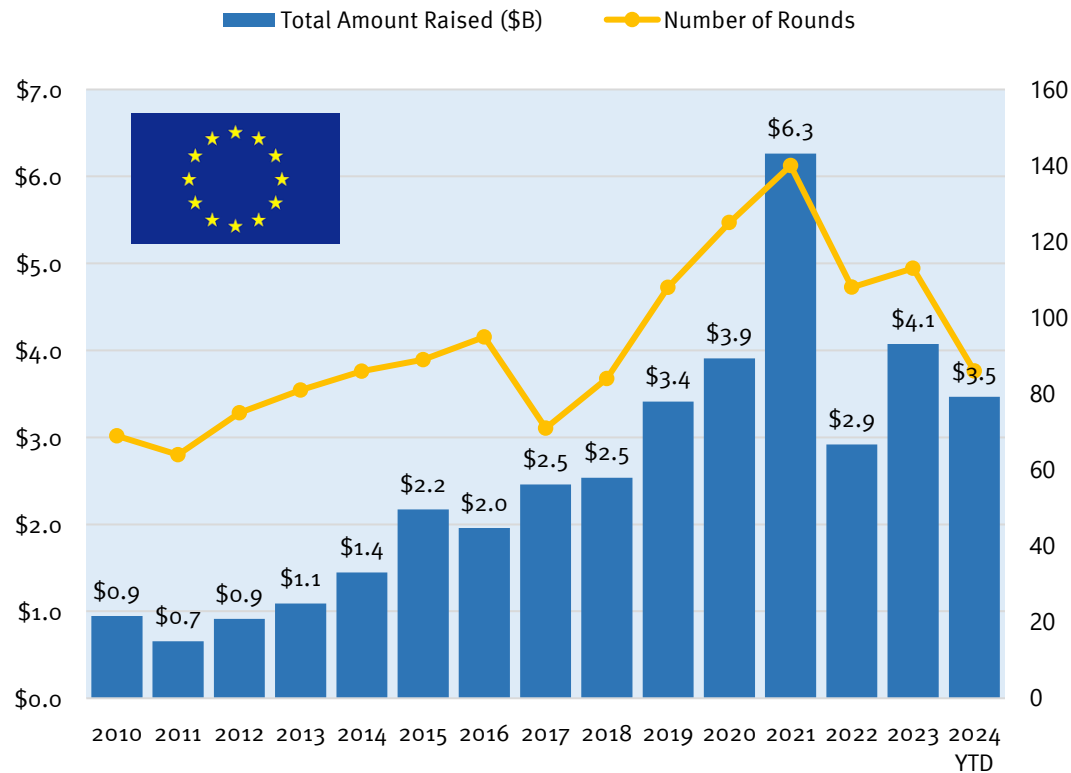


Source: DealForma Database

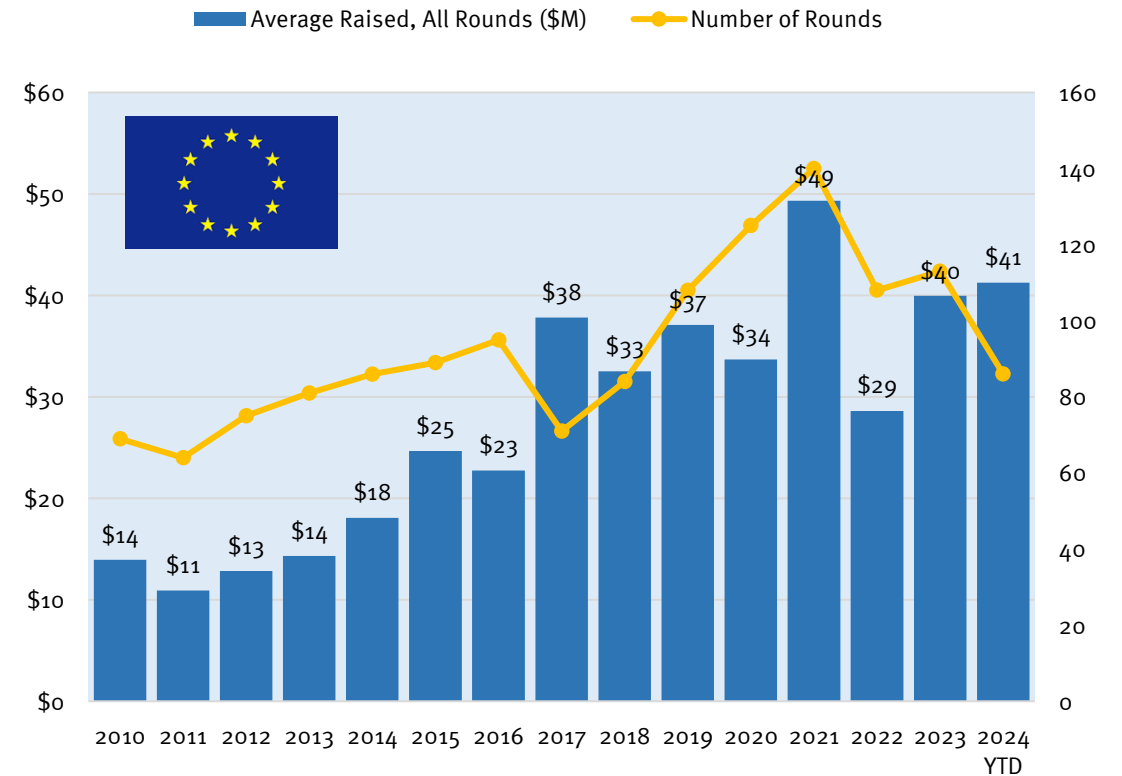


# Europe Biotech Venture Investment Holding Up in 2024 and Average Round Size Stable (But Half the U.S.)

Venture Totals - Biopharma Tx and Platforms – Europe,  
Q1 2010 to Q3 2024



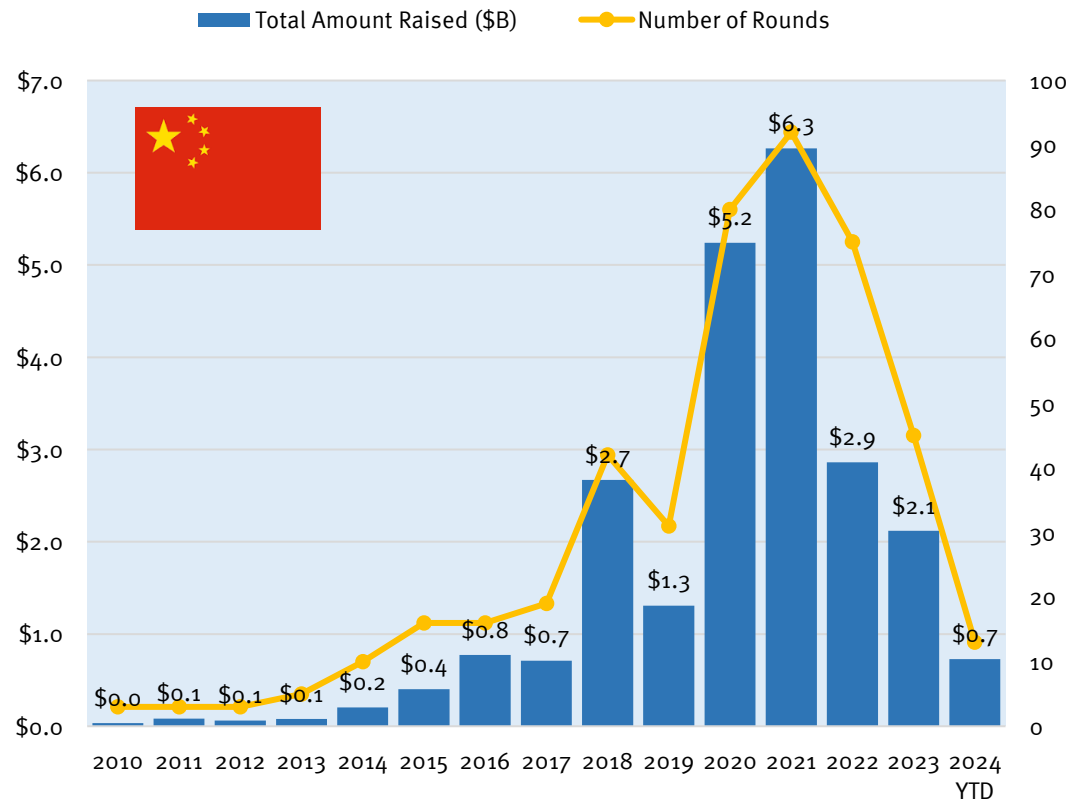
Venture Averages - Biopharma Tx and Platforms – Europe,  
Q1 2010 to Q3 2024



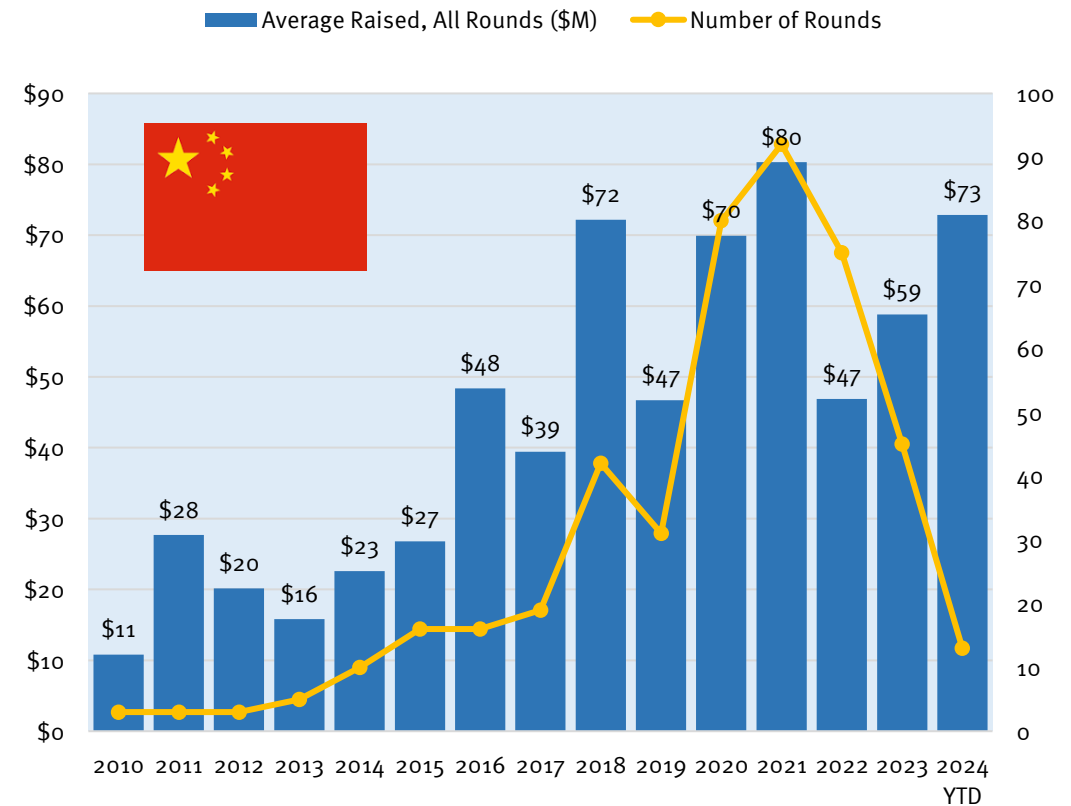
Source: DealForma Database

# China Biotech Investment Way Down in 2024 But Round Size is Up

Venture Totals - Biopharma Tx and Platforms – China, Q1 2010 to Q3 2024

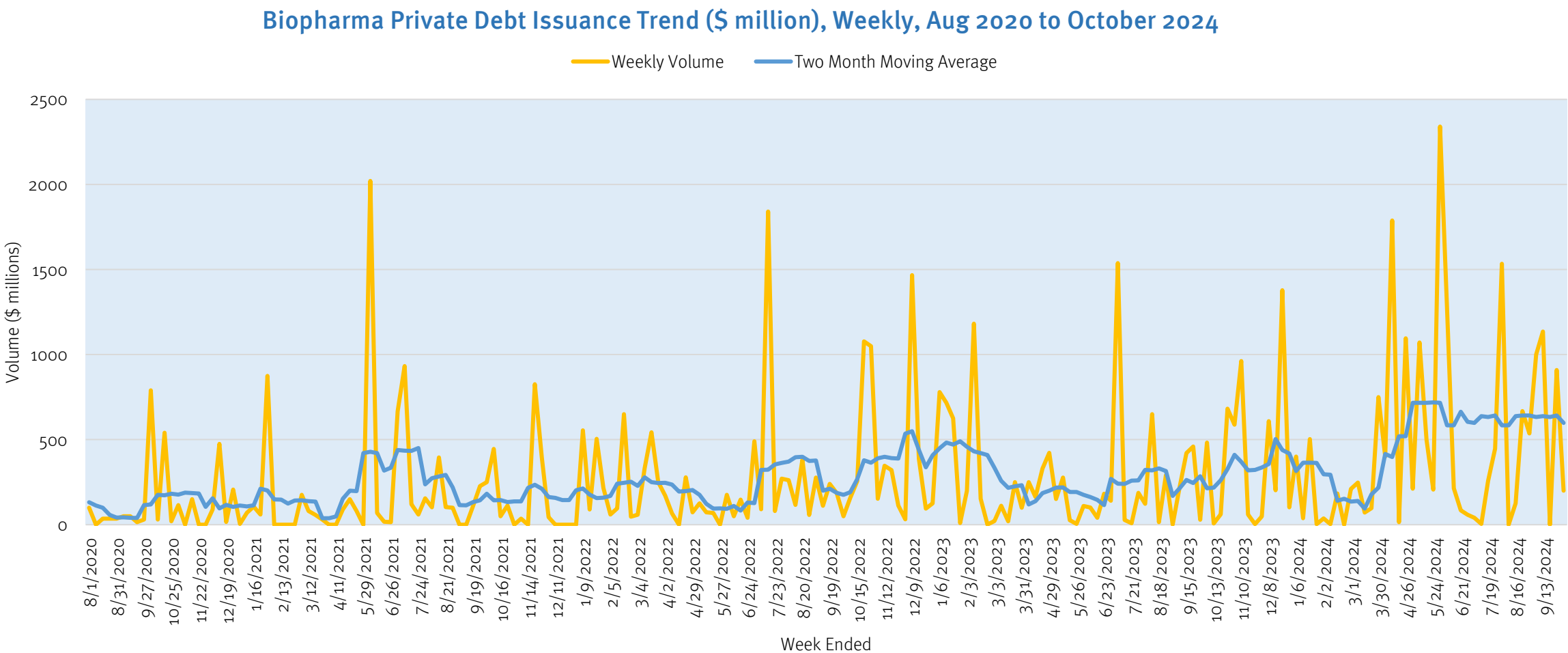


Venture Averages - Biopharma Tx and Platforms – China, Q1 2010 to Q3 2024



# Biopharma Private Debt Market Remains Strong

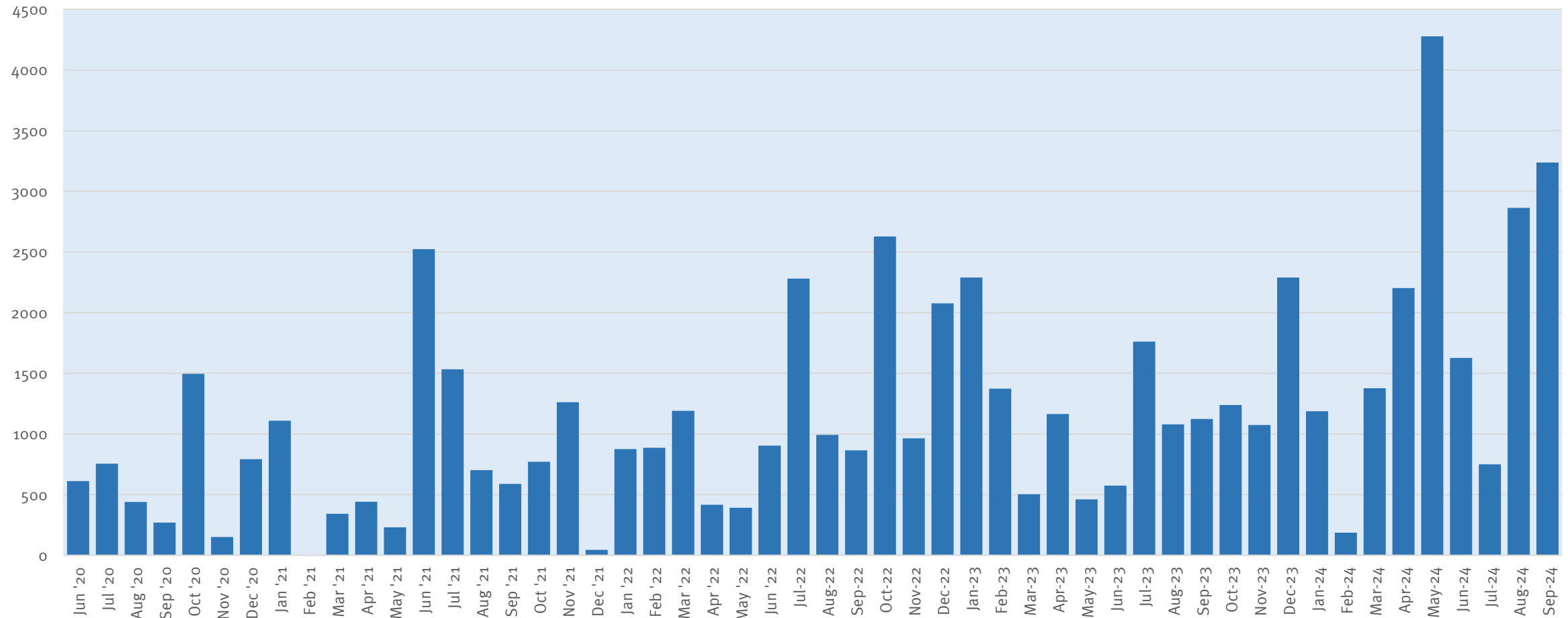
Volumes in the private debt market have been elevated in the last several months. The issuance volume seen in the last four weeks have been in line with the levels seen since May.



Source: Data from CapitalIQ, Crunchbase, Stifel research.

# September Life Sciences Sector Private Debt Issuance Volume Was the Second Highest We've Seen in Years

Private Debt Issuance (\$volume, \$mm), June 2020 to September 2024



Source: Data from CapitalIQ, Stifel research.



# Deal News

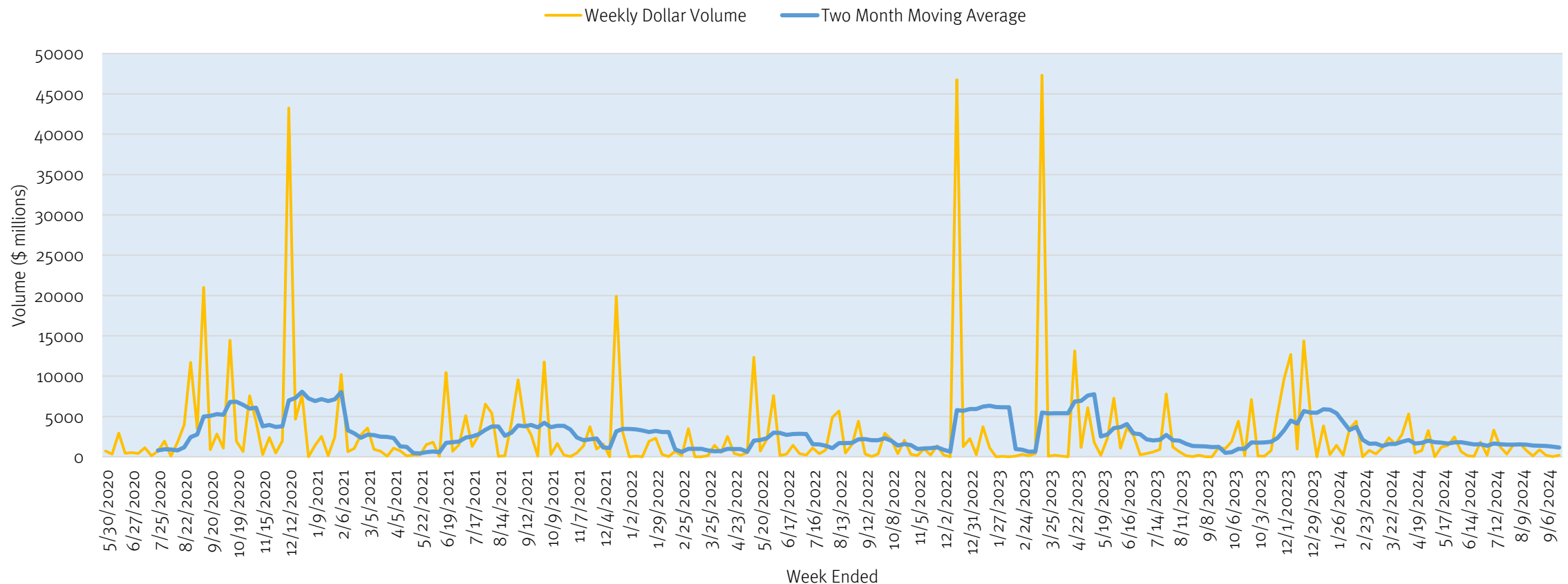




# Last Week Saw Light Biopharma M&A Volume

M&A volume has been very muted in September and last week was no exception. Last week saw two asset deals but no traditional M&A type deals of any size. Recordati acquired Enjaymo® from Sanofi for \$825 million and Genentech bought a portfolio of CDK inhibitors from the Chinese company Regor for \$850 million.

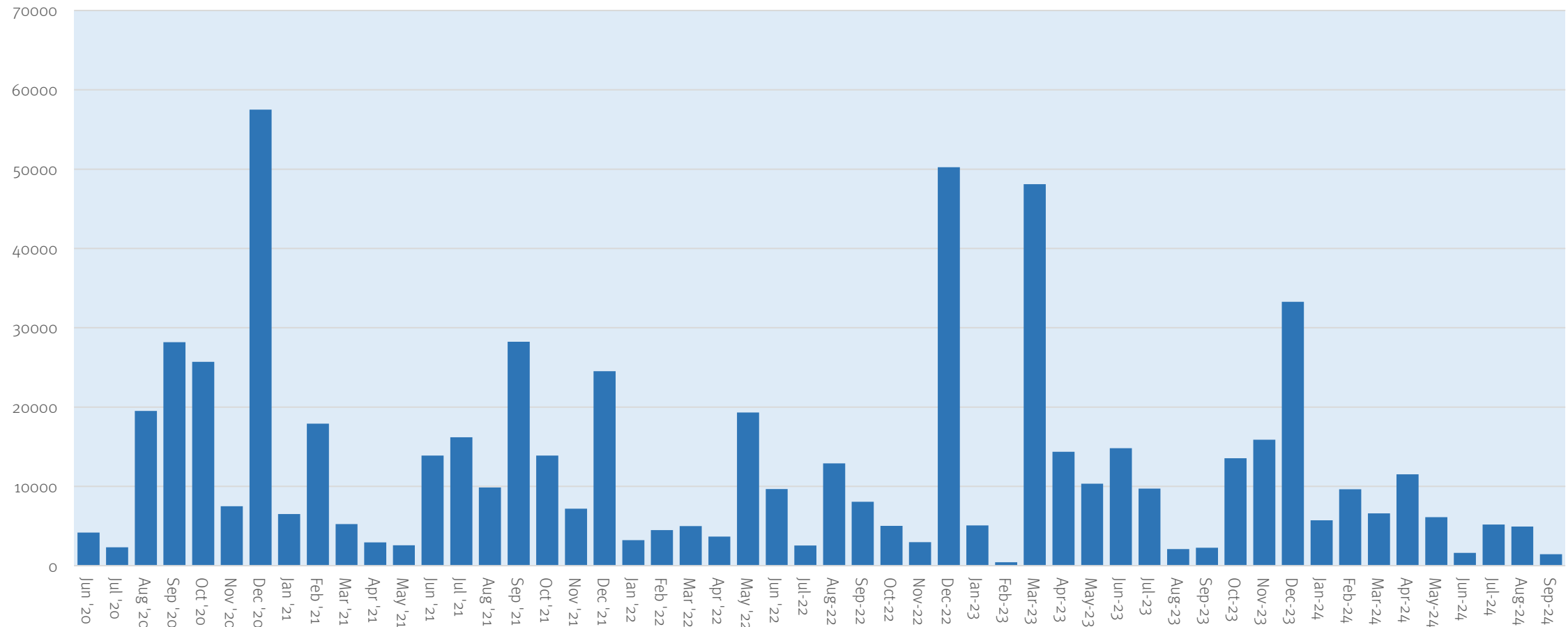
Biopharma M&A Volume Trend (\$ million), Weekly, May 2020 to Sep 2024



# We are in the Midst of Biopharma M&A Doldrums

September 2024 was the slowest month for M&A volume since Feb 2023. As we have gotten closer to the U.S. Presidential election the volume of M&A has slowed to a crawl. We do expect volume to pick up after the election, no matter the outcome.

Monthly M&A Activity (\$volume, \$mm), Jun 2020 to Sep 2024

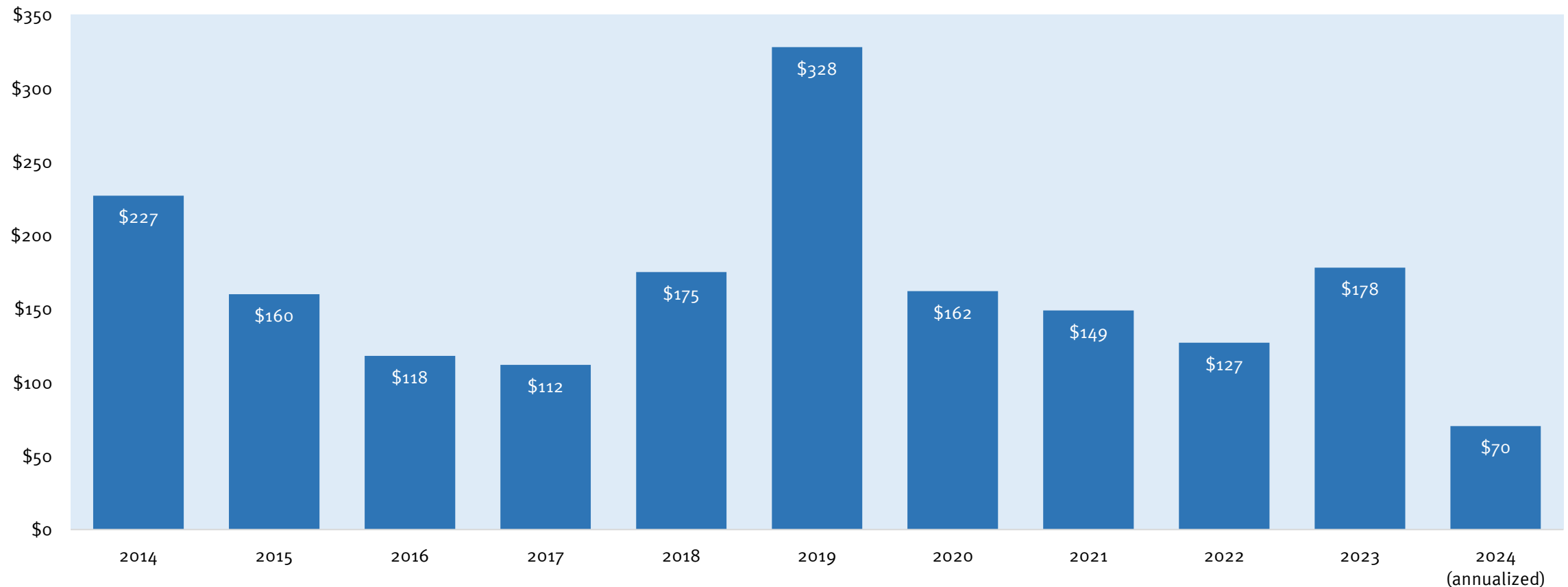


Source: Data from CapitalIQ, Stifel research.

# Data Through Q3 of This Year Points to an Historically Quiet M&A Year

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

(\$ Billions, Worldwide)



Source: Data from CapitalIQ, Stifel research.



# Regor Enters into a Definitive Purchase Agreement for Genentech to Acquire its Portfolio of CDK Inhibitors for the Treatment of Breast Cancer for \$850 Million

Press Release, Sep 30, 2024

Regor Pharmaceuticals (USA) ("Regor") has entered into a definitive purchase agreement whereby Genentech, a member of the Roche Group, will acquire a portfolio of next-generation CDK inhibitors from Regor for the treatment of breast cancer.

Under the terms of the agreement, Regor will receive an upfront cash payment of \$850 million and is eligible to receive additional cash payments based on the achievement of certain predetermined development, regulatory and commercial milestones. Genentech will be responsible for clinical development, manufacturing and commercialization worldwide. Regor will continue to manage the two ongoing Phase 1 trials to their completion: Regor will also advance its other distinct assets, unrelated to this deal, in oncology, metabolic diseases and auto-immunity.

"Genentech is well-positioned to bring these novel therapeutics to their full potential to benefit patients with breast cancer around the world," said Xiayang Qiu, Ph.D., founder and CEO of Regor. " We are proud of the strong data we have generated to date. We look forward to bringing more innovative therapies to patients around the world."



# Recordati Buys Rights to Rare Immune Disorder Drug from Sanofi for \$825 mln

Reuters, Oct 4, 2024

Italian pharma group Recordati said on Friday it would buy from Sanofi the global rights to a drug used to treat cold agglutinin disease (CAD), a rare autoimmune disorder, for \$825 million, sending both stocks up in early trade.

The deal includes additional commercial milestone payments of up to \$250 million and will be completed by year-end, subject to regulatory approval, the Italian company said.

Recordati shares had jumped 5.3% by 0744 GMT, while Sanofi was up 1.3%.

The deal is "very positive" as it will lead to optimised production and an increase in revenues for the Italian firm, a Milan-based trader told Reuters.

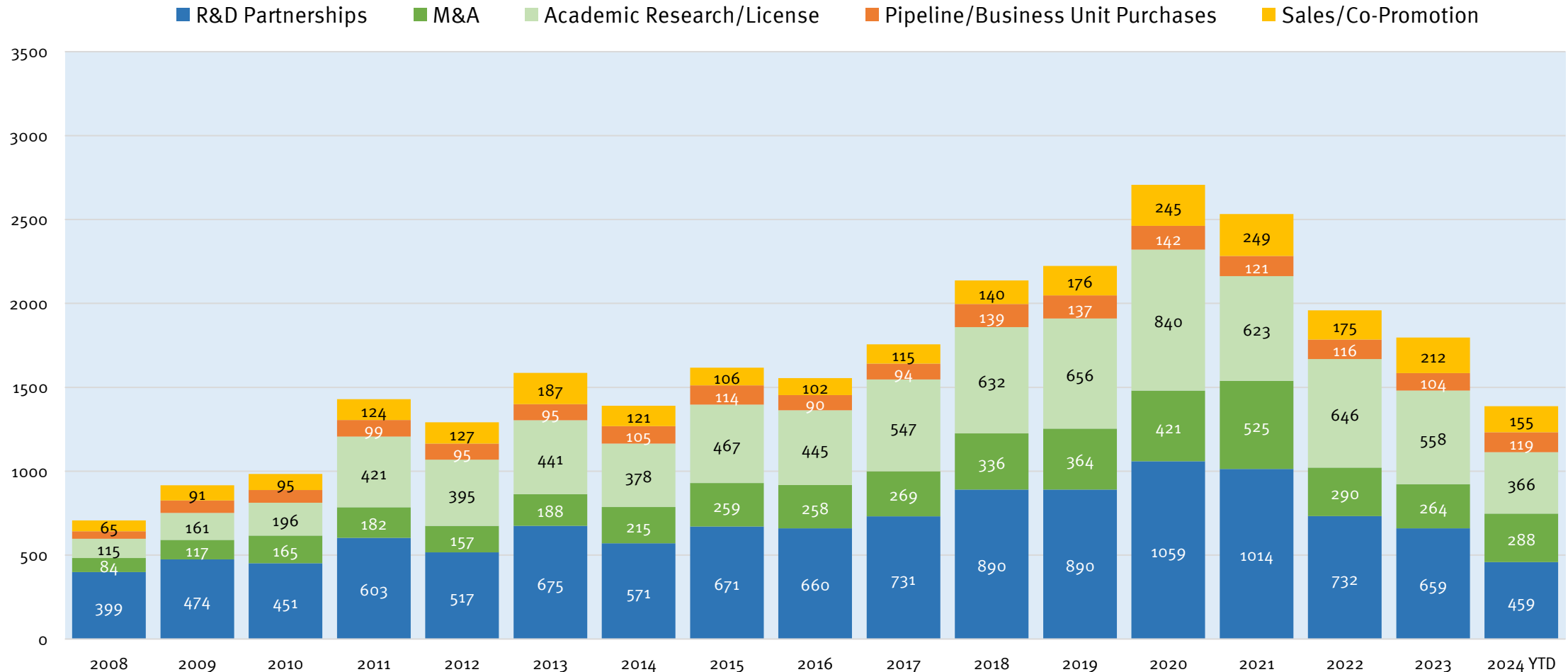
CAD is a rare B-cell lymphoproliferative disorder characterized by the premature destruction of red blood cells.

Recordati said the agreement it signed was for the rights to Enjaymo, a biologic which is the only targeted product for the treatment of CAD approved by the U.S. Food and Drug Administration (FDA).



# We are Seeing an Ongoing Decline in License and Partnership Activity Deal Count vs. 2020/2021 Period

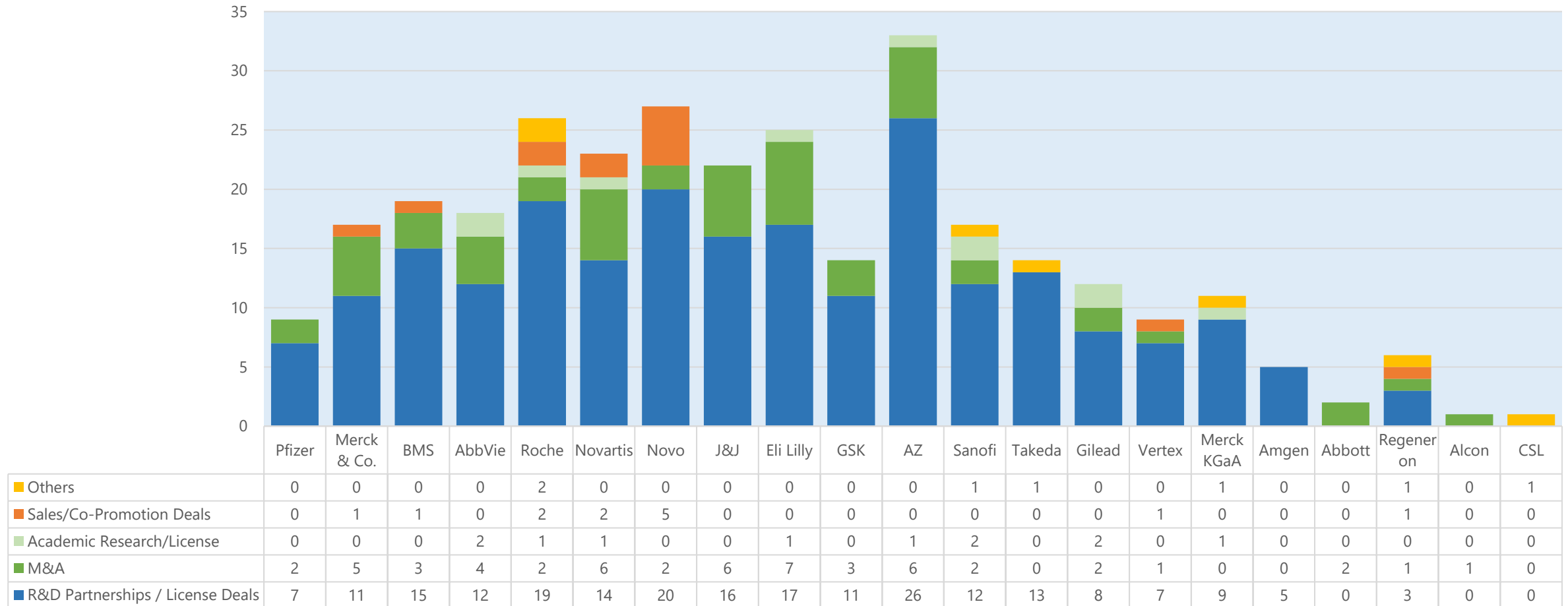
Number of Deals by General Structure - All Healthcare and Life Sciences, Q1 2008 – Q3 2024



# AstraZeneca, Novo Nordisk and Roche Lead in Partnership Deal Activity Since 2023

## Large-Cap Pharma Dealmaking by Type of Transaction, Q1 2023 to Q3 2024

Transaction Count (sorted by number of R&D-stage partnership/license deals)



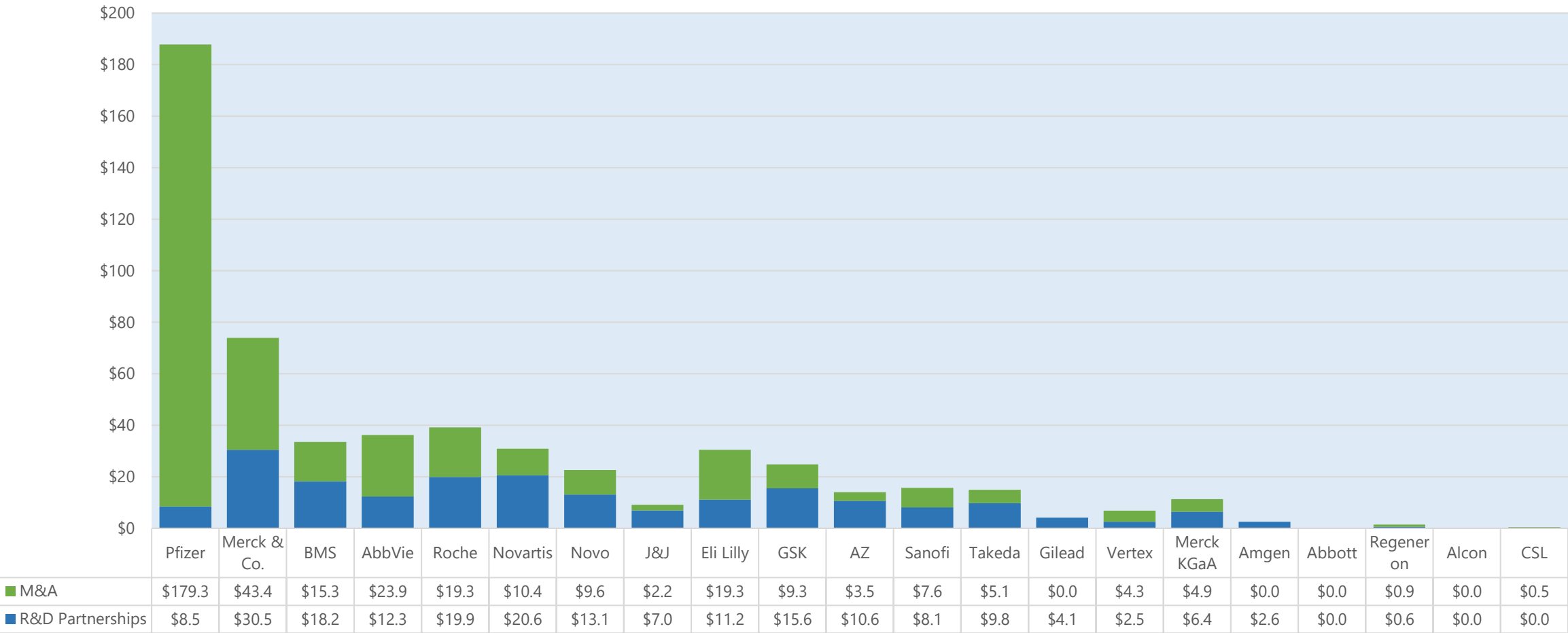
Source: DealForma Database. R&D Partnerships incl. CTAs.



# Pfizer and Merck Lead in Dollar Volume of Big Pharma Dealmaking Activity Since 2023

Large-Cap Pharma Dealmaking by Type of Transaction, Q1 2023 to Q3 2024

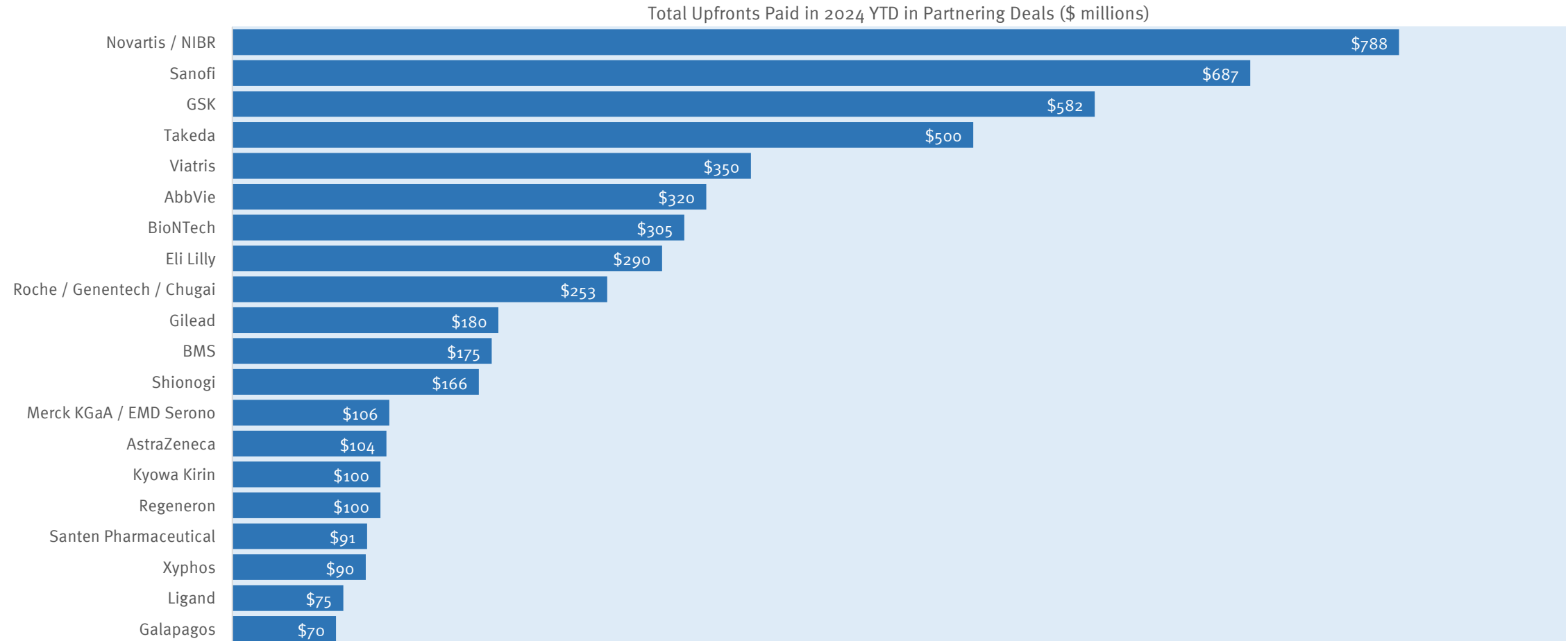
Transaction dollar volume (\$ billions)



Source: DealForma Database. R&D Partnerships incl. CTAs (can filter them out). Financials based on disclosed figures. Asset purchase transactions not included.

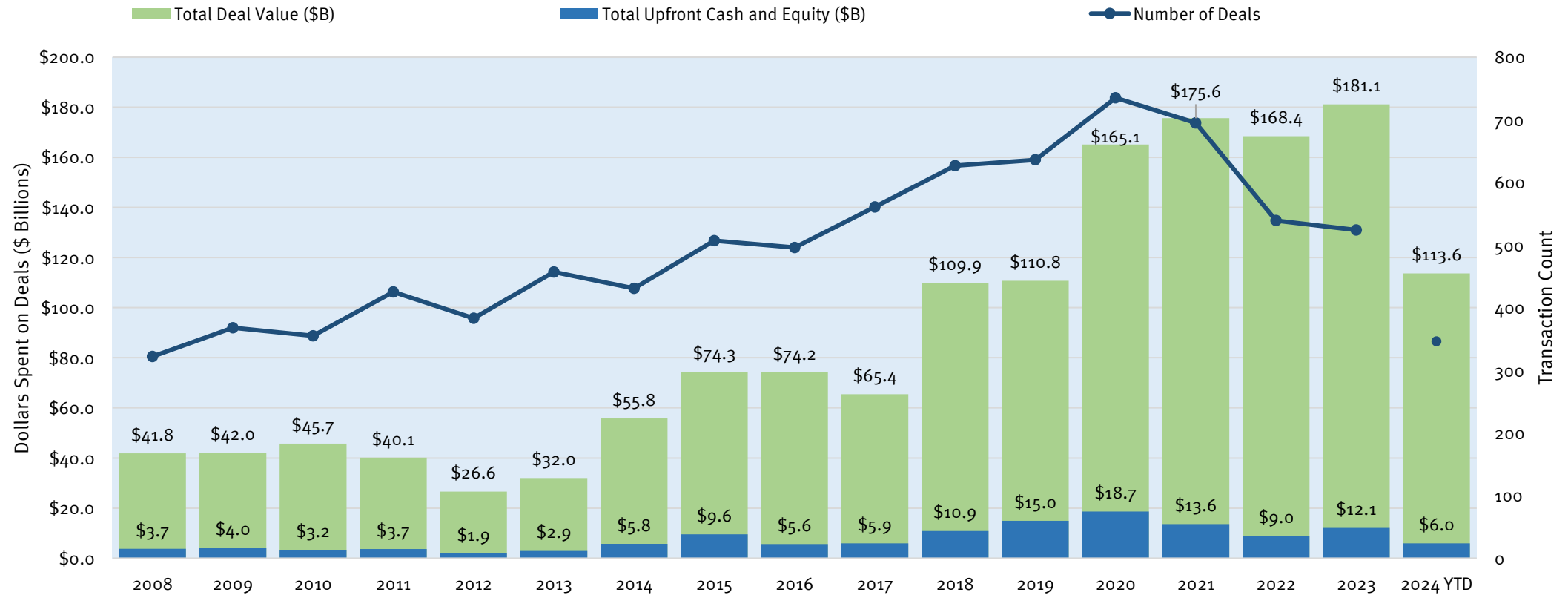
# Novartis, Sanofi and GSK lead by Dollars Spent on Licensing Deal Upfronts in 2024

## Top 20 Companies by Upfronts Paid (including Equity) in R&D Partnership/Licensing Deals, Q1 to Q3 2024



# The Pace of Biopharma Licensing Deals Continues to Drop in 2024

Total Deal Value, Upfronts and Deal Count, All Biopharma Partnership/License Deals, Q1 2008 to Q3 2024



# Global Biopharma Licensing/Partnership Deal Activity and Typical Terms by Therapeutic Area, Q1 2023 to Q3 2024

Primary Therapy Area	Number of Deals	Total Deal Value (\$Billions)	Total Upfront Cash and Equity (\$Millions)	Average Upfront Cash and Equity (\$Millions)	Median Upfront Cash and Equity (\$Millions)
Cancer	323	\$151.1	\$10,715	\$104	\$40
Neurologic	124	\$31.8	\$1,286	\$39	\$26
Cardiovascular	32	\$18.3	\$1,091	\$109	\$60
Autoimmune	51	\$15.2	\$1,124	\$62	\$13
Endocrine / Metabolic	42	\$14.5	\$727	\$61	\$43
Pulmonary	15	\$8.5	\$172	\$43	\$10
Infectious	39	\$6.3	\$1,274	\$127	\$30
Ophthalmic	24	\$4.0	\$244	\$35	\$20
Inflammation	23	\$3.8	\$248	\$50	\$48
Hepatic	13	\$3.7	\$82	\$20	\$22
Musculoskeletal	11	\$2.4	\$308	\$62	\$80
Hematologic	10	\$1.1	\$93	\$23	\$16
Dermatologic	12	\$1.0	\$36	\$12	\$12
Renal	6	\$0.5	\$45	\$23	\$23
Gastrointestinal	7	\$0.4	\$4	\$2	\$2
Genitourinary	5	\$0.0	\$7	\$7	\$7
Transplant	3	\$0.0	\$0	\$0	\$0

**740**

**\$262.6**

**\$17,453**



# Typical Big Pharma Terms for Transactions with Biotechs, Q1 2023 to Q3 2024

Stage of Development Underway at Time of Deal	Number of Deals	Total Deal Value (\$Billions)	Total Upfront Cash and Equity Paid (\$Millions)	Average Upfront Cash and Equity (\$Millions)	Median Upfront Cash and Equity (\$Millions)
Platform / Discovery	105	\$87.2	\$3.2	\$63.2	\$42
Preclinical / IND	23	\$17.0	\$0.8	\$49.9	\$49
Phase I	18	\$20.0	\$1.6	\$106.0	\$100
Phase II *	11	\$37.0	\$6.0	\$599.7	\$168
Phase III **	8	\$12.2	\$1.6	\$196.3	\$95
	<b>740</b>	<b>\$262.6</b>	<b>\$17,453</b>		

Platform: Discovery technologies; Preclinical: Lead compounds prior to Phase I; Clinical phases: Compound is in the stage or has not advanced beyond that stage at time of deal signing

\*Daiichi / Merck \$4B upfront, \$22B total, Phase II, Oct. 2023

\*\*Phase III deals are more often regional rather than worldwide, hence the smaller upfront.

# Industry News



# WuXi Companies May Sell Units Impacted by Biosecure

Jared Whitlock, *Endpoints News*, October 3, 2024 (excerpt)

WuXi AppTec and WuXi Biologics are reportedly looking to sell part of their operations that have struggled because of proposed federal legislation that's targeting the companies on national security grounds.

On Thursday, the *Financial Times* said that WuXi AppTec wants to sell its business WuXi Advanced Therapies, which operates labs and manufacturing facilities in Philadelphia.

Companies like Kyverna Therapeutics rely on the WuXi unit to manufacture cell and gene therapies, according to regulatory filings. In an interim financial report in July, WuXi AppTec partly blamed WuXi Advanced Therapies' falling revenue on "insufficient new business wins due to the proposed US legislation," a reference to the proposed Biosecure Act that bans US drugmakers from contracting with the WuXi companies after 2032.



**Wuxi Advanced Therapies Site in Philadelphia**



# LEK Study of the IRA: Effective Discounts to be Muted

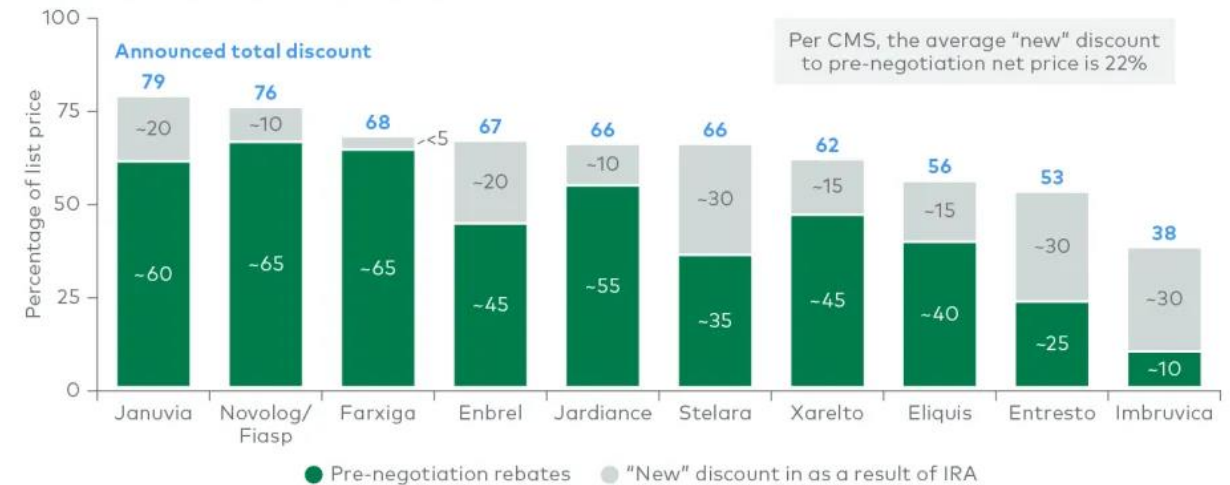


## EXECUTIVE INSIGHTS

### Understanding the Inflation Reduction Act Negotiation Prices After the Dust Has Settled

Nearly one year after announcing the 10 drugs for negotiation under the Inflation Reduction Act (IRA),<sup>1</sup> the Centers for Medicare & Medicaid Services (CMS) announced on August 15<sup>2</sup> that the negotiated prices would have saved approximately \$6B in net covered prescription drug costs, resulting in about 22% lower net spend in aggregate. Most drugs will now be sold at a discount of 65%-80% off list price. But what does all this mean for biopharmas and for patients?

Announced discounts\* vs pre-negotiation\*\*



<sup>1</sup>Exact net pricing paid by Part D plans is confidential and not disclosed but has been credibly estimated by third parties. The "pre-negotiation rebates" shown aim to isolate the commercial discounts negotiated between manufacturers and payers by estimating the difference between gross and net sales, then subtracting discounts to Medicaid, 340B and the Medicare Part D coverage drug program.<sup>5</sup>

\*Discounts are shown from list price (i.e., 79% discount indicates a price of 21% of list)

\*\*Pre-negotiation rebates represents the net price relevant to the negotiation (i.e., removes discounts to Medicaid, 340B and the Medicare Part D coverage drug program) and does not represent the pharmaceutical manufacturer's total gross-to-net discount; based on Hernandez et al. (JMCP) estimates

Note: IRA=Inflation Reduction Act; JMCP=definition; CMS=Centers for Medicare & Medicaid Services

Source: L.E.K. research and analysis; CMS; JMCP

# Blue Shield of California Bypassing PBMs

Ron Leuty, *San Francisco Business Times*, October 2, 2024 (excerpt)

Blue Shield of California ditched traditional drug middlemen and agreed to pay roughly a quarter of the going rate for a popular inflammatory disease drug — and it says it can do the same with other drugs as well.

The Oakland-based nonprofit health insurer said Evio Pharmacy Solutions, a company it co-owns with other Blue Shield plans, negotiated a \$525 monthly price with German drug maker Fresenius Kabi for a lookalike, or biosimilar, version of the drug Humira. Today the net price of the branded version of the drug, made by AbbVie Inc., is about \$2,100 a month, after drug middlemen known as pharmacy benefit managers, or PBMs, negotiate discounts, rebates and fees.

The deal also marks a timely collision of Blue Shield of California's new way of working with PBMs — or not — emerging competition among makers of biosimilar Humira, known scientifically as adalimumab, and fresh scrutiny of PBMs and what they mean to drug pricing.

"We will no longer take part in a pharmacy system that is designed to maximize the profit of participants instead of the quality, convenience and cost-effectiveness for consumers," Blue Shield of California CEO Paul Markovich said in a statement.



**Paul Markovich**

*Chief Executive Officer*  
Blue Shield of California



# Novo Nordisk CEO Lars Jorgensen Blames ‘Complex US Healthcare System’ for Steep Ozempic Prices

Victoria Vesovski, *Moneywise*, October 2, 2024 (excerpt)

Novo Nordisk CEO Lars Fruergaard Jorgensen has called attention to the complexities of the U.S. healthcare system while justifying the company’s drug pricing – prices that Senator Bernie Sanders has slammed as “outrageously high.”

Sanders accused the company of potentially driving up healthcare expenses for all Americans.

“The prices for these drugs are so high in the United States that everyone — regardless of whether they use the products or not — will likely be forced to bear the burden of Novo Nordisk’s profit maximizing strategy through higher insurance premiums and taxes,” Sanders wrote in a public letter to Jorgensen.

In response, Jorgensen defended the company’s pricing at a senate hearing in front of the Committee on Health, Education, Labor and Pensions (HELP), attributing the high costs to the U.S. healthcare system rather than corporate greed. While he acknowledged that Americans pay more than consumers in Europe and the U.K., Jorgensen emphasized that many patients still access the drugs at affordable rates between \$25 and \$50 per month.

The debate underscores growing tensions around the skyrocketing demand for GLP-1 drugs, which, though originally developed for type 2 diabetes, have surged in popularity because of their effectiveness for weight loss.



# FDA Makes End of Zepbound, Mounjaro Shortage Official

Kristen Jensen, *Biopharma Dive*, October 3, 2024 (excerpt)

Mounjaro and Zepbound are part of the GLP-1 class of drugs that also includes Novo Nordisk's Ozempic and Wegovy. The medicines' powerful effects in fighting obesity, and many other related health problems, have supercharged a market that analysts say could reach \$100 billion or more by 2030.

But demand for the new medications has far outstripped supply. Both Lilly and Novo Nordisk have been frantically working to increase production, with Lilly announcing a \$5 billion investment in manufacturing capacity for the drugs in May.

While the drugs faced shortages, direct-to-consumer operators stepped in, taking advantage of rules that allow compounding pharmacies to make medicines with supply issues. Now that the shortage for Lilly is over, the FDA on Wednesday warned that facilities can't make compounded drugs that simply copy agency-approved ones.

However, the law does allow exemptions in certain cases, including for compounded drugs that are personalized for a specific patient. And executives at one of the leading companies that relies on compounding, Hims and Hers, see that exception as a path for continued business.

"Our personalization dosages that exist on the platform today are offering fantastic high-touch care to patients that otherwise really wouldn't be able to experience the benefits of GLP-1," CEO Andrew Dudum told analysts on a conference call in August. "And I would expect in the future, in a post-shortage world, this also continues to exist for patients as an access point."

Hims and Hers currently offer compounded versions of semaglutide, the active ingredient in Ozempic and Wegovy. The FDA's database continues to list semaglutide in shortage.

The FDA warned consumers that there may still be local interruptions in supply of Mounjaro and Zepbound as manufacturers and distributors move the medicine to pharmacies around the country. Lilly has also warned patients of potentially "choppy" availability as shortages ease.

# The US has Passed Peak Obesity, a New Survey Suggests. Is it the Ozempic Effect?

Julia Musto, *The Independent*, October 5, 2024 (excerpt)

The United States has passed peak obesity, according to new data, suggesting that the sweeping uptake of weight-loss drugs could be having an effect.

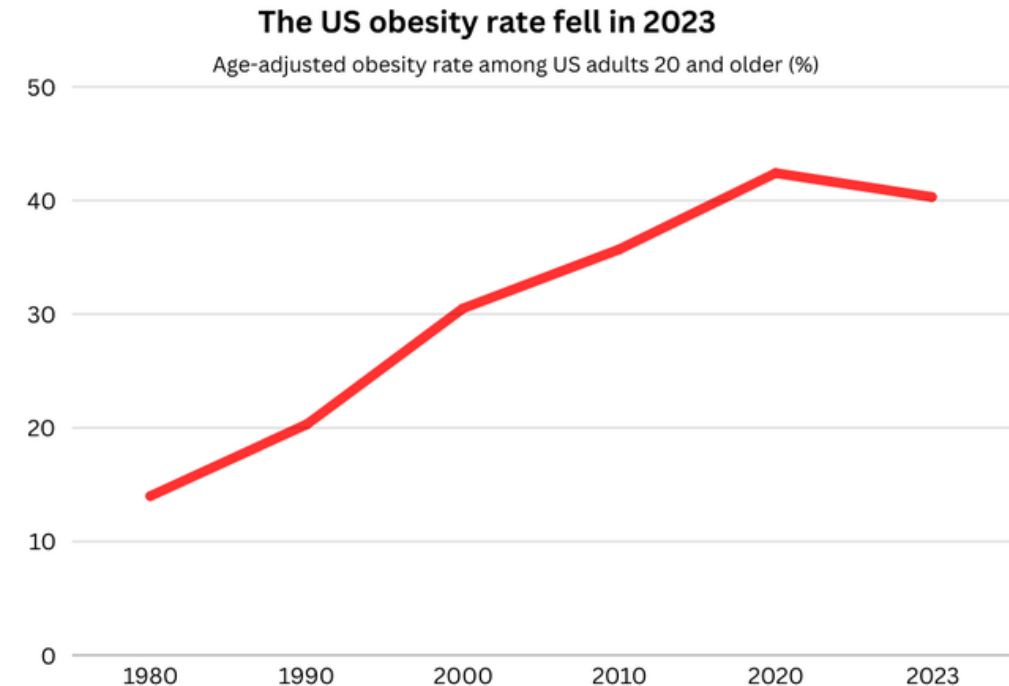
The obesity rate in American adults fell by 2 percent between 2020 and 2023, according to a US National Health and Nutrition Examination survey.

It also found that the prevalence of obesity was lower in adults with a bachelor's degree or and higher in adults with less education.

A study using data from 2020 to 2023, published in May, found a 594 percent increase of young adults and teens using this new generation of weight loss drugs each month.

Meanwhile the new survey showed that rates of obesity were dropping faster among college graduates, according to analysis of the data byThe Financial Times.

Two in five adults and nearly 15 million children and teenagers are obese in the US with rates rising more than 11 percent from the late 1990s through 2020. Obesity increases the risk of certain types of cancer, stroke, heart disease, high blood pressure, Type 2 diabetes, and premature death.



# How Roche Plans to Fill a Projected \$8B Sales Gap

Amy Baxter, *PharmaVoice*, Oct. 2, 2024 (excerpt)

Roche is in the midst of a revamp. With a renewed focus on slashing some R&D areas to streamline its pipeline, the Swiss drugmaker is betting on sales growth from its portfolio and a new stream of acquisitions to offset oncoming headwinds.

By 2028, Roche anticipates an \$8 billion — reported as 6.8 billion Swiss francs — sales gap compared to 2023 from biosimilar competition, which includes copycats to several blockbusters from its wholly-owned company Genentech, according to a new company presentation to investors.

But the pharma giant isn't sweating too hard.

According to CEO Thomas Shinecker, the company can cover the loss from “biosimilar erosion” with “the momentum we have in our portfolio,” he told investors Monday. The market portfolio has more than \$16 billion (nearly 14 billion Swiss francs) in growth, the company projected, and more than \$4 billion (3.7 billion Swiss francs) worth of sales in the pipeline.

Shinecker said the expected growth far outstrips the losses. The improved sales outlook stems from products Roche has already brought to market, but still have upside. And there's more to come.

“We went from eight blockbusters in 2013 to 16 blockbusters this year,” Shinecker said. “By the end of the year, we may have 17 blockbusters.”

Source: <https://www.pharmavoice.com/news/roche-8b-sales-gap-portfolio-strategy-thomas-shinecker/728608/>





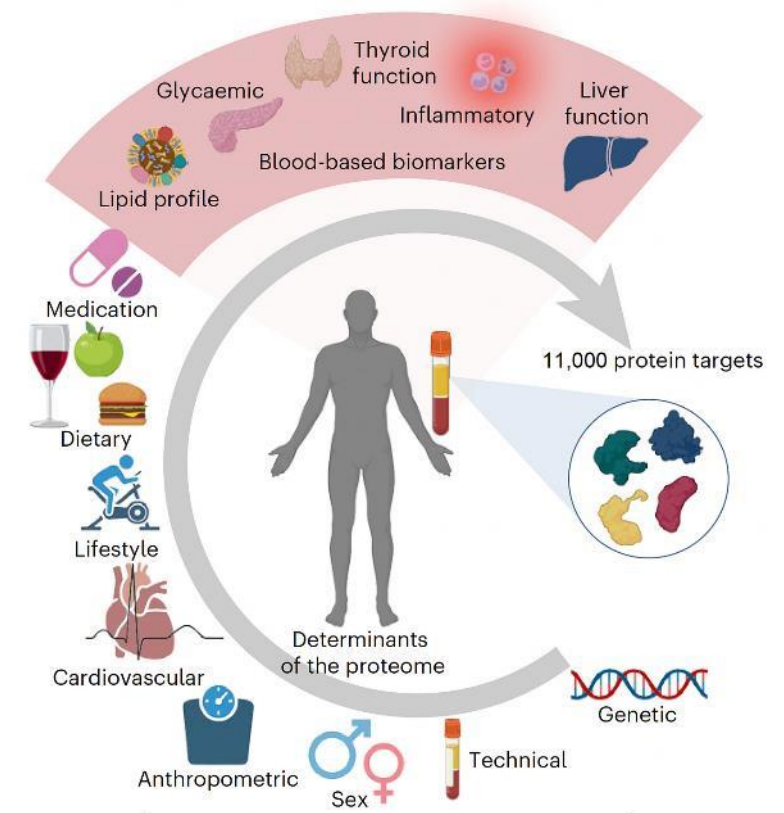
# What Can 11,000 Proteins In Our Blood Tell Us?

Eric Topol, Substack, October 5, 2024 (excerpt)

Last week in *Science*, I published an essay entitled “The revolution in high-throughput proteomics and AI.” But in the few weeks since I wrote it, there’s been much more to add to the story. Let me first summarize the background and we’ll build from there.

The recent capability to measure thousands of plasma proteins from a tiny blood sample has provided a new dimension of expansive data that can advance our understanding of human health. For example, the company SomaLogic has developed the means to measure 11,000 proteins and Thermo Fisher’s Olink assays over 5,400 proteins from as little as 2 µl. (This is real; not Theranos!) When these rich data are integrated with other layers of information from large patient cohorts, such as the UK Biobank’s genetic, health, and lifestyle information from half a million participants, we get new insights about the underpinnings of disease, the aging process, and the potential ability to forecast an individual’s health trajectory.

Lars Lind and colleagues recently published the proteomic data (O-link assay, 2,919 proteins) data from over 52,000 UK Biobank participants and replicated their findings in the China Kadoorie biobank. Using the protein data along with Mendelian Randomization (MR) from the genomic data (for a nice explanation on MR, see the transcript of my podcast with Pradeep Natarajan, starting at 7:13), they found 3 causal proteins for cardiovascular outcomes (heart attack, ischemic stroke, heart failure) that likely fulfilled a cause-and-effect relationship, including FURIN, FGF5, and PROCR. None of these proteins are currently targets in clinical trials, but all have potential to be druggable for prevention of adverse cardiovascular outcomes.





# Artificial Intelligence Algorithm for Subclinical Breast Cancer Detection

Jonas Gjesvik et.al., *JAMA Network Open*, Oct. 3, 2024 (excerpt)

**Design, Setting, and Participants** This retrospective cohort study of 116 495 women aged 50 to 69 years with no prior history of breast cancer before they underwent at least 3 consecutive biennial screening examinations used scores from an AI algorithm (INSIGHT MMG, version 1.1.7.2; Lunit Inc; used September 28, 2022, to April 5, 2023) for breast cancer detection and screening data from multiple, consecutive rounds of mammography performed from September 13, 2004, to December 21, 2018, at 9 breast centers in Norway. Artificial intelligence algorithm score indicating suspicion for the presence of breast cancer. The algorithm provided a continuous cancer detection score for each examination ranging from 0 to 100, with increasing values indicating a higher likelihood of cancer being present on the current mammogram.

**Results** The mean (SD) age at the first study round was 58.5 (4.5) years for 1265 women with screening-detected cancer in the third round, 57.4 (4.6) years for 342 women with interval cancer after 3 negative screening rounds, and 56.4 (4.9) years for 116 495 women without breast cancer all 3 screening rounds. The mean (SD) absolute differences in AI scores among breasts of women developing screening-detected cancer were 21.3 (28.1) at the first study round, 30.7 (32.5) at the second study round, and 79.0 (28.9) at the third study round. The mean (SD) differences prior to interval cancer were 19.7 (27.0) at the first study round, 21.0 (27.7) at the second study round, and 34.0 (33.6) at the third study round. The mean (SD) differences among women who did not develop breast cancer were 9.9 (17.5) at the first study round, 9.6 (17.4) at the second study round, and 9.3 (17.3) at the third study round. Areas under the receiver operating characteristic curve for the absolute difference were 0.63 (95% CI, 0.61-0.65) at the first study round, 0.72 (95% CI, 0.71-0.74) at the second study round, and 0.96 (95% CI, 0.95-0.96) at the third study round for screening-detected cancer and 0.64 (95% CI, 0.61-0.67) at the first study round, 0.65 (95% CI, 0.62-0.68) at the second study round, and 0.77 (95% CI, 0.74-0.79) at the third study round for interval cancers.

**Conclusions and Relevance** In this retrospective cohort study of women undergoing screening mammography, **mean absolute AI scores were higher for breasts developing vs not developing cancer 4 to 6 years before their eventual detection.** These findings suggest that commercial AI algorithms developed for breast cancer detection may identify women at high risk of a future breast cancer, offering a pathway for personalized screening approaches that can lead to earlier cancer diagnosis.

# Lancet Editorial on Endometriosis

Editorial, Endometriosis: Addressing the Roots of Slow Progress, *Lancet*, Oct 5, 2024

A recent paper in *Nature Genetics* has detailed a comprehensive map of the endometrium across the menstrual cycle, uncovering new information on the processes that might be involved in endometriosis. Endometriosis is a chronic condition that occurs when tissue similar to the endometrium grows outside of the uterus. Symptoms vary, but many women experience severe period pain along with other gynaecological and systemic symptoms such as heavy bleeding, difficulty conceiving, and fatigue. Cellular mapping could help determine the cause of endometriosis and might pave the way for novel diagnostics and therapeutics. Although this development is promising, basic science is a long way from reaching the clinic.

Consistently poor outcomes for women with endometriosis highlights the profound effect of the women's health gap. Decades of neglect from funding and research has stifled medical innovation, and gender bias and sexism prevent women from receiving optimal care. Menstrual pain in particular is widely normalised, which—along with taboos on discussing periods and other symptoms such as painful intercourse—means that many women delay seeking medical intervention, or never seek it at all. If they do seek help, symptoms are frequently dismissed or belittled. There are volumes of data to this effect from high-income countries, but data are urgently needed from low-income and middle-income countries too.

Advancing basic science is important because it is nearly impossible to develop better treatments or diagnostics without a better understanding of the natural course of endometriosis. But no amount of medical innovation will change outcomes if women are prevented from accessing care. To improve outcomes for endometriosis, all governments need to formulate plans that not only include measurable targets and interventions across the care pathway but also address the need to change the culture around women, pain, and periods. ■ *The Lancet*

# UC Irvine Researchers are First to Reveal Role of Ophthalmic Acid in Motor Function Control

Irvine, Calif., Oct. 4, 2024

A research team from the University of California, Irvine is the first to reveal that a molecule in the brain – ophthalmic acid – unexpectedly acts like a neurotransmitter similar to dopamine in regulating motor function, offering a new therapeutic target for Parkinson’s and other movement diseases.

In the study, published in the October issue of the journal *Brain*, researchers observed that ophthalmic acid binds to and activates calcium-sensing receptors in the brain, reversing the movement impairments of Parkinson’s mouse models for more than 20 hours.

The disabling neurodegenerative disease affects millions of people worldwide over the age of 50. Symptoms, which include tremors, shaking and lack of movement, are caused by decreasing levels of dopamine in the brain as those neurons die. L-dopa, the front-line drug for treatment, acts by replacing the lost dopamine and has a duration of two to three hours. While initially successful, the effect of L-dopa fades over time, and its long-term use leads to dyskinesia – involuntary, erratic muscle movements in the patient’s face, arms, legs and torso.

“Our findings present a groundbreaking discovery that possibly opens a new door in neuroscience by challenging the more-than-60-year-old view that dopamine is the exclusive neurotransmitter in motor function control,” said co-corresponding author Amal Alachkar, School of Pharmacy & Pharmaceutical Sciences professor.

“Remarkably, ophthalmic acid not only enabled movement, but also far surpassed L-dopa in sustaining positive effects. The identification of the ophthalmic acid-calcium-sensing receptor pathway, a previously unrecognized system, opens up promising new avenues for movement disorder research and therapeutic interventions, especially for Parkinson’s disease patients.”

Alachkar began her investigation into the complexities of motor function beyond the confines of dopamine more than two decades ago, when she observed robust motor activity in Parkinson’s mouse models without dopamine. In this study, the team conducted comprehensive metabolic examinations of hundreds of brain molecules to identify which are associated with motor activity in the absence of dopamine. After thorough behavioral, biochemical and pharmacological analyses, ophthalmic acid was confirmed as an alternative neurotransmitter.

“One of the critical hurdles in Parkinson’s treatment is the inability of neurotransmitters to cross the blood-brain barrier, which is why L-DOPA is administered to patients to be converted to dopamine in the brain,” Alachkar said. “We are now developing products that either release ophthalmic acid in the brain or enhance the brain’s ability to synthesize it as we continue to explore the full neurological function of this molecule.”

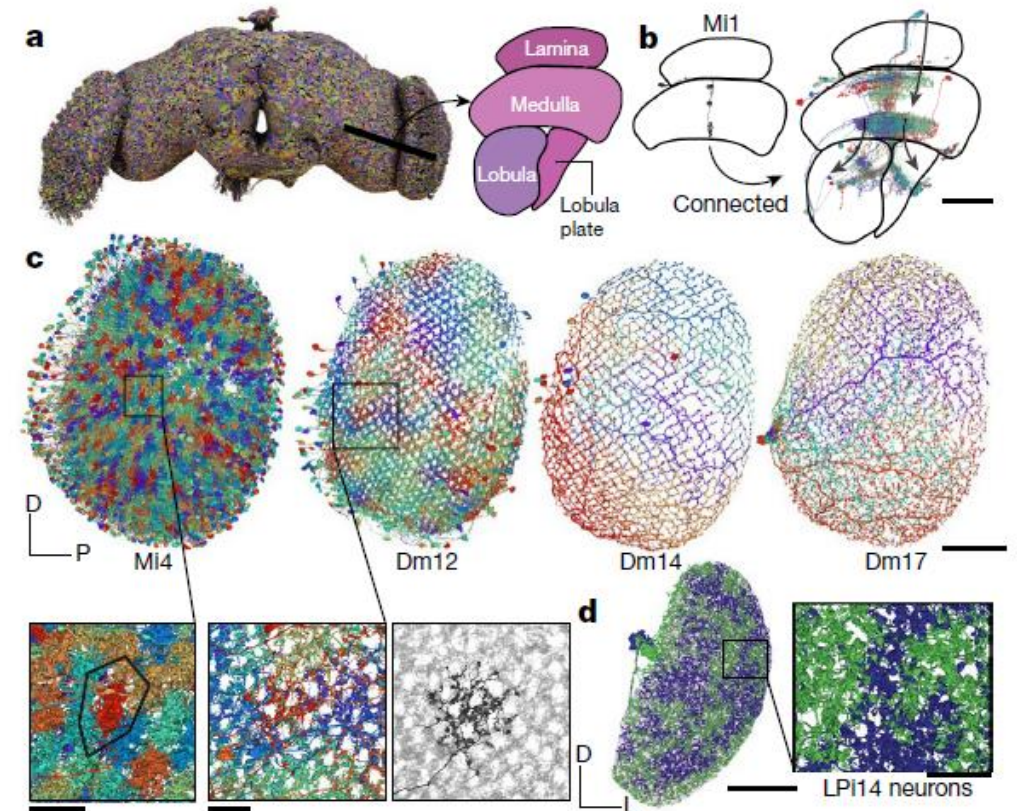
Team members also included doctoral student and lab assistant Sammy Alhassen, who is now a postdoctoral scholar at UCLA; lab specialist Derk Hogenkamp; project scientist Hung Anh Nguyen; doctoral student Saeed Al Masri; and co-corresponding author Olivier Civelli, the Eric L. and Lila D. Nelson Chair in Neuropharmacology – all from the School of Pharmacy & Pharmaceutical Sciences – as well as Geoffrey Abbott, professor of physiology & biophysics and vice dean of basic science research in the School of Medicine.



# Neuronal Wiring Diagram of an Adult Fruit Fly Brain

Sven Dorkenwald et.al., *Nature*, Oct 2, 2024 pp. 124-138.

Connections between neurons can be mapped by acquiring and analysing electron microscopic brain images. In recent years, this approach has been applied to chunks of brains to reconstruct local connectivity maps that are highly informative, but nevertheless inadequate for understanding brain function more globally. Here we present a neuronal wiring diagram of a whole brain containing  $5 \times 10^7$  chemical synapses<sup>7</sup> between 139,255 neurons reconstructed from an adult female *Drosophila melanogaster*<sup>8,9</sup>. The resource also incorporates annotations of cell classes and types, nerves, hemilineages and predictions of neurotransmitter identities<sup>10-12</sup>. Data products are available for download, programmatic access and interactive browsing and have been made interoperable with other fly data resources. We derive a projectome—a map of projections between regions—from the connectome and report on tracing of synaptic pathways and the analysis of information flow from inputs (sensory and ascending neurons) to outputs (motor, endocrine and descending neurons) across both hemispheres and between the central brain and the optic lobes. Tracing from a subset of photoreceptors to descending motor pathways illustrates how structure can uncover putative circuit mechanisms underlying sensorimotor behaviours. The technologies and open ecosystem reported here set the stage for future large-scale connectome projects in other species.

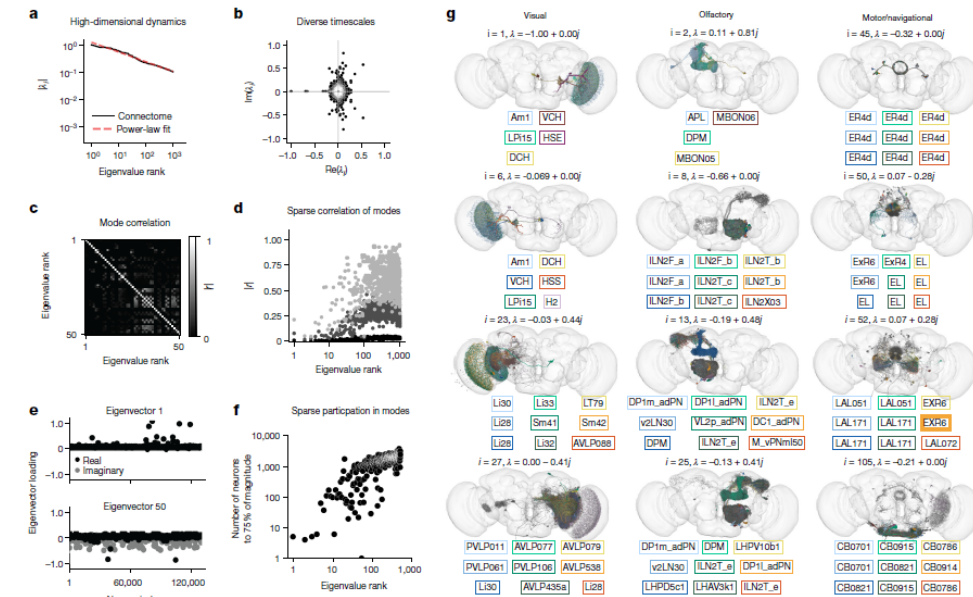


**Fig. 5 | Optic lobes.** **a**, Rendering of a subset of the neurons in the fly brain. A cut through the optic lobe is highlighted and neuropils are annotated. **b**, A single Mi1 neuron (left) and all neurons that share a connection with the single Mi1 neuron (at least five synapses) (right). Three large neurons (CT1, OA-AL2b2 and Dm17) were excluded for the visualization. **c**, Top, Mi4, Dm12, Dm14 and Dm17 neurons in the right optic lobe, as annotated by Matsliah et al.<sup>11</sup>. Bottom, expanded views of the outlined regions in Mi4 and Dm12 show the local structure. For Dm12, the right image shows a single neuron in black and all other Dm12 neurons are in background. **d**, The two LPI14 neurons in the right lobula plate (neuropil shown in background). Scale bars: 50  $\mu\text{m}$ , **b** and **c**, **d** (main image); 10  $\mu\text{m}$ , **c**, **d** (expanded views).

# Comment: The Fly Connectome Reveals a Path to the Effectome

Dean Posposil et.al., *Nature*, Oct 2, 2024

A goal of neuroscience is to obtain a causal model of the nervous system. The recently reported whole-brain fly connectome specifies the synaptic paths by which neurons can affect each other, but not how strongly they do affect each other in vivo. To overcome this limitation, we introduce a combined experimental and statistical strategy for efficiently learning a causal model of the fly brain, which we refer to as the ‘effectome’. Specifically, we propose an estimator for a linear dynamical model of the fly brain that uses stochastic optogenetic perturbation data to estimate causal effects and the connectome as a prior to greatly improve estimation efficiency. We validate our estimator in connectome-based linear simulations and show that it recovers a linear approximation to the nonlinear dynamics of more biophysically realistic simulations. We then analyse the connectome to propose circuits that dominate the dynamics of the fly nervous system. We discover that the dominant circuits involve only relatively small populations of neurons—thus, neuron-level imaging, stimulation and identification are feasible. This approach also re-discovers known circuits and generates testable hypotheses about their dynamics. Overall, we provide evidence that fly whole-brain dynamics are generated by a large collection of small circuits that operate largely independently of each other. This implies that a causal model of a brain can be feasibly obtained in the fly.



**Fig. 3 | Putative global dynamical properties of the fly central nervous system.** **a**, Magnitude of the top 1,000 eigenvalues of the putative effectome (scaled matrix of signed synaptic counts extracted from the connectome) and power-law fit. **b**, Eigenvalues plotted in the complex plane. **c**, Correlation of eigenvectors sorted by associated eigenvalue magnitude. **d**, Median (black), 99th percentile (dark grey) and maximum (light grey) correlation between each eigenvector and all other top 1,000 eigenvectors, showing that the first 10–20 eigenvectors are nearly orthogonal to other eigenvectors and the

correlation between other eigenvectors is highly sparse. **e**, Per neuron eigenvector loadings for the first (top) and 50th (bottom) eigenvector. **f**, Concentration of eigenvector loadings, quantified by the number of neurons needed to account for 75% of the power of the eigenvector. **g**, Anatomical renderings of neurons needed to account for 75% of the eigenvector's loading power. Eigenvectors are drawn from the top 100 eigenvectors, and each column displays eigenvectors with neurons predominantly associated with either visual, olfactory or motor/navigation anatomical locations.



# Disclosure



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