Biopharmaceutical Sector

Weekly Update – August 12, 2024

John Curtin School of Medical Research at the Australian National University, Canberra

STIFEL | Healthcare

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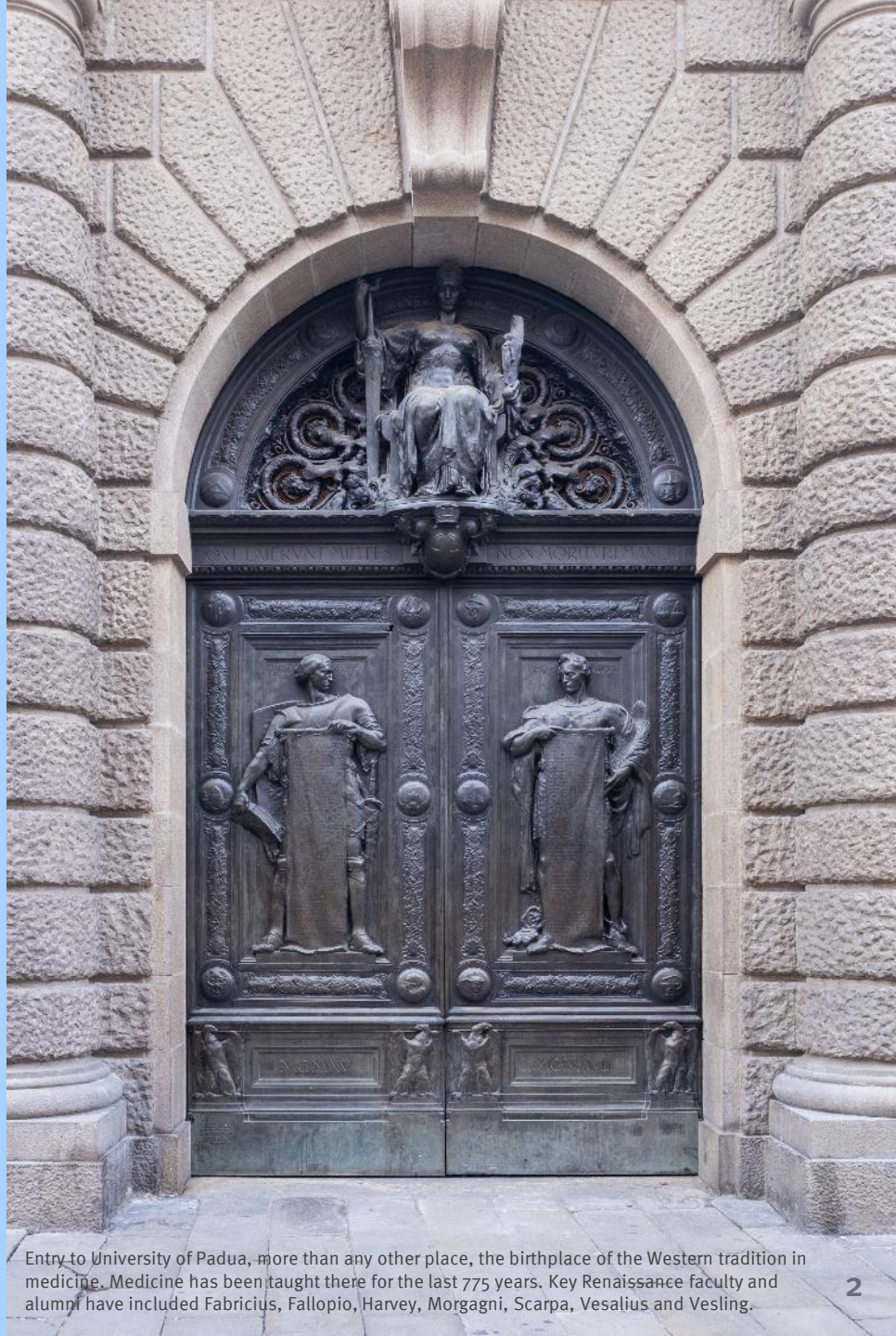

Entry to University of Padua, more than any other place, the birthplace of the Western tradition in medicine. Medicine has been taught there for the last 775 years. Key Renaissance faculty and alumni have included Fabricius, Fallopio, Harvey, Morgagni, Scarpa, Vesalius and Vesling.

Past Issues

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

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July 8, 2024 (Obesity Market Update)
June 17, 2024 (Lab Market)
June 8, 2024 (Oncology Review)
May 27, 2024 (GLP-1's)
May 20, 2024 (Returning Capital)
May 13, 2024 (Brain, AlphaFold 3)
May 6, 2024 (Earnings, Obesity)
April 29, 2024 (M&A, Japan)
April 22, 2024 (Pharma Pricing)
April 15, 2024 (AI in Pharma)
April 8, 2024 (The Buyside)
April 1, 2024 (Biotech Balance Sheets)
March 25, 2024 (Women's Health)
March 18, 2024 (Inflammasome)
March 11, 2024 (IRA, Immunology)
March 4, 2024 (Biotech Employment)
Feb 26, 2024 (Biotech Strategy)
Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Jan 22, 2024 (AI in medicine)
Jan 5, 2024 (Sector Outlook for 2024)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 22, 2023 (Bullish on Biotech)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
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September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

Hitting the books in a medical library.

Join Us at Biotech Hangout This Friday

To Learn More
https://www.biotechhangout.com/

Macroeconomics Update

Boston Lying-In Hospital, October 31, 1927

Boston Lying-In Hospital, August 8, 2024
(now 221 Longwood Avenue, Brigham & Women's Hospital, Harvard Medical School)

Fed Policymakers Signal Rate Cuts Ahead, But Not Because of Market Rout

Ann Saphir, *Reuters*, August 9, 2024 (excerpt)

Federal Reserve policymakers are increasingly confident that inflation is cooling enough to allow interest-rate cuts ahead, and they will take their cues on the size and timing of those rate cuts not from stock-market turmoil but from the economic data.

That was the shared message of three U.S. central bankers speaking on Thursday who otherwise had slightly different takes on exactly where the economy stands a week and a day after they decided to hold the policy rate steady but signaled a reduction as soon as next month.

A jump in the July U.S. unemployment rate reported on Friday helped spark a global stock market rout that continued into Monday before equities partially recovered, as investors and analysts worried the U.S. was headed for a recession and the Fed would need to react aggressively" he said.

"It's hard to make the case that something has just happened that is monumental on the equity side," Richmond Federal Reserve Bank President Thomas Barkin said on Thursday, noting major U.S. stock-market indices are still up from the start of the year.

"Financial conditions can both reveal important information on the trajectory of the economy and can also spillover to impact the real economy," he said in remarks prepared for delivery to the Kansas Bankers Association's annual meeting in Colorado Springs, Colorado. "However, the Fed has to remain focused on achieving its dual mandate" of full employment and price stability.

On that score, he said, recent "encouraging" data showing inflation around 2.5% gives him more confidence inflation is headed to the Fed's 2% goal.

"If inflation continues to come in low, my confidence will grow that we are on track to meet the price stability part of our mandate, and it will be appropriate to adjust the stance of policy," he said.

Source: https://www.reuters.com/markets/us/feds-barkin-sees-inflation-coming-down-time-assess-policy-2024-08-08/

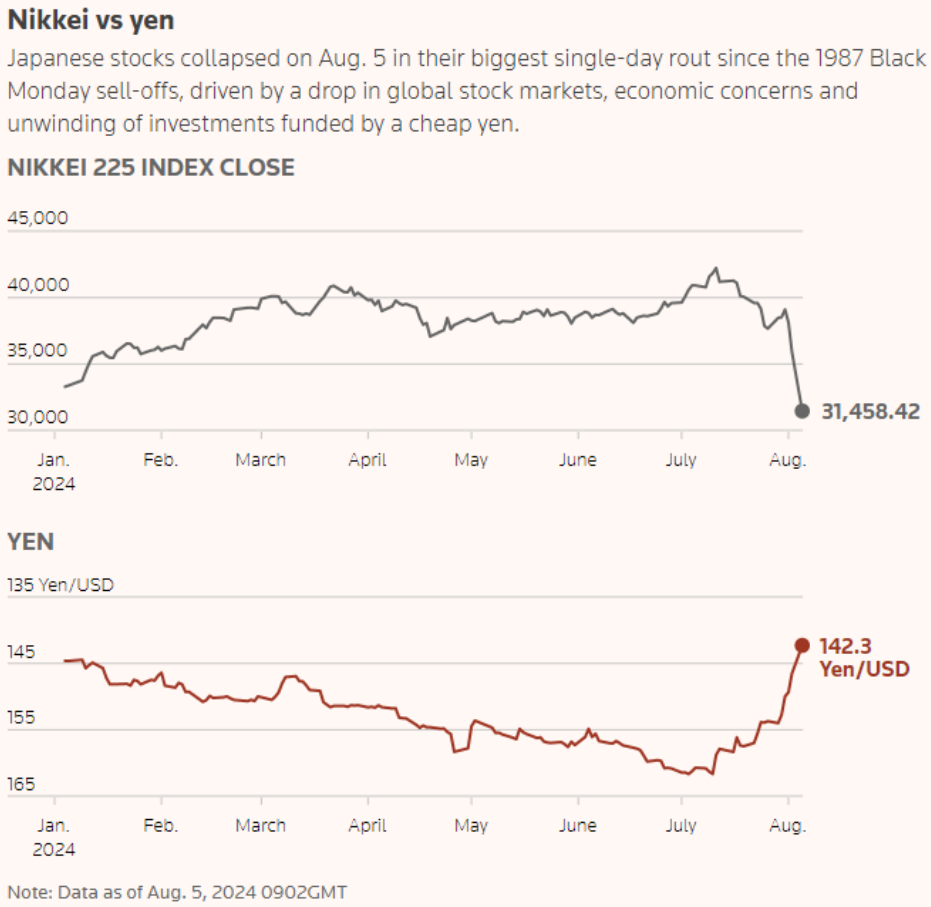
Bank of Japan Move to Raises Rates on July 31 Triggers Big Rally in Yen and Decline in Japanese Stocks

Reuters, Aug 8, 2024

The yen lost more than 20% against the dollar since the outset of 2022, prompting several rounds of intervention by Tokyo to prop up the currency in September and October that year. It kept falling despite further intervention in April and May 2024, touching a 38-year low of 161.96 to the dollar on July 3. Japan is suspected to have stepped in again in mid-July to put a floor under the yen.

The yen's downtrend has reversed in recent days, following the Bank of Japan's July 31 decision to raise interest rates and ahead of an expected loosening of U.S. monetary policy.

The BOJ's hawkish move, along with investors' concerns about U.S. growth, jolted global stock and bond markets. It triggered an unwinding of the carry trade, whereby investors borrow cheaply in yen to invest in higher-yielding assets. The yen rebounded sharply against the dollar, but remains relatively weak by the standards of the past few decades.

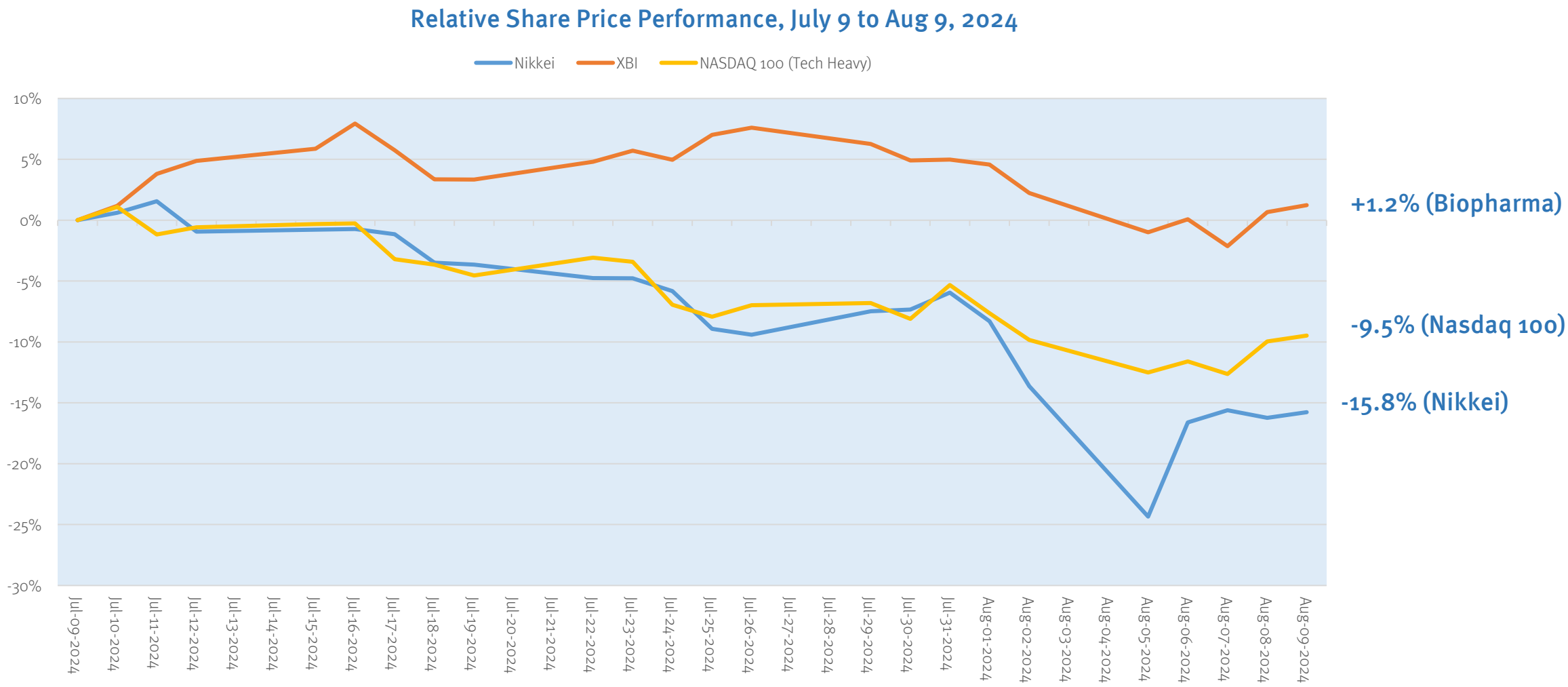


Source: https://www.reuters.com/graphics/JAPAN-YEN/EXPLAINER/xmvjnxjmbvr/

The Bank of Japan's move at the start of the month to finally take Japan away from a world of zero interest rates had unexpected effects on global markets.

Because so many traders were borrowing cheap Yen and investing it in stocks (including Japan stocks and U.S. tech stocks), investors moved quickly to unload those stocks. This unwinding of the "carry trade" over last weekend caused markets to hit a critical point, triggering a thousand-point drop in the Dow and a drop of more than 10% in the Nikkei.

XBI Unscathed in Tech Market / Japan Market Fracas



+1.2% (Biopharma)

-9.5% (Nasdaq 100)

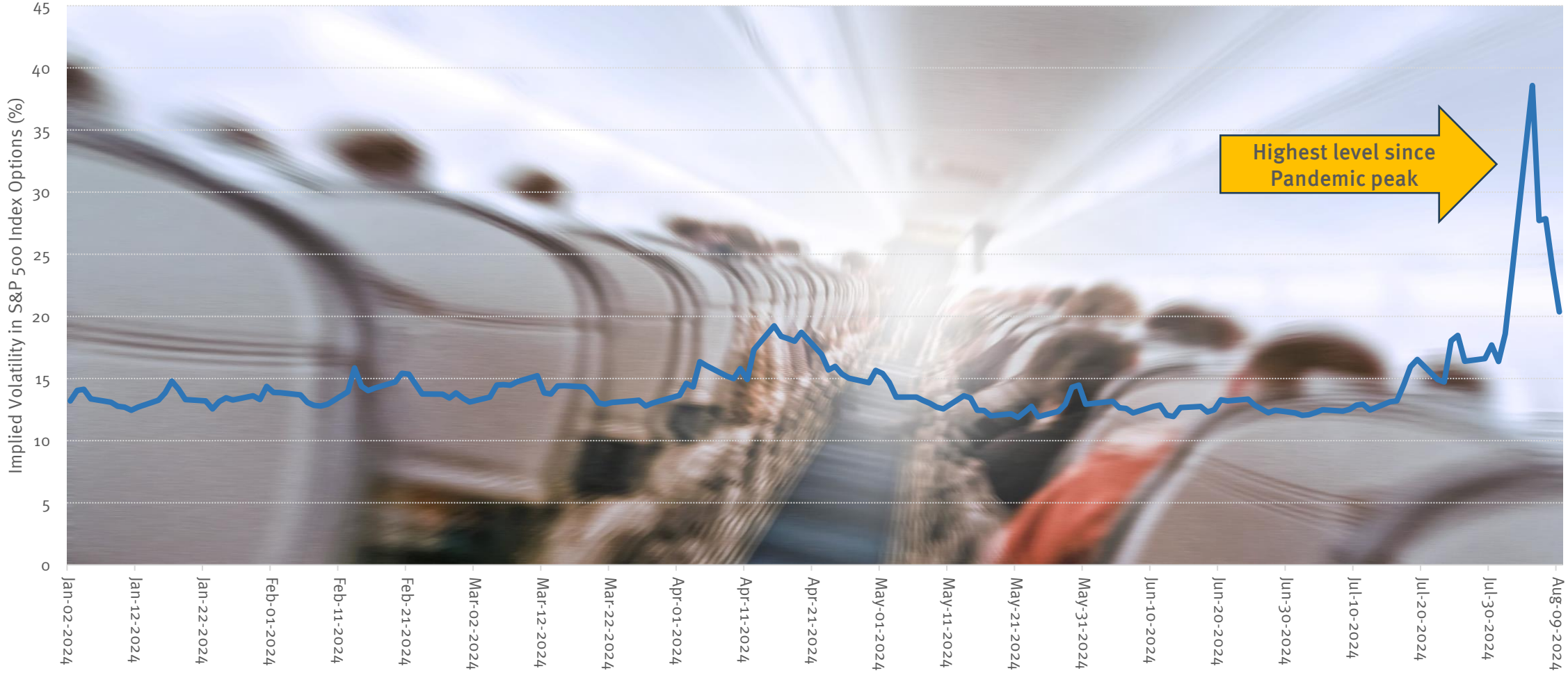
-15.8% (Nikkei)

Source: S&P CapitalIQ

Buckle Up. The US Equity Market Gets Very Bumpy

Rumors of giant losses on Yen/dollar carry trades on Monday sent the Dow down 1000 points. The XBI dropped 3% and the VIX skyrocketed. By Friday, the situation had substantially normalized.

CBOE Implied Volatility in S&P 500 Index Options (VIX), Jan 1 to Aug 9, 2024



Source: S&P CapitalIQ

Wall Street on Edge After a Week of Wild Swings

Joe Rennison and Danielle Kaye, *New York Times*, Aug 9, 2024 (excerpt)

After a wild week in the markets that rekindled fears about the strength of the U.S. economy, investors are wondering what comes next.

Until recently, Wall Street was focused on inflation, hoping that its slowdown would lead the Federal Reserve to cut interest rates, giving support to stocks. The recent havoc has brought back an additional consideration: the risk that markets could tank in response to signs that the economy was slowing too fast.

For now, markets seem to have recovered a sense of calm. On Thursday, the S&P 500 index recorded its biggest gain, up 2.3 percent, since late 2022, propelled by an often overlooked weekly report on unemployment claims that came in better than expected. After a rise of 0.5 percent on Friday, the index still ended lower for a fourth consecutive week, but only marginally — a significant turnaround after a global rout on Monday.

A similar story is unfolding around the world. In Japan, which bore the brunt of the recent selling, stocks remained volatile but pared losses after their biggest drop since 1987. The Europe-wide Stoxx 600 index enjoyed four days of gains that erased its drop on Monday.

Taking a step back, the S&P 500 is up roughly 12 percent for the year. For all its short-term ferocity, the magnitude of the recent sell-off since the index peaked in mid-July has not been particularly remarkable, historically speaking. Stocks fell a total of 8.5 percent through the end of Monday.

Source: https://www.nytimes.com/2024/08/09/business/stock-market-inflation.html

Investors Borrowed Like Crazy During the Rally. Now They're Paying the Price.

Behind the market tumult of the past month: the rapid unwind of several popular trades and the heavy use of leverage

Greg Zuckerman, Jack Pitcher, Vicky Ge Huang and David Uberti, WSJ, Aug 12, 2024

They built over months: Big bets on the Japanese yen. Complex cryptocurrency wagers. Investments in hot tech companies.

Common to all the trades were heavy doses of leverage, or borrowed money, which investors used to amplify expected gains. As markets rose through the first half of 2024, the investments generated windfall profits, inspiring copycat traders to get on board and pushing prices higher.

Now the tide has turned. Unrest has returned to global markets over the past month, and investors are now in retreat from these once-unstoppable trades. While the market has calmed in recent days and the Dow industrials remain within 5% of their record high, traders caution that there is reason to brace for more upheaval.

What's behind the tumult? Recent losses were caused in large part by a "deleveraging," said Andy Constan, chief executive of Damped Spring Advisors, a consultant for macro hedge funds.

Changes in economic or financial conditions can force investors to sell one piece of their portfolios, such as U.S. or Japanese equity holdings, to deal with losses from another, such as leveraged bets on a weak yen. The messy process to reduce risk takes time before traders can reload.

This deleveraging came at perhaps the worst time for markets—smack in the middle of summer months in which many traders and investors are vacationing. While more trading than ever is automated, decisions made by individuals still matter. Fewer pros in the office mean a shortage of seasoned individuals on trading desks, and fewer investors around to step in to buy as prices plunge.

It is a reason August has seen examples of panic in the past, such as the August 1998 collapse of the hedge fund Long-Term Capital Management and August 2007's "quant quake."

During the tumult of the past week, "The liquidity was worse or equal than during the Covid market crash," said Patrick Heusser, head of crypto lending at Trident Digital.

Other popular leveraged trades have turned painful. For more than a year, hedge funds, computer-driven quantitative funds and others piled into big U.S. technology stocks by using borrowed money, often while betting against small-cap stocks, according to investors and analysts. The trade flipped on its head in July, thanks to lackluster earnings that hurt tech shares and unleashed a long-awaited rally in small-cap shares, partly on the expectation that they would benefit from lower borrowing costs. Over the past month, longtime investor favorites such as Tesla, Amazon.com and Nvidia have dropped by 15% or more.

Source: https://www.wsj.com/finance/investors-borrowed-like-crazy-during-the-rally-now-theyre-paying-the-price-60811567

Traders Bet on Wild Swings With CPI Print Set to Test the Market

Jess Menton, *Bloomberg*, Aug 11, 2024 (excerpt)

Wall Street's summer to forget is approaching its climax, with all eyes on this week's consumer prices report, which traders hope will give the Federal Reserve the ammunition it needs to begin cutting interest rates at its next meeting in September.

But for now, the bet is for more volatility.

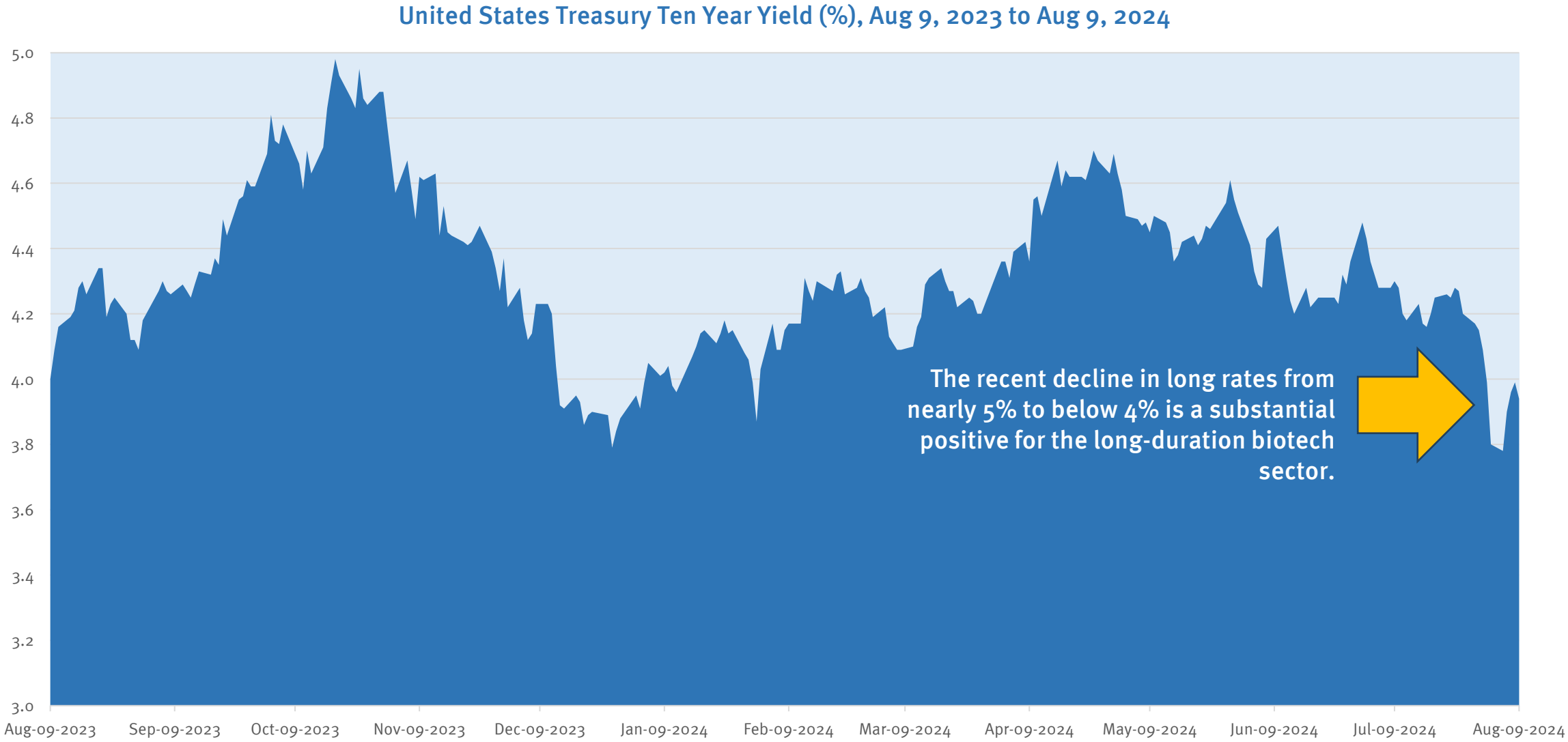
Some wild swings last week brought the Cboe Volatility Index, or VIX, which measures the magnitude of price moves in the S&P 500 Index, to levels not seen since the height of the pandemic in 2020. Based on the cost of at-the-money put and call options, traders are positioning for the S&P 500 to move 1.2% in either direction on Wednesday when the consumer price index report is released, according to Citigroup Inc.

Should that pricing hold through Tuesday's close, it would be roughly in line with the implied moves on Aug. 23, when Chair Jerome Powell is expected to deliver remarks at the Jackson Hole economic symposium, and Aug. 29, the day after Nvidia Corp.'s earnings report.

"The options market isn't sending an all-clear signal just yet for stocks," said Rocky Fishman, founder of derivatives analytical firm Asym 500. "When volatility is high, it's historically a good time to buy equities, but to some extent that's already happened, so CPI will be an important catalyst."

Source: https://www.bloomberg.com/news/articles/2024-08-11/traders-bet-on-wild-swings-with-cpi-print-set-to-test-the-market

Long Treasury Bond Yield at its Lowest Point in a Year



Source: S&P CapitalIQ

Polls Show Kamala Harris Building Lead over Trump in 2024 Election

Martin Pengelly, *The Guardian*, Aug 9, 2024 (excerpt)

Kamala Harris continues to gain strength in the US presidential election, as polls nationally and in battleground states show her building leads or catching Donald Trump.

On Friday morning, FiveThirtyEight, a leading polling analysis site, puts Harris, the Democratic party's presumptive nominee for president, up by 2.1 points over her Republican rival in its national average.

In averages for swing states, where control of the White House rests, Harris led in Michigan by two points, Pennsylvania by 1.1 point and Wisconsin by 1.8 points. Trump led in Arizona by less than half a point and in Georgia by half a point.

In battleground states without enough polls to calculate averages, Trump was ahead by about three points in North Carolina and the candidates were about level in Nevada. In the latter state, recent CBS and Bloomberg polls have given Harris two-point leads while on Friday the Nevada Independent reported a poll showing the Democrat six points up.

Now, just in the time that Harris has been in the race, you have seen those numbers move pretty significantly toward Harris, four- or five-point shifts in those battleground states, which is mirroring what we're seeing in the national poll as well.

Source: https://www.theguardian.com/us-news/article/2024/aug/09/us-election-polls-kamala-harris-trump

Biopharma Market Update

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

Research Facility, WashU School of Medicine

The XBI Closed at 95.5 Last Friday (Aug 9), Down 1% for the Week

The XBI was down last week despite positive developments in interest rates as the market was impacted by volatility caused by unwinding of Japanese carry trades.

Biotech Stocks Down Last Week

Return: Aug 3 to Aug 9, 2024

Nasdaq Biotech Index: -1.4%
Arca XBI ETF: -2.7%
Stifel Global Biotech EV (adjusted): +1%*
S&P 500: -0.04%

Return: Dec 29, 2023 to Aug 9, 2024 (YTD)

Nasdaq Biotech Index: +6.7%
Arca XBI ETF: +7.0%
Stifel Global Biotech EV (adjusted): +16.7%*
S&P 500: +12.0%

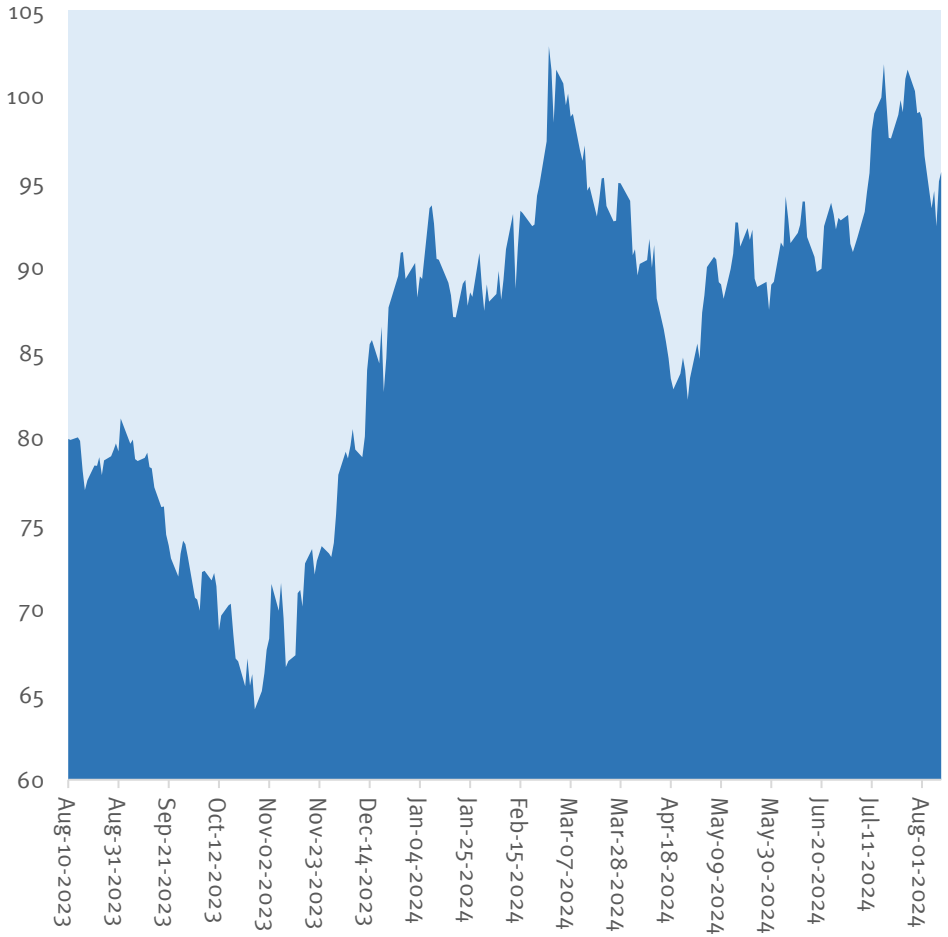
VIX Declined

July 21, 2023: 13.6%
Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Mar 29, 2024: 13.0%
May 17, 2024: 12.0%
Jun 14, 2024: 12.7%
Aug 2, 2024: 23.4%
Aug 9, 2024: 20.4%

10-Year Treasury Yield Rose

July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Mar 29, 2024: 4.20%
May 17, 2024: 4.42%
Jun 14, 2024: 4.2%
Aug 2, 2024: 3.80%
Aug 9, 2024: 3.94%

XBI, Aug 10, 2023 to Aug 9, 2024



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

Source: S&P Capital IQ and Stifel analysis

What the Meltdown in the Stock Market Means for Biotech and Pharma

Drew Armstrong, *Endpoints News*, August 5, 2024 (excerpt)

On Monday, global market indices crashed after a week of soft corporate earnings, a macroeconomic warning, and concerns that the Federal Reserve had waited too long to cut interest rates. Biotech and pharma weren't spared.

There are a lot of different things going on, some of which are very much about the markets and some of which are more about economic fundamentals.

Last week there was an earnings-related sell-off in the huge tech stocks that make up much of major stock indices. Then, on Friday, the US posted weak job numbers that led to worries about a recession or a "hard landing" that the US had until now avoided.

On top of that, get ready to hear a lot about the carry trade over the next couple of days. The short version is: Traders who make bets on the differing interest rates between countries like the US (where rates are high) and Japan (where rates are very low) use lots of leverage to bet on stocks. When it seemed like the interest rate policies of both countries were going to reverse, they started unwinding those bets by selling US stocks. That can cause some very big, very sudden moves.

"I think what we're seeing in a broad sense is a loss of confidence and fear creeping back into the market, and that's related to the declines in stocks like Nvidia, Apple, Microsoft," said Tim Opler, a managing director in Stifel's Global Healthcare Group.

It's going to be bumpy out there for a bit. Market and economic turmoil tend to take a while to sort itself out, and things tend to be volatile before they settle into any kind of narrative.

The US Federal Reserve has held off on making a long-expected rate cut, saying it was waiting for more data about the state of the economy. But last week's jobs report was a hint the US economy was slowing, and traders who wager on interest rates made bets that they would come down. Monday's sell-off has some hoping for an emergency rate cut, and arguing that the Fed shouldn't have waited.

The long term might be a different matter, said John Maraganore, the former Alnylam CEO who now sits on boards across the industry. On Monday morning he said interest rates were "number one, two, and three for the capital markets as it relates to biotech."

Source: https://endpts.com/what-the-meltdown-in-the-stock-market-means-for-biotech-and-pharma/

Has Tech vs Biotech Stock Divergence Gone Away?

Over the last 3 years, the XBI is down 30% while the S&P 500 is up 25.6%. At its widest, the spread between the two measures hit 63%. Now, it's at 56%. Despite the events of recent weeks, biotech relative underperformance is still largely intact.

Relative Outperformance of the S&P 500 Index Over the XBI Since June 14, 2021 (Raw Percentage)

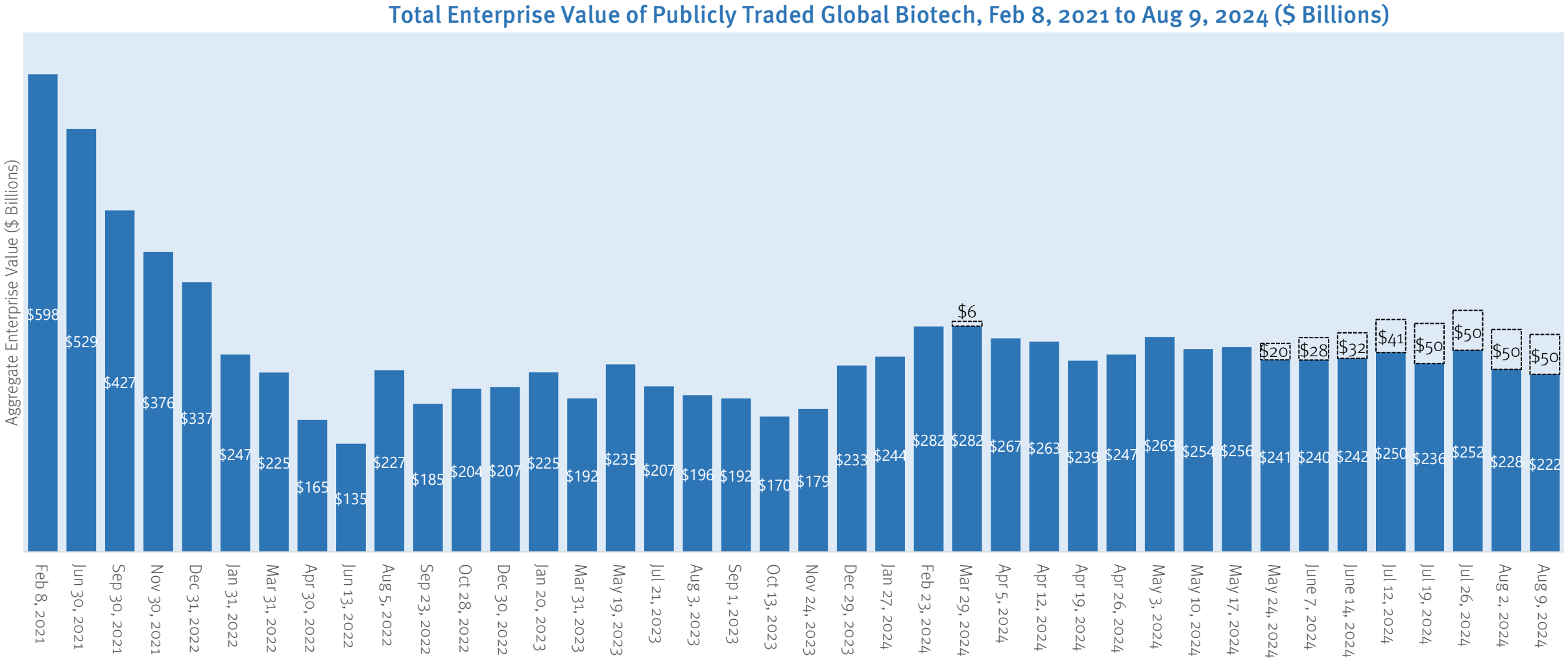
The XBI has underperformed the S&P 500 by a whopping 56% over the last 38 months.

We have seen this performance gap narrow by only eight percentage points in the recent tech stock swoon.

Source: CapitalIQ.

Total Global Biotech Sector Down 2.7% Last Week and 11.9% in Two Weeks

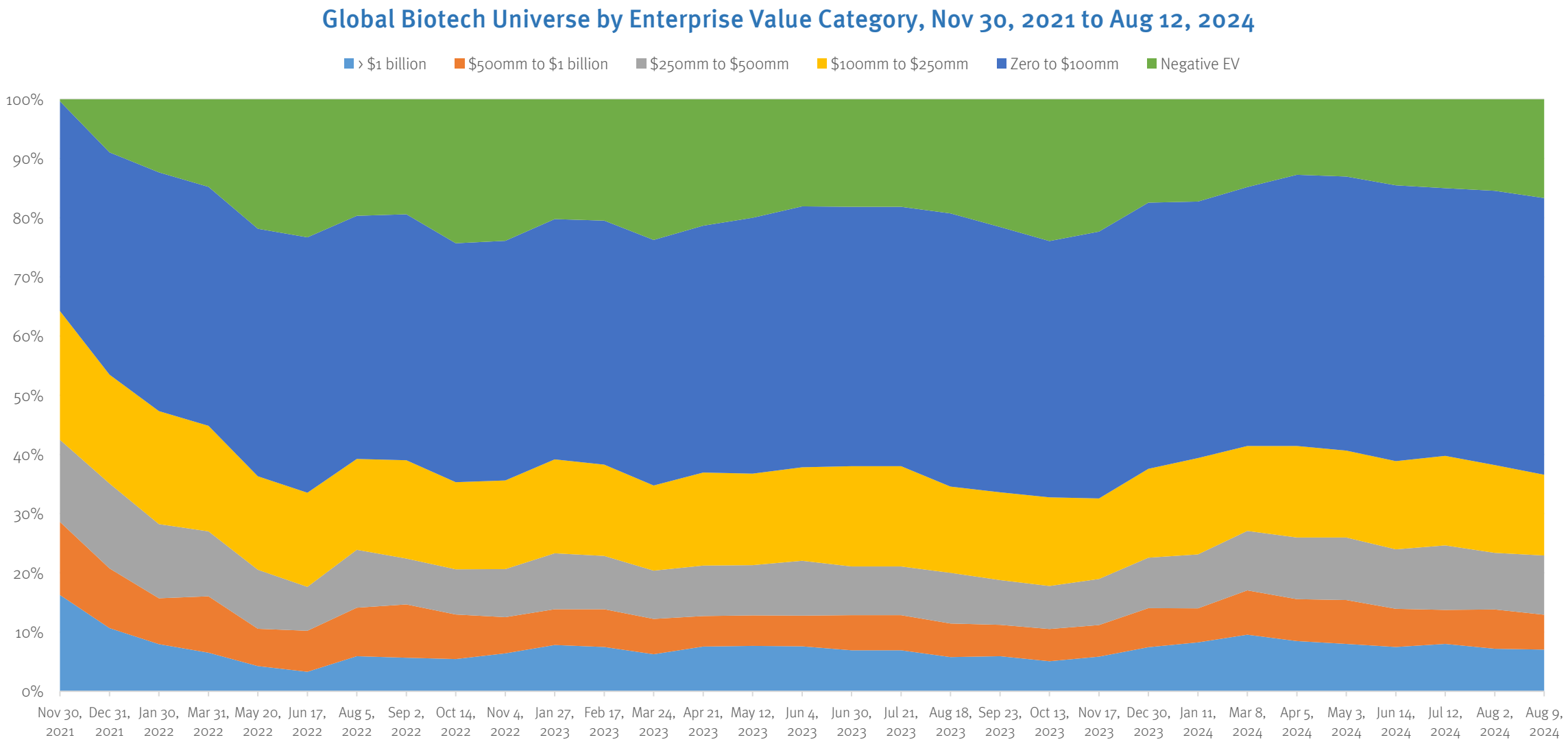
Biotech stocks are down nearly 12% in the last two weeks with most of the impact hitting in the first week of August. On a disappearance adjusted basis, biotech is up 16.7% for the year to date.



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 value companies has shrunk rather dramatically over the last month.

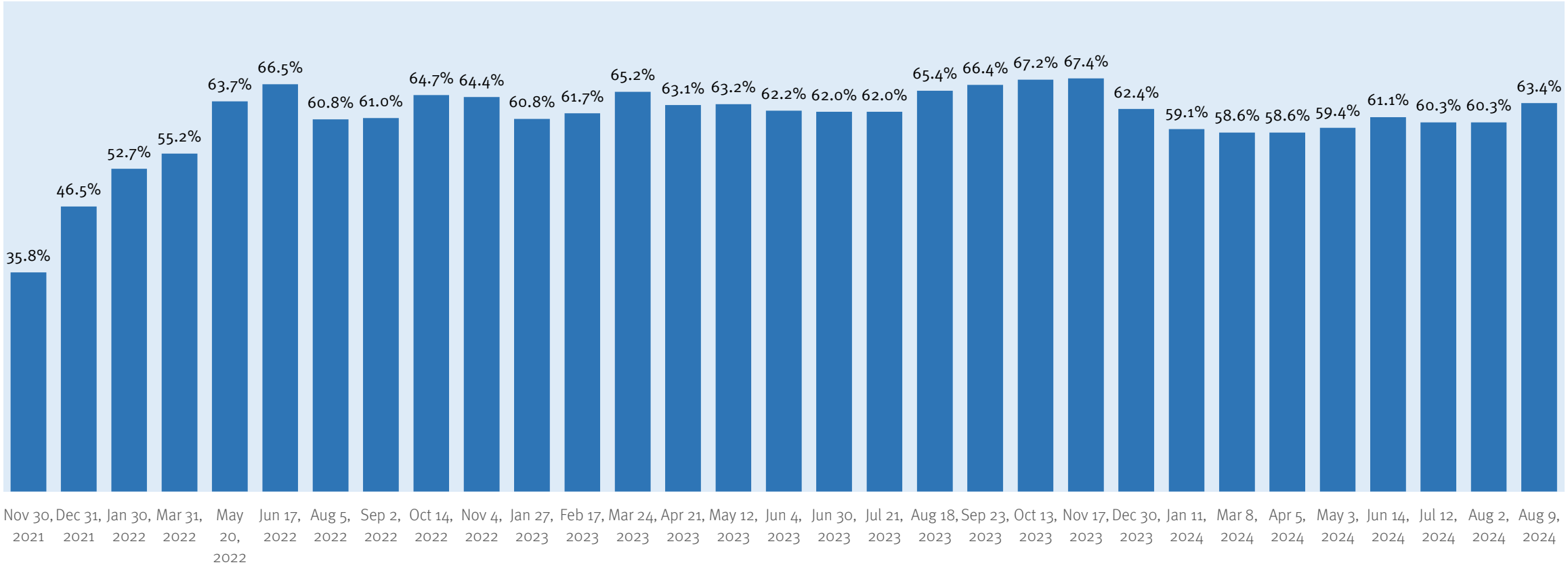


Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Population of Sub $100mm Biotechs Going in the Wrong Direction in Recent Weeks

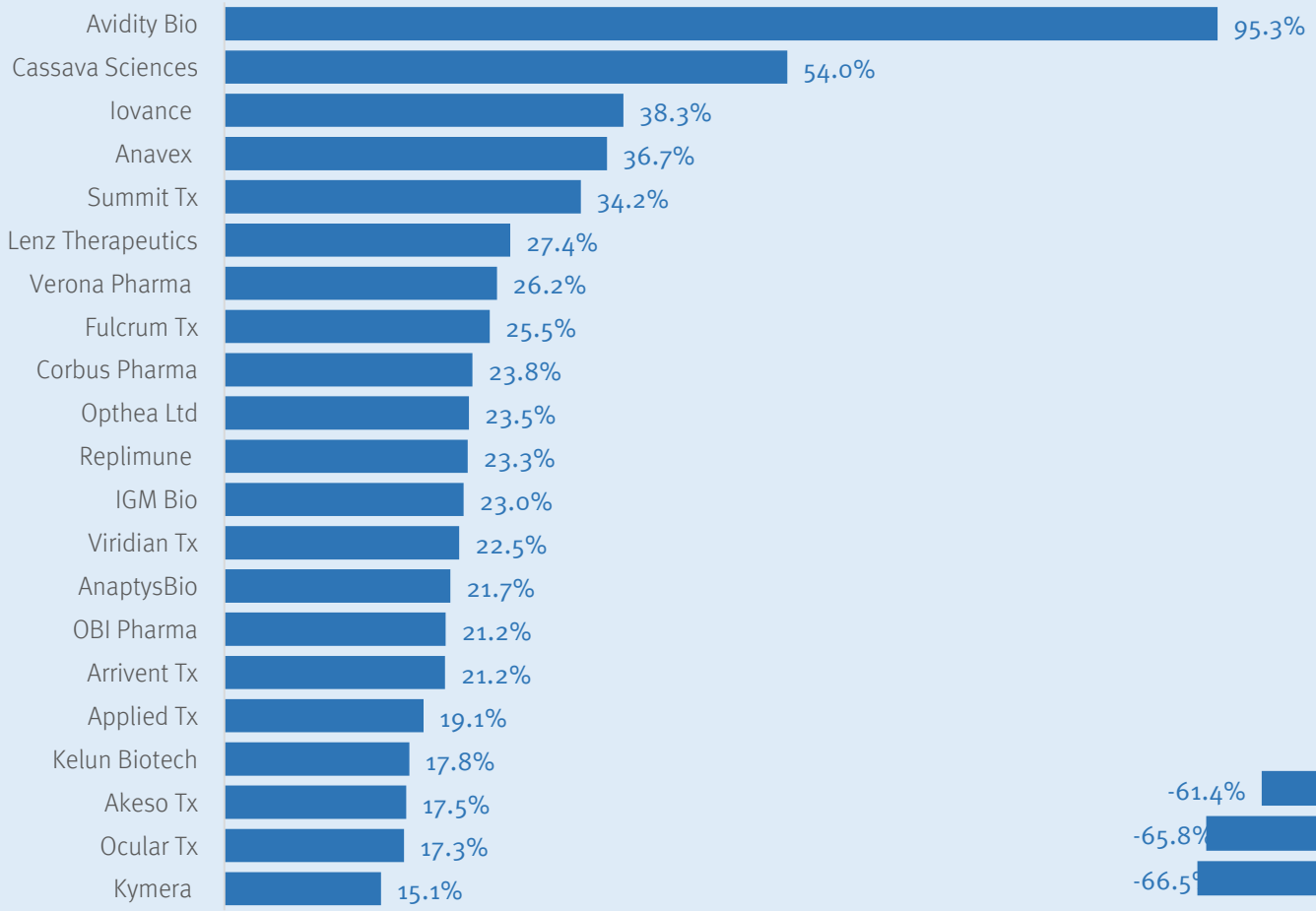
The broad recovery in small cap biotech stocks has, unfortunately, reversed substantially in the last week.

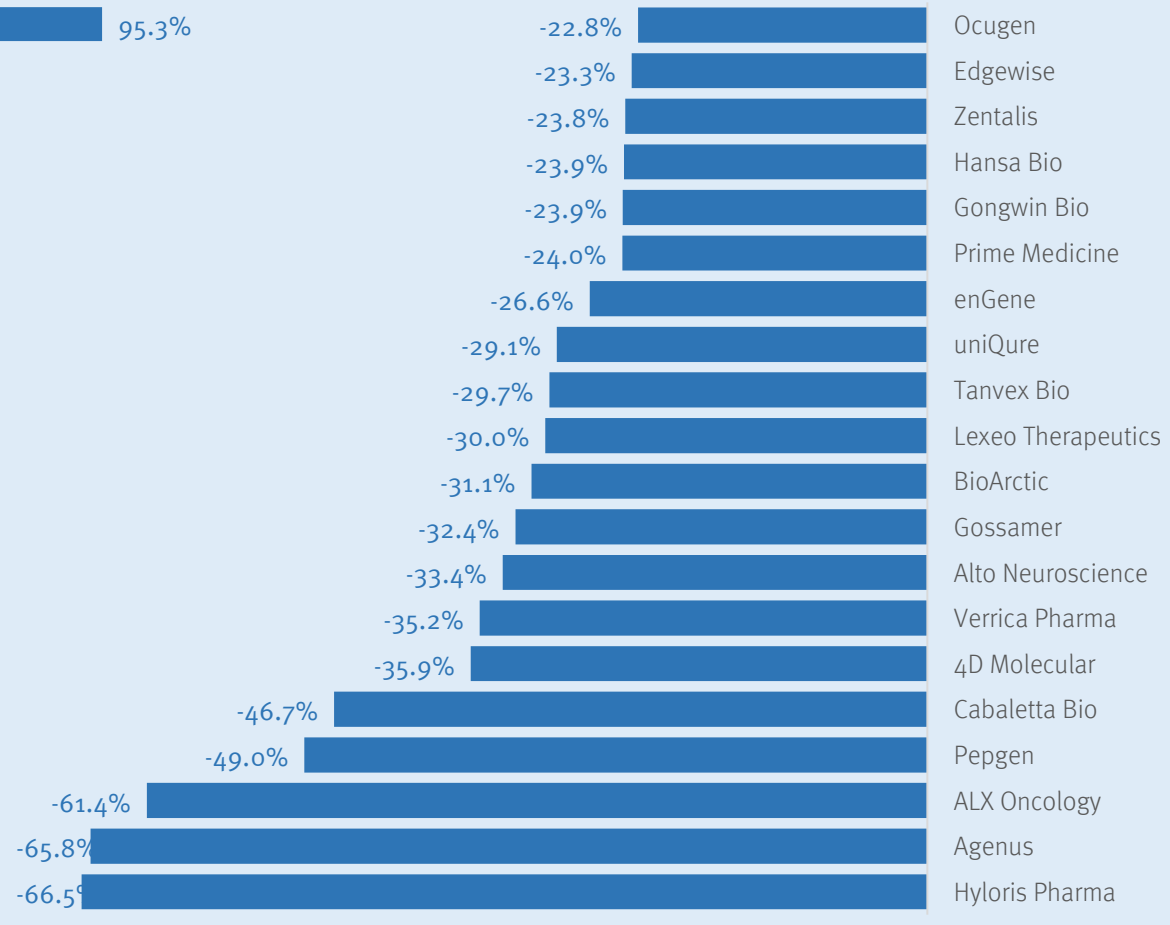
Percent of Biotechs with an Enterprise Value Under $100mm, Nov 2021 to Aug 2024



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

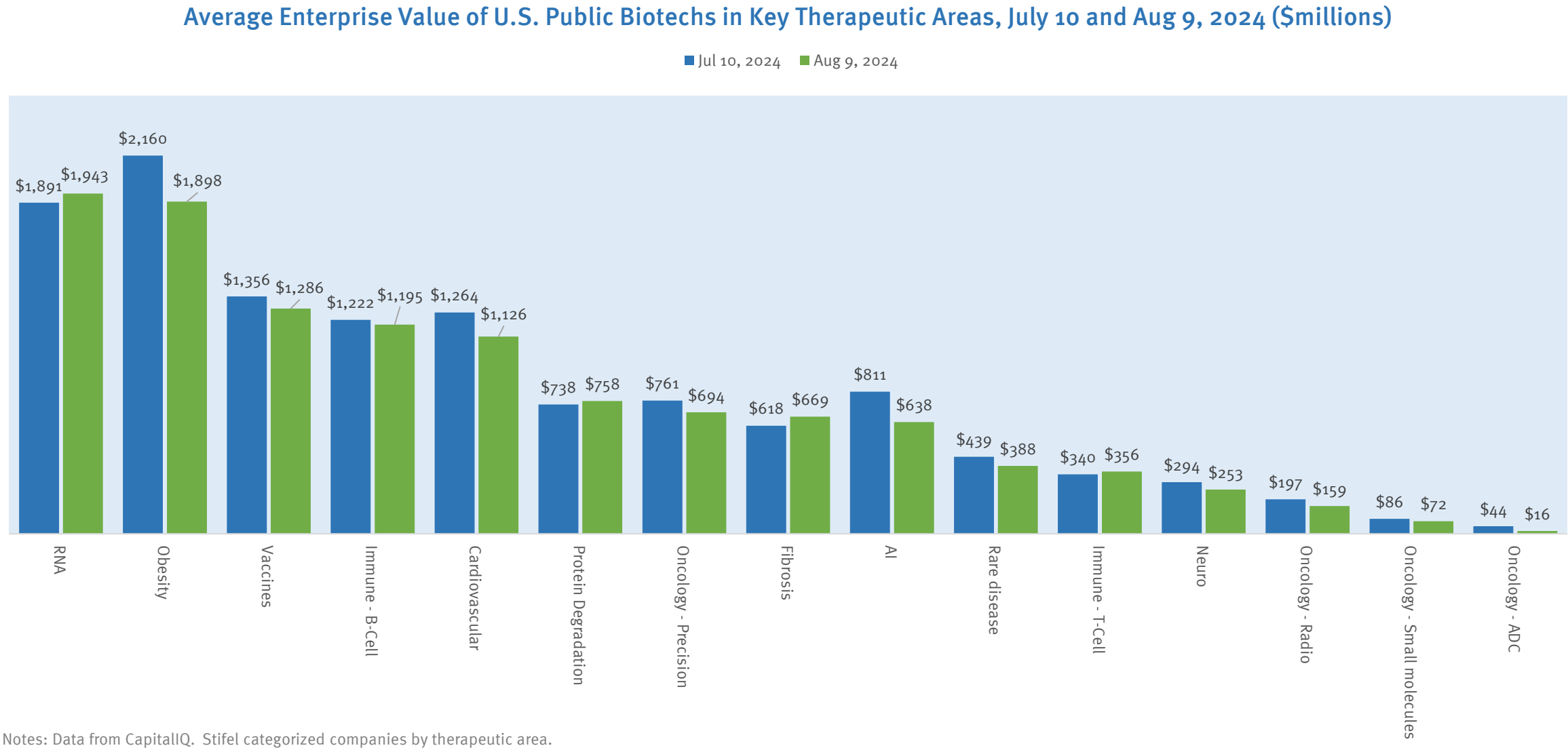
Top Biotech Performers Have Been Spread Across Neuro, RNA and Oncology. Decliners Concentrated in Oncology and Hospital





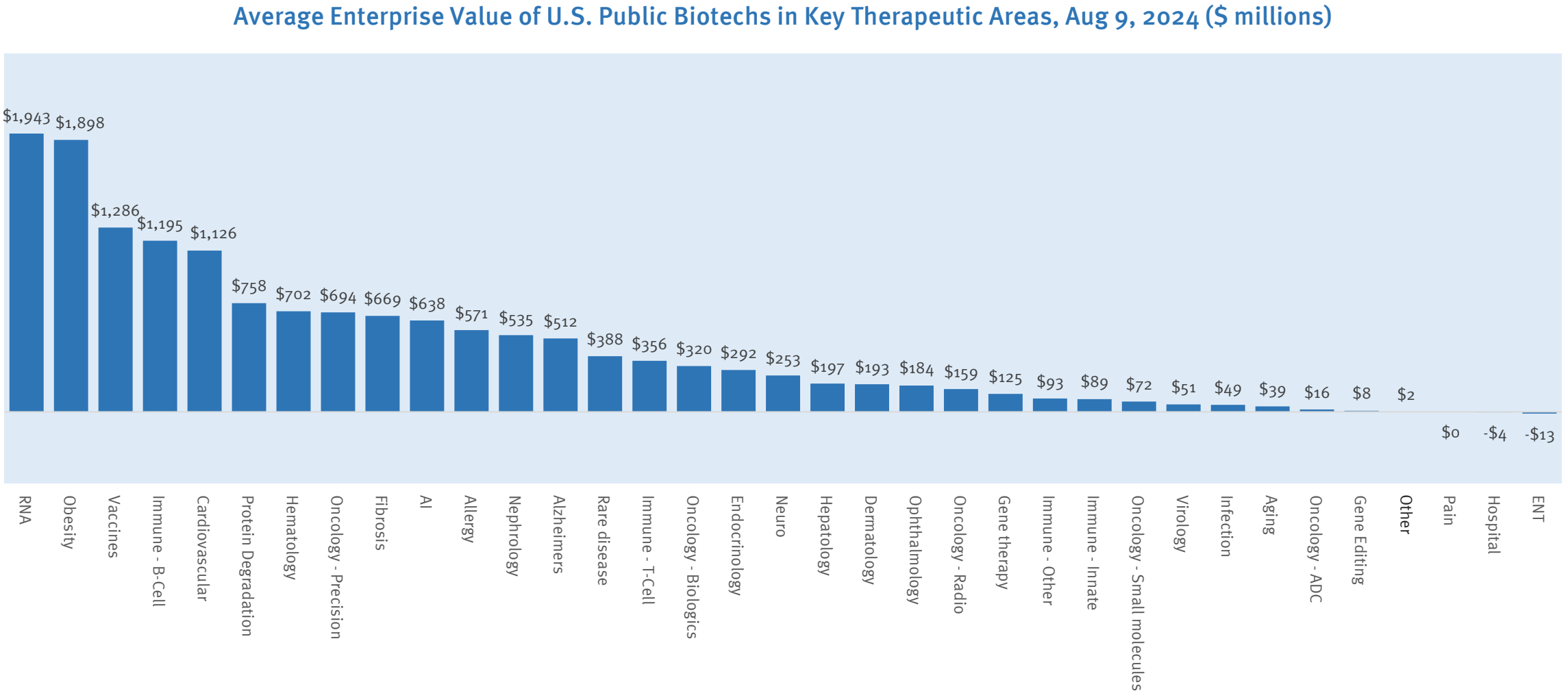
Notes: Data from CapitalIQ. Returns computed from July 9, 20224 to Aug 9, 2024. Only companies with a market cap of $250mm or higher on Jul 9, 2024 were included in this analysis.

RNA Stocks Overtake Obesity Stocks Last Month as Biotech Value Kings



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

CV, B-Cell, Vaccine, Obesity and RNA Biotech Stocks Maintain Average Valuations Over $1 Billion

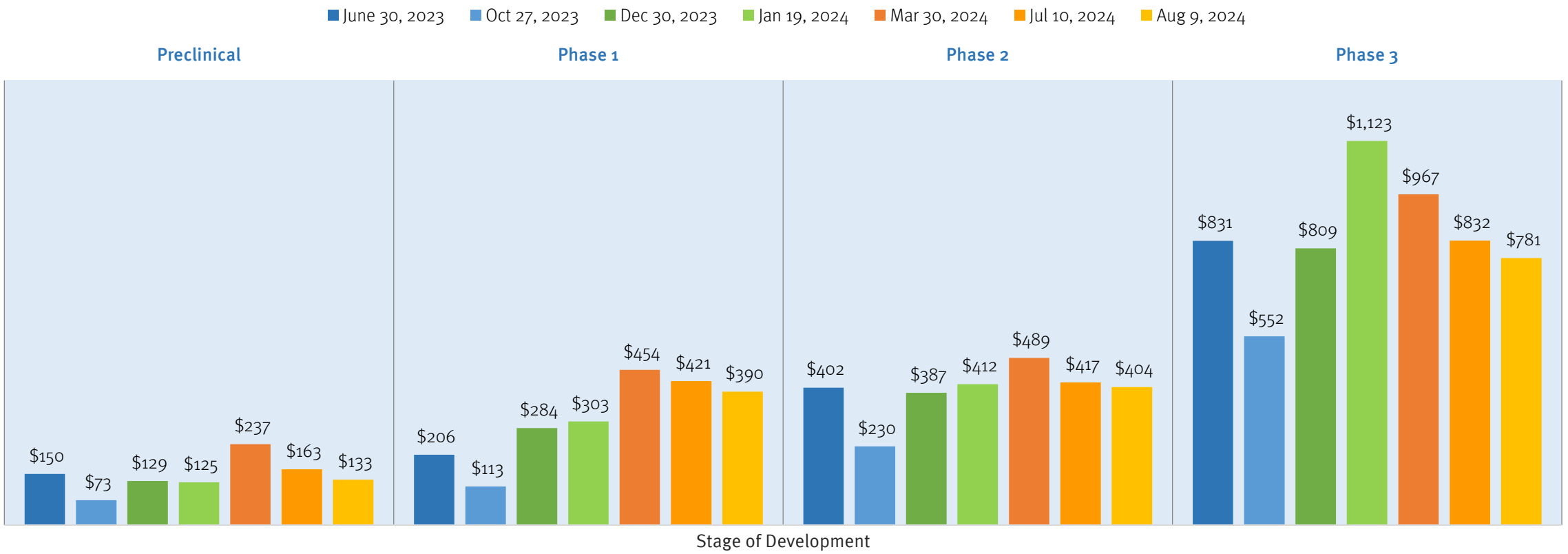


Notes: Data from CapitalIQ. Stifel categorized companies by therapeutic area.

Late-Stage Biotech Values Continue to Drop

The average value of a Phase 3 biotech today is $781 million – down from $1 billion at the end of Q1 and down from $809 million at the start of 2024. In contrast, the average preclinical company value today of $133 million is flat to its value of $129 million at the start of 2024.

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development, June 30 2023 to Aug 9, 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.

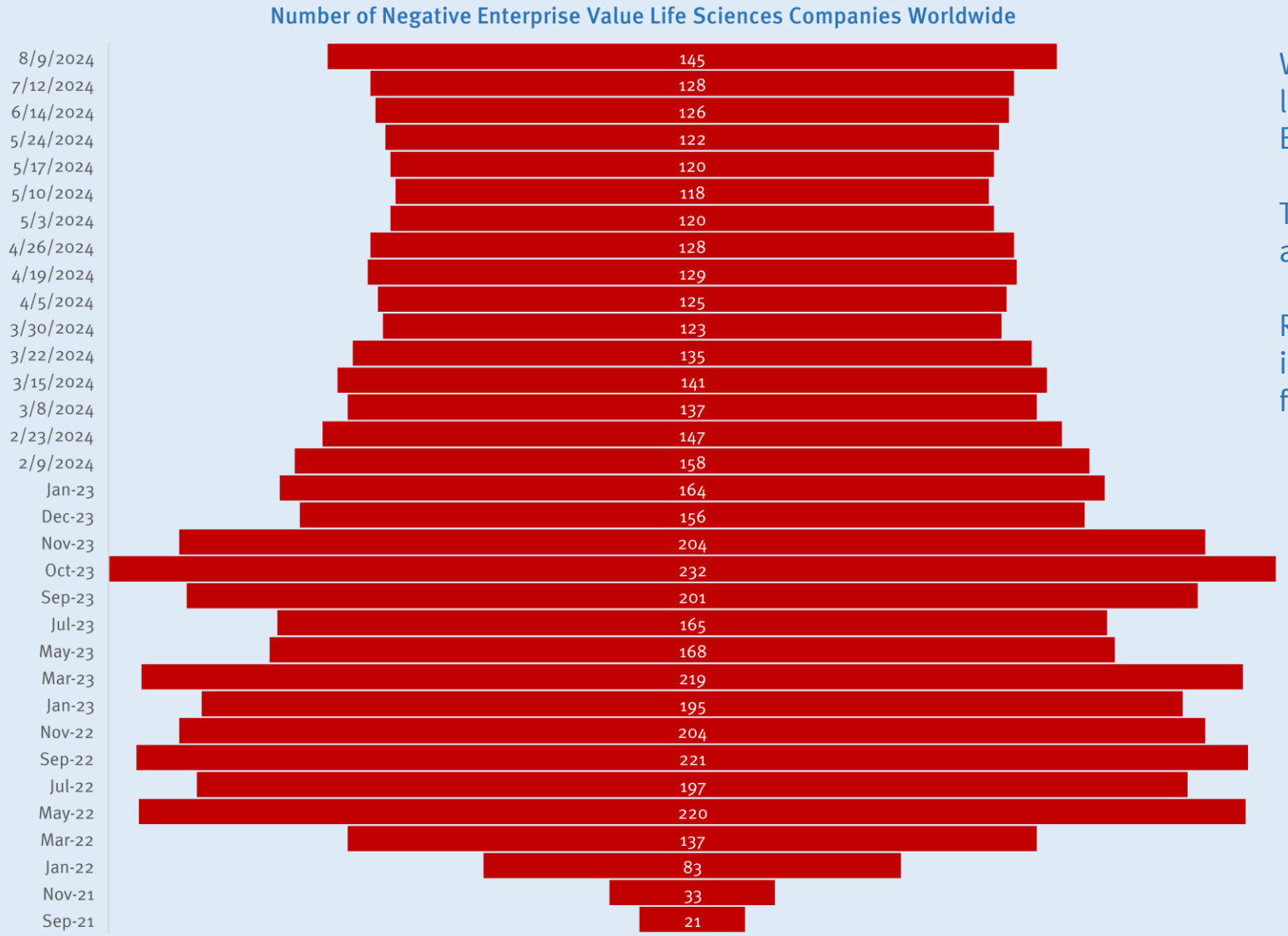
Life Sciences Sector Total Value Up 0.6% Last Week

Performance was mixed across the life sciences sector last week as biotech, life science tools and pharma services dropped while HCIT gained on a major earnings beat from Doximity. Further, commercial pharma gained on outstanding earnings at Eli Lilly.

Sector	Firm Count	Enterprise Value (Aug 12, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$87,362	-0.4%	6.1%	9.3%
Biotech	774	$222,475	-2.7%	-6.8%	-5.1%
CDMO	39	$159,819	1.0%	9.8%	-6.9%
Diagnostics	81	$244,618	1.3%	-6.0%	-5.8%
OTC	29	$26,606	1.1%	0.4%	-16.5%
Pharma	716	$6,719,505	1.1%	1.3%	13.9%
Services	38	$179,091	-1.9%	-0.3%	-13.9%
Tools	50	$713,599	-2.4%	7.0%	0.1%
Devices	180	$1,687,921	0.5%	-0.1%	4.6%
HCIT	10	$19,905	9.1%	11.1%	-15.5%
Total	**1998**	**$10,060,901**	**0.6%**	**1.2%**	**9.8%**

Source: CapitalIQ and Stifel analysis

Major Rise in Count of Negative Enterprise Value Life Sciences Companies in Last Four Weeks



We have seen a major jump up in the number of life science companies trading with a negative EV in the last few weeks.

This has been coupled with a rise in the VIX and a drop in small cap biotech values.

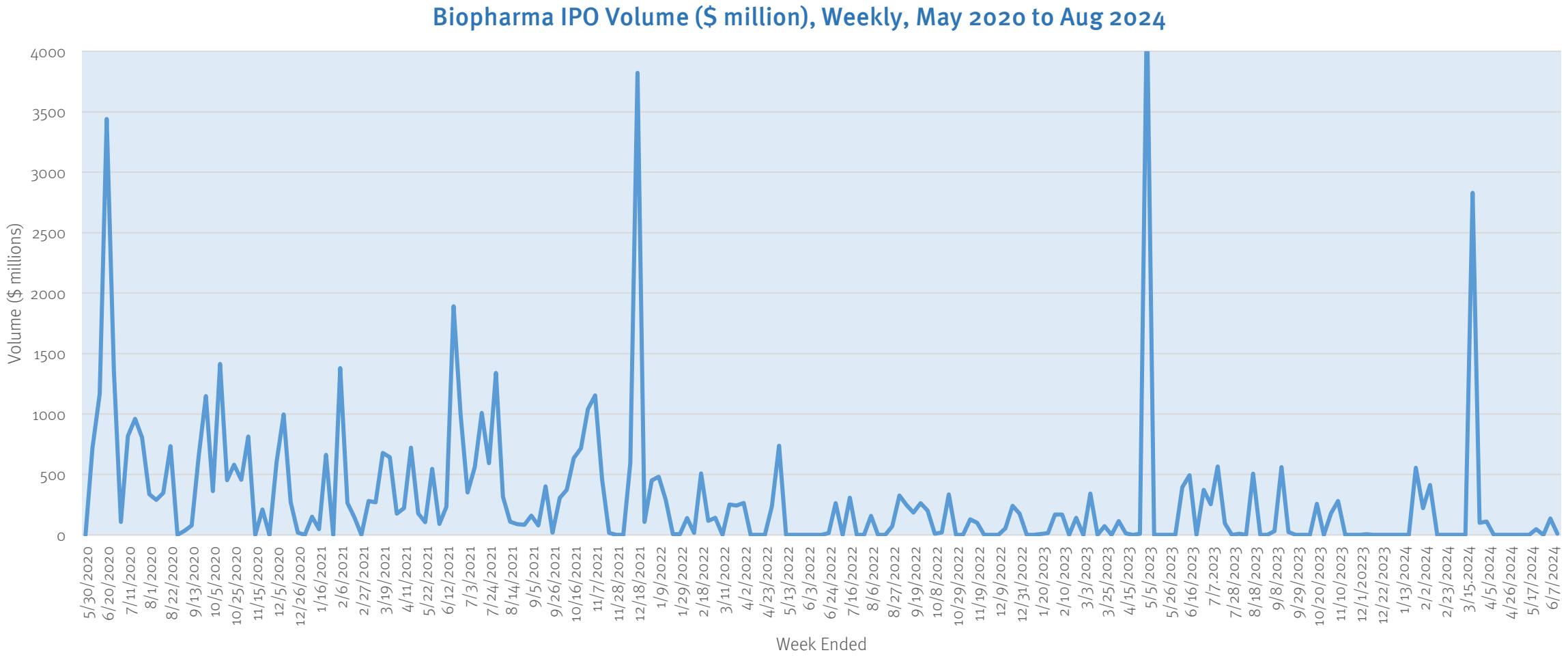
Regrettably, this metric indicates that the sector is starting to look more distressed than it was four or five months ago.

Source: CapitalIQ and Stifel analysis

Capital Markets Update

IPO Market Not Active in Last Month

The U.S. IPO market has remained inactive in recent weeks. The most recent company to go public was Artiva Biotherapeutics. This cell therapy IPO priced at $12/share on July 18th and closed at $11.30 last Friday.



Source: Data from CapitalIQ and Stifel research.

Market Conditions Impacting IPO Issuance Volume

Robert Barrie, *Pharmaceutical Technology*, Aug 6, 2024 (excerpt)

Initial public offerings (IPOs) for biotechs bounced back from years of dormancy to raise $3.72bn in Q1 2024, but the current global stock market crash means listing failures could lie ahead.

The $3.72bn raised in the first quarter of this year is six times the higher than the value reached in Q4 2023, marking the highest quarterly biotech IPO value in over a year on a quarter-on-quarter (QoQ) comparison, based on analysis by GlobalData's Pharmaceutical Intelligence Centre.

However, financial conditions significantly worsened earlier this week when global stock markets saw large falls amid fears of a US recession. It remains to be seen how the global stock sell-off will impact the biotech IPO rebound soon.

GlobalData business fundamentals senior analyst Ophelia Chan told Pharmaceutical Technology: "The current global stock market crash is likely to create a challenging environment for biotech companies planning IPOs later this year. Lower valuations will probably be necessary to attract investor interest, leading to less capital raised and therefore impacting overall funding strategies."

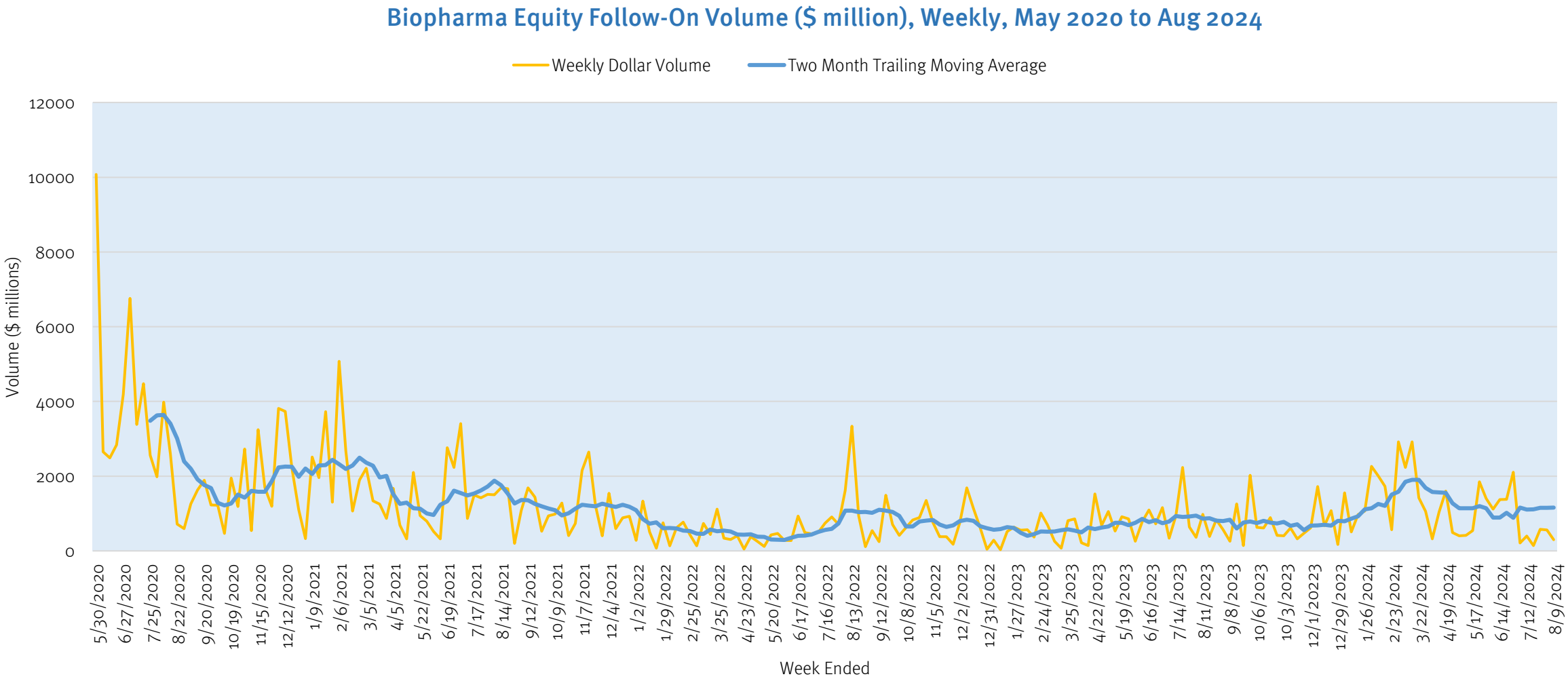
"In addition, since the US Federal Reserve has delayed interest rate cuts, this has also heavily impacted investor interest. Given the current volatile market conditions, biotech companies may delay their IPOs in hopes the market stabilises." In 2020, biotech IPOs boomed with $30.8bn being raised that year. Uncertainty in the market meant only $5.9bn was raised in 2022, which went further down to $4.4bn a year later.

Chan said: "High interest rates during 2022 and 2023 led investors to prioritise the existing portfolios over new opportunities, causing many biotechs to delay their IPOs until market conditions improved." The first and largest biotech IPO to date this year was CG Oncology, which raised $380m for its armed oncolytic virus therapy. Boundless Bio raised $100m in an IPO in March this year while Kyverna Therapeutics, Metagenomi, and Alto Neuroscience have all also made the jump. There have been six completed IPOs in H1 2024, each raising over $100m, as per disclosed values. This totals nearly $5bn, which is more than double the amount raised by five high-value IPOs in the same period last year.

Source: https://www.pharmaceutical-technology.com/news/global-stock-market-crash-likely-to-delay-biotech-ipos

Follow-On Market Quiet Given Market Volatility

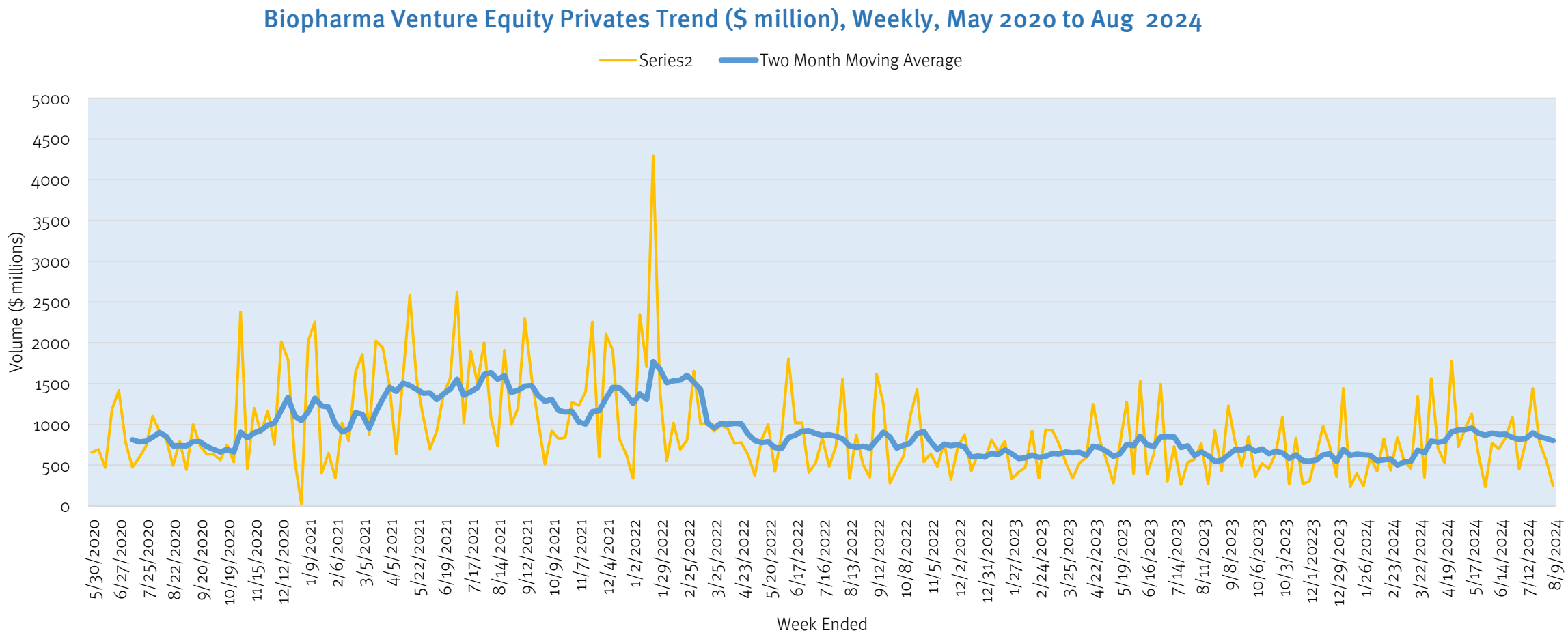
The follow-on market has been conspicuously slow in the last six weeks given the onset of deep Summer and a volatile market. Offerors have issued $2.2 billion in paper into the market. Compare this to $9.2 billion issued in the prior six week period.



Source: Data from CapitalIQ.

Private Venture Equity Market Normal Last Week

Weekly volume of venture privates this year has averaged $750mm. Volume in the last eight weeks has averaged $760mm (in light with the market all year). The market is basically flat overall.



Source: Data from CapitalIQ, Crunchbase.

IDRx Announces $120 Million Series B Financing to Advance Potential Best-in-class New Treatment for Gastrointestinal Stromal Tumor (GIST)

Plymouth, Mass (BUSINESS WIRE) – Aug 7, 2024: IDRx, Inc., a clinical-stage biopharmaceutical company dedicated to transforming cancer treatment with purpose-built precision therapies, today announced the completion of an oversubscribed $120 million Series B Preferred Stock financing. The financing was led by RA Capital Management, Commodore Capital, and Blackstone Multi-Asset Investing with additional new investors, including Rock Springs Capital and a U.S.-based healthcare-focused fund. Existing investors, including Andreessen Horowitz (a16z) Bio + Health, Casdin Capital, Nextech Invest Ltd. (on behalf of one or more funds managed by it), Forge Life Science Partners, co-founder Nick Lydon, Ph.D., and strategic partner Merck KGaA, Darmstadt, Germany also participated in the financing. Derek DiRocco, Ph.D., Partner at RA Capital Management, has joined the IDRx Board of Directors.

IDRx plans to use the proceeds from the financing to support the ongoing Phase 1/1b StrateGIST 1 study of its lead product candidate IDRX-42, a potent, oral, highly selective KIT inhibitor targeting all major categories of activating and resistance mutations in patients with KIT-mutant GIST. Additionally, proceeds will be used to fund the expected initiation of the first pivotal study for IDRX-42 in patients with second-line GIST.

At the 2024 American Society of Clinical Oncology (ASCO) annual meeting, IDRx presented preliminary Phase 1 data from the ongoing Phase 1/1b StrateGIST 1 trial. The data support the best-in-class potential of IDRX-42 in patients with GIST. This included a 23% objective response rate (ORR) across all patients (median four prior lines of therapy) and a 43% ORR in second-line patients, including those with either or both ATP binding site and activation loop mutations, with a favorable tolerability profile consistent with use in front-line and second-line settings. IDRx is now enrolling patients in the Phase 1b portion of the trial. In addition, the U.S. Food and Drug Administration (FDA) has recently granted Fast Track designation to IDRX-42 for the treatment of GIST after disease progression on or intolerance to imatinib.

Source: https://www.businesswire.com/news/home/20240806631982/en/IDRx-Announces-120-Million-Series-B-Financing-to-Advance-Potential-Best-in-class-New-Treatment-for-Gastrointestinal-Stromal-Tumor-GIST

"We are thrilled to announce this financing, which includes support from a top-tier syndicate of investors and positions us to accelerate the development of IDRX-42 for a broad population of patients with GIST, including in the second-line and front-line settings, where patients haven't seen a new treatment option in over 15 years."

Tim Clackson
Chief Executive Officer, IDRx

Biotech Financing: Darkest Before the Dawn

Melanie Senior, *Nature Biotechnology*, Aug 8, 2024 (excerpt)

"It was the best of times, it was the worst of times," wrote Charles Dickens in A Tale of Two Cities. The same might be said for biotech financing today.

On the plus side: flourishing innovation, robust mergers and acquisitions (M&A) activity, and average private biotech funding round sizes at a 15-year high (Fig. 1) On the downside: stubbornly muted public markets and cautious, choosy venture capitalists (VCs) struggling to raise their own new funds in "the worst [environment] I have ever seen" for VC fundraising, according to Antoine Papiernik, chairman and managing partner at Sofinnova. Most biotechs are stuck in a deep, long-lasting downcycle.

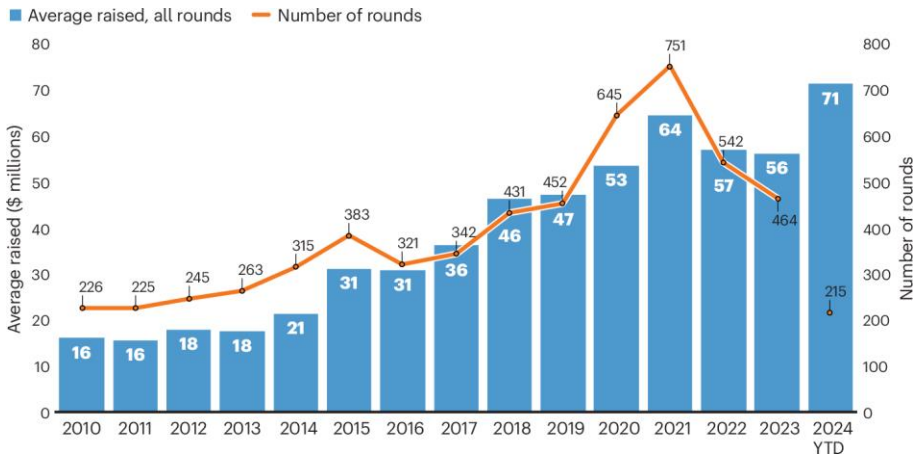
Most — but not all. Three years since the start of its fall from record-breaking pandemic peaks, biotech remains a sector of wildly divergent fortunes.

The fat cats: companies with — and investors in — clinical-stage assets on big pharma's acquisition radars, or management teams with a strong track record. The paupers: earlier-stage groups for whom the music stopped before proof of concept.

Capitalism drives a widening wedge between haves and have-nots. Investors and companies on the right side of the line "can attract funds, talent and entrepreneurs," says Sander Slootweg, managing partner at Naarden, Netherlands-based VC firm Forbion, itself flush with proceeds from six billion-dollar-plus portfolio company acquisitions by big pharma within the last 14 months. Experienced teams working in hot therapy areas are raising outsized rounds — like the $400 million in March 2024 for immuno-inflammation startup Mirador Therapeutics, founded by Mark McKenna, former CEO at Prometheus Biosciences (the latter of which was acquired by Merck & Co. for $10.8 billion in 2023).

Source: https://www.nature.com/articles/s41587-024-02357-2

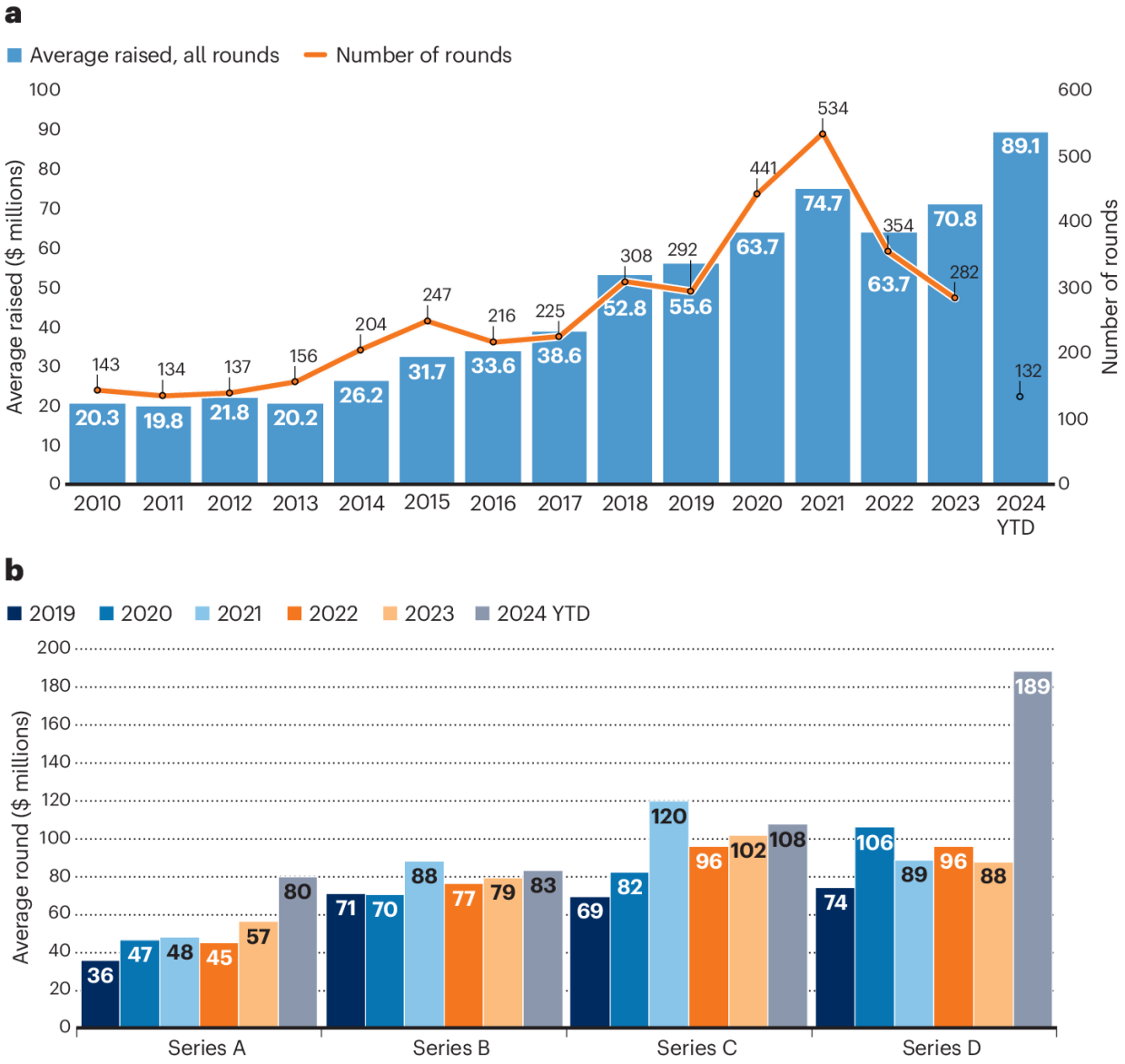
Fig. 1: Venture averages for biopharma therapeutics and platform companies (global).



Neuropsychiatry-focused Seaport Therapeutics launched the following month with $100 million. It is founded and run by Daphne Zohar, co-founder of Karuna (acquired by Bristol Myers Squibb for $14 billion in late 2023). Cancer-focused Synnovation Therapeutics, which raised a $102 million series A in January, is run by a team with experience developing kinase inhibitors at Incyte.

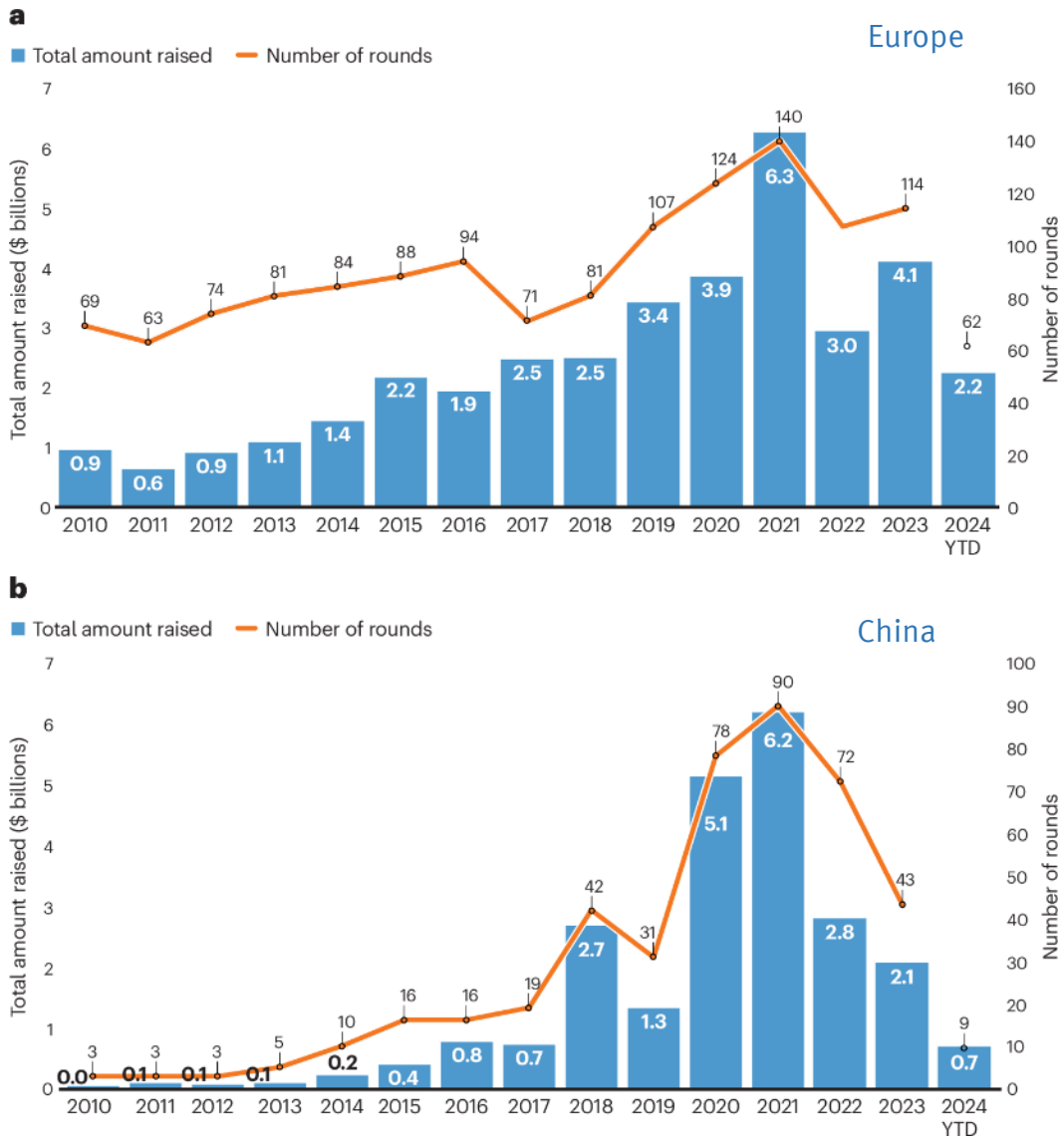
Those biotechs and investors left behind — including the early-stage, the new and the unlucky — must streamline, refinance on less favorable terms, merge or shut down. "Financing early-stage innovation has been very challenging," says David Schilansky, co-founder and CEO of European seed financier and biotech builder Home Biosciences.

Fig. 3: Biopharma therapeutics and platforms venture averages



Source: https://www.nature.com/articles/s41587-024-02357-2

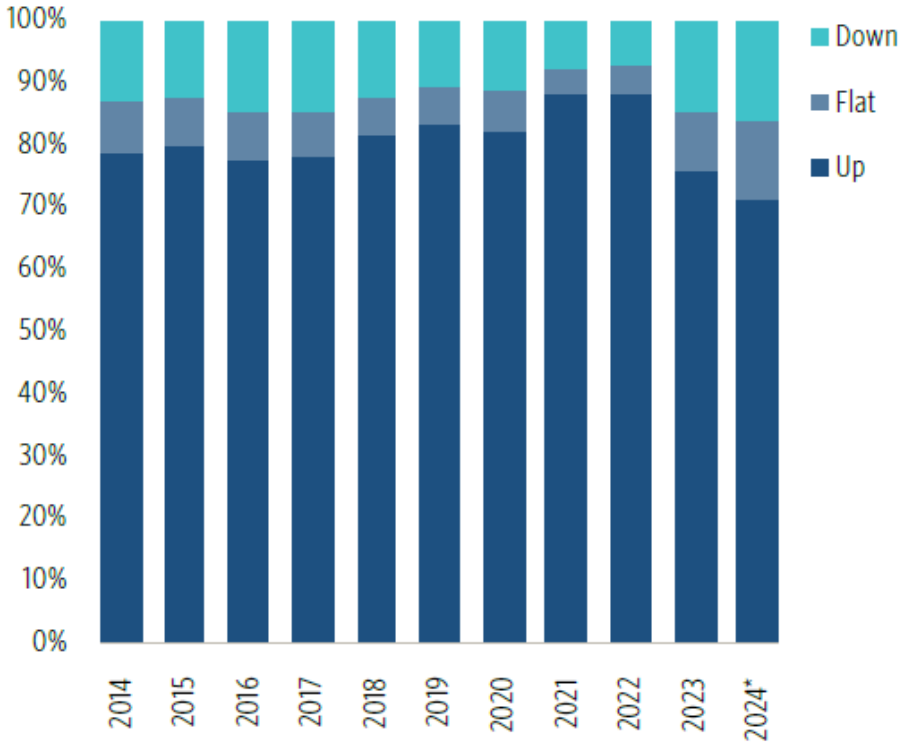
Fig. 5: Venture totals in Europe and China.



Pitchbook U.S. Venture Study (Q2 2024) Shows Heavy Pressure on Valuations in Venture Deals (All Sectors)

Greatest percentage of flat and down rounds in a decade

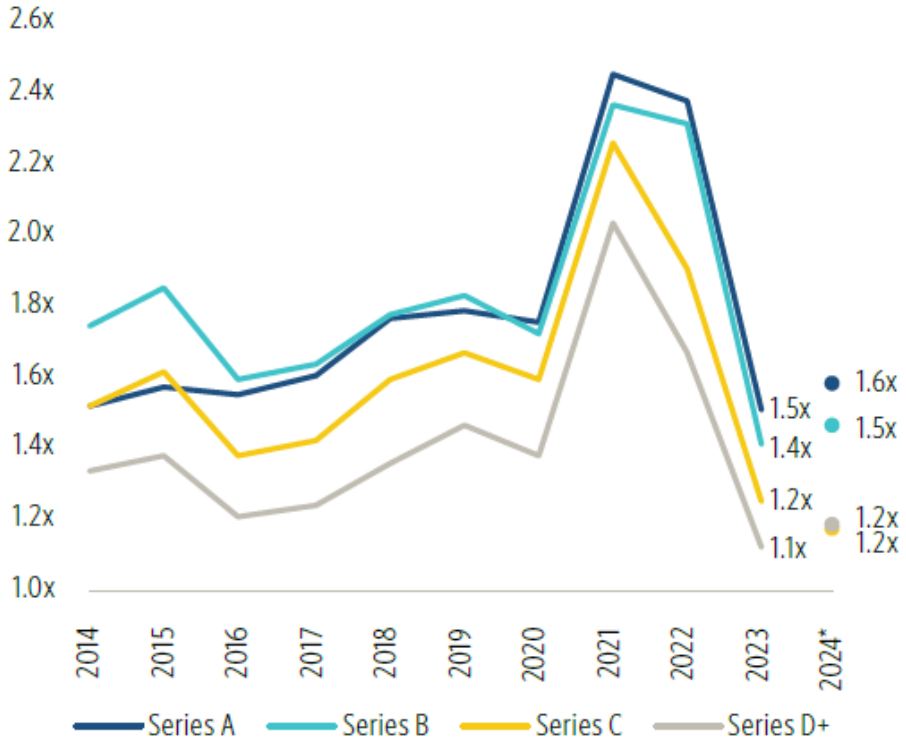
Share of VC deal count by up, down, and flat rounds



Source: PitchBook • Geography: US • *As of June 30, 2024

Step-ups decrease to pre-pandemic levels

Median VC step-up by series



Source: PitchBook • Geography: US • *As of June 30, 2024

Source: https://pitchbook.com/news/reports/q2-2024-us-vc-valuations-report

What is a Crossover Round?

Peter Kolchinsky, Managing Partner, RA Capital, July 2024

Recently I invited people in the biotech community on LinkedIn to share their definitions of a “crossover” round. I had long been hearing people use the term in ways that didn’t quite align with how I understood it. I received a variety of responses that only deepened my sense that we’re not all saying the same thing when we’re saying the same thing.

And that’s a challenge, if not necessarily always a problem, in an industry that’s only becoming more scientifically and financially complex as it matures. Because to understand one another and avoid unnecessary hiccups it helps to have a common language.

If a company says they want to raise a crossover round but doesn’t understand that it’s not positioning itself for a crossover round, then it will struggle to raise a crossover round because investors would quickly recognize that it doesn’t meet the conditions for a crossover round. However, if it recognized that what it was really positioned for was a straightforward venture round and approached the raise like a venture round, then it would find that many of the same investors might be willing to engage in discussions.

Source: https://racap.docsend.com/view/hdsk6stbie4dr9sv

Some reading this might wonder what the difference is between a venture and a crossover round if not the investors participating. Isn’t a crossover round just the round before an IPO in which crossover investors participate? And a venture round… isn’t that some regular private round that maybe venture investors invest and that won’t be followed by an IPO? Indeed, it seems that this is what many people think, but these definitions don’t explain how investors behave. There’s a better definition of a crossover round that would more fully explain investor behavior.

TomaAYto TomAHto… Why does it matter?

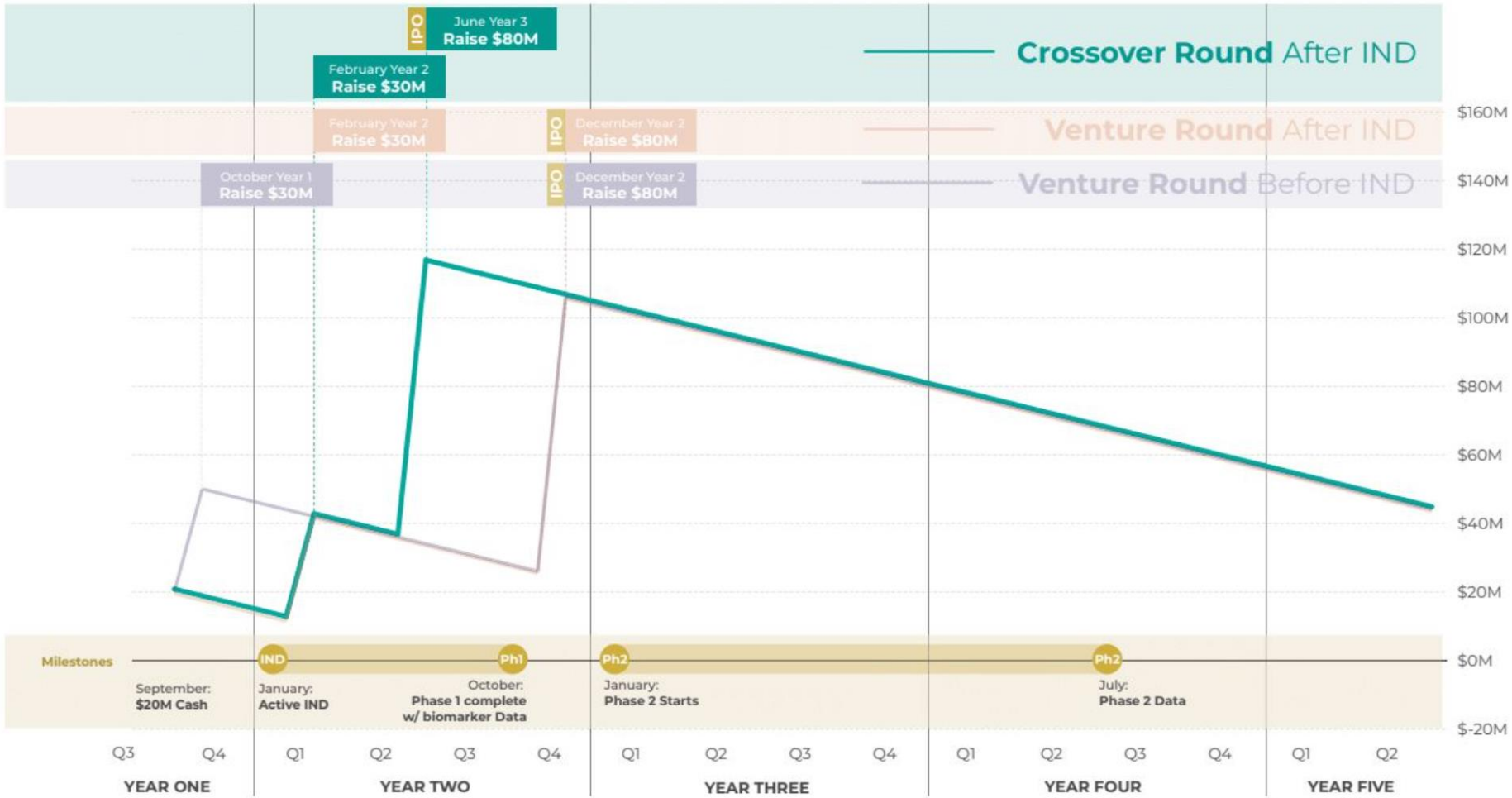
Venture vs Crossover. Why am I making a big deal about the terminology? Why does it matter?

Think about it this way: if investors consider the Series B round a venture round, they will wear their venture hats… which means their “oh damn, this is a risky private investment that might stay private for a long time, especially if the markets fall apart… so I might need a big discount relative to where I think the company could do an IPO today given current market conditions” hats. It’s a lot to fit on a hat, I know.

Investors that see the Series B as a venture round, or see the company as very risky, and/or assume the IPO is far away (i.e., risky) might not agree with the company about its IPO prospects because market conditions might change, Phase 1 might enroll slowly, there might be tox, etc.). Therefore those investors could be looking for a bigger discount or might not even be willing to consider the investment at any price because they can’t lock up their cash for that long.

Crossover investors looking to do crossover deals often have a limit on how much of their funds can be locked up in private companies, kind of like a restaurant can only seat so many people and needs parties to move along to make room for the next seating. A crossover fund can also do venture deals, but it does those consciously not expecting that cash to free up soon for more deals. So what the crossover fund wants to avoid is doing a crossover deal that later turns out to be a venture investment that stays private longer than expected. That can dramatically cut back on a fund’s ability to do more deals.

The goals of a crossover round are to bring on investors who would help the company with insider price discovery and underwrite most if not all of the IPO.



Source: https://racap.docsend.com/view/hdsk6stbie4dr9sv

To recap:

1. A proper crossover round is a private round done in such a way, in terms of pricing, investors, and timing, that there is very little risk to the company also getting the intended proceeds of an IPO at the same or higher price.

2. The goals of a crossover round are to bring on investors who would help the company with insider price discovery and underwrite most if not all of the IPO (check out our **Series I explainer** to understand this process deeply).

3. The alternative to a crossover round is a regular venture round, which just means that investors know that the situation could change a fair bit between the round and the next round, which may or may not be an IPO, and that it's hard to know whether one will invest in that next round and at what price.

4. A true crossover round includes investors who are true crossover investors, which means that they can be trusted to honor their commitment to participate in insider price discovery ahead of the IPO and to put in a meaningful order in the IPO at prices higher than the crossover round *if indeed nothing material has changed between the crossover round and IPO.*

5. Crossover investors may or may not make venture investments. Venture investors might or might not be crossover investors (e.g., they might make private investments but not participate in pre-IPO price discovery, in which case they aren't crossover investors by my definition since they aren't helping the company derisk the IPO).

6. A crossover round is not merely a private round done before the IPO, regardless of who invests in it. Nor is a crossover investor merely any investor who normally invests in public companies but sometimes does private deals.

Hopefully this helps management teams understand when they are doing a crossover vs a venture round and recognize when they are talking to an investor who is or isn't capable of being a crossover investor and, even if they are, whether they are wearing their crossover vs venture hat.

Source: https://racap.docsend.com/view/hdsk6stbie4dr9sv

The key point of this article is that a crossover financing round is fundamentally different than a venture round.

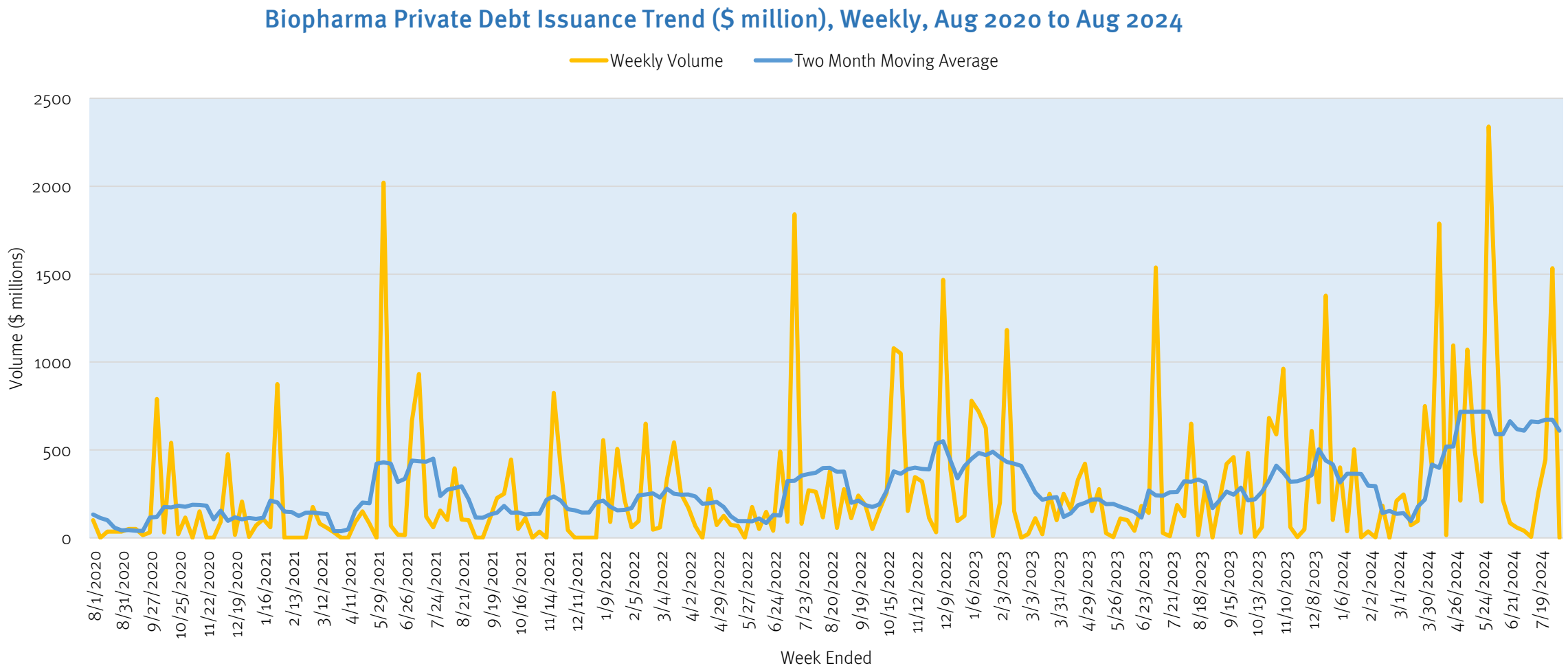
The term "crossover financing" has indeed been used in a very plastic and indefinite way in conversations we have had with issuers over the last three or four years.

A related phrase we often hear is "family office" financing. This is often code that means that an issuer is looking for valuation insensitive investors who are not particularly sophisticated.

In our experience, these type of investors are almost universally mythical beasts that do not exist.

Biopharma Private Debt Market Remains Elevated

Volumes in the private debt market have remained elevated in the last several months. We have been averaging around $700mm a week in this market – the same volume as seen in the venture equity market.

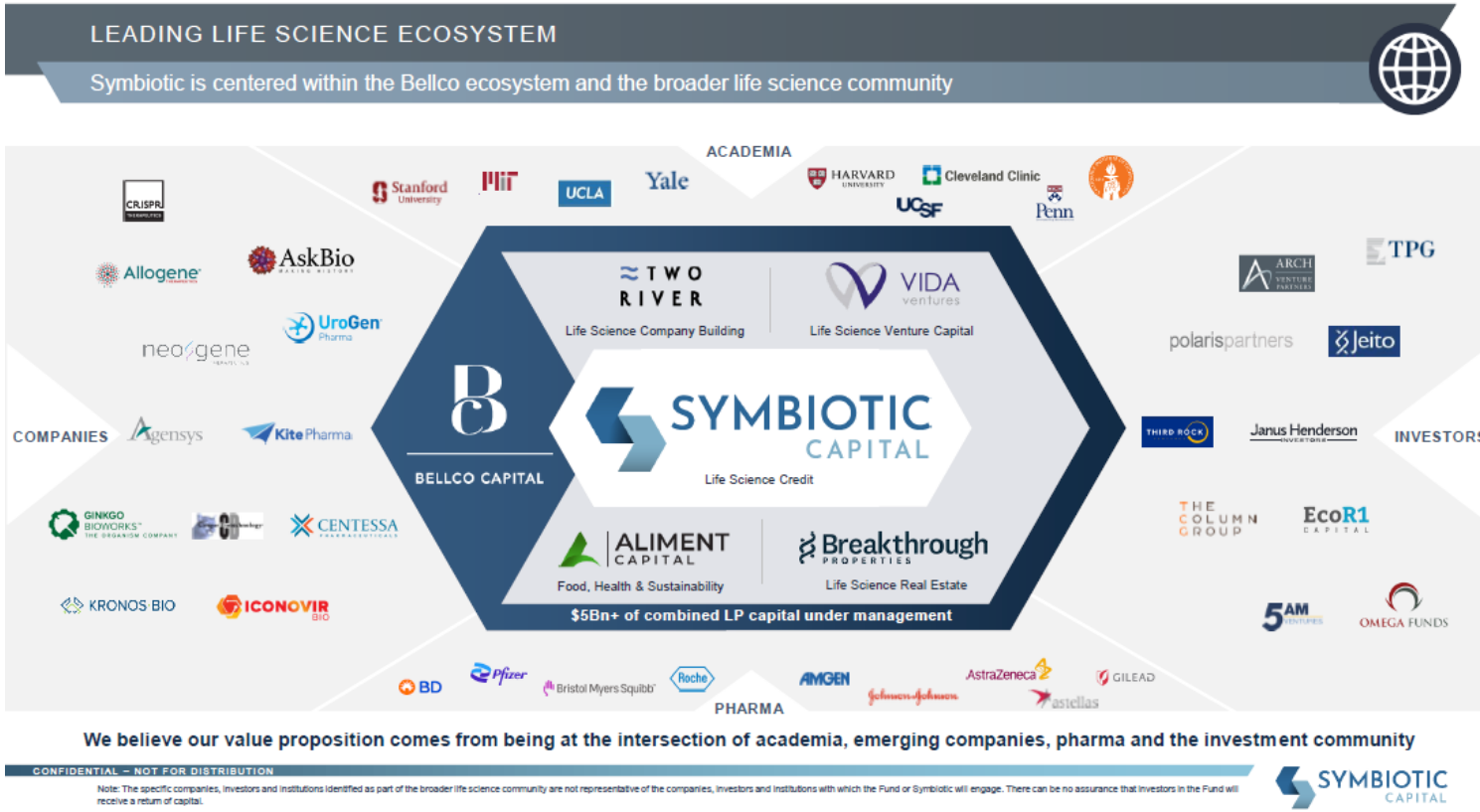


Source: Data from CapitalIQ, Crunchbase, Stifel research.

Biotech Entrepreneur Arie Belldegrun Launches New ‘Science-First’ Credit Firm

Delilah Alvarado, *Biopharma Dive*, Aug 6, 2024 (excerpt)

- Arie Belldegrun, the founder of Allogene Therapeutics and Kite Pharma, unveiled a new credit firm Tuesday with $600 million to put to work providing loans to biotechnology, medical device and other life sciences companies.
- Called Symbiotic Capital, the firm pitches itself as a new kind of lender that understands the complexities of life sciences businesses, which may be years away from generating the kind of regular revenue that typically makes loan repayments manageable.
- The new firm is affiliated with Bellco Capital, which was founded by Belldegrun. Along with Kite, which he sold to Gilead Sciences for $11.9 billion, and Allogene, the biotech executive also co-founded the venture firm Vida Ventures and started a real estate company called Breakthrough Properties.



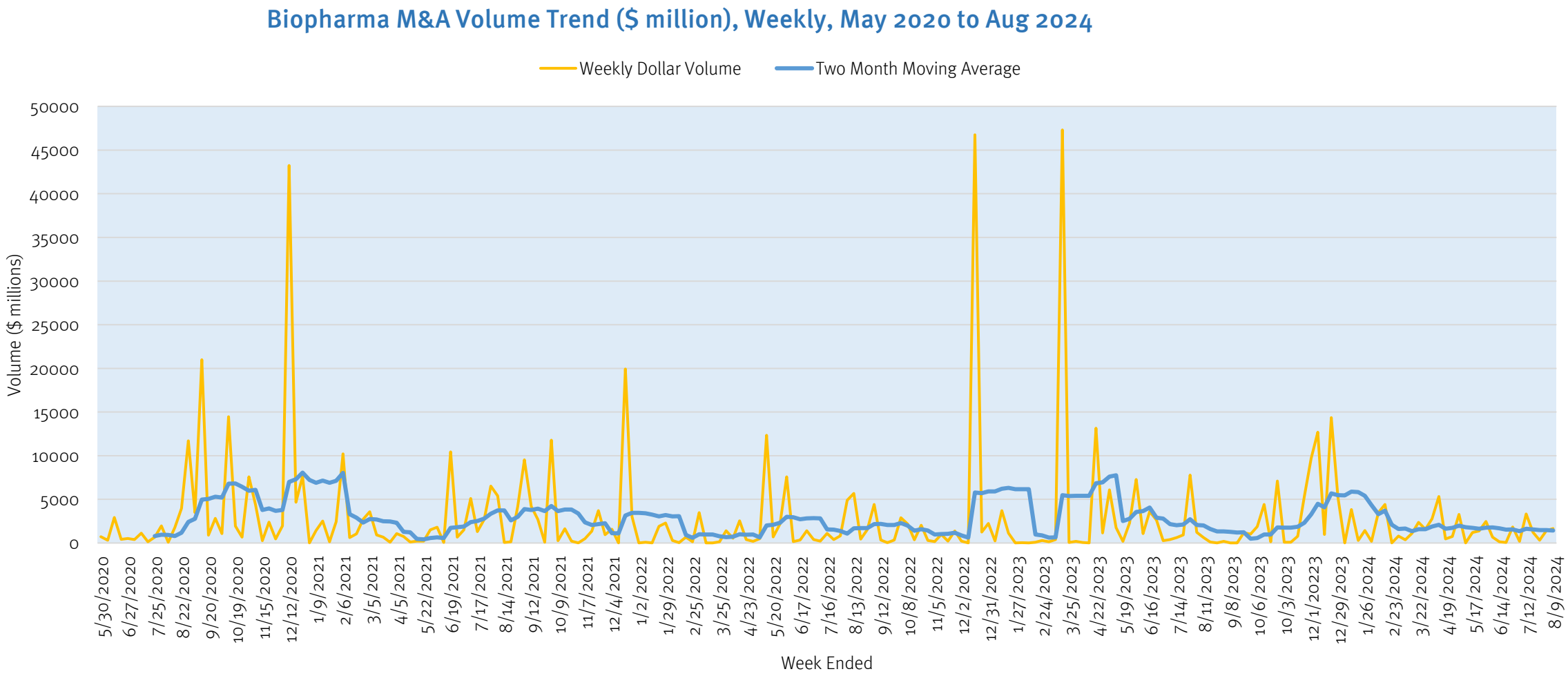
Source: https://www.biopharmadive.com/news/arie-belldegrun-symbiotic-capital-credit-biotech-lending/723414/

Deal News

Hotel Dieu, Lyon, France, a Functional Hospital from 1454 to 2010.

Last Week Saw Moderate Biopharma M&A Volume

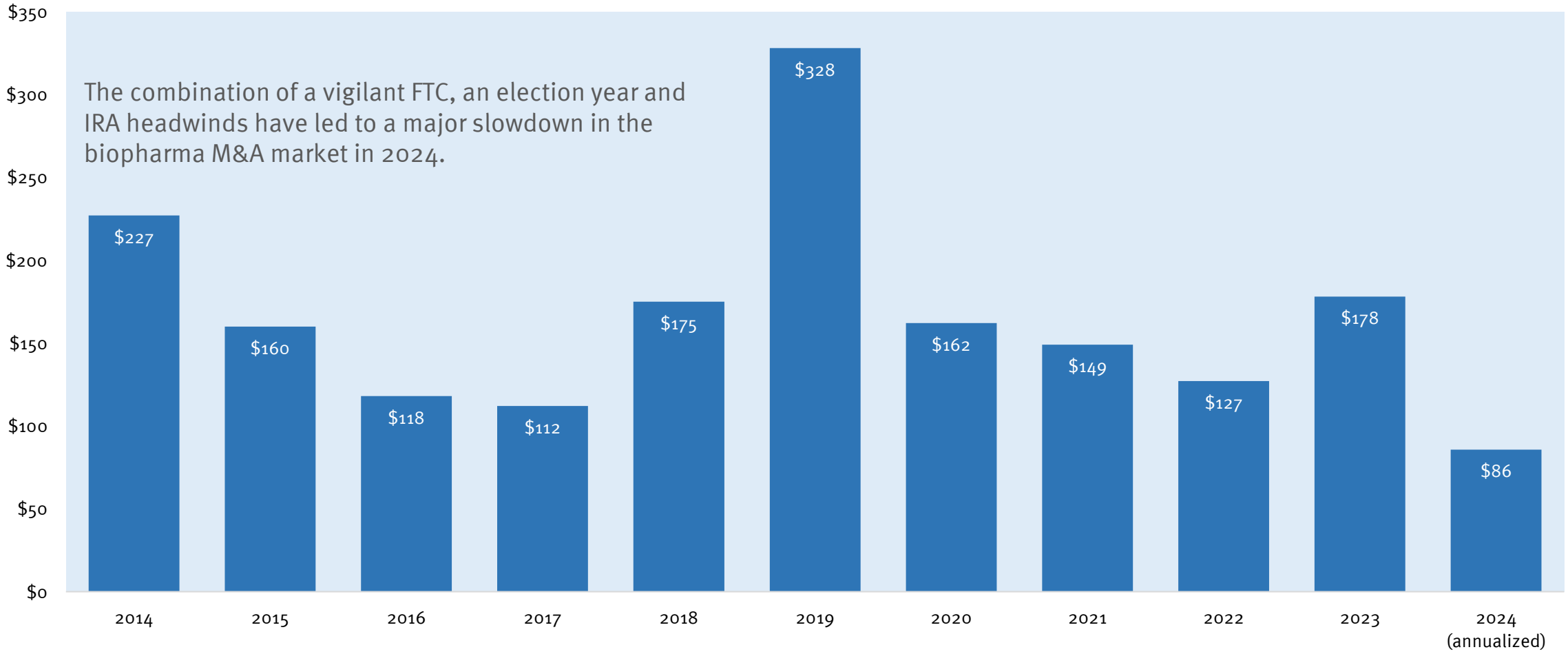
We are seeing weekly M&A volume run between $1bn and $1.5bn in the last several months. There is a conspicuous paucity of large deals.



Source: S&P CapitalIQ

Large M&A Doldrums Continue

M&A Volume in the Biopharma Sector, Jan 2014 – Aug 10 2024 (annualized)
($ Billions, Worldwide)



Source: S&P CapitalIQ and Stifel research.

Big Drugmakers Doing Smaller Deals

Jared Hopkins and Laura Cooper, Wall Street Journal, August 12, 2024

Merck has made four small acquisitions this year to diversify and deepen the company's drug pipeline. For years the world's biggest drugmakers paid up for deals. Now they are writing much smaller checks.

After shelling out tens of billions of dollars for single biotech companies, pharmaceutical giants such as AbbVie, AstraZeneca and Merck & Co. have shifted to smaller targets costing $5 billion or less. Many of the companies getting taken out are private.

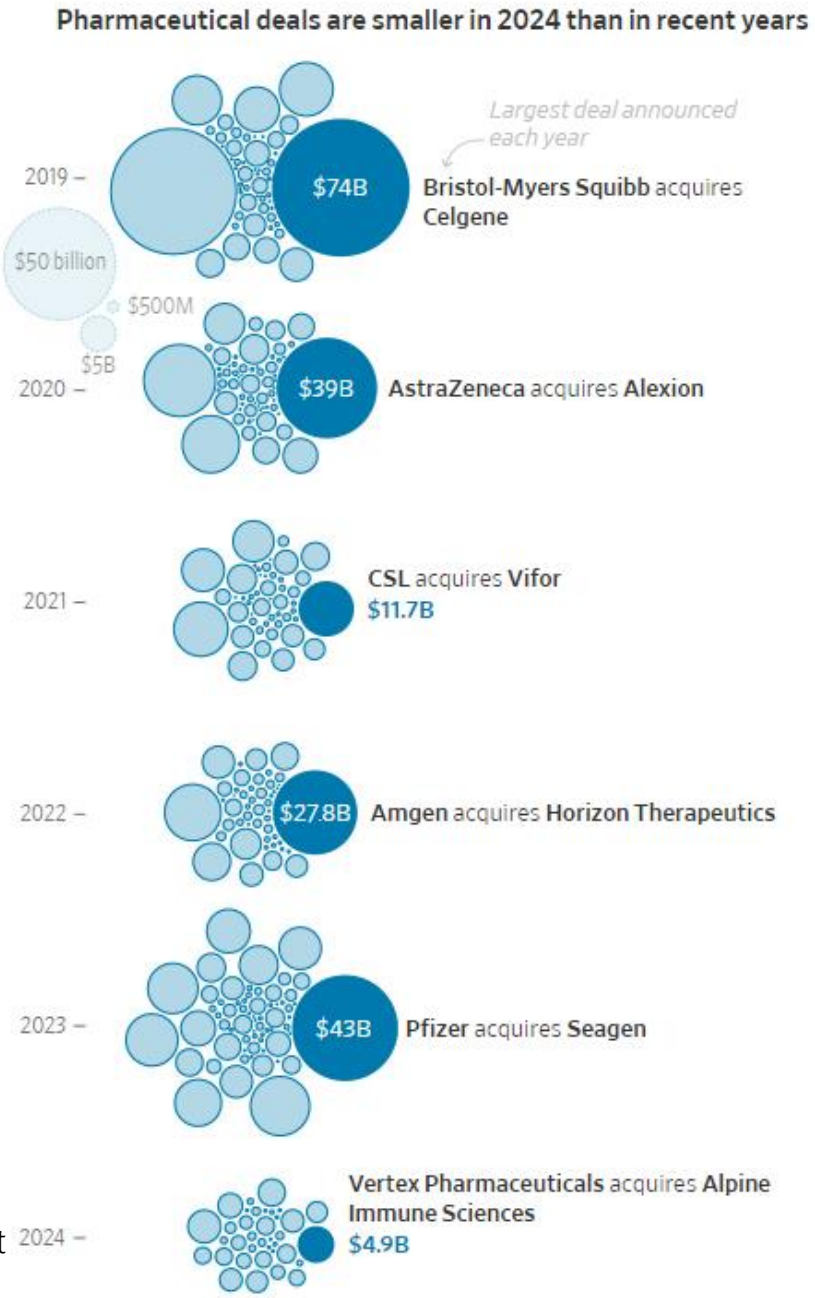
The reason, according to executives, bankers and lawyers: Smaller deals are just easier to do in the current regulatory environment, and the sector is looking pretty picked over.

All 17 deals announced by big pharmaceutical companies during the first six months of the year were valued at $5 billion or less, according to research firm DealForma. During the same period last year, big drugmakers agreed to nine deals, including two that were $10 billion or larger.

Nine of the 17 deals were for privately held companies, compared with one during the same period last year, DealForma said. Its data was for deals with disclosed values and upfront cash and equity amounts. Large drugmakers were defined as having a market value of more than $50 billion.

Last year's big acquisitions were led by Pfizer's $43 billion purchase of cancer biotech Seagen. By contrast, the biggest pharmaceutical deal so far this year was Vertex Pharmaceuticals' $4.9 billion purchase of Alpine Immune Sciences and its experimental kidney drug.

"The size of this deal was just about perfect for Vertex. It was easy to afford and left us with a balance sheet to do more deals," said Vertex Chairman Jeffrey Leiden.



Source: https://www.wsj.com/health/pharma/big-drugmakers-are-clinching-smaller-deals-0c039593

Mallinckrodt to Sell Therakos to CVC for $925 Million

DUBLIN and LUXEMBOURG – August 5, 2024 -- Mallinckrodt plc ("Mallinckrodt" or the "Company"), a global specialty pharmaceutical company, and CVC Capital Partners ("CVC"), one of the world's leading investment firms, today announced that they have entered into a definitive agreement1 under which CVC Capital Partners Fund IX will acquire the Company's Therakos business for a purchase price of $925 million, subject to customary adjustments.

Therakos is a fully integrated extracorporeal photopheresis (ECP) delivery system for autologous immunomodulatory therapy. With approvals for use in the U.S., Canada, Europe, Japan, Australia and Latin America, it is the platform-of-choice among healthcare providers and patients to treat a range of immune-related diseases. CVC has deep expertise in healthcare and a global portfolio of life sciences businesses spanning pharma, med-tech and healthcare services. The firm intends to make additional investments in the continued research, development, indication expansion and geographic expansion of Therakos.

Under the terms of the agreement, key employees who work on Therakos will transition with the business and continue supporting the product and its stakeholders.

On behalf of CVC's Healthcare team, Cathrin Petty and Phil Robinson said, "We see significant opportunities ahead to expand Therakos' indications, enter new geographies and bring this innovative treatment to more patients around the world. We look forward to working closely with the talented Therakos team and adding this best-in-class ECP system with an unparalleled efficacy, safety and tolerability profile to our portfolio of healthcare businesses."

"Today's announcement underscores our commitment to executing on our strategic priorities and creating value for our stakeholders," said Siggi Olafsson, President and Chief Executive Officer of Mallinckrodt.

"This transaction provides the Therakos business with an ideal partner to invest in its continued growth, and we look forward to closely working with CVC to transition Therakos for the benefit of patients, healthcare providers, partners and employees. I thank the Therakos team for their ongoing commitment and dedication to improving the lives of patients."

Source: https://www.cvc.com/media/news/2024/2024-08-05-mallinckrodt-reaches-agreement-to-sell-therakos-business-to-cvc/

Pharmacosmos to Acquire G1 Therapeutics for $405 Million

RESEARCH TRIANGLE PARK, N.C. and HOLBAEK, Denmark, Aug. 07, 2024 -- G1 Therapeutics, Inc. (Nasdaq: GTHX), a commercial-stage oncology company focused on delivering next-generation therapies that improve the lives of those affected by cancer, and Pharmacosmos A/S, a leader in the development of innovative treatments for patients suffering from iron deficiency and iron deficiency anemia, today announced that they have entered into a definitive merger agreement under which Pharmacosmos A/S, through its U.S. subsidiary Pharmacosmos Therapeutics Inc., will acquire all outstanding shares of G1 Therapeutics common stock for U.S. $7.15 per share in cash for a total equity value of approximately $405 million, which represents a 68% premium to G1's closing share price on August 6, 2024 and a 133% premium to G1's prior 30-day volume weighted average price. The Boards of Directors of the parties have unanimously approved the transaction, which is expected to close late in the third quarter of 2024.

G1's COSELA is the first and only product approved by the U.S. Food and Drug Administration to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

Together, Pharmacosmos and G1 Therapeutics will execute on the shared vision to grow and accelerate the availability of COSELA for all appropriate patients with ES-SCLC. G1 brings a well-established and successful commercial, sales, and medical platform to Pharmacosmos, which has complementary expertise in commercializing hematology and supportive care products, a robust global commercial presence, and significant resources to maximize the penetration of COSELA into the ES-SCLC market. Together, the combined company will be able to optimize the commercial reach to oncologists and expand the availability of COSELA among patients living with ES-SCLC.

Under the terms of the merger agreement, Pharmacosmos has agreed to commence a cash tender offer to acquire all issued and outstanding shares of G1 common stock for US $7.15 per share in cash. The transaction will be fully financed by Pharmacosmos' existing cash on hand and existing corporate credit facilities.

The closing of the tender offer will be subject to customary conditions, including the tender of shares which represent at least a majority of the total number of G1's outstanding shares of common stock and the expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act. Upon successful completion of the tender offer, Pharmacosmos would acquire all shares not acquired in the tender offer through a second-step merger for the same consideration that the tendering stockholders will receive in the tender offer.

Source: https://www.globenewswire.com/news-release/2024/08/07/2925767/0/en/Pharmacosmos-Group-to-Acquire-G1-Therapeutics.html

Pharma AI Powerhouses Recursion and Exscientia to Merge

SALT LAKE CITY and OXFORD, United Kingdom, Aug. 08, 2024 (GLOBE NEWSWIRE) -- Recursion (Nasdaq: RXRX) and Exscientia plc (Nasdaq: EXAI) today announced the companies have entered into a definitive agreement, combining Recursion, a leading clinical stage technology-enabled biotech company decoding biology to industrialize drug discovery, with Exscientia, a technology-driven clinical stage drug design and development company, committed to creating more effective medicines for patients, faster.

“We believe the proposed combination is deeply complementary and aligned with our missions to industrialize drug discovery to deliver high quality medicines and lower prices for consumers,” said Chris Gibson, Ph.D., Co-Founder and CEO of Recursion as well as the planned CEO of the combined entity. “Exscientia’s precision chemistry tools and capabilities, including its newly commissioned automated small molecule synthesis platform, will augment our tech-enabled biology and chemistry exploration, hit discovery and translational capabilities. I am excited to continue building the best example of the next generation of biotechnology companies. It still feels like we are just getting started.”

“Adding Exscientia’s best-in-class focused precision oncology internal pipeline to Recursion’s first-in-class focused pipeline spanning rare disease, precision oncology and infectious disease is highly complementary as we look to bring treatments to patients faster,” said David Hallett, Ph.D., Interim Chief Executive Officer and planned Chief Scientific Officer of Recursion post-closing of the transaction. “We look forward to bringing our teams together and integrating Recursion's high throughput and target biology capabilities with Exscientia's highly scalable molecular design and automated chemistry synthesis capabilities to truly accelerate the discovery of better drugs for patients.”

Once integrated, the companies believe the extended and evolved Recursion OS will enable the discovery and translation of higher quality medicines more efficiently and at a higher scale with a full-stack technology-enabled small molecule discovery platform. In addition, the combined company expects to read out approximately 10 clinical trials in the next 18 months.

The proposed business combination will also advance significant therapeutic discovery collaborations with some of the most prominent biopharma companies in the world, including Roche-Genentech, Sanofi, Bayer, and Merck KGaA. Moreover, there is the potential for approximately $200 million in milestone payments over the next 2 years from these current partnerships and there is the potential for more than $20 billion in revenue before royalties on net-sales of partnership programs which range from mid single-digit to double-digit royalties over the course of the partnership.

Source: https://www.globenewswire.com/news-release/2024/08/08/2926843/0/en/Recursion-and-Exscientia-Enter-Definitive-Agreement-to-Create-a-Global-Technology-Enabled-Drug-Discovery-Leader-with-End-to-End-Capabilities.html

Biotech Firm Recursion to Buy Smaller Peer Exscientia for $688 Million

Anirban Sen, *Reuters*, Aug 8, 2024 (excerpt)

Recursion Pharmaceuticals, a biotech firm which uses artificial intelligence to discover new drug candidates, has agreed to buy smaller rival Exscientia for $688 million in an all-stock deal, according to a statement seen by Reuters.

The deal, which is expected to be announced as early as Thursday morning, comes as major drugmakers double down on AI to boost drug development, find patients for clinical trials quickly or reduce the number of people needed to test medicines, both accelerating drug development and potentially saving millions of dollars.

Human studies are the most expensive and time-consuming part of drug development as it can take several years to recruit patients and trial new medicines in a process that can cost more than a billion dollars to get a newly discovered drug over the finishing line.

"Recursion and Exscientia coming together is extraordinarily complementary in terms of using end-to-end in discovery from biology to all the way through chemistry. It enables you to make medicines better and faster and that's what we're trying to do," said Najat Khan, chief R&D officer at Recursion.

Founded in 2013, Recursion is a phase 2 clinical-stage firm, which has a pipeline of treatments for rare diseases and some forms of cancers. It became a publicly-listed company in 2021 and has partnerships with large pharmaceutical companies including Roche AG and Bayer.

Earlier this year, it launched an Nvidia-powered supercomputer called BioHive-2, which helps accelerate the process of drug discovery. Nvidia is also an investor in Recursion. UK-headquartered Exscientia also operates an AI-powered drug discovery platform and is developing a pipeline of treatments for immunology and oncology.

Source: https://www.reuters.com/markets/deals/biotech-firm-recursion-buy-smaller-peer-exscientia-688-million-2024-08-08/

With Pharma in 'Catbird Seat,' Biotechs Get Less Upfront in Drug Partnerships

Gwendolyn Wu, *Biopharma Drive*, Aug 9, 2024 (excerpt)

The recent downturn in the biotechnology sector affected startups in many ways, from the availability of financing to the types of research they pursued.

In 2019 and 2020, upfront payments accounted for about 13% and 12%, respectively, of the overall value of drug alliances struck those years. That number has fallen steadily since and hit 6% over the first half of 2024. If that figure holds up, it would be the lowest share since at least 2015, per the report. Deals are becoming more heavily backloaded, with the bulk of the money biotechs are eligible to receive coming in the form of "bio-bucks" that may never materialize. These promised — but not guaranteed — payouts are making up a larger share of deal totals, with the largest portion often tied to post-approval sales targets, the report shows.

To some industry insiders, the shift reflects the reality of a more risk-averse environment. Last decade, before being bought by Bristol Myers Squibb, Celgene modeled a flexible type of dealmaking that, at times, involved handing unusually large checks to unproven startups. That strategy was replicated by other big firms hoping, like Celgene, to become a partner of choice.

Pharma companies now appear more discerning, putting biotechs under greater pressure to deliver results before getting a financial reward. The deal terms startups can get are changing as a result. "The world is not receptive to that kind of a deal structure anymore," said Tom Duley, a partner at the law firm Sidley Austin, who works on collaborations and M&A deals in the life sciences sector. "The economics of these deals are more closely tied to actual real-world progress than they were 10 years ago."

Meanwhile, their prospective partners sit on piles of cash they can be selective in deploying. They also have a deeper pool of potential drugs to choose from. More China-based biotechs have advanced assets to offer, creating competition for U.S.-based startups and driving licensing prices down, said Duley, of Sidley Austin. Pharma is "in the catbird seat" and can choose what will "drive the most value for them," Dupont said. Biotechs "can't be as aggressive about their terms and upfront payments" as a result.

Source: https://www.biopharmadive.com/news/biotech-startups-pharma-licensing-deals-terms-partnerships-upfront-trends/723347/

Merck to Acquire B-Cell Depletion Therapy, CN201, from Curon Biopharmaceutical for $700mm Upfront

RAHWAY, N.J.--(BUSINESS WIRE) – August 9, 2024. Merck and Curon Biopharmaceutical (Curon), a privately held biotechnology company, today announced that the companies have entered into a definitive agreement under which Merck, through a subsidiary, has agreed to acquire CN201, a novel investigational clinical-stage bispecific antibody for the treatment of B-cell associated diseases.

"We continue to identify opportunities to expand and diversify our pipeline," said Dr. Dean Y. Li, president, Merck Research Laboratories. "Early clinical data have provided robust evidence for the potential of CN201 to target and deplete circulating and tissue B cells with the potential to treat a range of malignant and autoimmune diseases."

Under the terms of the agreement, Merck through a subsidiary will acquire full global rights to CN201 for an upfront payment of $700 million in cash. Curon is also eligible to receive up to $600 million in milestone payments associated with the development and regulatory approval of CN201.

CN201 is currently being evaluated in Phase 1 and Phase 1b/2 clinical trials for the treatment of patients with relapsed or refractory non-Hodgkin's lymphoma (NHL) and relapsed or refractory B-cell acute lymphocytic leukemia (ALL), respectively. Preliminary data suggest CN201 has activity in patients with relapsed or refractory B-cell hematologic malignancies and is well tolerated, with the potential to induce significant and sustained reductions in B-cell populations. Merck plans to evaluate CN201 as a treatment for B-cell malignancies as well as investigate its potential to provide a novel, scalable option for the treatment of autoimmune diseases. "This agreement reflects the drive and dedication of the Curon team," said Zhihong Chen, president and chief executive officer, Curon. "As a pioneer in immuno-oncology, Merck is well positioned to build upon the work done to-date and investigate the wide-ranging, first-in-class potential of CN201."

Closing of the proposed transaction is subject to approval under the Hart-Scott-Rodino Antitrust Improvements Act and other customary conditions. The transaction is expected to close in the third quarter of 2024 and be accounted for as an asset acquisition. Merck expects to record a pre-tax charge of approximately $750 million (reflecting the upfront payment and other related costs), or approximately $0.28 per share, to be included in non-GAAP results in the quarter that the transaction closes.

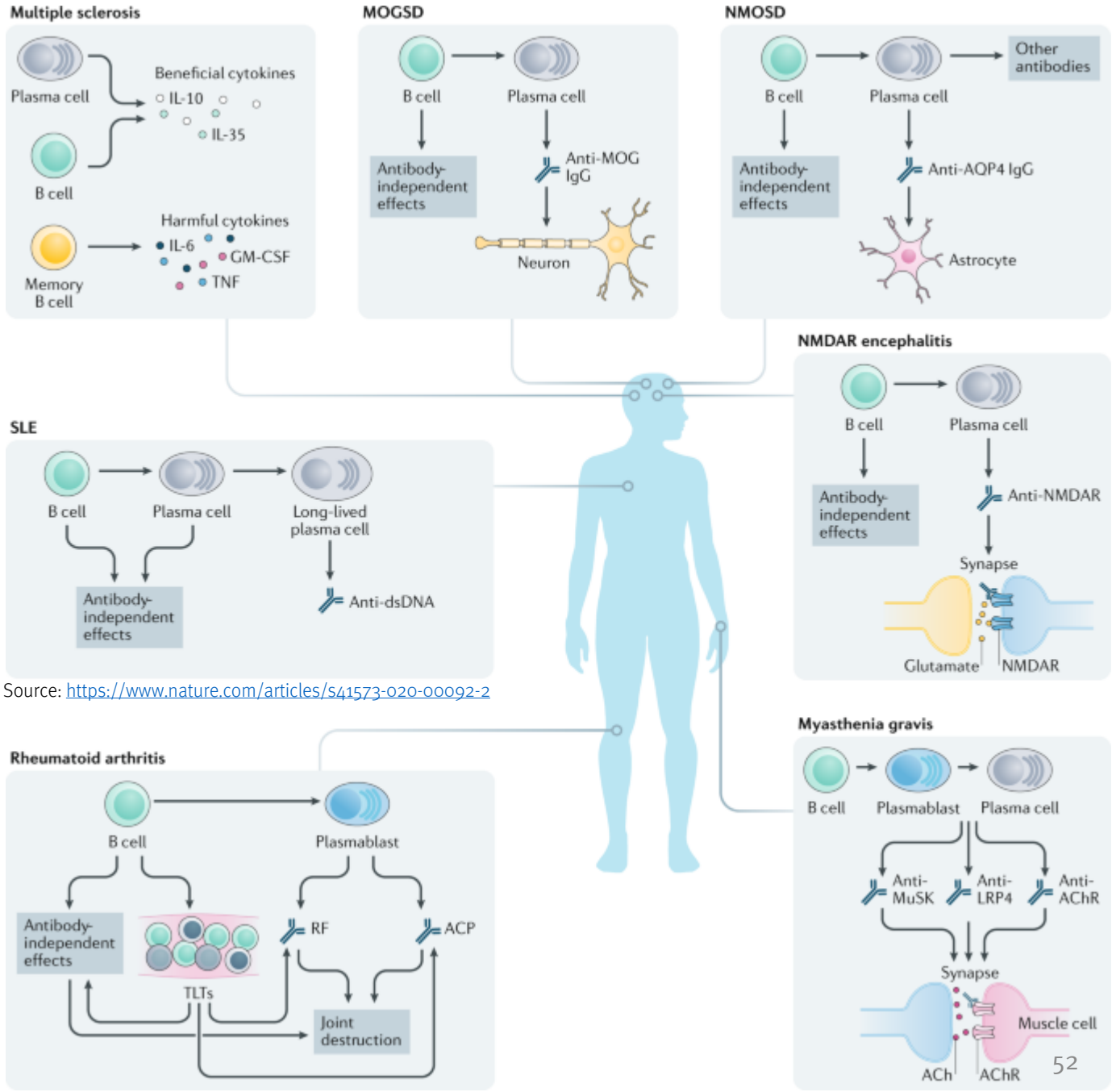
Source: https://www.merck.com/news/merck-to-acquire-investigational-b-cell-depletion-therapy-cn201-from-curon-biopharmaceutical/

B Cells Are a Good Target for Autoimmunity

Lee et.al., *Nature Reviews Drug Discovery*, 2021

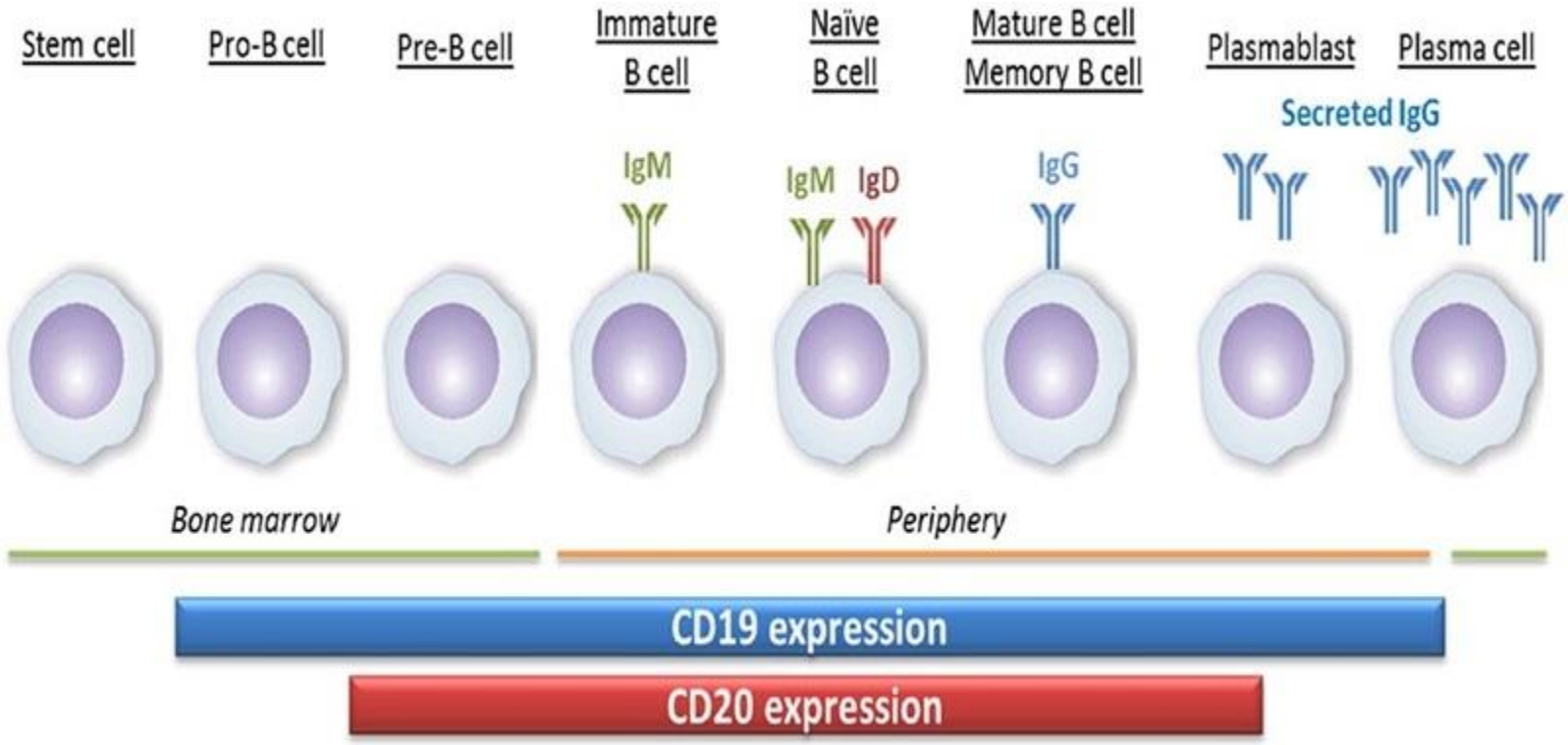
B cells and their effectors such as antibodies and cytokines differ in their contributions to pathobiology depending on the disease. Seven autoimmune disorders (multiple sclerosis, N-methyl-D-aspartate receptor (NMDAR) encephalitis, myasthenia gravis, systemic lupus erythematosus (SLE), rheumatoid arthritis, myelin–oligodendrocyte glycoprotein (MOG) spectrum disorder (MOGSD) and neuromyelitis optica spectrum disorder (NMOSD)), their targets, and the implicated B cell subtype or pathogenic autoantibodies are shown. Based on the vast options for how B cells can influence pathobiology, patients must be carefully assessed to ensure that B cell depletion therapy reduces pathogenic but not beneficial B cell subsets. ACh, acetylcholine; AChR, nicotinic acetylcholine receptor; ACP, anti-citrullinated protein; AQP4, aquaporin 4; dsDNA, double-stranded DNA; GM-CSF, granulocyte–macrophage colony-stimulating factor; MuSK, muscle-specific tyrosine kinase; RF, rheumatoid factor; TLT, tertiary lymphoid tissue; TNF, tumour necrosis factor.

Source: https://www.nature.com/articles/s41573-020-00092-2



Source: https://www.nature.com/articles/s41573-020-00092-2

CD19 Expressed on Most Relevant B Cell Lineages for Autoimmunity



Source: https://www.news-medical.net/whitepaper/20211109/Antibody-drug-development-Targeting-CD20-and-CD3.aspx

Why Bispecific T-Cell Engagers? Response Rates Double

MAYO CLINIC

Bispecific Antibodies in Relapsed Refractory Myeloma

Bispecific Antibody	Target	ORR
Teclistamab[1]	BCMA	65%
REGN-5458[2]	BCMA	63%
Elranatamab[3]	BCMA	70%
Talquetamab[4]	GPRC5D	53%
Cevostamab[5]	FcRH5	53%
TNB 383B[6]	BCMA	60%

1. Usmani. Lancet. 2021;398:665. 2. Madduri. ASH 2020. Abstr 291.
3. Bahlis. ASCO 2021. Abstr 8006. 4. Berdeja. ASCO 2021. Abstr 8008. 5. Cohen. ASH 2020. Abstr 292. Kumar S, ASH 2021

Multiple Myeloma is cancer caused by pathogenic B cells.

Response rates in this disease are much better when T-cell engagers are used rather than naked antibodies.

Source: Mayo Clinic Presentation, ASH, Dec 2023

Industry News

UCLA School of Medicine

We Lost a Giant of our Sector Last Week: Sandy Robertson

Sujeet Indap, *Financial Times*, Aug 9, 2024 (excerpt)

Sanford “Sandy” Robertson, the pioneering Silicon Valley financier whose initial public offerings helped turn a sleepy Northern California peninsula into a global economic powerhouse, has died at age 93.

Robertson was one of the earliest bankers to sense the potential of technological innovations emerging from the suburbs south of San Francisco in the 1970s and 1980s, at a time when major New York investment banks evinced little interest in the high-risk and little-known inventions that would come to dominate every aspect of modern life.

He and a handful of like-minded money men launched boutique investment banks catering to the emerging industry, collectively becoming known as the so-called Four Horsemen firms that dominated technology stock market listings for almost three decades.

Robertson’s firm, Robertson Stephens, went on to underwrite hundreds of technology companies, some of which would ultimately become household names: Pixar Studios, eBay, E*Trade, AOL and Dell among them.

Robertson and his then wife Jeanne, like Benioff, would become important benefactors of the hospital at the University of California, San Francisco. Politics also rose as an important outlet for Robertson who counted fellow San Franciscans, Nancy and Paul Pelosi, as close friends.

Robertson had been a life-long Republican until he met Bill Clinton in 1992 at an event at Apple where the Democratic Arkansas governor’s commitment to the North American Free Trade Agreement impressed him. Robertson hosted a fundraiser for Clinton soon thereafter, with the festivities spilling into the wee hours at Robertson’s home in the Russian Hill neighbourhood of San Francisco.

Sanford Robertson, Biotech financier, 1931-2024

Source: https://www.ft.com/content/22bc8d19-6f32-4e85-b6ee-418d4840766d

Stifel's Mark Simon Reminisces on Working for Robertson

I was blessed to have worked for Sandy for 10 years at Robertson Stephens and staying close to him for another 25 years after he left Robertson Stephens.

Over the 35 years, he was an extraordinary leader and mentor.

He placed great value on the importance of relationships over fees. He started his second career after his 40 years as a pioneering investment banker on the West Coast in his late 60's, when most retire.

He always put the integrity of a deal over the fees that we might earn. He always backed me up when I made controversial research calls – even when banking didn't agree. Those calls usually turned out to be right and we kept our firm's reputation strong.

He was a pioneer in making principal investments off of the Robertson Stephens platform.

His second career in a co-founding a private equity firm (Francisco partners) was even more spectacular than his first as an investment banker.

I really like the quote on him from DJ Deb of Francisco Partners: "Sandy was far more than the industries he contributed to building and the illustrious company he kept. What stands out to me is not what he accomplished; rather, it was how he made people feel. He treated everyone equally, and with respect and appreciation. We will miss him dearly as will his family. He was a mentor and father figure to so many of us and while others may be compared to Sandy, he will never be compared with anyone else."*

Mark Simon, Stifel Biotech Advisor

* Source: https://www.franciscopartners.com/media/francisco-partners-mourns-the-passing-of-co-founder-sandy-robertson

Eli Lilly Is Gaining on Novo Nordisk in the Obesity Race

David Wainer, *Wall Street Journal*, Aug 9, 2024 (excerpt)

Novo Nordisk had a big head start in the race to dominate the weight-loss market. But Eli Lilly is catching up fast. The two companies' divergent earnings reports this week showed that Indianapolis-based Lilly is moving faster than its Denmark-headquartered counterpart in the race to win the GLP-1 war.

On Wednesday, Novo Nordisk reported that quarterly sales of Wegovy, its weight-loss medication, came in about 14% short of Wall Street expectations. Its stock cratered, bringing Lilly down as well. The next day, Lilly provided a more sanguine picture. Its fast-growing GLP-1 medications, Mounjaro and Zepbound, beat analysts' estimates, allowing the company to increase its revenue outlook for the year by $3 billion. Its stock surged 9.5% on Thursday, lifting Novo with it.

For the quarter, Lilly posted $4.3 billion in combined sales for Zepbound and Mounjaro. That compares with about $5.9 billion for Novo's Ozempic and Wegovy. By 2026, analysts expect Zepbound and Mounjaro to bring in $30 billion, compared with over $40 billion for Novo's two key products, according to consensus estimates on FactSet. But a quicker manufacturing ramp-up by either company could change things.

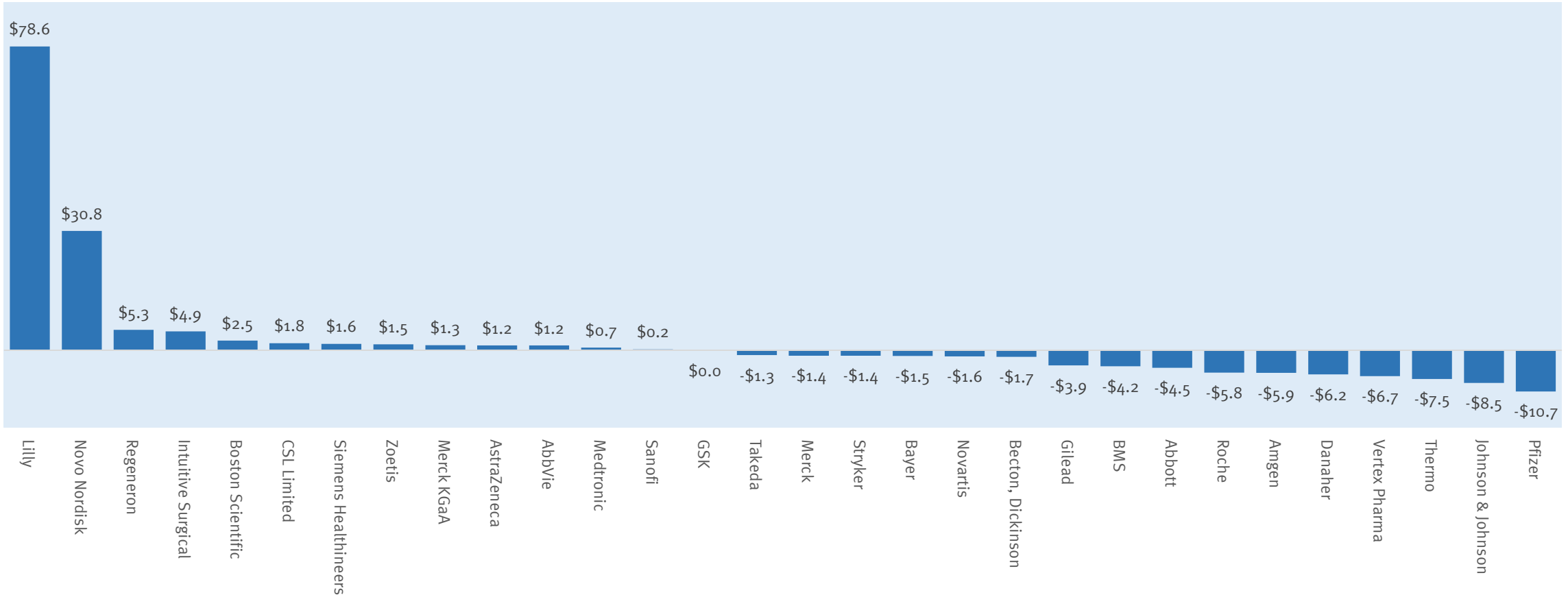
At this point, the market will buy as much as Lilly and Novo can make. Excess demand is being supplied by a range of pharmacy compounders across the country. So Eli Lilly's significant guidance bump indicates it feels increasingly confident about its ability to increase manufacturing as it invests heavily in plants in Indiana, North Carolina, Ireland and Germany. Novo also boosted its sales-growth guidance range, though not as significantly.

Source: https://www.wsj.com/health/pharma/eli-lilly-is-gaining-on-novo-nordisk-in-the-obesity-race-843bbfa9

Lilly / Novo Doubters Eat Humble Pie Last Week

Lilly shares were weak going into earnings. After releasing stunning tirzepatide numbers, Lilly shares jumped up by $78.6 billion. This is one of the largest one-week pops in the history of the life sciences sector. Novo shares jumped by $31 billion in value. No one else in the sector was close in value added.

Change in Enterprise Value of Top 30 Life Science Companies by EV, Aug 2 to Aug 9, 2024 ($ Billions)



Source: S&P Capital IQ

FDA Approves First Nasal Spray to Treat Allergic Reactions

Jonel Aleccia, *Associated Press*, Aug 10, 2024 (excerpt)

U.S. health officials on Friday approved a nasal spray to treat severe allergic reactions, the first needle-free alternative to shots like EpiPen. The Food and Drug Administration said it approved the spray from drugmaker ARS Pharmaceuticals Inc. as an emergency treatment for adults and older children experiencing life-threatening allergic reactions known as anaphylaxis.

Anaphylaxis occurs when the body's immune system develops a sudden, unexpected reaction to a foreign substance, such as food, insect stings, or medications. Common symptoms include hives, swelling, itching, vomiting, and difficulty breathing.

The device, marketed as Neffy, could upend treatment for the 33 million to 45 million Americans with severe allergies to food and other triggers. Anaphylaxis sends more than 30,000 people to emergency rooms and results in more than 2,000 hospitalizations and more than 230 deaths in the U.S. each year.

Of the 6 million prescriptions written for auto-injectors each year, more than 40% are never filled, Dr. Thomas Casale, an allergist at the University of South Florida, told an FDA advisory panel last year. Even when they are available to caregivers, many auto-injectors are used incorrectly, he said.

"There's a real unmet medical need for a large portion of the population," he said.

Neffy is intended for people who weigh at least 66 pounds. It is given in a single dose sprayed into one nostril. A second dose can be given if the person's symptoms don't improve.

Source: https://www.boston.com/news/health/2024/08/10/fda-approves-first-nasal-spray-to-treat-dangerous-allergic-reactions/

FDA Approves Citius' LYMPHIR™ Immunotherapy for the Treatment of Adults with Relapsed or Refractory Cutaneous T-Cell Lymphoma

CRANFORD, N.J., Aug. 8, 2024 /PRNewswire/ -- Citius Pharmaceuticals, Inc. (NASDAQ: CTXR) ("Citius", "Citius Pharma"), announced today that the U.S. Food and Drug Administration (FDA) has approved LYMPHIR™ (denileukin diftitox-cxdl), a novel immunotherapy for the treatment of r/r cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy. LYMPHIR is the only CTCL therapy that targets the interleukin-2 (IL-2) receptor found on malignant T-cells and Tregs. This is the first indication for LYMPHIR and the first FDA-approved product for Citius Pharma.

"LYMPHIR offers new hope for patients suffering from cutaneous T-cell lymphoma, a rare and chronic cancer characterized by debilitating skin lesions and severe itching. This approval is a significant milestone for CTCL patients. The introduction of LYMPHIR, with its potential to rapidly reduce skin disease and control symptomatic itching without cumulative toxicity, is expected to expand the CTCL treatment landscape and grow the overall market, currently estimated to be $300-$400 million," stated Leonard Mazur, Chief Executive Officer of Citius Pharmaceuticals.

LYMPHIR™
(denileukin diftitox-cxdl)
Injection 300 mcg

"LYMPHIR, with an initial indication in the treatment of CTCL, is the first of our pipeline candidates to receive FDA approval. Citius is dedicated to working closely with healthcare providers to ensure that all r/r CTCL patients have timely access to this important new therapy. We are preparing to launch LYMPHIR in the U.S. market within the next five months," added Mazur.

"We are grateful to the clinicians, patients, and researchers who contributed to the development of LYMPHIR. We believe LYMPHIR's unique IL-2 receptor-targeted treatment, which kills tumor cells directly, and concurrently depletes host Tregs in order to boost the body's immune response, is an important differentiator and offers clinically meaningful benefits to a significant percentage of r/r patients. As the only IL-2 receptor-targeted immunotherapy for CTCL, LYMPHIR provides a novel and non-cross-resistant treatment option without cumulative toxicity for Stage I-III r/r patients for whom symptomatic skin involvement interferes with their daily quality of life. LYMPHIR's median time-to-response of only 1.4 months (min, max: 0.7, 5.6) offers many patients rapid skin relief," added Dr. Myron Czuczman, Chief Medical Officer of Citius Pharmaceuticals.

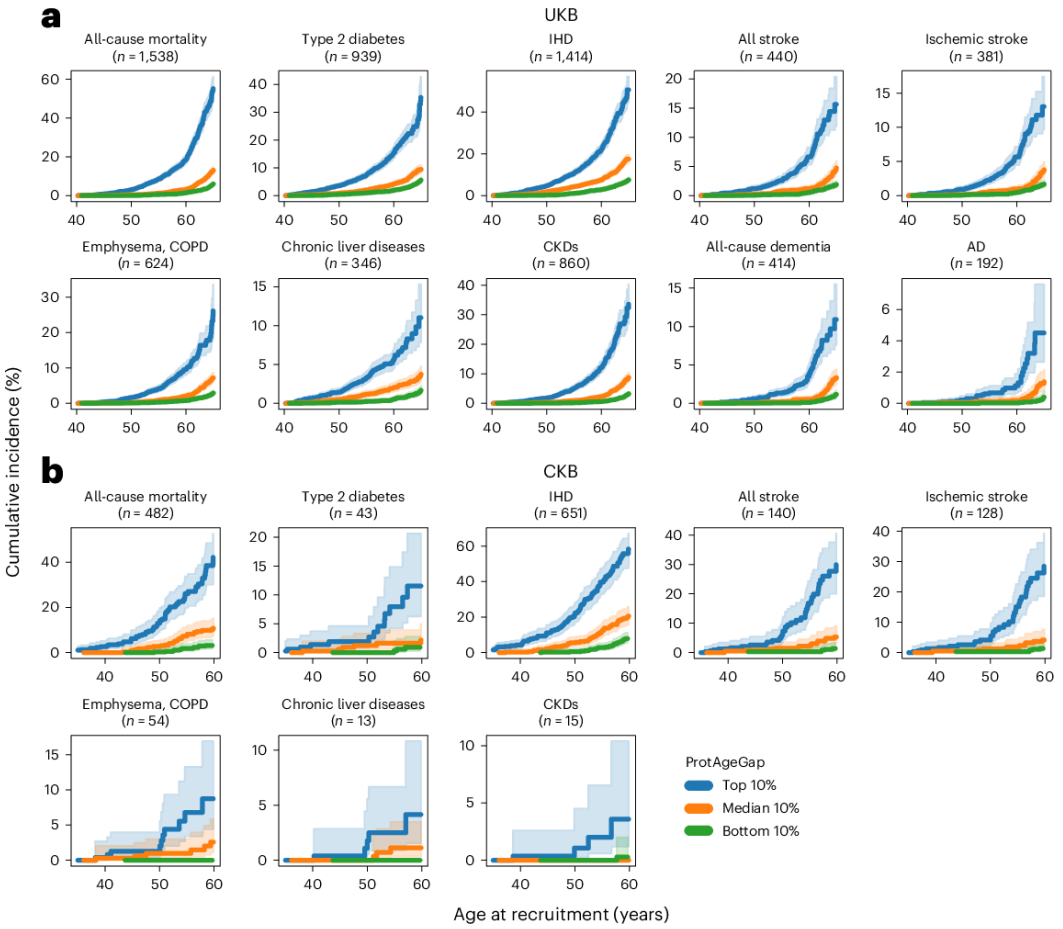
Source: https://www.prnewswire.com/news-releases/citius-pharmaceuticals-receives-fda-approval-for-lymphir-denileukin-diftitox-cxdl-immunotherapy-for-the-treatment-of-adults-with-relapsed-or-refractory-cutaneous-t-cell-lymphoma-302217630.html

Proteomic Aging Signatures Predict Disease Risk and Mortality Across Diverse Populations

Argentieri, M. A. et al., *Nat Med*, Aug 8, 2024.

We developed a machine learning model that uses blood proteomics information to estimate a proteomics age clock for a large sample of participants from the UK Biobank (UKB) (n = 45,441; age range, 40–70 years). We further validated this model in two biobanks across the world: the China Kadoorie Biobank (CKB) (n = 3,977; age range, 30–80 years) and FinnGen (n = 1,990; age range, 20–80 years). These biobanks represent geographically and genetically distinct populations that differ from the UKB in age range and morbidity profiles. We systematically assessed the influence of the proteomic age gap (defined as the difference between protein-predicted age and chronological age) on 27 aging-related phenotypes related to biological, functional and cognitive function; all-cause mortality; and incidence of 26 common age-related diseases.

We identified 204 proteins that accurately predict chronological age, and we further identified a set of 20 aging-related proteins that capture 91% of the age-prediction accuracy of the larger model. We demonstrated that our proteomics age clock showed age-prediction accuracy in independent participants from China and Finland similar to its performance for the UK Biobank. We found that proteomic aging was associated with the incidence of 18 major chronic diseases (including diseases of the heart, liver, kidneys and lungs, diabetes, neurodegeneration and cancer), multimorbidity and all-cause mortality.



Cumulative incidence of various diseases and mortality (above plots) by decile of proteomic age gap (ProtAgeGap) (in years) in the UKB (a) and CKB (b). Incidence rates are shown for the subsequent 11–16 years (UKB) or 11–14 years (CKB) of follow-up after recruitment for each given age at recruitment. All plots show the cumulative density of events at a given timepoint on the basis of the Kaplan–Meier survival function, with 95% confidence intervals (lighter shading).

Source: https://www.nature.com/articles/s41591-024-03170-9

Structures of the Dopamine Transporter Point to Ways to Target Addiction and Disease

Harald Sitte, *Nature*, Aug 7, 2024 (excerpt)

Dopamine is a key neurotransmitter molecule that cells called dopaminergic neurons use to signal to each other across synapses — the interfaces between these cells. Writing in *Nature*, Srivastava et al., Nielsen et al. and Li et al. provide exciting structural insights into how a variety of molecules bind to the human dopamine transporter (DAT). The papers, which gathered evidence using a technique called cryo-electron microscopy, are consistent with each other regarding many aspects of the structures. These studies mark a key turning point for the development of targeted drugs to treat DAT-related conditions.

DAT is a transport protein found in neurons close to a part of the cell called the presynaptic nerve terminal. After dopamine is released from the presynaptic region of a neuron by a process called exocytosis, DAT retrieves the molecule from the extracellular space to end dopamine signalling. DAT activity is coupled to a pre-existing gradient of sodium ions across the plasma membrane. The uptake of dopamine is an economical way to retrieve and reuse the neurotransmitter.

Dopamine not only serves as the precursor molecule needed to produce the key signalling molecules noradrenaline and adrenaline, but also has a crucial role in the brain, affecting appetite, mood, movement and reward-related behaviours. Loss of dopamine in dopamine-rich brain areas occurs in, and leads to, Parkinson's disease.

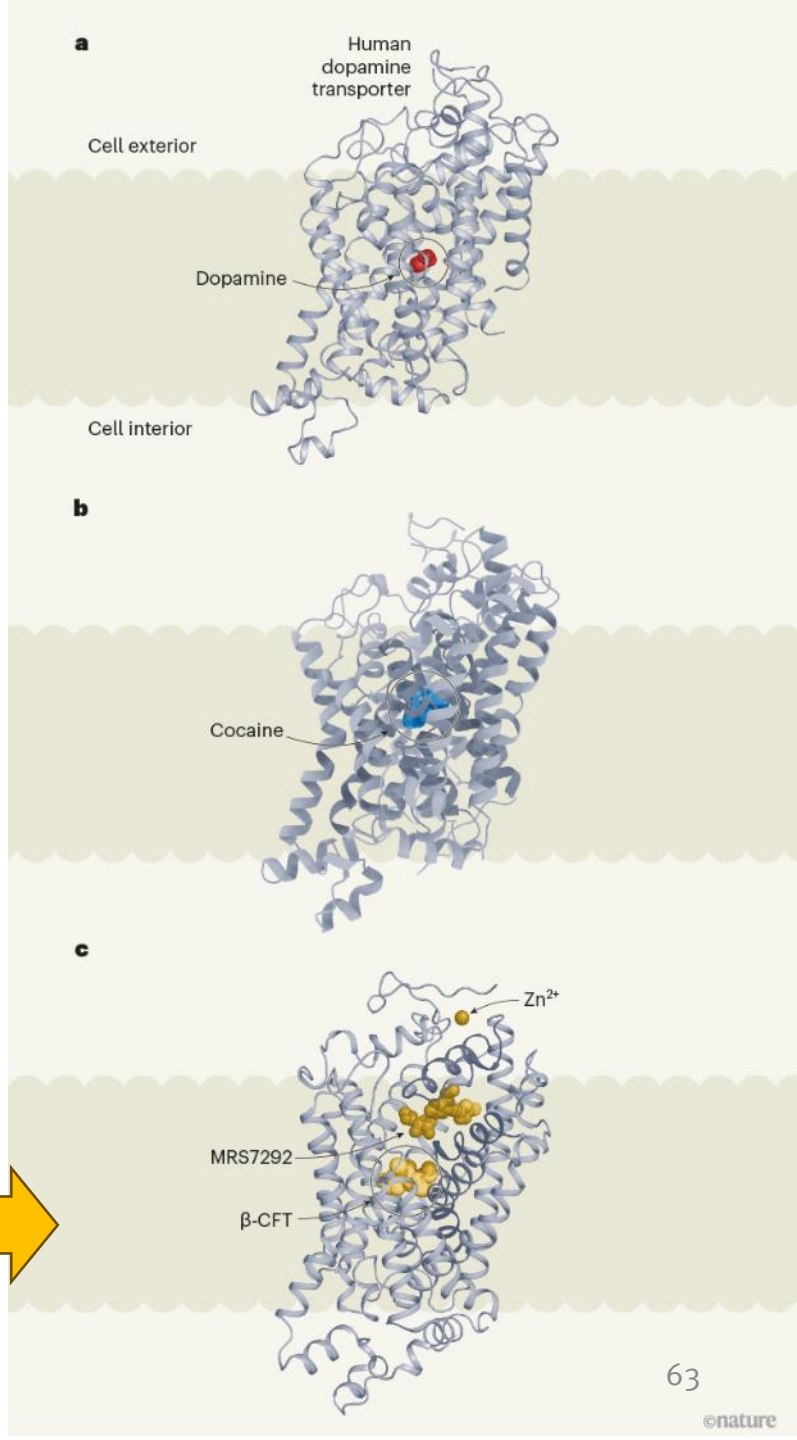


Figure 1 | The structure of the human dopamine transporter. Srivastava et al., Nielsen et al. and Li et al. present high-resolution structures of this protein obtained using a technique called cryo-electron microscopy, revealing a variety of sites that bind molecules. a, Li and co-workers reveal the binding site for the neurotransmitter dopamine. b, The transporter can bind to cocaine, as indicated in this structure by Nielsen and colleagues. c, Srivastava et al. report the binding sites of zinc ions (Zn^{2+}) and where the inhibitor molecules MRS7292 and β-CFT bind. (Adapted from Fig. 1 of ref. 3, Fig. 1 of ref. 2 and Fig. 3 of ref. 1.)

Source: https://www.nature.com/articles/d41586-024-02435-0

Disclosure

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