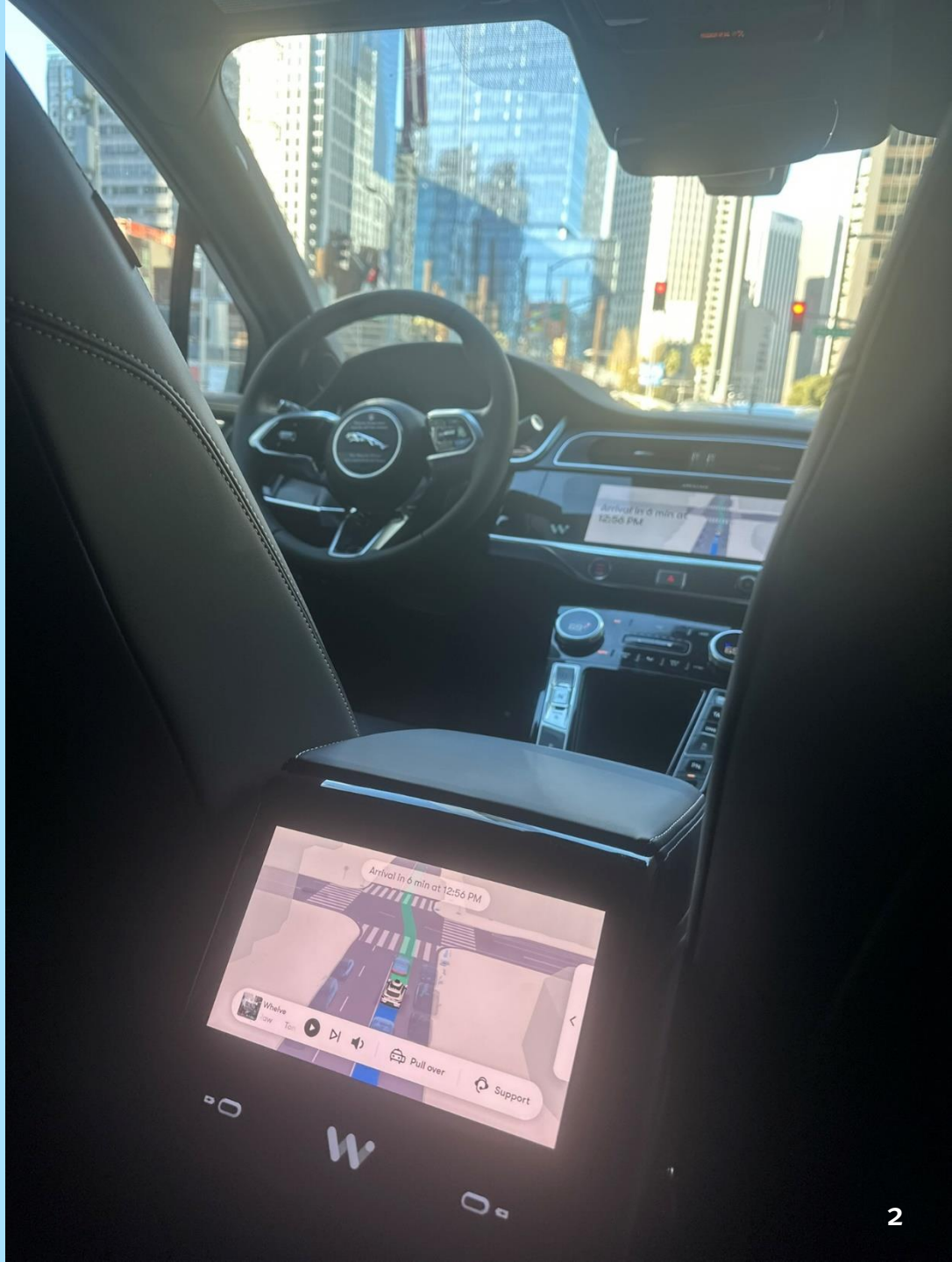
Biopharma Market Update

Jan 27, 2025

STIFEL | Healthcare

Table of Contents

STIFEL | Healthcare



Getting driven in autonomous Waymo to the next meeting at the #JPM25 conference events in San Francisco, January 25.

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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)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
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)

Resting in a big armchair with two friends during the #JPM25 conference in the Marine Memorial Club Library, San Francisco.

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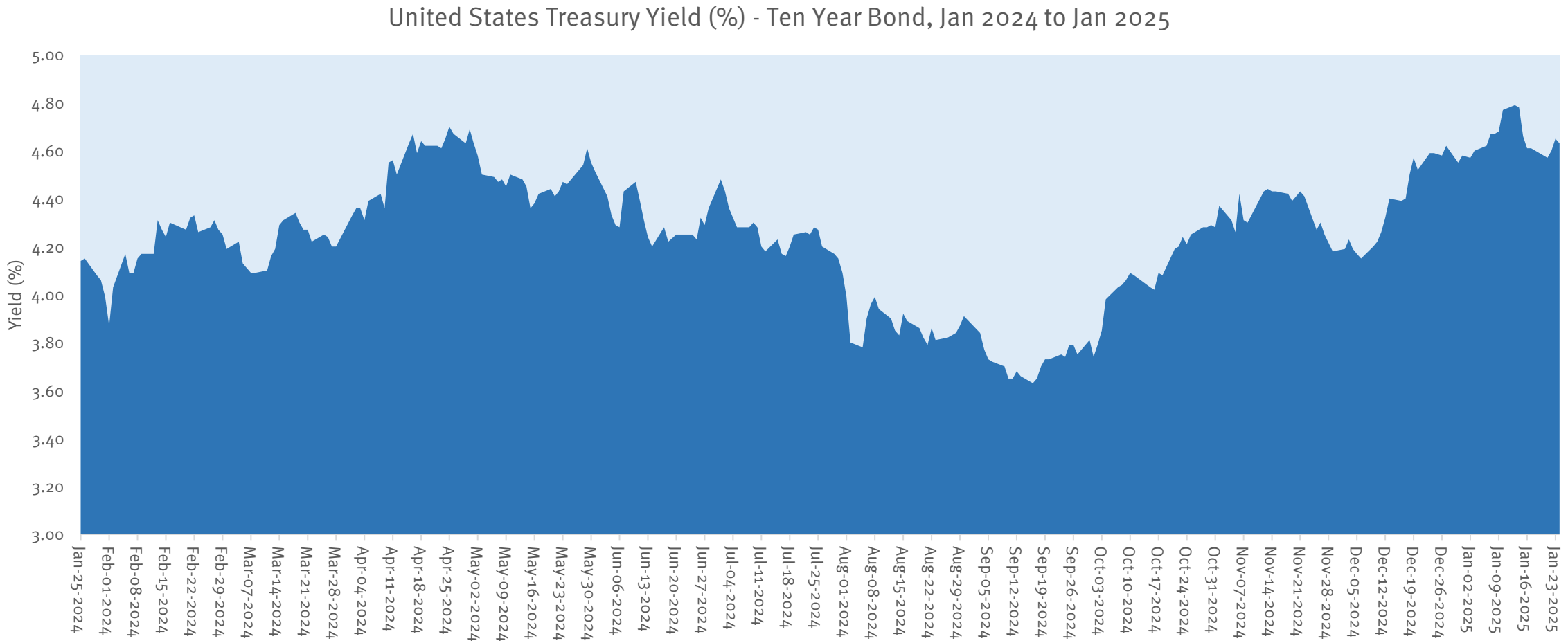
Macro Update

U.S. Treasury Bond Yields Remain Stubbornly High

While 10-year Treasury yields started to come in last week they remain high by recent standards. The Fed continues to be slow in lowering rates. This is tied very much to worries of inflation in a Trump presidency.



Source: S&P Capital IQ

So Far – Threatened Trump Tariffs Have Not Appeared

***Lu Wang and Liz Capo McCormick,* "Trump Unleashes Surprise Global Rally by Backing Off Key Promise", Bloomberg, Jan 24, 2025 (excerpt)**

Week one of the Trump administration was, as advertised, full of excitement in financial markets — just not the kind of excitement most investors had anticipated.

The Trump trades that became so popular during the campaign last year — load up on US stocks and the dollar, go light on international stocks and bet against Treasuries — only fared OK. US stocks jumped, sure, but not as much as they did in Japan and Germany or even parts of emerging markets. The dollar tumbled and the Treasury bond market was calm all week, with most yields quietly grinding lower.

President Donald Trump conducted plenty of business in his first week in office, signing executive order after executive order, holding impromptu press conferences, mugging for the camera, crisscrossing the country, but it was the one thing he failed to do — immediately slap tariffs on US trade partners — that triggered the surprising market response.

This had been a pledge he made throughout the campaign and it was a major piece of the Trump trade thesis: Punitive tariffs, as high as 60% on China, would hurt rival economies far more than the US, sinking their currencies against the dollar and rekindling inflation everywhere. It was the market interpretation of America First. For at least one week, though, it was America Last.

To be clear, US stock gains were robust. The 1.7% advance in the S&P 500 was the best start to a presidential term since Ronald Reagan in 1985. Yet the gains just weren't all that eye-catching in a market that's been on a tear for the better part of two years nor, more importantly, when compared to the rallies seen elsewhere. Stocks climbed some 2.4% in Germany, 3.9% in Japan and around 5% in Mexico.

Underneath the surface of the broad market gauges, winners and losers of the new era stood out. Oracle Corp., a major player in a Trump-backed $100 billion AI joint venture, soared 14%, the most in four months. Space stocks jumped on Trump's promise to land American astronauts on Mars while Tesla Inc. dropped after he told his administration to consider removing subsidies for the electronic vehicle industry.

As Trump tempered his rhetoric on tariffs, the dollar weakened against major currencies. By one measure, the greenback looked poised for the largest weekly slide since November 2023, marking the worst performance at the onset of a presidential term since at least the 1970s.

While its early days in the Trump Presidency, pro-inflationary tariffs have yet to appear. This was a relief to financial markets last week.

Source: https://www.bloomberg.com/news/articles/2025-01-24/trump-spurs-surprise-world-rally-in-first-week-on-trade-respite

Trump Promised Some Tariffs Immediately. They're Not Here — Yet.

Megan Messerly and Ari Hawkins, *Politico*, Jan 24, 2025 (excerpt)

Donald Trump vowed on the campaign trail to slap tariffs as high as 20 percent on everything from cars to food when he took the White House.

Four days into office, Trump hasn't immediately followed through on an issue that has consumed him for decades, including some levies that he promised to implement on Day One.

The approach is a sign that Trump has likely not made up his mind about exactly what paths he will use to levy tariffs, and when he will levy them, according to three people familiar with discussions inside the administration, granted anonymity to speak about policies that have yet to be decided. He also must decide whether he will target specific countries with extra-high trade duties, and whether he will make carve-outs for certain industries or products.

The striking level of uncertainty around tariffs is the first and most prominent example of a divide in Trump's circle on a major policy position.

But make no mistake, Trump insiders caution: Tariffs are coming.

"Tariffs are coming in the next couple months — broad based, universal tariffs," said one person familiar with discussions inside the administration, granted anonymity to speak about policies that have yet to be decided. "Literally, if you just listen to Trump talk — it is all he talks about."

"The president is serious about the universal tariff," a second person familiar with the discussions added.

The ambiguity around the rest of the tariff agenda is, in part, because Trump continues to take counsel from two camps. In one is Treasury secretary nominee Scott Bessent and Kevin Hassett, who Trump picked to lead his National Economic Council. They have historically expressed a more cautious view on trade and are arguing for more gradual and targeted tariffs that won't spook the markets or spike inflation.

Source: https://www.politico.com/news/2025/01/24/trump-tariffs-trade-policy-00006551

Stocks Hit a Record Amid Strong Earnings and Easing Inflation Concerns

Joe Rennison, *New York Times*, Jan 23, 2025 (excerpt)

The S&P 500 clambered back to a record high on Thursday, inching above a peak reached in early December, building on gains after President Trump reiterated his commitment to bring down oil prices — a major component of inflation.

The S&P 500 rose just 0.5 percent on Thursday, but the gain added to a winning streak that began more than a week ago with data that showed inflation slowing in December by more than economists had expected. With Thursday's rise the index is up 4 percent in the first three weeks of the year.

The recent rally arrived after the market had languished for weeks, as investors worried about the inflationary impact of policies promised by Mr. Trump — in particular, new tariffs and a mass deportation program that could push up consumer prices and wages.

Wall Street was concerned that the resulting inflation would prompt the Federal Reserve to leave interest rates higher than previously expected, as it sought to keep consumer price gains under control. Higher interest rates raise the cost of borrowing for consumers and companies and typically weigh on valuations in the equity market.

Source: https://www.nytimes.com/2025/01/23/business/stock-market-record-trump-inflation-earnings.html

Biopharma Market Update

Biotech Gloom Has Not Lifted

The overall gloom in biotech public market sentiment did not lift last week.

We continue to hear concerns about inflation and Treasury rates as a key brake on biotech market performance.

In a sort of surreal Trumpian moment we saw Larry Ellison of Oracle talk up mRNA stocks at last week's announcement of Project Stargate, an AI investment project (see press photo).

We also witnessed Larry Summers, economist and former Treasury Secretary speak of the huge potential for biotech innovation at the World Economic Forum, arguing that 'Miracle' drug innovation could see a new Wegovy launch every couple of years henceforth.

While normally one would hope that biotech insiders would get attention for talking up the sector, it does appear to be a tech world today.

So, why not accept from free publicity from the likes of Larry Ellison?

Last week saw Larry Ellison of Oracle talk up messenger RNA vaccines at a White House event on Project Stargate.

Worries About Hedge Fund Balance Sheets Persist

A further brake on biotech stocks has been concern about the balance sheet condition of specific hedge funds. There were quiet reports of forced selling caused by unwanted fund redemptions in December.

We spoke to one knowledgeable fund of funds manager who indicated that this stopped in January but worries in the market have persisted. We have received more than a few calls on this topic from worried trading desks.

Another fund manager expressed concern last week that a mid-sized fund was busy covering their short book due to pressure that they were under.

Our experience at Stifel is that it remains a “haves” and “have nots” biotech market.

On the one hand, we were an underwriter on the Disc Medicine follow-on last week which was upsized last week. We also saw the Ascentage IPO price and four other IPOs are publicly on file for possible near-term transactions

Market Participants Barely Noticed Last Week's Rally

However, a minority of investors remain uncomfortable, in general, about buying new paper and are not keen to wall cross on PIPE offerings until this year's market direction is clearer.

This is a public biotech market best described as "mixed". Perhaps "uncertain" or "skittish."

One of the oddest things about the market last week was how little remark was made regarding the reasonably robust rally in the XBI.

We noted no stories in the media and not a single positive call with an investor nor other market commentator on the subject.

In fact, the XBI was up over 5% last week. Our global biotech tracker popped by 7.8% last week. We'd call that meaningful.

We spoke to three knowledgeable parties about this. None of them were particularly aware that that the market was up at all, and one said it must have been caused by short covering. Another attributed it to the pop in Moderna stock and a third offered no explanation.

We'll take a look at this in today's issue and try to figure out what might be going on here.

The shell-shocked biotech community appears to have barely noticed last week's rally in the XBI.

Conditions for a Biotech Rally In Place

We'd repeat the comment made in our last issue which is that there remains a huge disjuncture today between tech stocks and biotech. Since the year began, tech stocks (measured by the NASDAQ 100 index) have indeed outperformed the XBI even further.

Our own sense is that there is a vast disequilibrium between biopharma stocks today and the broader market, at least in the U.S..

One observer we spoke to last week noted that the weight of healthcare stocks in the S&P 500 is at a twenty-year low. We have not checked this but it certainly feels right.

Many large endowments, sovereign funds and wholesale capital pools remain heavily underallocated to healthcare and biotech.

The conditions for a biotech rally certainly seem to be in place: (1) relative undervaluation, (2) improving macro picture, (3) a stronger M&A environment and (4) extraordinarily positive innovation fundamentals.

And don't forget: random sector endorsements from a bunch of guys named "Larry"… ??? ☺ ☺ ☺.

Who knows what's next?

In addition to fundamentals, there is always the mystery factor: random endorsements of biotech from guys called "Larry".

Venture Capitalist Mood Much More Positive

A further odd disjuncture in today's market is the difference in view between private market and public market participants in biotech. This is the time of year when we check in with many VC's to see how they are doing, what they like in their portfolios etc. Without exception, we have found VC's are really pumped about how good their portfolios are right now.

We have to agree. When we listen to what is scheduled to take place in 2025 with various investments in the venture area we have been struck by the shift towards "high innovation" companies. A lot less "me too" investments happening right now in the private markets.

It's hard not to get really excited when you hear what's in the works in the venture investment community.

If there is one difference that we are noticing, it is this: more "transformational" companies with "really big" drugs. VC's got the memo on what pharma wants and started avoiding "me too" and small market drugs a few years ago.

While VC's in general remained preferenced toward clinical stage assets we have also heard a willingness to go earlier and to invest in emerging technologies and platforms.

Investors Not that Impressed by M&A So Far in 2025

There is plenty of dry powder in the biotech venture community today and most groups are not that worried about the funk in the public markets.

Another area where dry powder appears to be plentiful is the M&A market. The year is off to quite a strong start on biopharma sector M&A. In the first three weeks of 2025 we have seen M&A volume of $21.6 billion.*

A number of observers have been arguing that the Intra-Cellular takeout by J&J was a bit of an exception and that we remain in a low M&A year.

J&J held an earnings call last week in which they made it clear that this was a large deal for them and that investors shouldn't except more deals like this from J&J anytime soon.

This isn't surprising. It would be exceptional to see one company undertake a series of $10bn+ M&A deals in any given year. But, we do think it's likely that we will see more $10bn+ deals from *others* this year.

Investors are obviously hungry for more M&A to lift the sector and seem impatient that there hasn't been even more M&A this year (never mind that we are on a pace for more than 50 $1bn+ deals in 2025).

We suppose that most farmers are slow to acknowledge the effect of rains after a long drought.

We understand, it would be great if there would be a lot more M&A done by now.

Farmers are often slow to acknowledge the effect of rains after a long drought.

* Source: CapitalIQ

First Three Weeks of 2025 Quite Strong for M&A

But consider this.

If you were to *exclude* the Intra-Cellular deal this year you would have seen $7 billion in M&A thus far in 2025. That is 1.5 times more than all M&A in the first three weeks of 2024; twice the amount of all M&A in the first three weeks of 2023 and 1.7 times the amount of all M&A in the first three weeks of 2022.*

Another way of thinking about it is as follows: were the M&A pace of the first three weeks of 2025 to continue, we would surpass 2024's full-year M&A dollar volume total in the **first quarter** of this year.

By any measure, 2025 is looking like a much better M&A year.

We would note that based on our own deal pipeline at Stifel and recent conversations with others in the market, we believe it's going to be quite a strong year for both M&A and licensing. We do expect to see more U.S. public biopharma takeouts, more China licensing deals and more "high science" type private deals take place in the months to come.

Time will tell.

* Source: CapitalIQ

The XBI Closed at 92.5 Last Friday (Jan 24), Up 5.1% for the Week

The XBI gained substantial ground last week. The XBI is up 2.6% so far this year.

Biotech Stocks Up Last Week

Return: Jan 18 to Jan 24, 2025

Nasdaq Biotech Index: +4.1%
Arca XBI ETF: +5.1%
Stifel Global Biotech EV (adjusted): +7.8%*
S&P 500: +1.7%

Return: Dec 31, 2024 to Jan 24, 2025 (YTD)

Nasdaq Biotech Index: +4.2%
Arca XBI ETF: +2.2%
Stifel Global Biotech EV (adjusted): -0.5%*
S&P 500: +3.8%

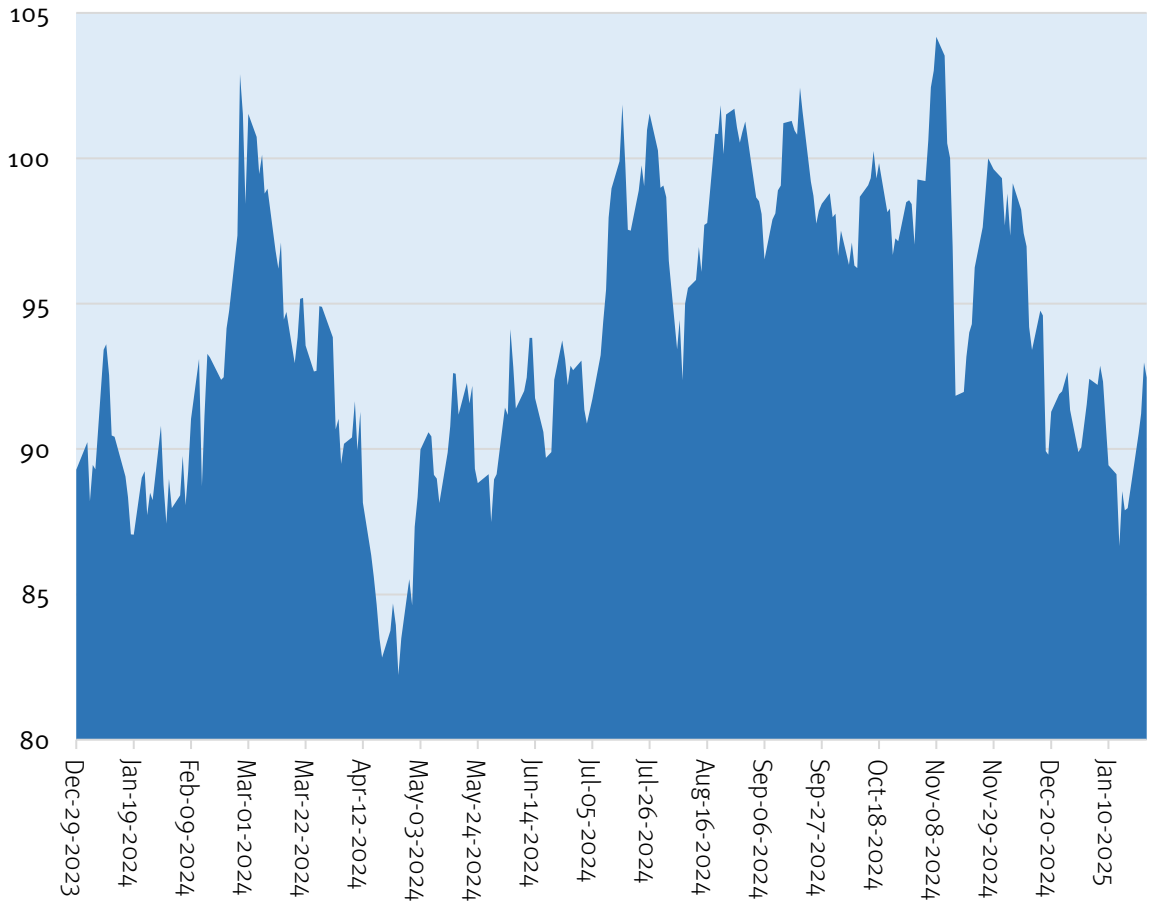
VIX Flat

Dec 29, 2023: 12.45%
Mar 29, 2024: 13.0%
May 17, 2024: 12.0%
Aug 2, 2024: 23.4%
Sep 20, 2024: 16.1%
Oct 19, 2024: 18.0%
Dec 13, 2024: 13.8%
Jan 24, 2025: 14.2%

10-Year Treasury Yield Flat

Dec 29, 2023: 3.88%
May 17, 2024: 4.42%
Aug 2, 2024: 3.80%
Sep 20, 2024: 3.73%
Oct 19, 2024: 4.08%
Nov 23, 2024: 4.41%
Dec 13, 2024: 4.4%
Jan 24, 2025: 4.6%

XBI, Dec 29. 2023 to Jan 24, 2024



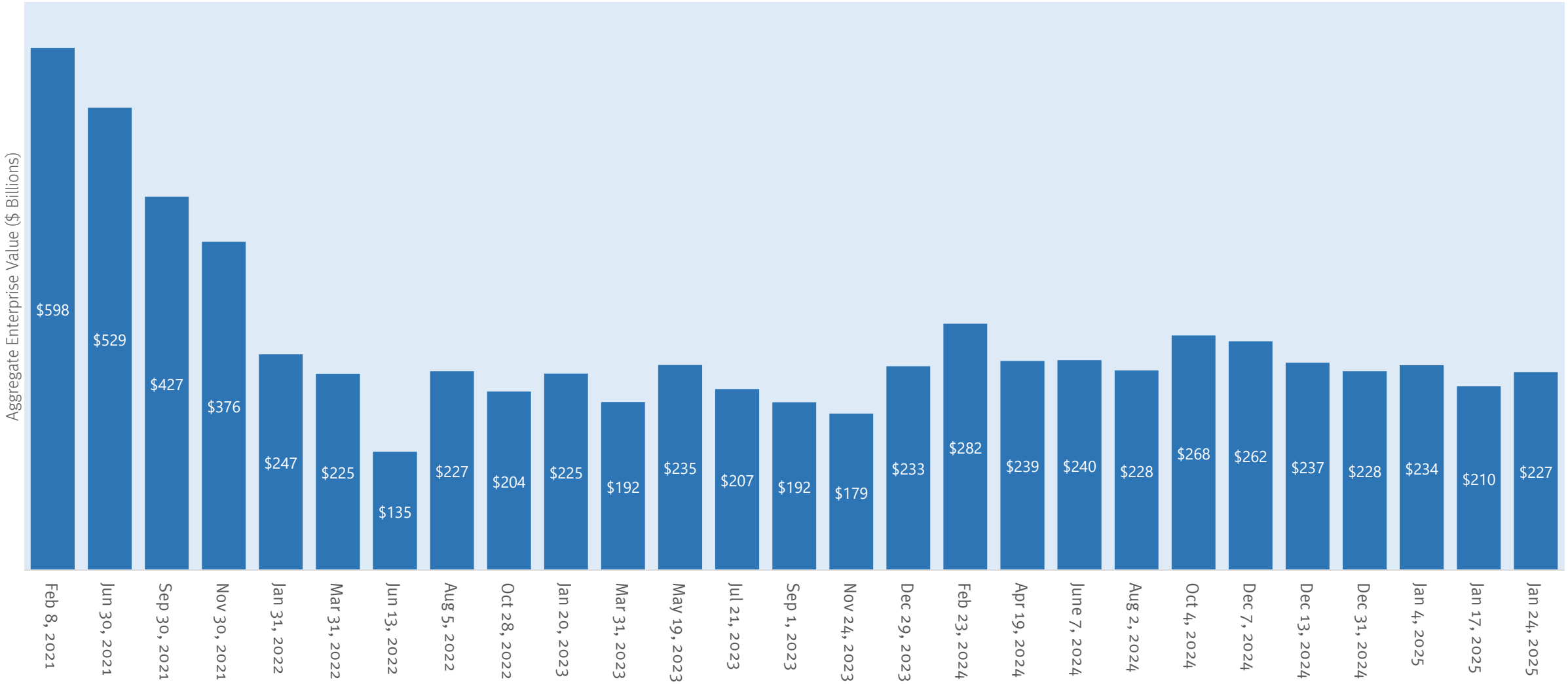
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs. The annual change by market cap is even higher.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Rose 7.8% Last Week

Biotech stocks rose 7.8% in the last week – substantially more than the XBI. However, biotech has been weak all year. By our math, the total global biotech sector is flat for the year (-0.5%).

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Jan 24, 2025 ($ Billions)

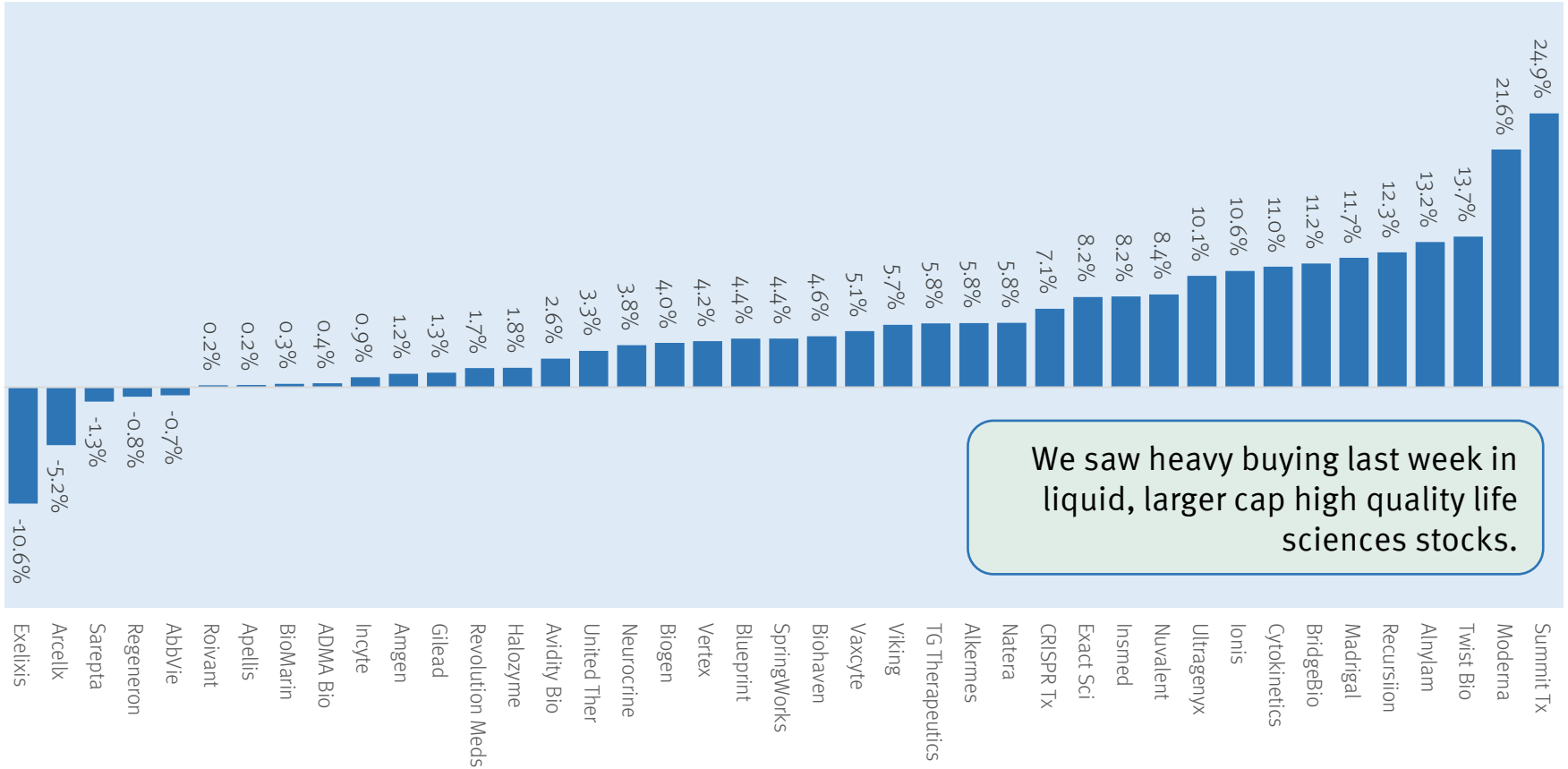


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

A Good Week for XBI Stocks

This chart shows the change in market cap last week for the 41 most influential stocks in the XBI. These stocks comprise 70% of the weight of the XBI (out of 138 stocks total). The mean percentage change in value was +5.4% (median 4.4%). Summit rose 25% last week and Moderna was up 22% on the Larry Ellison endorsement. We also saw strong performance of Twist, Alnylam, Recursion, Madrigal and BridgeBio.

Top 41 XBI Influencers, Pecent Change in Market Cap, Week of Jan 18 to Jan 25, 2025



So Why Did the XBI Pop Last Week?

The big risers in the XBI were not heavily shorted so the short-selling story does not hold water. The Moderna story was a small part of the story. A tenth of the rise in the XBI was caused by the 21.6% pop in Moderna stock. The real cause of the rally was **buying in select liquid mid/large cap biopharma and diagnostic names**.

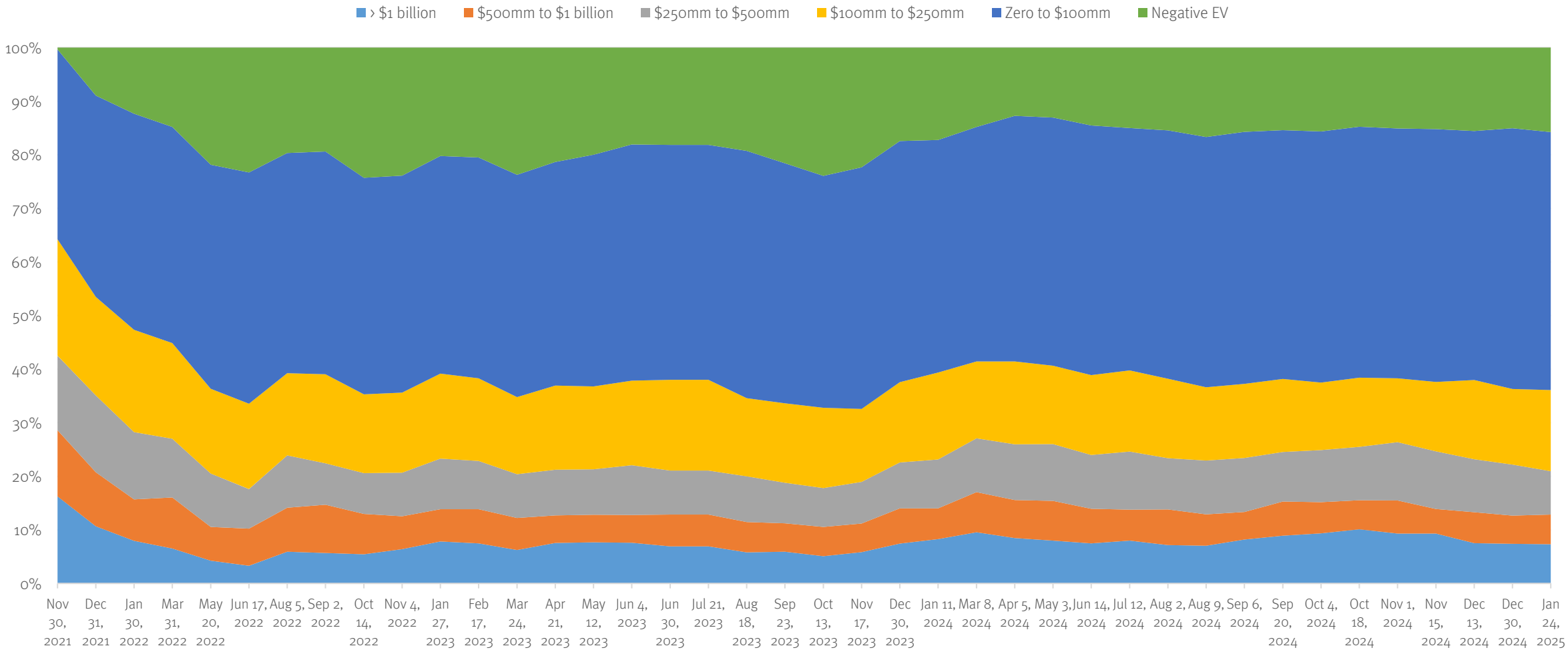
Roughly half the pop in the XBI can be attributed to good performance in a dozen stocks which are (in order): Moderna, Alnylam, Summit Tx, Madrigal, Insmed, BridgeBio, Exact Sciences, Cytokinetics, Ionis, Natera, Twist Bio, Vaxcyte and Neurocrine.

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

Global Biotech Neighborhood Analysis

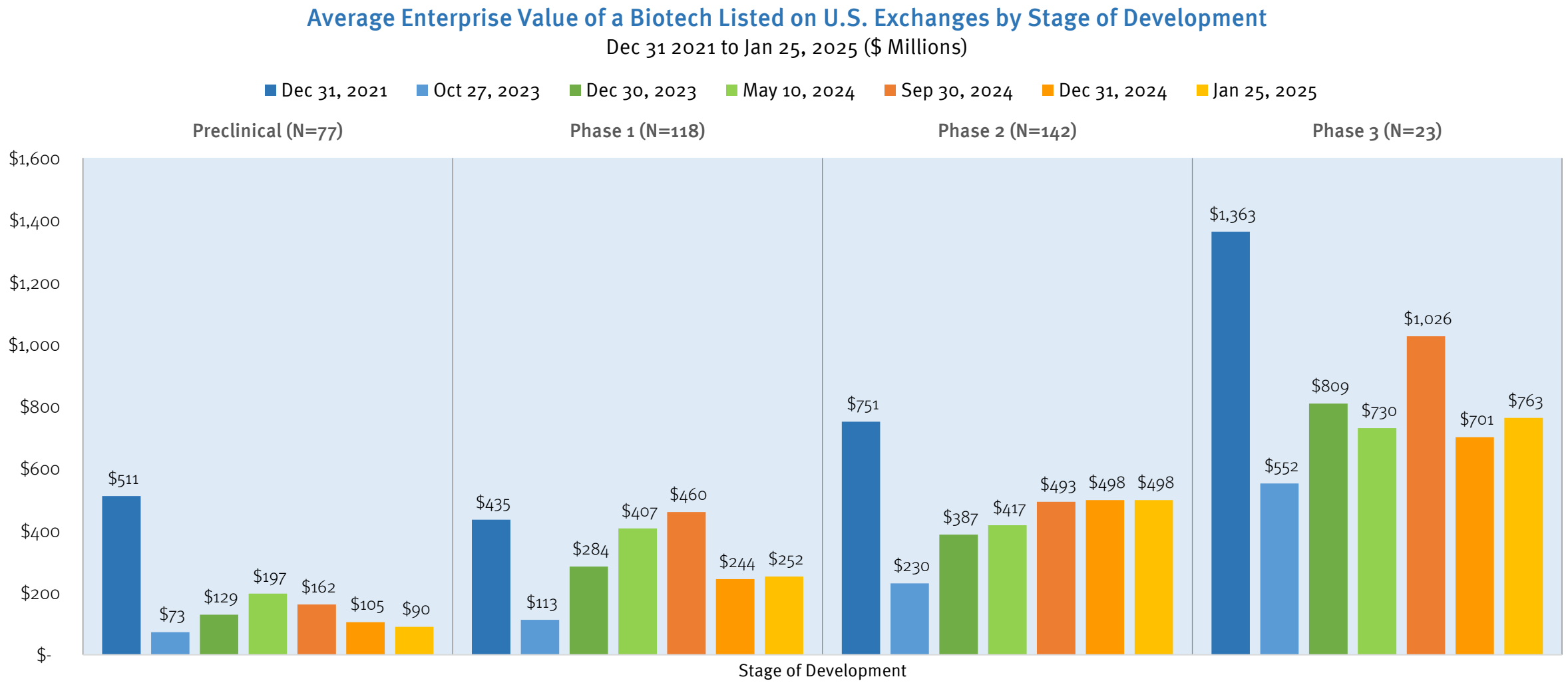
This year has seen big growth in the number of companies worth $250mm in EV or less. The population of companies trading for more than $250mm has shrunk the most in the relatively tough biotech tape of 2025.

Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Jan 24, 2025



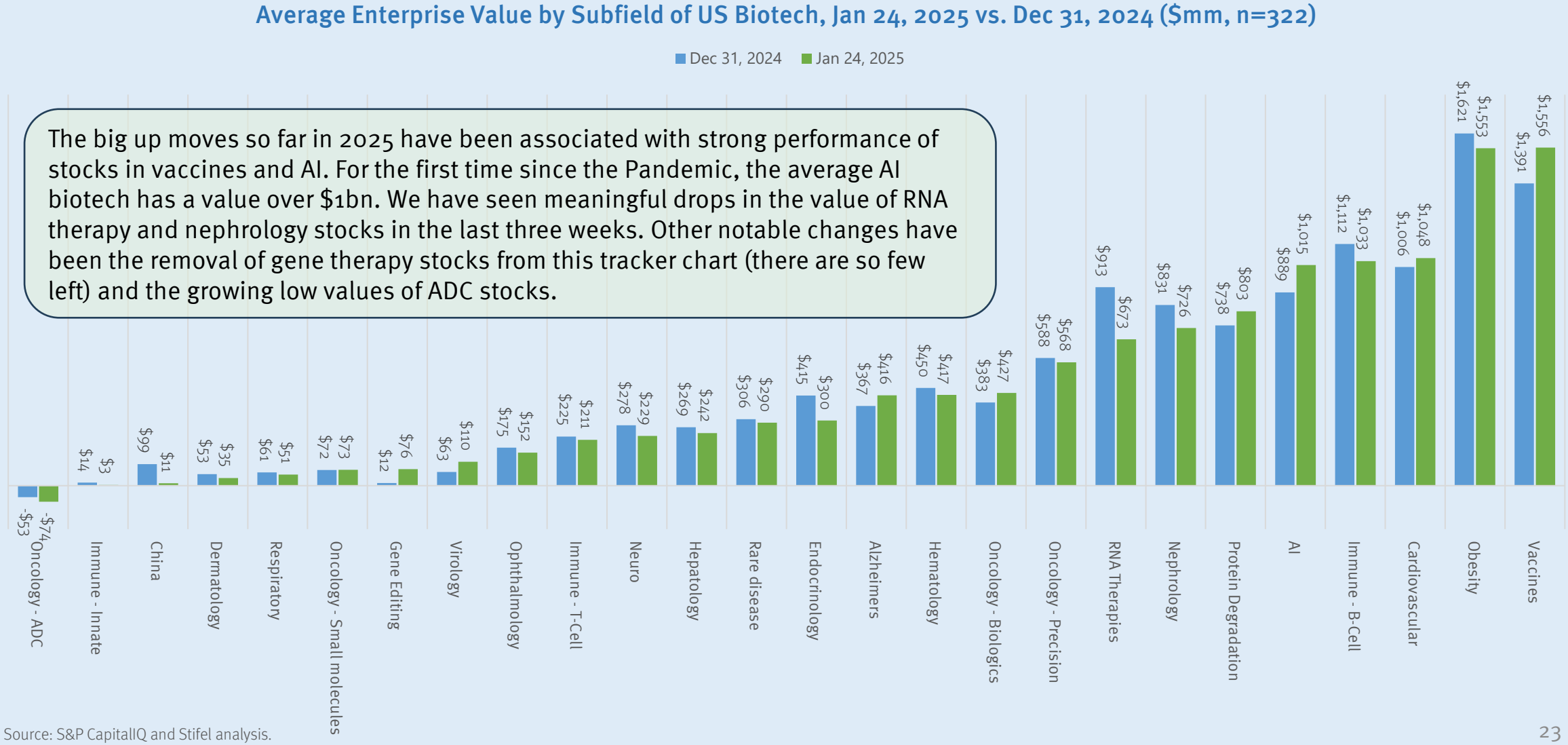
Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

We are Seeing Pre-Clinical Names Drop in 2025 While Phase 3 Biotech Stocks are Rising



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.

Vaccines, Obesity, CV, B-Cell and AI Biotechs Most Highly Valued U.S. Biotech Categories Thus Far in 2025



Source: S&P CapitalIQ and Stifel analysis.

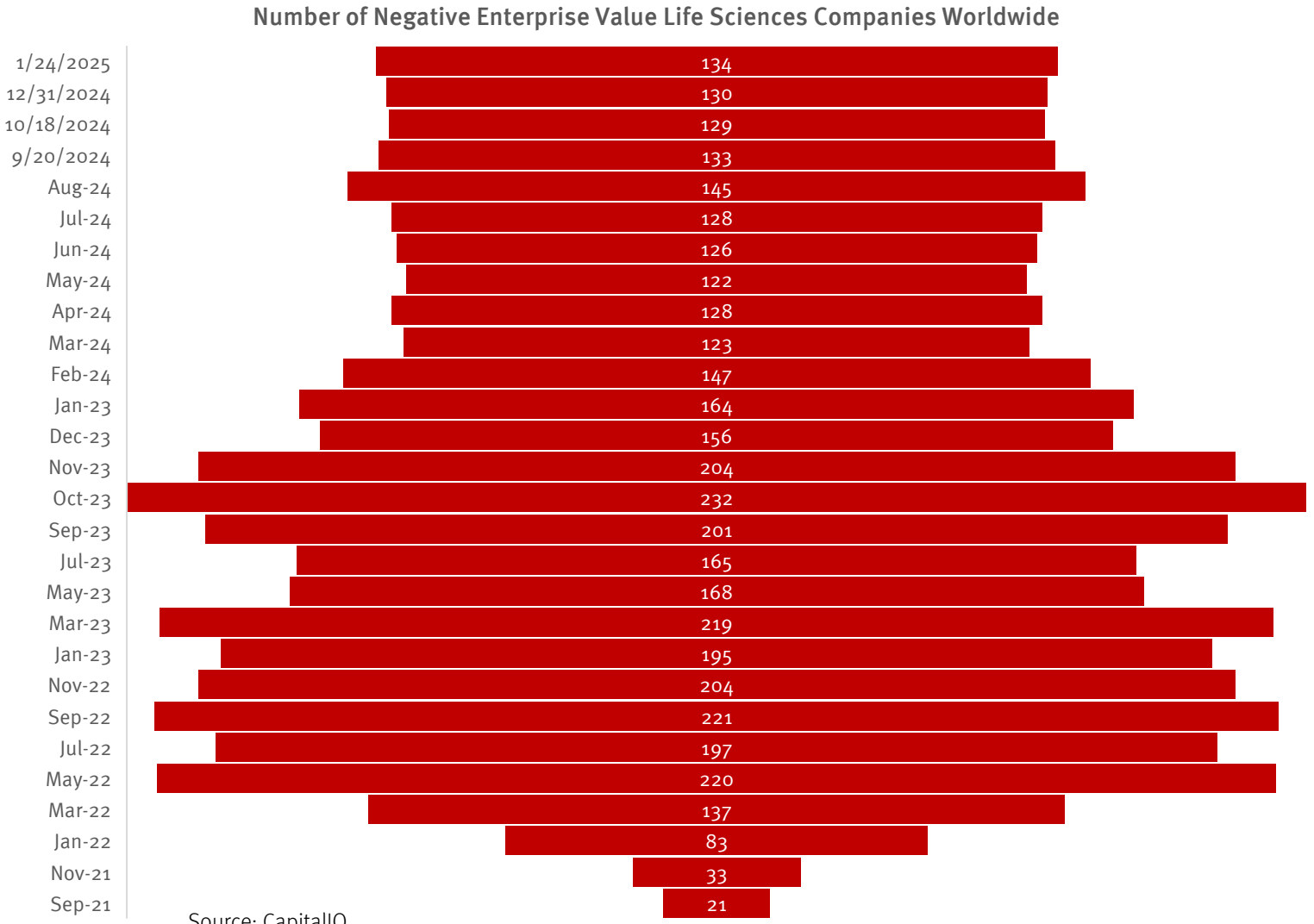
Life Sciences Sector Gained $279 Billion in Value Last Week (3%)

Last week was quite strong for the life sciences sector with big gains in biotech, CDMO's, HCIT, diagnostics, commercial pharma, pharma services, medical devices and life science tools.

Sector	Firm Count	Enterprise Value (Jan 24, 2025, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	79	$88,861	0.0%	-3.8%	11.4%
Biotech	733	$234,085	7.8%	-4.2%	-5.1%
CDMO	38	$150,191	5.9%	8.1%	14.3%
Diagnostics	77	$261,348	4.6%	4.3%	-1.2%
OTC	29	$23,960	1.1%	-1.3%	-12.6%
Commercial Pharma	701	$6,054,432	2.8%	0.6%	1.5%
Pharma Services	38	$171,570	3.1%	-0.3%	-9.9%
Tools	50	$699,780	2.5%	6.6%	2.7%
Devices	174	$1,875,639	2.9%	5.6%	14.8%
HCIT	7	$21,859	5.3%	-1.8%	7.8%
Total	**1926**	**$9,581,725**	**3.0%**	**2.0%**	**4.1%**

Source: CapitalIQ and Stifel analysis

Number of Negative Enterprise Value Life Sciences Companies Unchanged in Recent Months



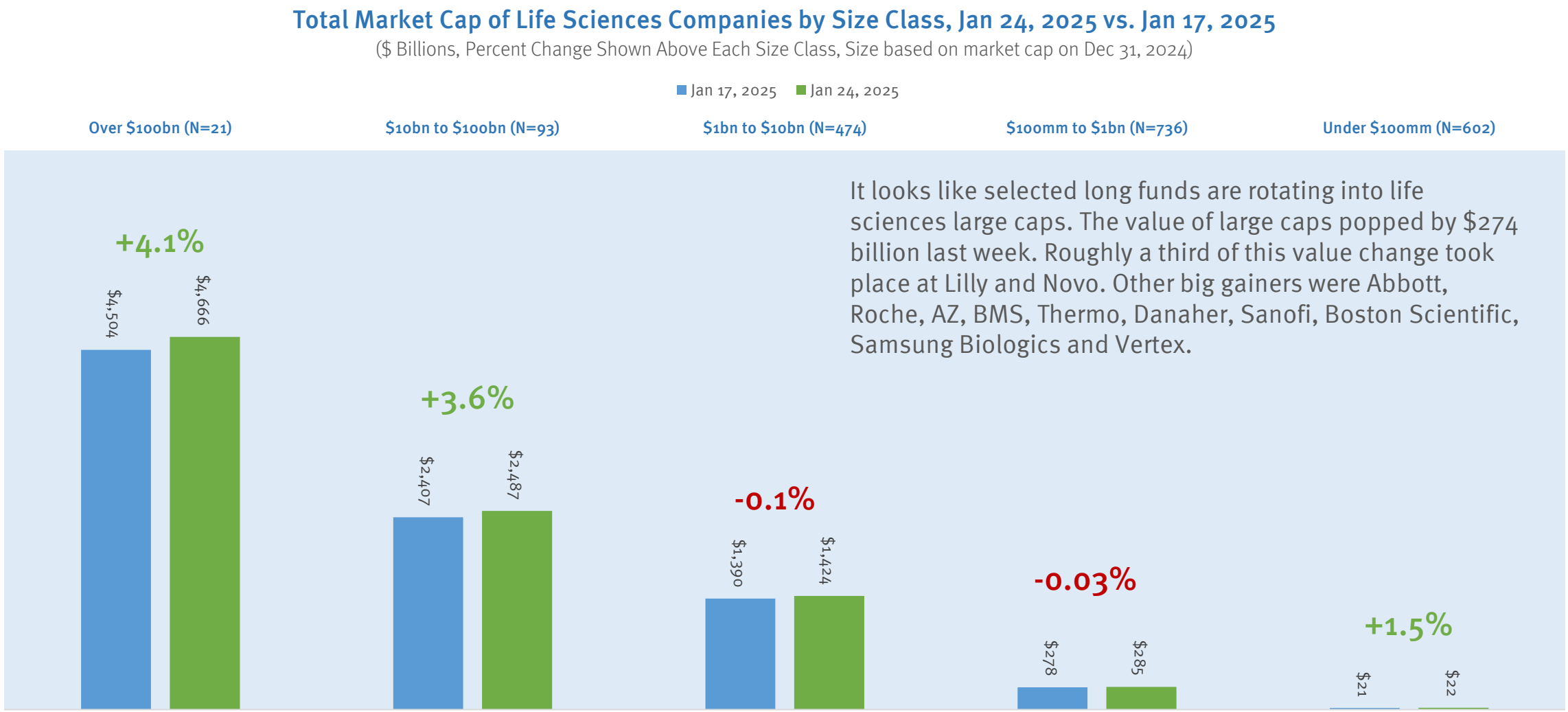
Source: CapitalIQ

The count of negative EV life sciences companies worldwide rose from 130 at year end 2024 to 134 last Friday.

This measure of sector distress has been quite steady for ten months.

We only expect to see a big change once the Fed starts to more meaningfully reduce the discount rate.

Big and Medium Caps Life Sciences Rallied Last Week



Beaten Down Under Biden, Big Pharma Hopes for New Chapter Under Trump

David Wainer, *Wall Street Journal*, Jan 20, 2025 (excerpt)

The past two years have been punishing for the biotech and pharma space. As Wall Street chased the artificial-intelligence boom, drugmakers were left behind, with pharma stocks trading at a major discount to the broader market. The SPDR S&P Biotech ETF, meanwhile, was basically unchanged last year despite huge gains for innovation counterparts in the tech sector.

Politics hasn't helped. After decades of wielding significant influence in Washington, the pharma lobby suffered a major blow when the Biden administration pushed through Medicare's drug-price negotiation law. Now as Donald Trump takes office, the industry is cautiously optimistic that its fortunes might finally begin to shift—or at least not get any worse. At last week's annual JPMorgan Healthcare Conference in San Francisco, industry executives pointed to Trump's promises to cut taxes and to crack down on pharmacy-benefit managers as evidence that his policies might benefit the industry as a whole.

While Trump's victory and his decision to name Robert F. Kennedy Jr. as his top health official initially unsettled executives and investors, many are now warming up to the new administration. No one is betting that Trump will suddenly fall in love with big pharma. During his first administration he repeatedly railed against the industry and tried to pass a rule linking some Medicare drug prices to international drug prices. But at this point an unpredictable leader, some argue, is better than a predictably unfriendly one.

During a lunch with reporters in San Francisco, Pfizer Chief Executive Albert Bourla was particularly blunt, describing the previous administration as heavily influenced by progressive priorities on everything from taxes to antitrust. By contrast, Bourla noted that the Trump administration appears more inclined to address misaligned incentives for PBMs, which act as drug middlemen, rather than pursuing sweeping drug-pricing legislation.

"He doesn't like, of course, that here people are paying a lot for their medicines compared to Germany," said Bourla, who dined with Trump at Mar-a-Lago last month. "But he appreciates that here there is the middleman that is inflating the out-of-pocket [cost] disproportionately."

Concerns about the incoming administration remain, however, particularly given Robert F. Kennedy Jr.'s rhetoric on vaccines and drugs more broadly. But even on that front, the thinking in some corners is that Kennedy's more extreme impulses could be somewhat tempered. Last week, The Wall Street Journal reported that two vaccine skeptics who had been advising RFK Jr. have been sidelined by Trump transition officials. Some believe he might be steered toward focusing on other issues, like food safety or fluoride, while more industry-friendly voices could play a larger role in shaping policy.

Source: https://www.wsj.com/health/pharma/pharmaceutical-companies-trump-presidency-da79b394

A Tale of Two Sentiments: JPM 2025

Aimee Raleigh, Atlas Venture, *LifeSciVC*, Jan 21, 2025 (excerpt)

"It was the best of times, it was the worst of times…"

Another JPM is behind us, and while much of the small talk was centered on the beautiful weather, impressive sea of pink in support of the Biotech CEO Sisterhood, and Monday's deals (congratulations to ITCI, Scorpion, and IDRx teams!), overall sentiment was bifurcated. While many early-stage private VCs (and especially those participating in recent M&A) are feeling good going into 2025, public investors lamented the poor performance of public portfolios and indices.

Similarly on the company side, a few megaround darlings have captured a large share of the capital in the past year (nearly 100 raises ›$100M). In contrast, the mood is more apprehensive for those companies with data or timing setbacks, especially on top of one of the highest rates of RIFs in 2024. The past year has been a mixed bag, especially when factoring in tenuous macro headwinds such as uncertainty regarding the new administration, debate on drug pricing, and persistently high interest rates.

You'll hear from other outlets that JPM sentiment ranged from poor to cautiously optimistic – while I won't add more adjectives to the pile, below are some of my key takeaways as we start the new year.

Brave New World: China Assets are Here to Stay

Despite grandstanding from Washington, China out-licenses to U.S. and EU-based biotech and Pharma have never been more abundant than in the past year. While our industry will continue to debate whether the rapid timelines and abundant programs available in China are a boom or a bust for our biotech economy, there is no denying the landscape for therapeutic development is shifting (and especially for "validated" targets for "best-in-class" plays). Pharma in particular increased China-sourced deal volume substantially last year, a vote of confidence for the strong discovery and development talent there as well as more efficient timelines to clinical proof-of-concept.

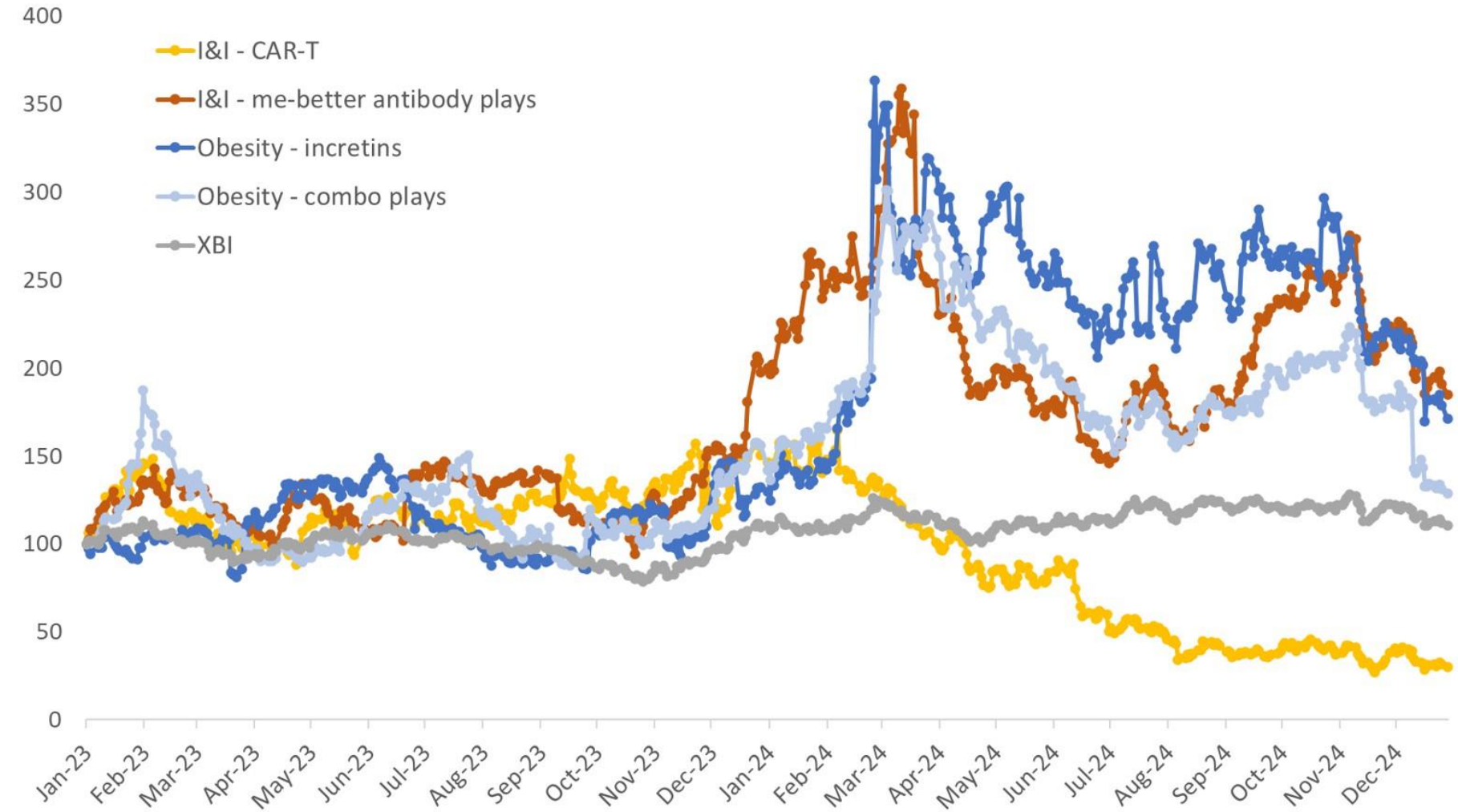
There and Back Again: Investors Tiring of "Me-Too" Plays

Relatedly, investor excitement for asset-centric plays has played a role in the rush to source (largely clinical-stage) assets from China. Thus, when you are evaluating the 7th antibody program against Target X, consider whether the buyer pool is saturated and what incremental opportunity is offered by any differentiated features. I have no doubt many more of these programs will "work" clinically than can be feasibly commercialized. Perhaps in the near-future investors will again appreciate riskier but potentially higher-reward biology and deals – we may already be starting to see that in 2025 with some of the large follow-on financings for next-gen modalities. A common refrain this past JPM was that of public investors lamenting lack of "originality" in the private deals they were evaluating.

Source: https://lifescivc.com/2025/01/a-tale-of-two-sentiments-jpm-2025/

Fig. 2: Fates & Furies – Aggregate Stock Performance for "Hot" Trades

2023 – 2024



Source: Analysis of Yahoo Finance

Source: https://lifescivc.com/wp-content/uploads/2025/01/Fig.-2.jpg

A Tale of Two Sentiments (Continued)

New Opportunities & Headwinds in Clinical Development: So where does an investor or entrepreneur look when some indications feel saturated? One area of focus might be indications where trial landscapes are evolving such that probability of success is higher today than previously. As an example, consider asthma – up until the early 2010s asthma trials did not use eosinophil levels as an inclusion criteria or stratifier, but rather some flavor of Th2 marker (e.g., periostin).

Changing development paradigms offer a path forward for new or previously discarded mechanisms – a few of my favorites from the past ~year are: COPD, HFpEF, urticaria, solid tumors. While these changing paradigms can help drive further development, there are also plenty of indications where the trial landscape is in dire need of new insights on patient stratification, endpoint selection, and treatment duration. Atopic Dermatitis in particular stands out – while the pipeline of active agents is increasing, so too is the collective uncertainty re: constraining placebo response. Likewise for ALS, we continue to see failed mechanisms across trials (the past year alone it was ATXN2, eIF2B, RIPK1, 15-Lipoxygenase, and others) and it's unclear whether we are seeing trial design noise or true negative reads on the biology.

Within Neuro, Epilepsy Continues to be a Darling for Investors: 2024 saw many gains in the neuro space, including repurposing anti-amyloid antibodies with TfR1 shuttles for improved brain penetration, the first approval in Schizophrenia in over 30 years in Cobenfy, and positive mHTT and NfL readouts in Huntington's. Last year was also marked by numerous compelling datasets for epilepsy. In particular, data in pediatric developmental and epileptic encephalopathies (DEE) and adult focal epilepsy suggests a paradigm shift to best-in-class activity with safer profiles. Some of the compelling readouts in the past year, and those on tap for 2025, are below:

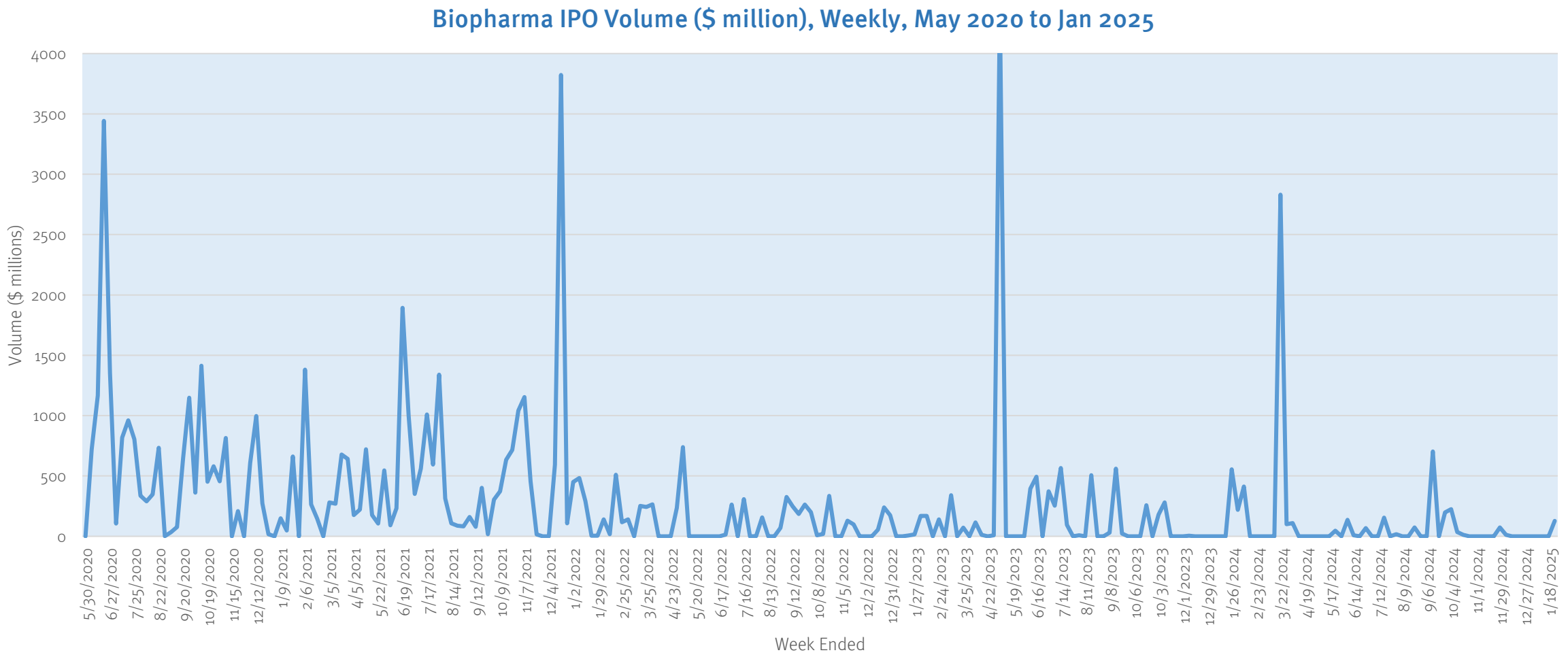
Closing Thoughts – Exits Will Continue to Dictate Sentiment: Ultimately investors are judged on their exits, so M&A and public portfolio performance will continue to play an oversized role in sentiment for 2025. On the former, Pharma patent cliffs continue to loom large and thus will likely drive sustained acquisitions for clinical or near-clinical plays. On the latter, we are still seeing strong data being rewarded (e.g., BMPC, DNLI, others last week). Even if stocks aren't at their all-time highs, there is opportunity to pick winners and do well in this market, especially considering some of the undervalued names.

There is a bimodal distribution in investor and company sentiment and it's unlikely to change in the very near-term. Instead of focusing on what is out of our control (geopolitical agita, pricing pressure, stubborn inflation), let's put energy into what we can control: doing everything in our collective power to bring medicines to patients. Cheers to a productive 2025 for our industry.

Source: https://lifescivc.com/2025/01/a-tale-of-two-sentiments-jpm-2025/

Capital Markets and Deals Update

Ascentage Prices First Biotech IPO of the Year Last Week



Source: Data from CapitalIQ and Stifel research.

Ascentage Prices First Biotech IPO of 2025, Raising $126M

Gwendolyn Wu, *Biopharma Dive*, Jan 23, 2025 (excerpt)

亞 盛 醫 藥
Ascentage Pharma

Ascentage Pharma, a cancer drug developer based in Suzhou, China, on Thursday raised just over $126 million in the first U.S. initial public offering by a biotechnology company this year.

The company, which is already publicly traded in Hong Kong, sold 7,325,000 American depositary shares at $17.25 apiece, a lower price than it had projected earlier this week. Shares will begin trading on the Nasdaq Stock Exchange Friday under the ticker symbol "AAPG."

Ascentage will use the proceeds to develop treatments for cancer, among them a leukemia drug called olverembatinib that's approved in China. Its IPO comes amid increased dealmaking involving drugs from China, a trend industry watchers expect to continue this year. Ascentage is one such beneficiary, having licensed olverembatinib to Takeda last year.

Ascentage's Wall Street debut is a test of U.S. investors' interest in the progress China's biotech sector has made.

Efforts by the Chinese government to boost the country's capabilities have produced a burgeoning ecosystem of drug companies, many of which are trying to improve on medicines either on the market or in development. That, combined with tight funding in biotech, has led to a flurry of licensing deals.

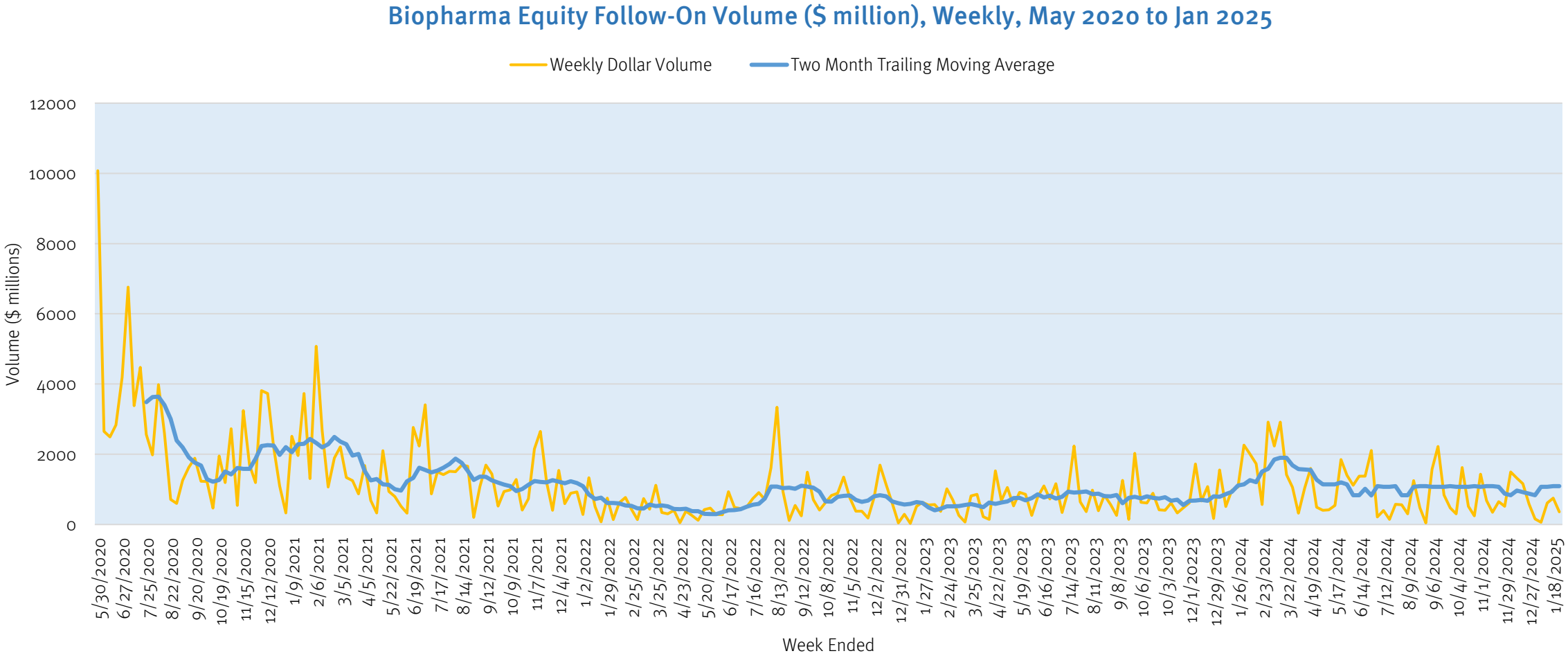
Though relatively few China-based biotechs have reached public markets in the U.S., some, like oncology-focused drug developers Legend Biotech and BeiGene, have prospered.

Ascentage is developing small molecule drugs that block or degrade protein targets implicated in cancer. Its most advanced prospect is olverembatinib, which is cleared in China for certain people with chronic myeloid leukemia. It's in multi-country Phase 3 trials in CML, as well as for two other forms of cancer.

Source: https://www.biopharmadive.com/news/ascentage-ipo-china-biotech-cancer-drugs/738051/

January Has Been Soft For Follow-On Financings

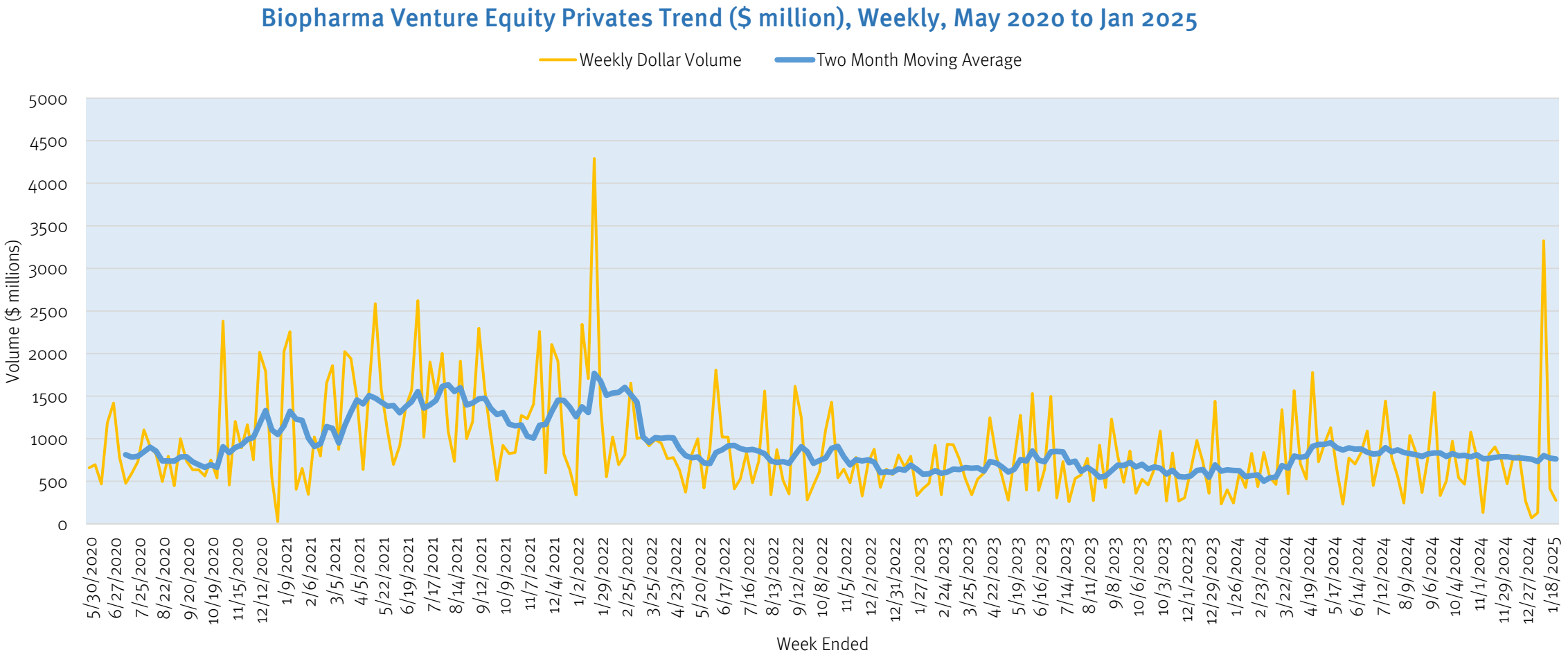
The first three and a half weeks of 2025 have seen $1.8 billion in follow-on biopharma offerings. This is well below the $1bn a week pace of activity that was seen in Q4 2024. We expect that clarification of market uncertainty will help revive this market in the months ahead.



Source: Data from CapitalIQ and Stifel research.

This Month Has Been Running Hot in the Privates Market

The market for venture privates has seen $4.1 billion in issuance in the first three and a half weeks of the year. This pace is up 50% from what we saw in Q4 last year.



Source: Data from CapitalIQ, Crunchbase.

Biotech Venture Investors Optimistic, but Uncertainties Persist

Brian Gormley, *Wall Street Journal*, Jan 23, 2025 (excerpt)

Biotechnology venture capital is recovering from its slide and investors are expressing optimism about 2025, even as they confront uncertainties weighing on their industry.

U.S. and European biotech venture funding climbed to $28.1 billion in 2024 from $21.2 billion the prior year, according to HSBC Innovation Banking, which works with startups and venture investors.

The outlook for biotech M&A is encouraging because drugmakers need to fill gaps from medicines coming off patent, the overhang from the presidential election is gone, and inflation is more under control, said Roel van den Akker, principal, pharmaceutical and life science deals leader, for PricewaterhouseCoopers U.S.

"If you have a more-stable and predictable environment it's likely that we're going to see people lean into dealmaking a bit more in '25 than perhaps we've seen over the past two years," he said. Last week, Johnson & Johnson agreed to buy publicly held Intra-Cellular Therapies, for $14.6 billion, and GSK said it would pay up to $1.15 billion to purchase venture-backed IDRx. "We have been talking about cautious optimism for the last two years," said Arda Ural, EY Americas life sciences sector leader. "We can finally drop the 'cautious.'"

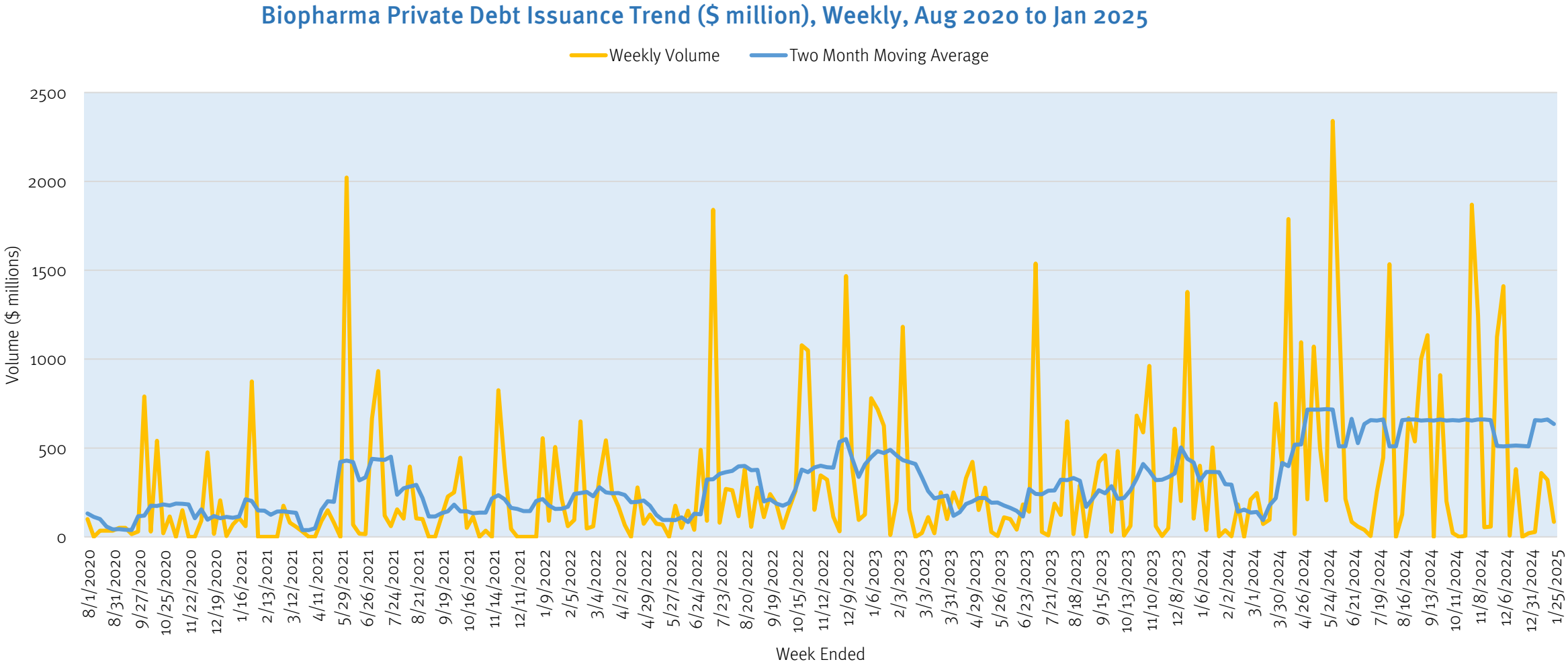
The recovery, however, is uneven and new headwinds could slow it. "I think things look really good, but I do have concerns regarding the macroeconomic policies that could impact biotech investing through inflationary results," said Robert Williamson, president, acting chief executive and director of venture-backed biotech company Triumvira Immunologics.

Investors have responded to uncertainty by placing what appear to be surer bets, channeling more money to fewer companies. Biotech venture financings fell to 569 last year from 573 in 2023, and financings of $100 million or more—mega-rounds—grew 70% from 2023 to 106 deals in 2024, according to HSBC. As capital markets constricted in 2022 and 2023, venture firms tended their own portfolios, propping up companies with insider rounds. By last year firms were ready to focus more on new investments, but often favored startups led by repeat entrepreneurs who could raise giant financings to target big markets.

Source: https://www.wsj.com/articles/biotech-venture-investors-optimistic-but-uncertainties-persist-038ofdca

Global Biopharma Private Debt Placement Market Cool So Far in January

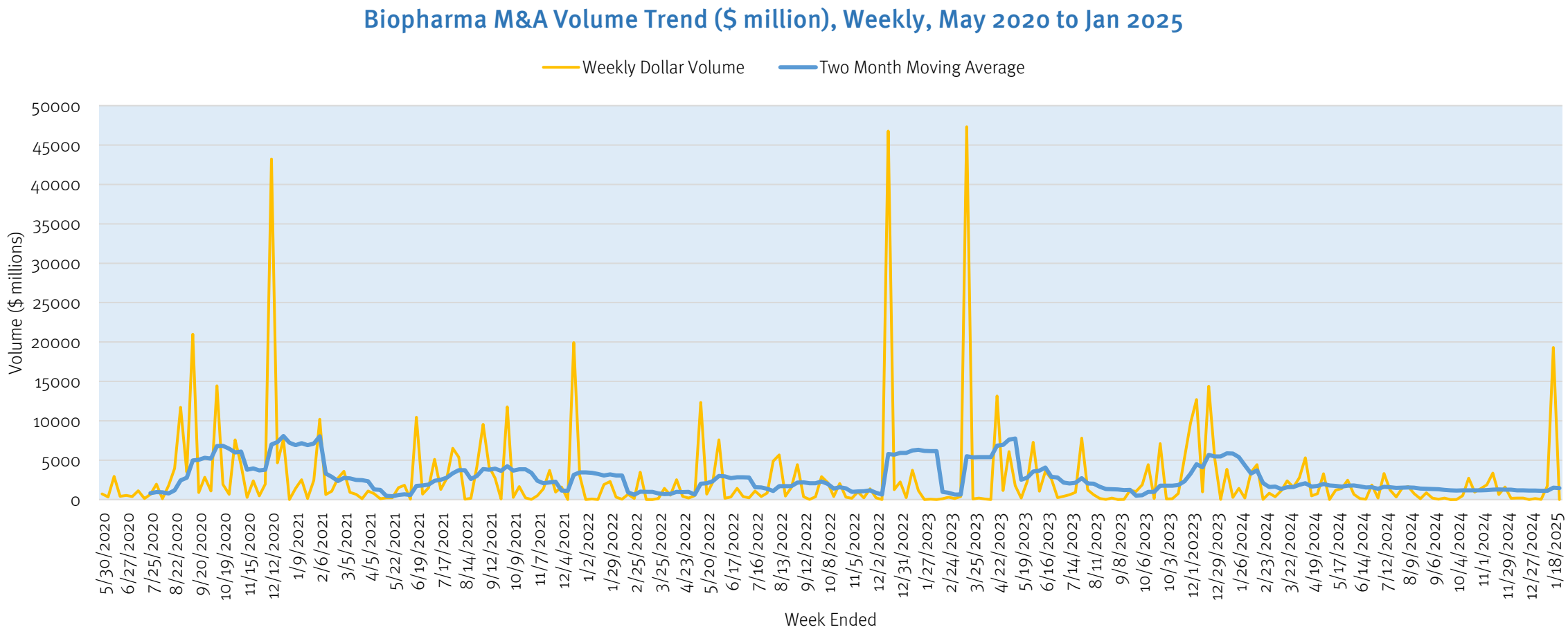
We have seen $800 million in private debt deals get done so far this month. This is well below the blistering pace seen in Q4 2024.



Source: Data from CapitalIQ, Crunchbase.

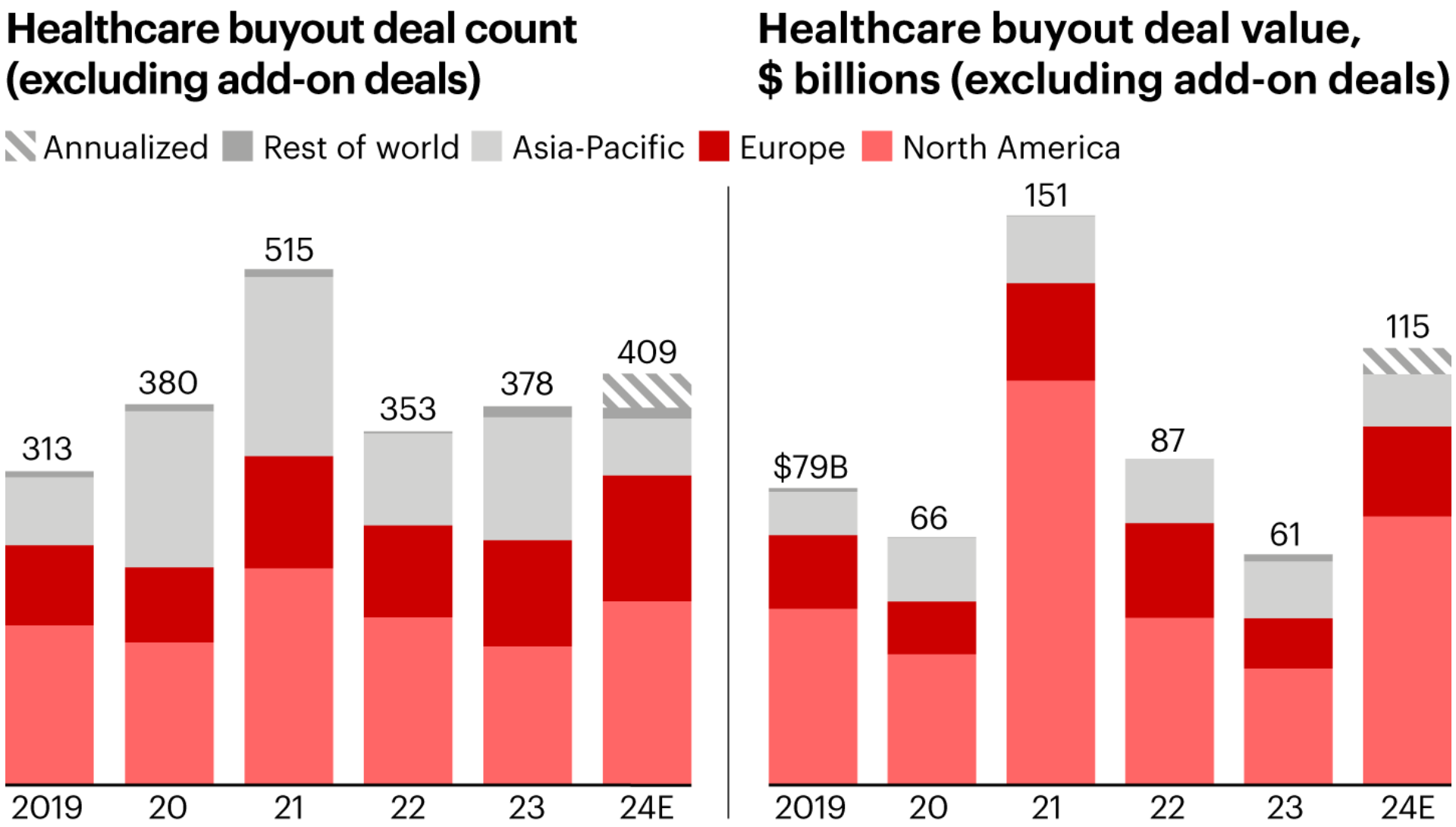
M&A Market Running Strong

We have seen $21 billion in M&A volume in the first three and a half weeks of 2025. This is one of the strongest starts to the year seen in a long time. One key exception year was 2019 when we saw the Celgene acquisition announced on the Jan 3rd. One comparison metric is the number of $1bn+ deals announced. So far this year, we have seen three such deals. Compare this to 15 total $1bn+ M&A deals seen in all of last year.



Source: S&P, CapitalIQ

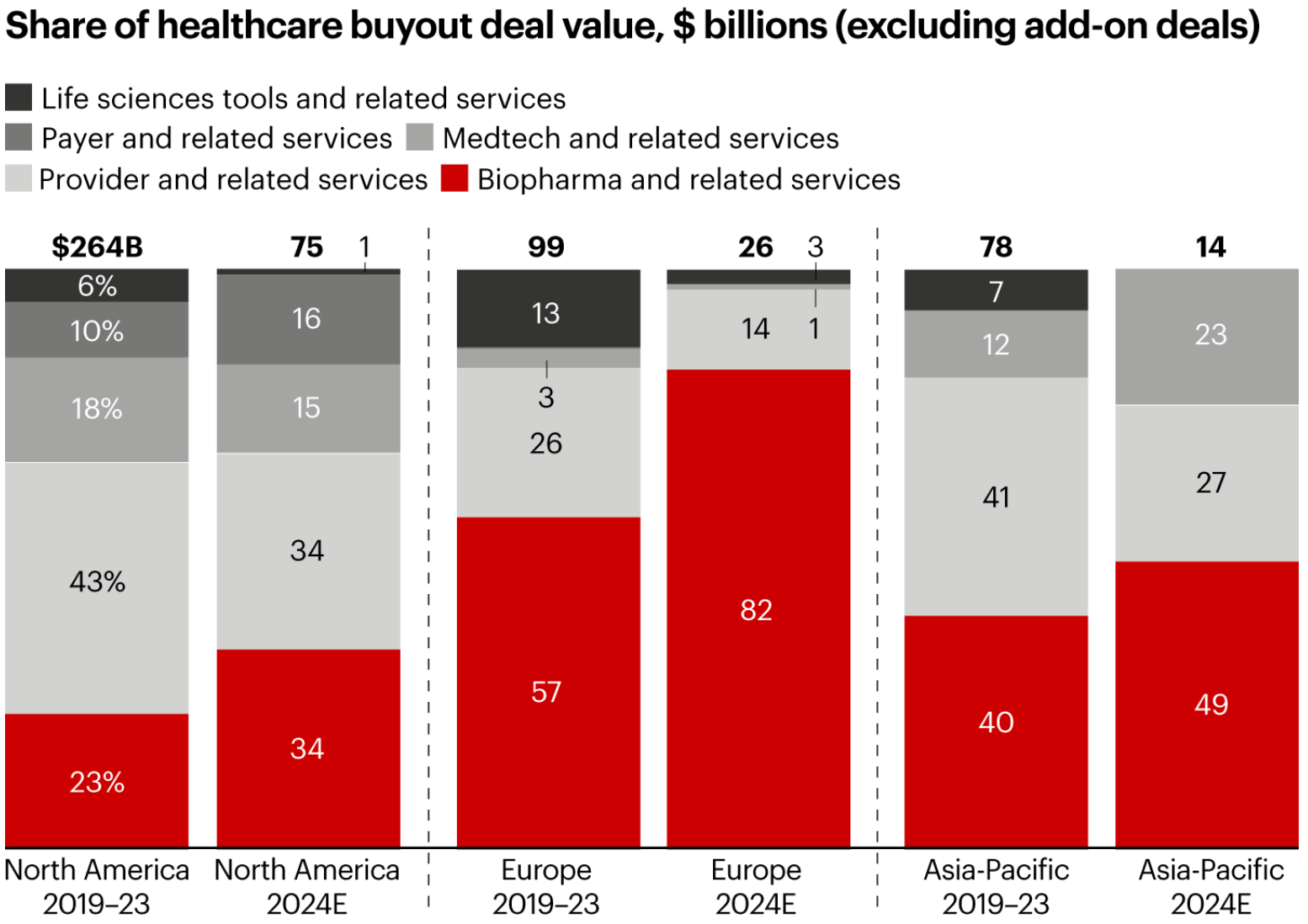
Bain: North American and European PE Deal Activity Surged in 2024



Source: https://www.bain.com/insights/year-in-review-and-outlook-global-healthcare-private-equity-report-2025/

Bain: Biopharma Led Healthcare Buyout Activity in 2024

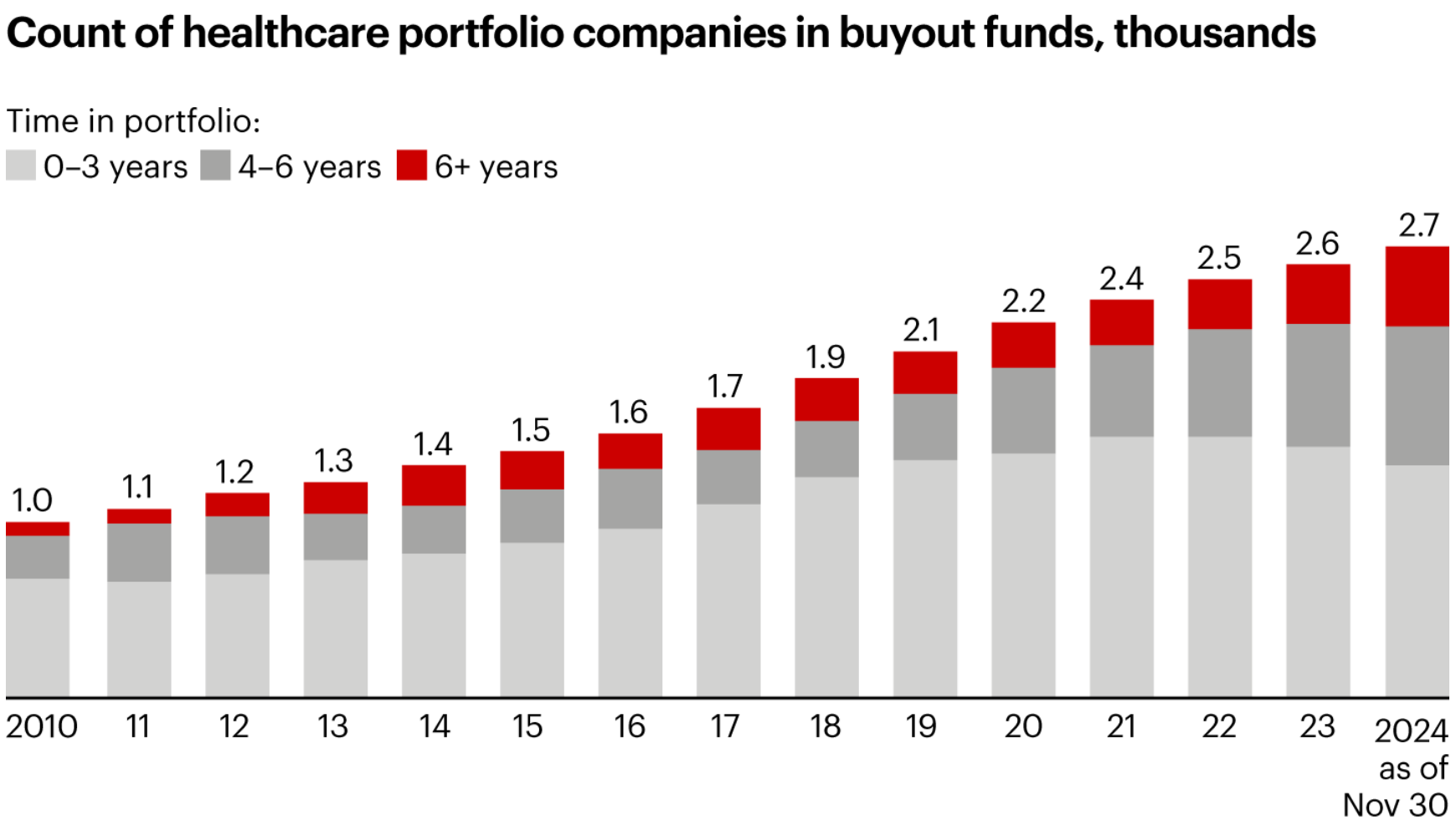
Biopharma and related services led all other segments in deal value in 2024



Source: https://www.bain.com/insights/year-in-review-and-outlook-global-healthcare-private-equity-report-2025/

Bain: Healthcare PE Deal Hold Times Getting Longer

Average PE hold times for portfolio companies peaked in 2024



Source: https://www.bain.com/insights/year-in-review-and-outlook-global-healthcare-private-equity-report-2025/

Industry Update

The Biotech CEO Sisterhood Assembles in Union Square, SF on Jan 14, 2025.

Trump Presence Being Felt in Health R&D and Foreign Aid

STAT+ | POLITICS

Jan 24, 2025

Trump's restrictions spark chaos across health and science agencies

Ongoing experiments, research funding, and scientists' careers are all at stake

Trump Withdraws U.S. From World Health Organization

NYT, Jan 22, 2025

Public health experts say U.S. withdrawal from the W.H.O. would undermine the nation's standing as a global health leader and make it harder to fight the next pandemic.

Trump hits NIH with 'devastating' freezes on meetings, travel, communications, and hiring

Researchers facing "a lot of uncertainty, fear, and panic"

Science, Jan 22, 2025

US freezes almost all foreign aid

By Jennifer Hansler, CNN

4 minute read · Updated 1:26 PM EST, Sat January 25, 2025

CBS News, "FDA pauses updates on foodborne outbreak probes as health agencies regroup on communications," Jan 24, 2025

Multiple federal health agencies have stopped releasing some key health information – including updates on some outbreak investigations – amid a department-wide communications "pause" ordered by the Trump administration, though many other "mission critical" updates are still being released, CBS News has learned.

1. Stops work battling a deadly Marburg outbreak in Tanzania and a wide outbreak of a mpox variant killing children in west Africa before it spreads further.

2. Stops monitoring of bird flu in 49 countries, a disease which already killed an American on home soil.

McKinsey Study Analyzes Women's Health Opportunity

Nearly half of the global population—and 80 percent of patients in therapeutic areas such as immunology—are women. And yet, treatments are frequently developed without tailored insights for female patients. Too often, researchers have viewed "women's health" narrowly through the lens of reproductive organs, treated women as "small men" for other conditions, and ignored critical biological differences such as cellular sex (every cell in the body has a sex), hormonal impacts, and genetic factors. Addressing these differences is not just about equity—it drives more precise and effective healthcare for everyone.

A recent analysis by the World Economic Forum, in collaboration with the McKinsey Health Institute (MHI), revealed that women, on average, **spend 25 percent more of their lives in poor health compared with men, partially because of a lack of sex-based treatment development and delivery.** Addressing this disparity could improve quality of life for women and unlock more than $1 trillion in annual global GDP by 2040 and create new market opportunities for conditions with significant unmet needs.

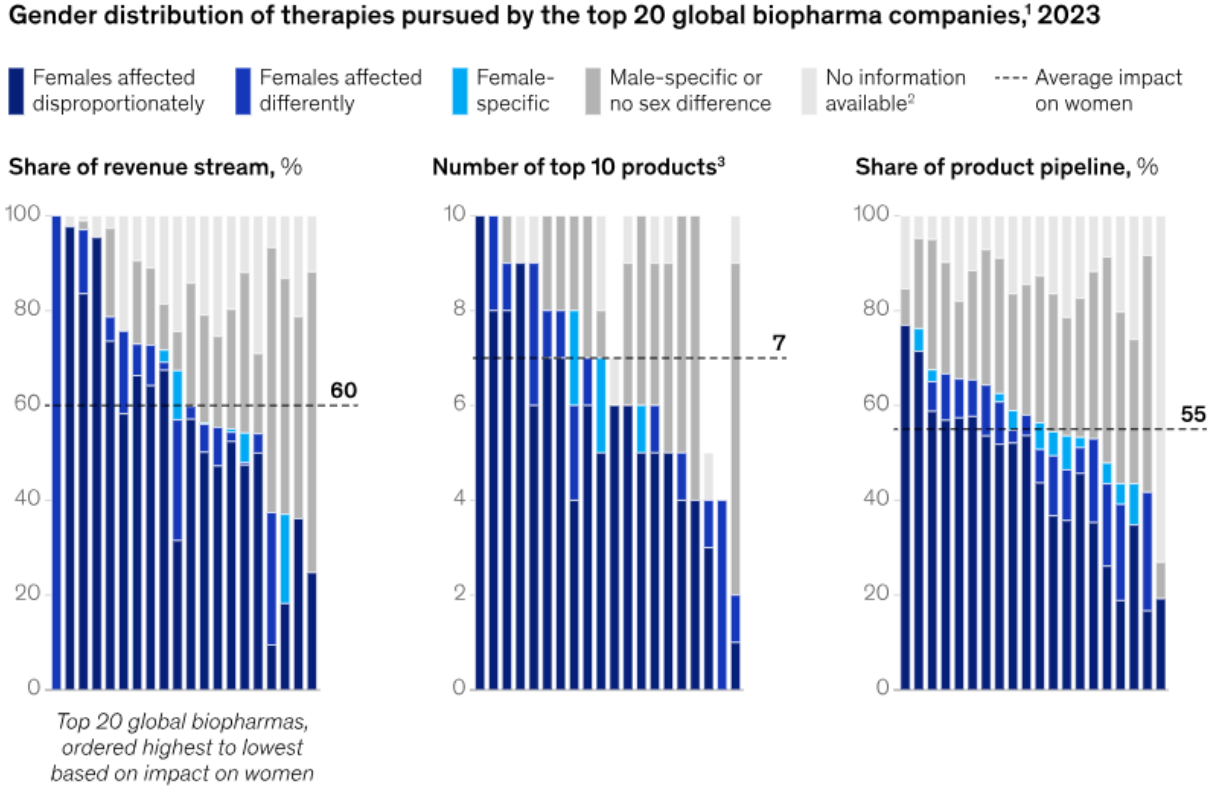
Source: https://www.mckinsey.com/industries/life-sciences/our-insights/closing-the-womens-health-gap-biopharmas-untapped-opportunity

Pharma Already Big in Women Health But May Not Know It

Beyond expanding into areas of high unmet needs for women, pharma companies can also close the health gap by simply recognizing and amplifying the substantial role women's health already plays in their portfolios. The majority of the top 20 pharma companies derive more than 60 percent of their revenue from treatments for conditions that uniquely, differently, or disproportionately affect women (Exhibit 1).

A substantial portion of revenue for 16 of these players comes from treatments for such conditions as autoimmune diseases, mental health disorders, osteoporosis, cardiovascular disease, and certain cancers. Additionally, more than 55 percent of assets in Phase II and III clinical trials target conditions that disproportionately, or more intensely, affect women.

Most of the top 20 global biopharma companies focus on conditions that disproportionately affect women.



[1]Top 20 global biopharma companies by 2023 total sales.
[2]"No information available" means the company has grouped several products in the "other" category, data is missing, or the condition has no available data.
[3]Top 10 products in FY 2023 revenue. Three of the companies had fewer than 10 products overall.
Source: Evaluate Pharma; McKinsey Value Intelligence Platform; S&P Capital IQ; S&P Global Market Intelligence, June 2024; McKinsey analysis

Source: https://www.mckinsey.com/industries/life-sciences/our-insights/closing-the-womens-health-gap-biopharmas-untapped-opportunity

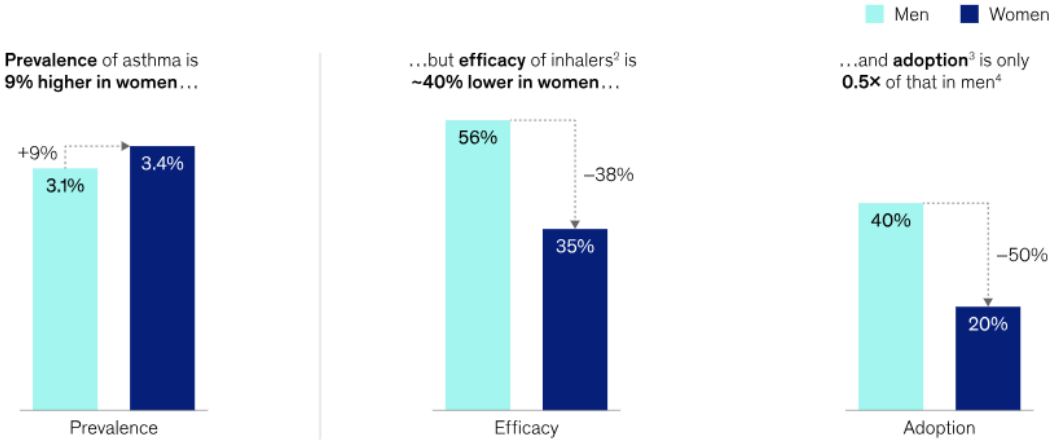
Why Sex-Based Drug Development Matters

Emerging evidence about sex-based disease differences highlights the need for more targeted R&D for therapeutic interventions. Such differences include the active role of the second X chromosome in women, particularly in immune responses, and physiological distinctions between women and men in fat distribution and metabolism that affect drug efficacy and safety in cardiometabolic treatments.

Closing the sex gap can have a profound impact on treatment adoption and efficacy for women. For instance, asthma is more prevalent in women, yet they experience lower efficacy of treatments and lower adherence rates. Inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) inhalers, for example, demonstrate roughly 40 percent lower efficacy in women, and adoption rates are only half that of men, partly due to hormonal fluctuations and access barriers. Achieving sex parity in asthma treatment could result in a 27 to 35 percent increase in the number of women effectively treated, benefiting an additional 16 million female patients and preventing approximately 1.6 million disability-adjusted life years (DALYs) (Exhibit 2).

Closing the sex gap on adoption and efficacy of ICS/LABA[1] inhalers for asthma could increase the number of patients treated by 27 to 35 percent.

Overview of prevalence, efficacy, and adoption of ICS/LABA inhalers for asthma, disaggregated by sex



[1]Inhaled corticosteroid (ICS)/long-acting beta agonist (LABA).
[2]Pharmacological treatment with combined ICS and LABA in combined inhaler device; includes beclometasone with chlorofluorocarbon propellant, beclometasone with hydrofluoroalkane propellant, budesonide chlorofluorocarbon, budesonide hydrofluoroalkane, ciclesonide chlorofluorocarbon, flunisolide, fluticasone propionate, mometasone, and triamcinolone.
[3]Engelkes, Marjolein et al. "Medication adherence and the risk of severe asthma exacerbations: a systematic review." European Respiratory Journal 45 (2014): 396–407.
[4]Calculated maximum % increase in patients treated by assuming equal adoption between men and women, minimum calculated by assuming 60% of the adoption gap can be addressed, 1990 prevalence rates applied to 2024 global population
Source: McKinsey Health Institute Research, Institute for Health Metrics and Evaluation Global Burden of Disease 2019; BMJ 2014 Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis; Medication adherence and the risk of severe asthma exacerbations: a systematic review Eur Respir J

Source: https://www.mckinsey.com/industries/life-sciences/our-insights/closing-the-womens-health-gap-biopharmas-untapped-opportunity

Achieving sex parity in drug adoption and efficacy can prevent substantial loss of healthy life years.

Example conditions selected based on prevalence and existence of adoption and efficacy gaps between sexes

Condition and intervention	Impact on number of patients receiving intervention	% increase in patients	Impact on DALYs[1]
Asthma Combined ICS/LABA[2] inhalers	+16 million	35	480,000 Reduction in DALYs due to achieving sex parity in treatment efficacy and adoption
Atrial Fibrillation Anticoagulation	+680,000	5	130,000 Reduction in DALYs due to achieving sex parity in treatment efficacy and adoption
Tuberculosis Supervised multidrug regiment treatment	+27 million	3	1.3 million Reduction in DALYs due to increased adoption of therapeutic treatment in women

[1]Disability-adjusted life years.
[2]Inhaled corticosteroid (ICS)/long-acting beta agonist (LABA).
Source: Closing the women's health gap: A $1 trillion opportunity to improve lives and economies, IHME GBD 2019

Source: https://www.mckinsey.com/industries/life-sciences/our-insights/closing-the-womens-health-gap-biopharmas-untapped-opportunity

IQVIA INSTITUTE FOR HUMAN DATA SCIENCE

Research Brief

2025 Indicators of Progress for the Life Sciences Sector

HOW WILL WE KNOW IF THE SECTOR IS ADVANCING IN 2025?

January 2025

IQVIA Institute Report on Progress Indicators

The year ahead for the life sciences sector will be defined by advances in science, research and development, marketplace dynamics, economics, and politics. There will be successes and challenges along the way, and no shortage of uncertainty. This research brief outlines several factors that can be used as indicators of positive progress in 2025 for the life sciences industry across multiple domains, including industry reputation, research and clinical development productivity, biotech funding, early intervention, therapeutic innovation, patient access to healthcare services, and health policy. These indicators are not intended as predictions of what will happen — but rather a series of explicit markers that will reflect progress if they are achieved by the end of the year.

1. **Greater trust in life sciences companies**: A lack of public trust in the pharmaceutical industry leads to diminished political support and credibility, patient hesitancy, and less use of medicines. Progress will be recognized if the positive public view of the pharmaceutical industry improves to 25% in 2025 from 20% last year.
2. **Reduction in out-of-pocket costs for patients**: Drug prices are perceived by the public to be too high largely through the out-of-pocket costs borne by patients with or without insurance, and are a flashpoint for policymakers, leading to finger-pointing among stakeholders and driving misguided policies. Progress in 2025 will be achieved if average brand prescription out-of-pocket costs fall below $25 and the share of brand prescriptions carrying patient costs of more than $125 falls to less than 3% of the total.
3. **Expanded patient access to healthcare services**: Fewer interactions between patients and healthcare professionals result in fewer opportunities for medicines to be considered as treatment options and their full value delivered to patients.
4. **Inclusive progress on the "Make America Healthy Again" (MAHA) agenda**: As the next U.S. administration brings new approaches and priorities to the healthcare sector, the potential exists for policy and regulatory actions that bring uncertainty, delays and disruption for the industry. A positive indicator in 2025 will be an inclusive approach — including the life sciences sector.
5. **More focus on disease prevention and early intervention**: The life sciences sector remains heavily dependent on developing and commercializing treatments for late-stage disease and symptom management. Consistent with the MAHA agenda, progress in placing more focus and funding for disease prevention and early intervention will be an important indicator for the industry.

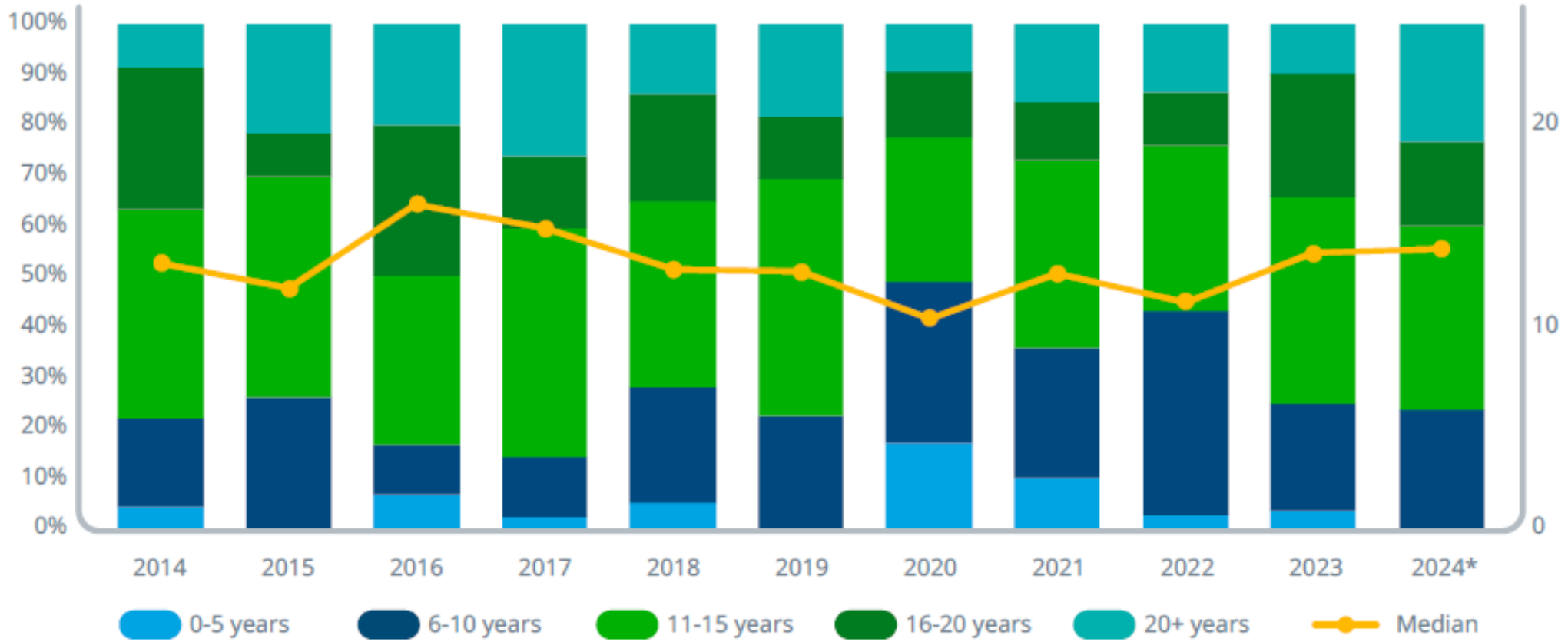
Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/2025-indicators-of-progress-for-the-life-sciences-sector

IQVIA Institute Report on Progress Indicators (continued)

6. **Restored growth in the emerging biopharma sector**: Emerging biopharma companies require stable funding sources and exit strategies, both of which have been challenging over the past three years. Since these companies represent about 60% of clinical trial activity globally, their strength and growth are vital to the broader sector.
7. **Improvements in clinical development decisionmaking, processes, and technology deployment**: Pharmaceutical research and development is highly risky and Phase II project success rates have hovered stubbornly around 30% in recent years at the total industry level — resulting in higher clinical development costs and more than 13 years elapsing from patent filing to patient availability of new medicines.
8. **Expanded use of novel advanced therapies**: The life sciences sector has made great progress in bringing through development and regulatory approval, and growing a number of novel cell and gene therapies and other advanced modalities. However, the limited access and use of these therapies brings uncertain sustainability to this area of innovation. Positive indicators of progress in 2025 would be the increased use of CAR T-cell therapies, for example, in third line or later multiple myeloma to more than 8% of treatment regimens in the U.S. and 5% in EU4+UK. Additionally, bringing approved sickle cell gene therapies approved in 2023 to treat just 2% of eligible patients by the end of the year would reflect positively on these novel advanced therapies.
9. **Higher Freshness Index for life sciences company product portfolios**: Balancing the cycle of investment in innovation with the generation of returns during a defined period of exclusivity is a hallmark of successful life sciences companies. In recent years, product portfolios have not been fully replenished at the rate needed to sustain investment in innovation. An indicator of progress in 2025 would be an improvement in the Freshness Index that would take the share of branded drug sales from launches in the prior five years from 20% to 25%, and the share of sales from launches in the prior decade from 60% to 65%.
10. **Increased contribution from markets outside of the U.S. to global sales of life sciences companies**: For global companies, over-dependence on a single market can concentrate commercial risk and increase the impact of policy changes that may be imposed to limit growth in payer expenditure on medicines. In this context, a metric of positive progress in 2025 would be the share of global branded drug sales from outside the U.S. increasing to more than 40%, a level not seen since 2013.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/2025-indicators-of-progress-for-the-life-sciences-sector

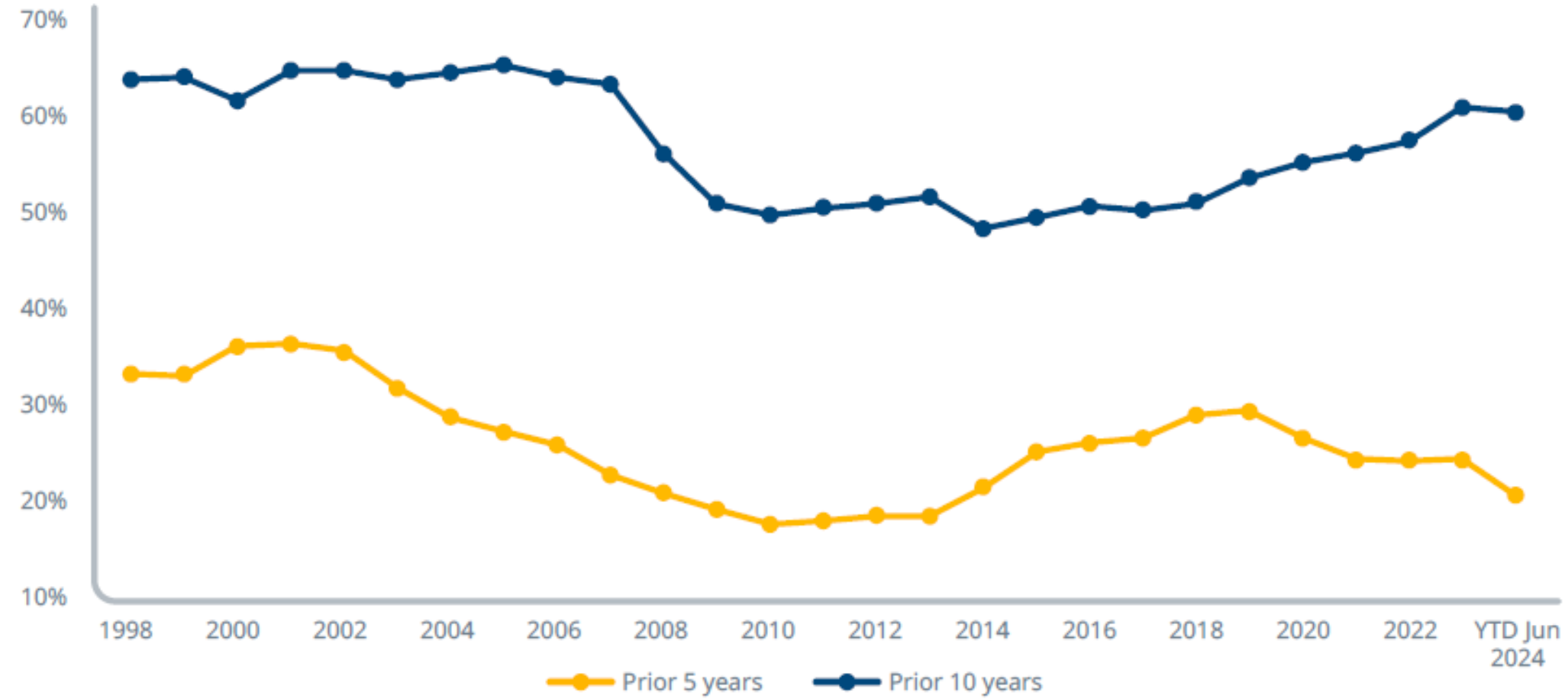
Exhibit 4: Time from first patent filing to U.S. launch for novel active substances, 2014 - 2024



Source: IQVIA Institute NAS Database, December 2024.
* YTD Sept 30, 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/2025-indicators-of-progress-for-the-life-sciences-sector

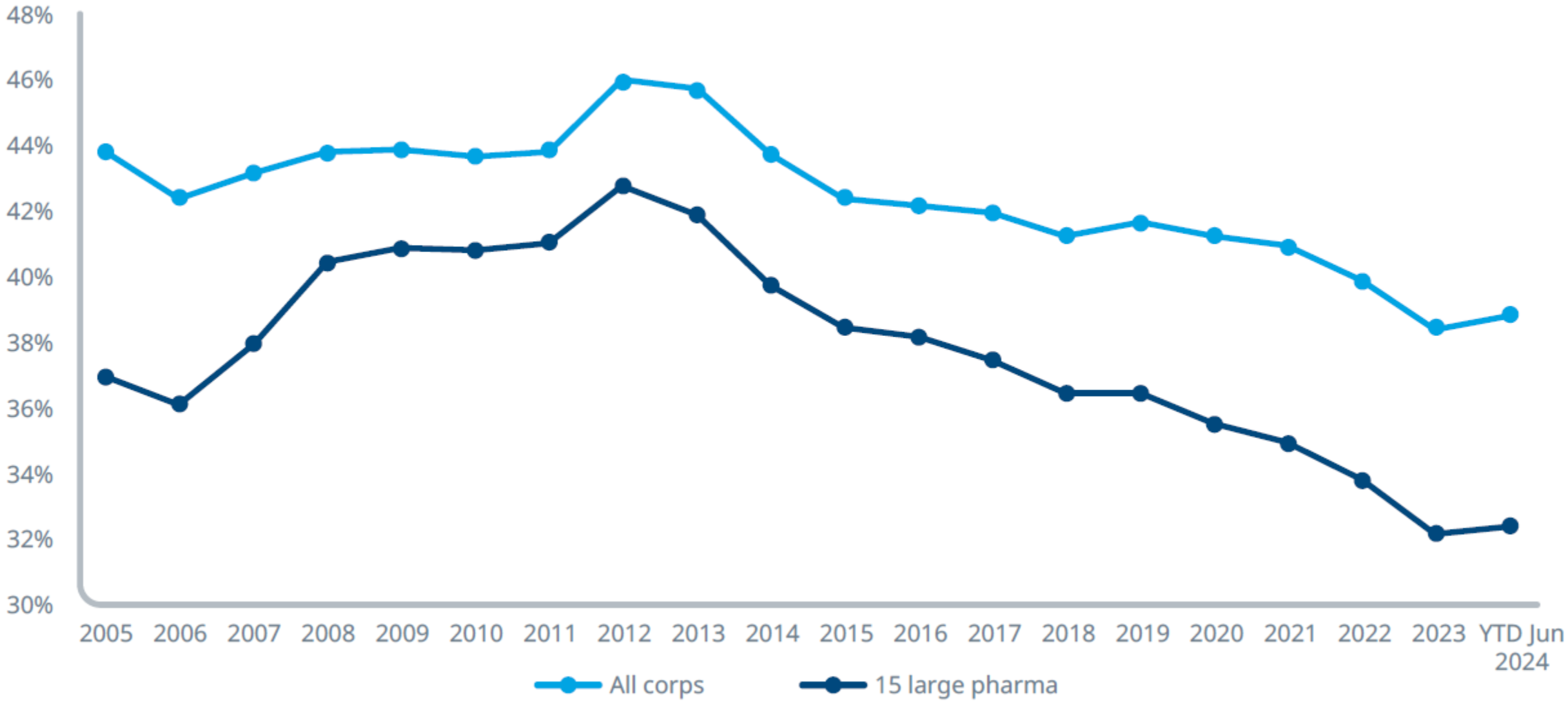
Exhibit 9: Freshness Index — Share of branded drug sales from launches in the prior 5 and 10 years



Source: Oncology Dynamics, Sep 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/2025-indicators-of-progress-for-the-life-sciences-sector

Exhibit 10: Share of global branded drug sales from markets outside of U.S.



Source: IQVIA MIDAS, Jun 2024; IQVIA Institute, Nov 2024.

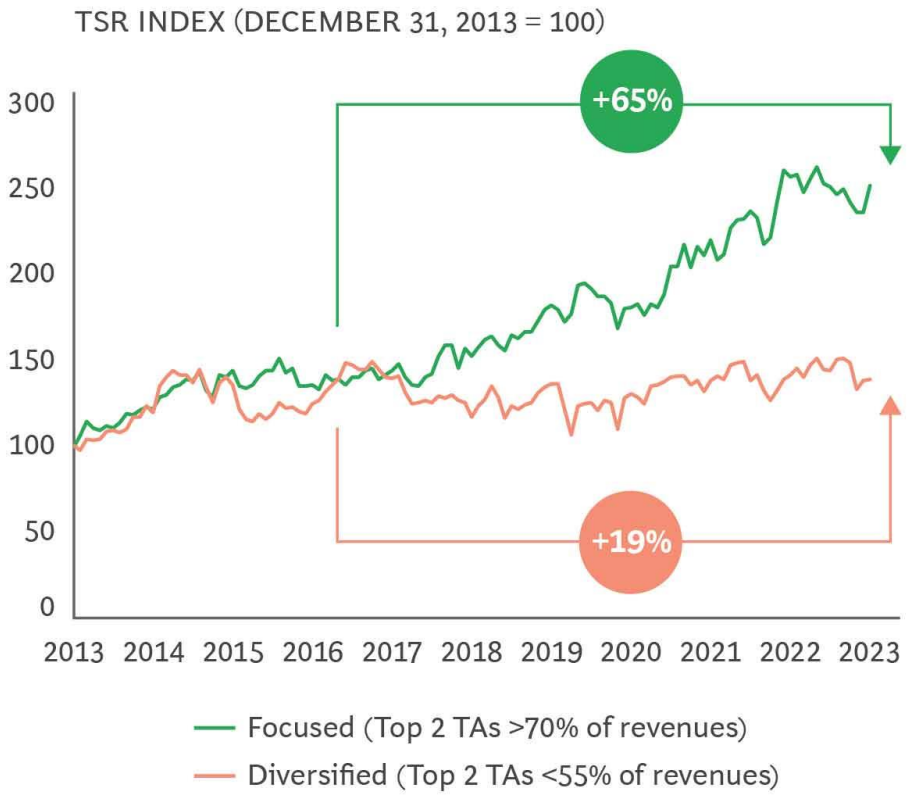
Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/2025-indicators-of-progress-for-the-life-sciences-sector

BCG Study: Focused Pharmas Have Done Better

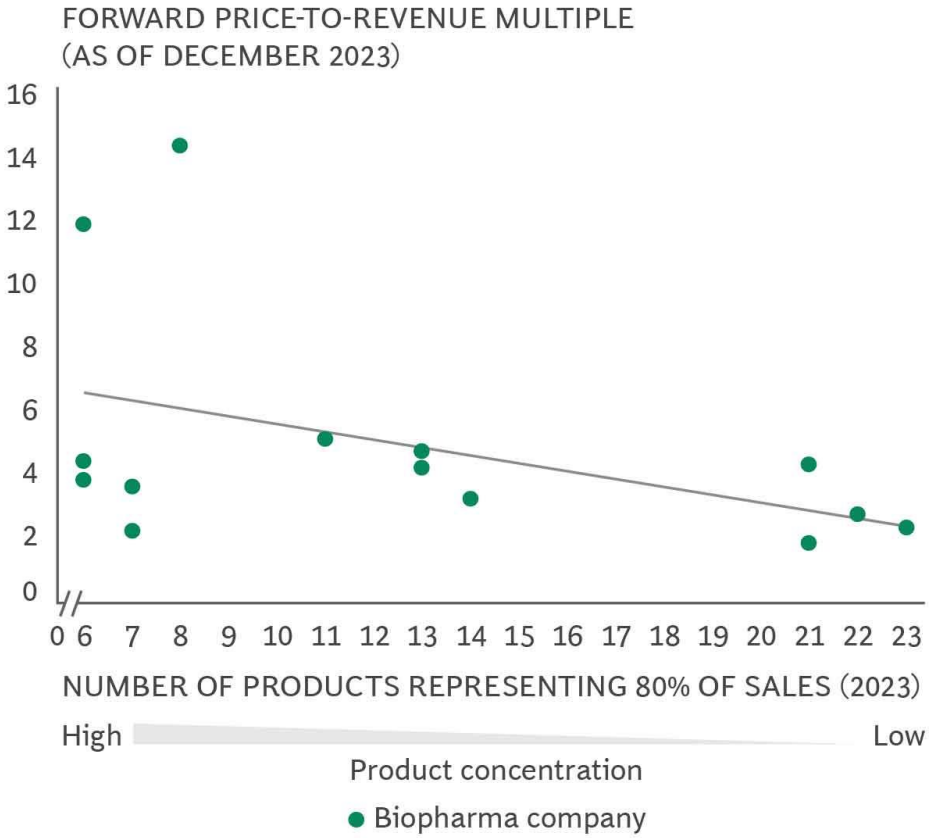
EXHIBIT 1

Investors Have Rewarded Companies Whose Portfolios Are Focused

TSRs favor companies whose portfolios are more focused



Equity valuations tend to be higher for companies with greater product concentration



Sources: S&P Capital IQ; EvaluatePharma; BCG ValueScience Center.
Note: Company names in the forward price-to-revenue multiple chart are New York Stock Exchange ticker abbreviations. TA = therapeutic area; TSR = total shareholder return.

Source: https://www.bcg.com/publications/2025/biopharma-trends

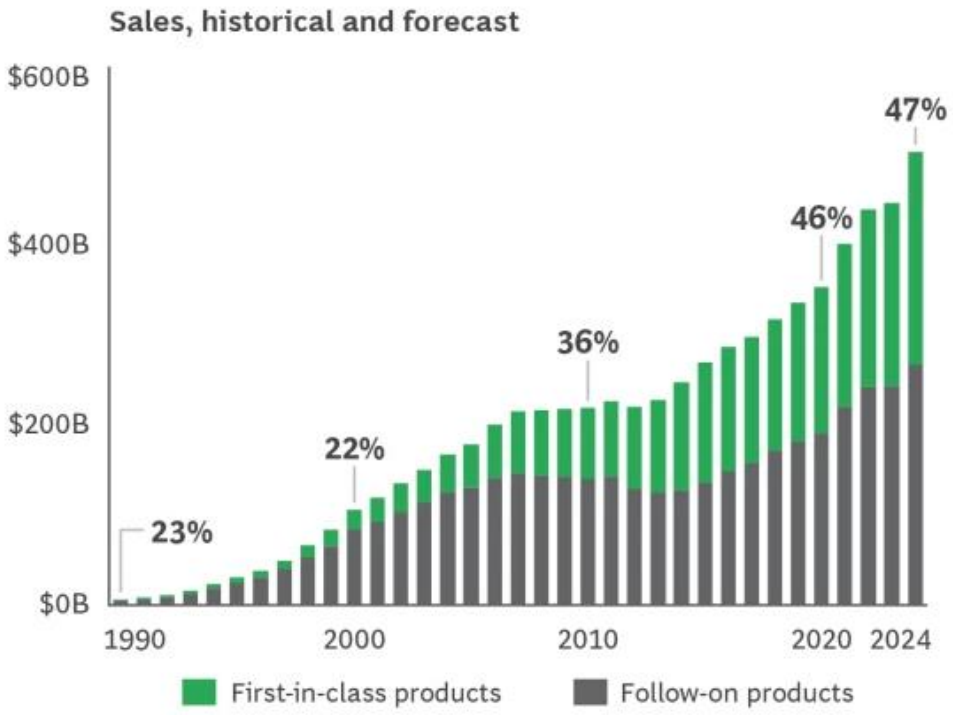
BCG Study: More First-in-Class Molecules

EXHIBIT 2

A Combination of Better Understanding of Causal Biology and Novel Modalities Is Fueling the Growth of First-in-Class Products

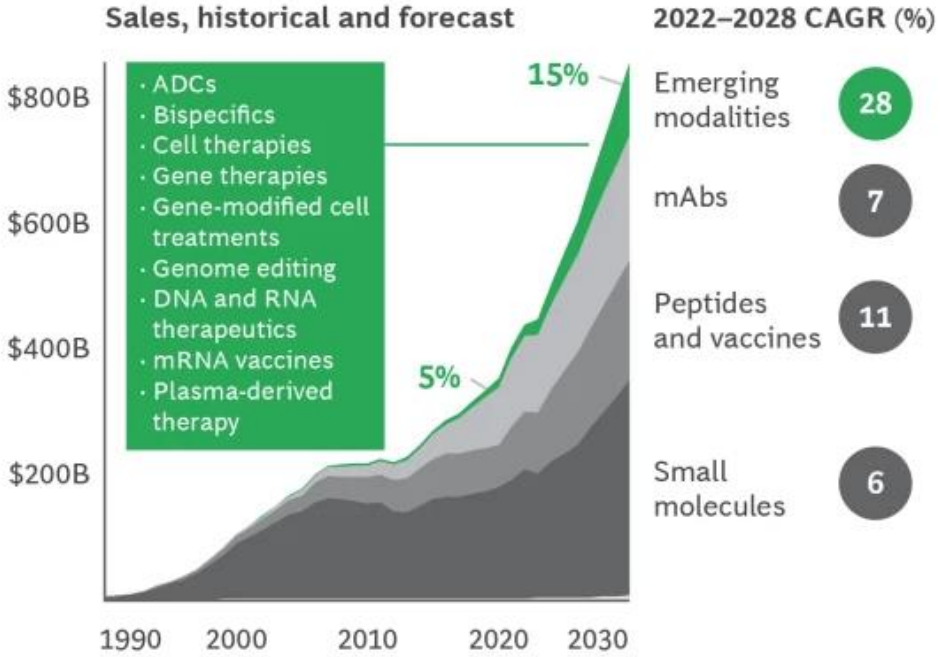
Market share of first-in-class products doubled in past 20 years

US SALES OF FIRST-IN-CLASS VS FOLLOW-ON PRODUCTS, 1990–2024 ($BILLIONS)



Novel modalities will account for 15% of total market by 2030

US SALES BY DRUG MODALITY, 1990–2030 ($BILLIONS)



Sources: EvaluatePharma; BCG analysis.
Note: Analysis includes all assets with 1990–2030 FDA approval. ADC = antibody drug conjugate; mAbs = monoclonal antibodies.

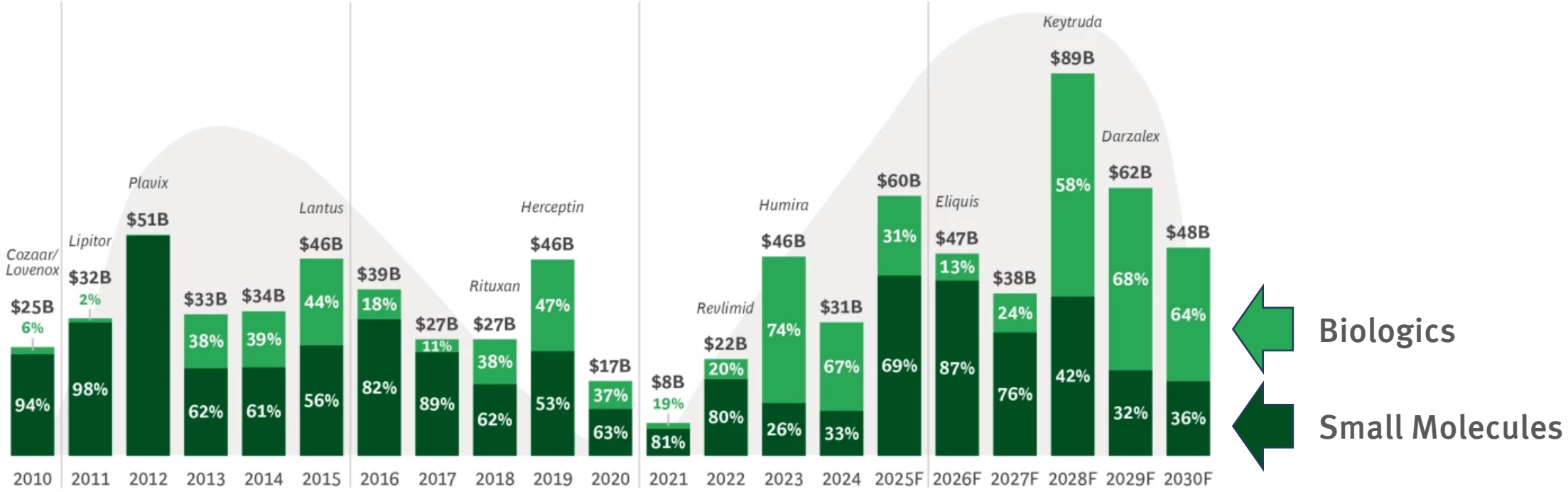
Source: https://www.bcg.com/publications/2025/biopharma-trends

BCG Study: More Biologics LOE's Coming Up than Before

EXHIBIT 3

Although the Share of Revenue That Will Lose Exclusivity by 2030 Is Roughly in Line With Previous Patent Cliffs, More Biologics Are at Risk This Time

TOTAL WORLDWIDE REVENUE IMPACT/REVENUE AT RISK FROM LOE FOR BIOLOGICS VERSUS SMALL MOLECULES, 2010–2030 ($BILLIONS)



Source: https://www.bcg.com/publications/2025/biopharma-trends

Retro Biosciences eyes $1B to Extend Lifespan by 10 Years

Kyle LaHucik, *Endpoints News*, Jan 24, 2025 (excerpt)

Disease-reversal startup Retro Biosciences is aiming for a $1 billion funding round, a spokesperson for the company confirmed in a Friday email to Endpoints News.

It would be one of the largest funding rounds for a private biotech startup in recent years, rivaling only AI-fueled Xaira Therapeutics and Altos Labs.

The Redwood City, CA-based startup hopes to add 10 years to humans' lifespans by winding back the clock on aging processes and treating various diseases like Alzheimer's. Part of its mission is to replace old cells with "zero age" cells, CEO Joe Betts-LaCroix said on a recent podcast.

The Financial Times first reported on the fundraise. Retro looks to enter human trials in Australia this year with a potential medicine for Alzheimer's, according to the FT.

Retro broke onto the scene in April 2022 with $180 million in funding. It was later revealed that OpenAI CEO Sam Altman is Retro's main investor. OpenAI and Retro are working on a language model for longevity science, MIT Technology Review reported this month. Altman has financially backed other scientific ventures and biotech startups, including the $500 million-funded Arcadia Science.

Source: https://endpts.com/with-sam-altmans-help-retro-biosciences-eyes-1b-to-extend-lifespan-by-10-years/

BioAge Reconnects with its Longevity Pipeline

Alexandra Pecci, *PharmaVoice*, Jan 22, 2025 (excerpt)

BioAge Labs is returning to its aging roots after a failed attempt in obesity R&D. To get the ball rolling again, the biotech has entered into a multi-year research collaboration worth up to $550 million with Novartis to identify and validate drug targets related to aging, specifically around exercise biology.

Since its founding a decade ago, BioAge has targeted what it calls the "biology of human aging." It hopped on the obesity bandwagon with azelaprag, a small molecule pill that became its lead candidate.

Although Fortney said the idea that BioAge is now going back to its aging roots is "one way of thinking about it," she noted that every target, including obesity, is drawn from its AI-driven discovery platform.

"Our focus has always been on those molecular mechanisms of healthy aging, and of course once you get to clinical development and you're focused on a particular indication, like obesity, you can forget the genesis," she said. "But those were also targets that emerged from the platform originally."

As part of its Novartis partnership, BioAge will tap that platform, which analyzes longitudinal data from a human biobank, along with detailed health records, "to identify and validate multiple novel therapeutic drug targets," the company said.

Kristen Fortney
Chief Executive Officer
BioAge Labs

Source: https://www.pharmavoice.com/news/obesity-bioage-labs-novartis-aging/737882/

Tris Pharma Reports Impressive Pain Data

Tris Pharma Press Release, Monmouth Junction, NJ, January 22, 2025 (excerpt)

Tris Pharma, Inc. (Tris), a commercial-stage biopharmaceutical company, today announced positive topline results from its ALLEVIATE-1 pivotal Phase 3 clinical trial evaluating cebranopadol, an investigational therapy, for the treatment of moderate-to-severe acute pain in patients following abdominoplasty surgery. These results add to the growing body of data underscoring the promising efficacy and safety profile of cebranopadol, a first-in-class pain therapy involving dual-nociceptin/orphanin FQ peptide (NOP) receptor and μ-opioid peptide (MOP) receptor (dual-NMR) agonism. .

The results of the clinical study demonstrated a statistically significant reduction in pain intensity as measured using the Pain Numeric Rating Scale (NRS) Area Under the Curve for the 44 hours following surgery (AUC4-48) as the primary endpoint. **Specifically, treatment with cebranopadol 400 μg once per day for two days resulted in a statistically significant reduction in pain intensity compared to placebo (LS Mean difference [SE] of 59.2 [14.36]; p<0.001). Additionally, cebranopadol was generally well tolerated and exhibited a favorable safety profile that was comparable to placebo, with no serious adverse events related to cebranopadol.** The most common adverse event was nausea.

“These are extremely encouraging results, emphasizing the important role cebranopadol could play in effectively and safely alleviating moderate-to-severe acute pain for patients,” said Harold Minkowitz, M.D., primary investigator in the ALLEVIATE-1 study and president of analgesics, perioperative & hospital-based research at Evolution Research Group.

Tris plans to submit full results from the ALLEVIATE-1 abdominoplasty clinical trial for presentation at an upcoming medical congress. In Q1 2025, Tris also plans to share results evaluating cebranopadol in two additional studies, an intranasal human abuse potential study and ALLEVIATE-2, a Phase 3 clinical study in patients following bunionectomy, with an NDA submission expected later this year. Tris plans to conduct cebranopadol studies in multiple chronic pain indications beginning in the second half of 2025.

Source: https://www.trispharma.com/tris-pharma-announces-positive-results-from-alleviate-1-phase-3-clinical-trial-of-cebranopadol-an-investigational-first-in-class-oral-dual-nmr-agonist-for-the-treatment-of-moderate-to-severe-acute-p/

Obesity Drug Market Update

Investors Lose their Appetite for the Obesity Trade

Hannah Kuchler and Oliver Barnes, *Financial Times*, Jan 23, 2025 (excerpt)

In a few short years, excitement about groundbreaking anti-obesity drugs made Novo Nordisk Europe's most highly valued company and Eli Lilly the biggest pharma group in the world. Just as quickly, investors are losing their appetite for the trade.

After a disappointing trial of a new Novo Nordisk drug last month and lower-than-expected sales figures from Eli Lilly for two consecutive quarters, shares in both have come down from all-time highs. Some investors are also unconvinced that the market will be worth the $100bn plus by the end of the decade that analysts predict. The result for now is that Novo Nordisk is no longer the most valuable company in Europe, and anti-obesity specialists have entered bear market territory.

Even so, a plethora of biotechs have sprung up around the world to try to compete with the two big players. They hope to be able to design treatments that are easier to manufacture, more convenient to administer — the current options must be injected — and have fewer side effects, the most common ones being sickness and diarrhoea.

Private investors have recently backed biotechs with exceptionally large funding rounds: Verdiva Bio and Kailera Therapeutics have raised more than $400mn each, while Metsera, which has filed for an IPO, secured $215mn in November. Big pharma companies are also rushing to buy anti-obesity drug candidates. But the vast majority of these drugs are still many years from the market and although sales of existing drugs continue to grow, investors have become unnerved by the high valuations of Novo Nordisk and Eli Lilly.

Even after its shares fell 7 per cent in one day earlier this month, Eli Lilly is trading on a price/earnings ratio of 55. Novo Nordisk trades at a p/e of 27, despite a more than 21 per cent drop in its shares in one day late last year.

We're not so sure investors have lost their interest in obesity drugs although we agree with the authors that sales and stocks have been volatile.

Last week saw Novo and Lilly shares add almost $100 billion in value.

The interest in this area remains quite strong.

Source: https://www.ft.com/content/963e548e-2bfe-43ef-b891-0ed6213630ae

Novo Nordisk Reports 22% Weight Loss with Amycretin

Novo Nordisk, *Press release*, Jan 24, 2025 (excerpt)

Bagsværd, Denmark, 24 January 2025 – Novo Nordisk today announced topline results from a phase 1b/2a clinical trial with amycretin, a unimolecular GLP-1 and amylin receptor agonist intended for once weekly subcutaneous administration.

The trial investigated the safety, tolerability, pharmacokinetics, and proof-of-concept after once-weekly subcutaneous administrations of amycretin in 125 people with overweight or obesity. The trial was a combined single ascending dose, multiple ascending dose and dose-response trial investigating three different maintenance doses with a total treatment duration of up to 36 weeks.

The primary endpoint was treatment emergent adverse events. The safety profile of amycretin was consistent with incretin-based therapies. The most common adverse events with amycretin were gastrointestinal and the vast majority were mild to moderate in severity.

When evaluating the effects of treatment if all people adhered to treatment1 from a mean baseline body weight of 92.7 kg, people treated with amycretin achieved an estimated body weight loss of 9.7% on 1.25mg (20 weeks), 16.2% on 5mg (28 weeks) and 22.0% on 20mg (36 weeks). People treated with placebo experienced an estimated 1.9%, 2.3% and 2.0% body weight gain, respectively.

“We are very encouraged by the subcutaneous phase 1b/2a results for amycretin in people living with overweight or obesity,” said Martin Lange, executive vice president for Development at Novo Nordisk. “The results seen in the trial support the weight lowering potential of this novel unimolecular GLP-1 and amylin receptor agonist, amycretin, that we have previously seen with the oral formulation.”

These data look really interesting.

However, they are not ITT data and only include weight loss for responders.

Novo did not report drop out rates or AE rates.

It’s interesting that amycretin performed so much better than cagrilintide which has the same MOA.

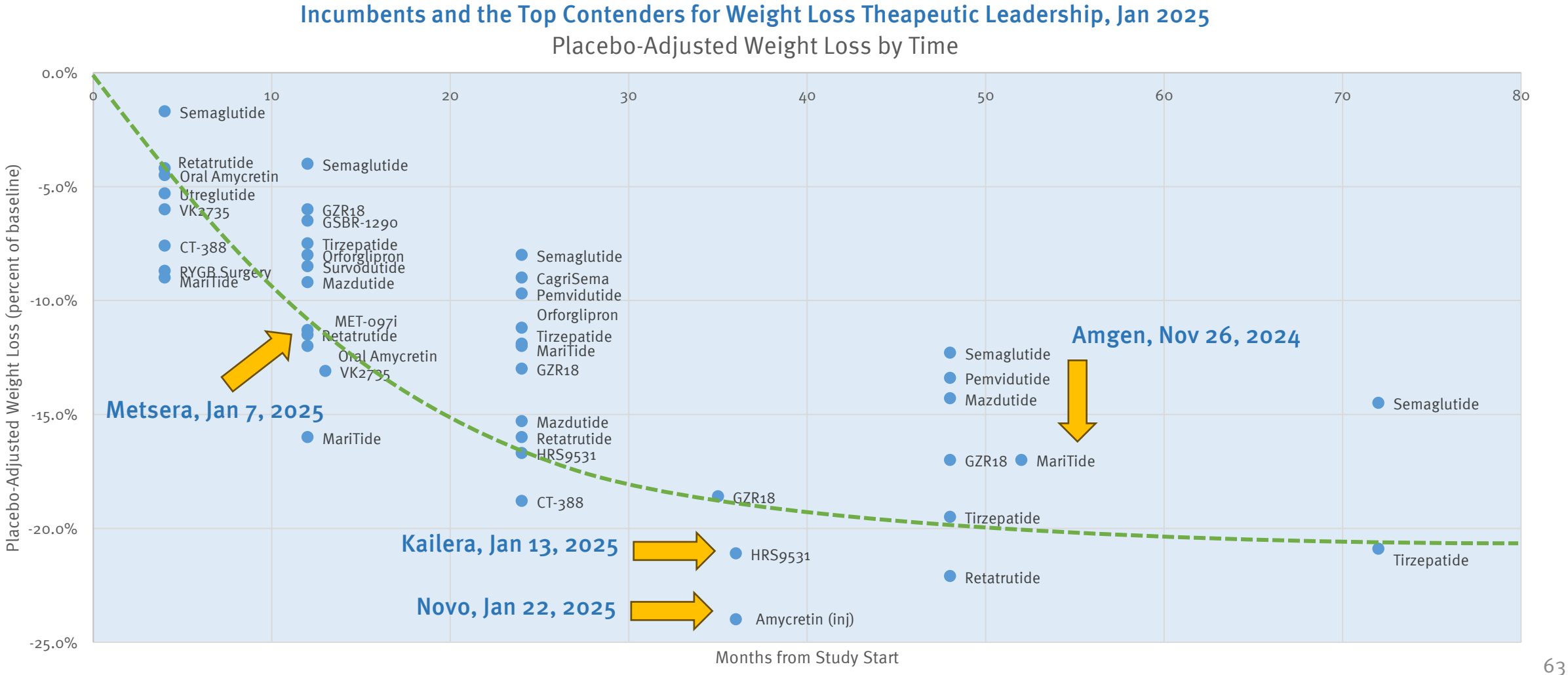
We have reviewed what we think the patent is for amycretin.* It’s important to note that this is a particularly complex molecule – with all that this implies for CMC costs and the like.

Source: https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=915251#

* https://patents.google.com/patent/US20230331803A1. As an example, the polypeptide GLP-1/amylin bridge in claim 6 of this patent involves 64 amino acids. This would almost certainly call for recombinant biologic manufacture rather than solid state synthesis with its attendant costs and complexity. On the positive side, generics would be slow to come and this would certainly qualify as a biologic rather than as a small molecule under current exclusivity rules.

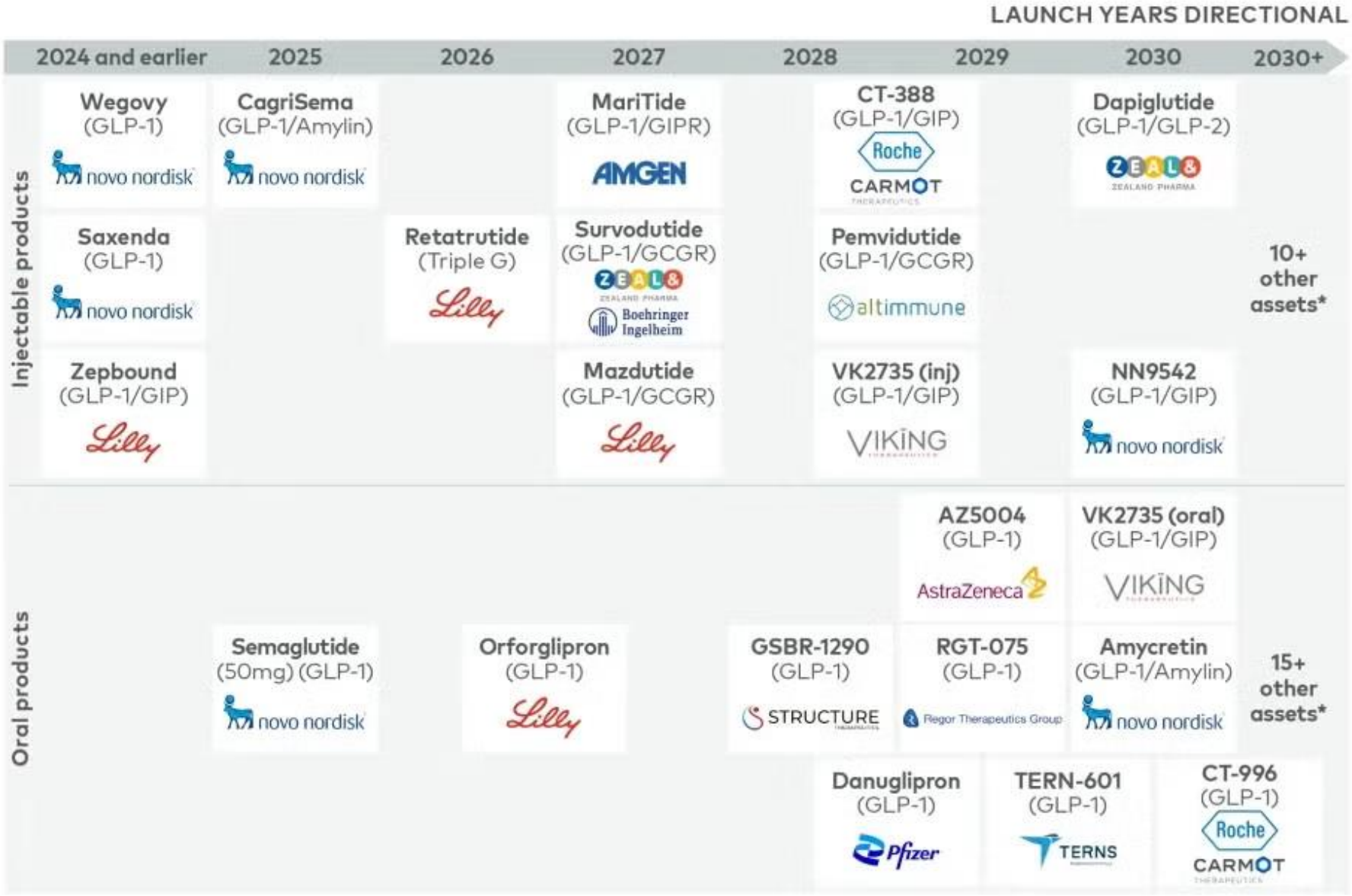
Novo Amycretin Data Look Good But Kailera Made Most Interesting Recent Report

We've seen a number of interesting recent obesity data releases. Last week's Novo data on Amycretin was "below the green line" which tracks tirzepatide performance. However, this was only barely below the line and these were not ITT data. We'll need to see a scientific presentation of the findings (inclusive of side effects) to evaluate. Kailera's recent data look as good as retatrutide (arguably better) and they reported more AE findings. Replicating this data in the U.S. will be the next step. Amgen's MariTide data appear far off the mark for weight loss. But, interestingly, MariTide performed quite well in diabetics and may end up being a better drug for that population (the same can be said of Cagrilintide).



LEK: Heavy Pace of Obesity Drug Launches Likely in 2028 to 2030 Window

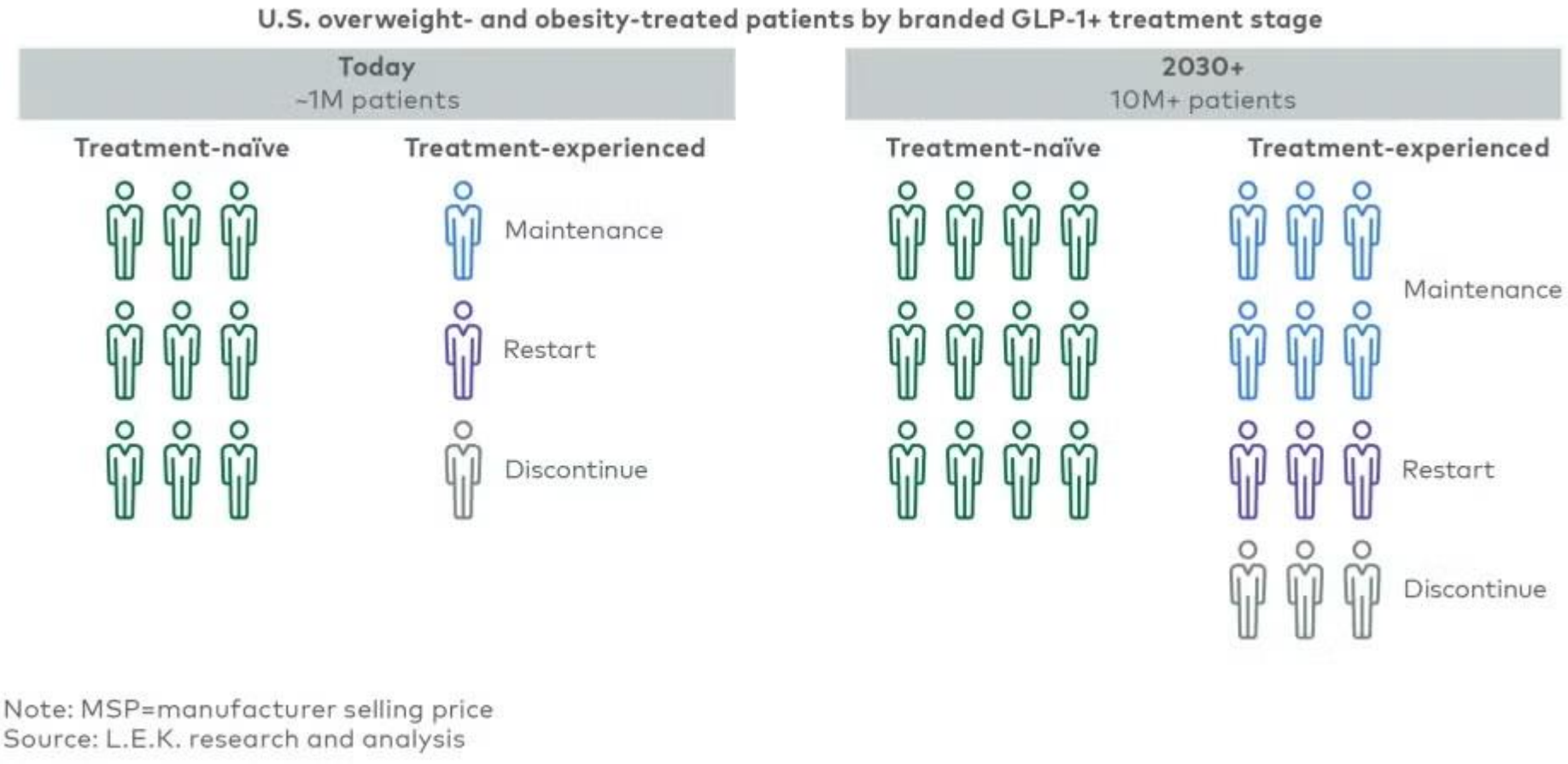
There are quite a few companies hitting the obesity market in the 2028 to 2031 window – which is the time that semaglutide will go generic. These new competitors will need to differentiate themselves against this inexpensive competition to justify a non-generic price.



Source: https://www.lek.com/insights/hea/us/ei/future-outlook-aom-market

*Includes earlier-stage assets, assets transitioning to U.S. studies whose launch dates are TBD (e.g., Kailera), and other mechanisms that affect GLP-1 (e.g., oral nutrient receptor agonists K-757 and K-833)
Note: GLP-1=glucagon-like peptide 1
Source: Company websites; EvaluatePharma; PharmaProjects

LEK: Obesity Market Segmentation Opportunities Will Expand by 2030



Source: https://www.lek.com/insights/hea/us/ei/future-outlook-aom-market

Pro's and Con's of GLP-1's

Xie Y, Choi T, Al-Aly Z. "Mapping the effectiveness and risks of GLP-1 receptor agonists," *Nature Medicine*, Jan 20 2025.

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are increasingly being used to treat diabetes and obesity. However, their effectiveness and risks have not yet been systematically evaluated in a comprehensive set of possible health outcomes. Here, we used the US Department of Veterans Affairs databases to build a cohort of people with diabetes who initiated GLP-1RA (n = 215,970) and compared them to those who initiated sulfonylureas (n = 159,465), dipeptidyl peptidase 4 (DPP4) inhibitors (n = 117,989) or sodium-glucose cotransporter-2 (SGLT2) inhibitors (n = 258,614), a control group composed of an equal proportion of individuals initiating sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors (n = 536,068), and a control group of 1,203,097 individuals who continued use of non-GLP-1RA antihyperglycemics (usual care).

We used a discovery approach to systematically map an atlas of the associations of GLP-1RA use versus each comparator with 175 health outcomes.

Compared to usual care, GLP-1RA use was associated with a reduced risk of substance use and psychotic disorders, seizures, neurocognitive disorders (including Alzheimer's disease and dementia), coagulation disorders, cardiometabolic disorders, infectious illnesses and several respiratory conditions.

There was an increased risk of gastrointestinal disorders, hypotension, syncope, arthritic disorders, nephrolithiasis, interstitial nephritis and drug-induced pancreatitis associated with GLP-1RA use compared to usual care. The results provide insights into the benefits and risks of GLP-1RAs and may be useful for informing clinical care and guiding research agendas.

Source: https://www.nature.com/articles/s41591-024-03412-w

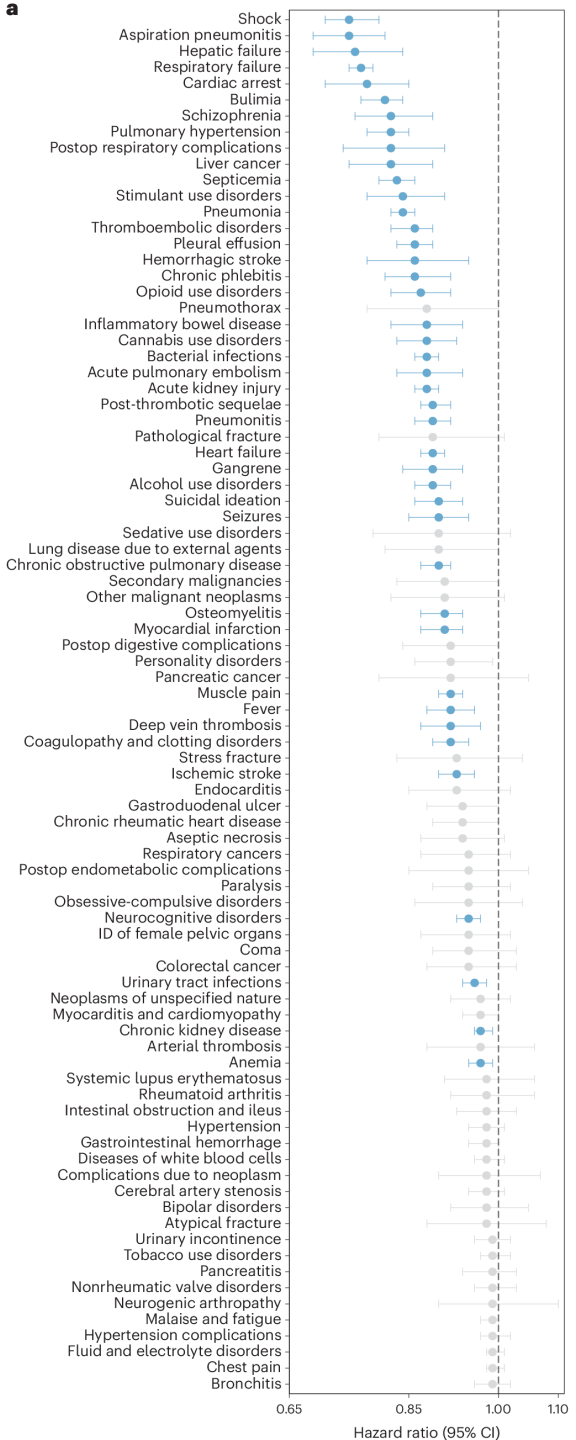
Pro's and Con's of GLP-1's

Xie Y, Choi T, Al-Aly Z. Mapping the effectiveness and risks of GLP-1 receptor agonists. Nat Med. 2025 Jan 20.

Fig. 5: Forest plots for systematic evaluation of the effectiveness and risks of incident GLP-1RA use compared to usual care.

a,b, Comparisons between the GLP-1RA use group (n = 215,970) and the usual care group who continued use of non-GLP-1RA antihyperglycemics (n = 1,203,097). a, Outcomes with HR <1 ranked by HR from low to high. b, Outcomes with HR ≥1 ranked by HR from high to low. Dots, HRs; 95% CIs of the HRs. Outcomes with statistically significant associations are shown in blue (reduced risk) or red (increased risk). P values were based on two-sided Wald chi-squared tests. Benjamini–Hochberg correction for multiple tests was applied. ID, inflammatory disease; Postop, postprocedural; schizophrenia, schizophrenia and other psychotic disorders; suicidal ideation, suicidal ideation, attempt or intentional self-harm.

Source: https://www.nature.com/articles/s41591-024-03412-w



Free Fatty Acid Receptor 4 Modulates Dietary Sugar Preference via the Gut Microbiota

Fayt et.al., *Nature Microbiology*, Jan 24, 2025 (excerpt)

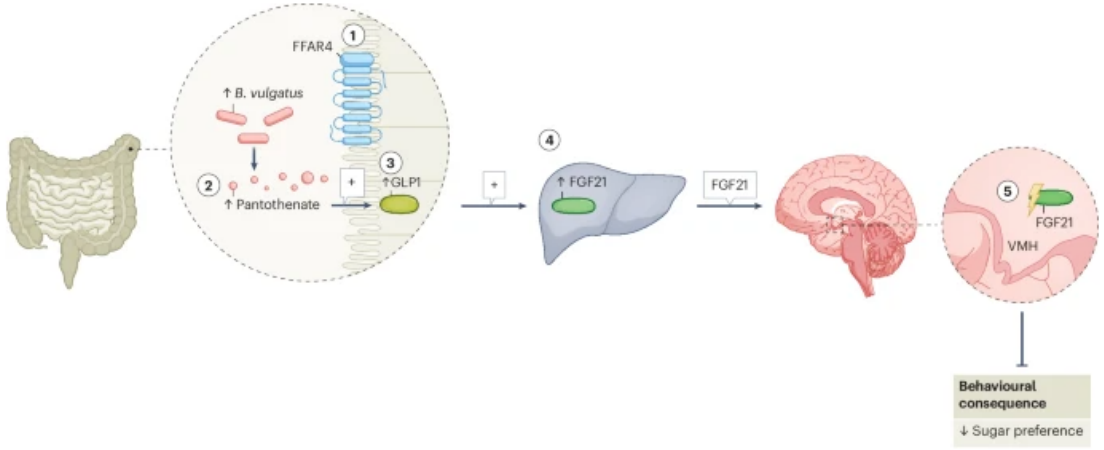
A *Bacteroides vulgatus* metabolite, pantothenate, induces secretion of the hormones GLP1 in the gut and FGF21 in the liver, which act on the hypothalamus to reduce sugar intake.

In this issue of *Nature Microbiology*, Zhang et al. report a mechanism underlying the interaction of gut microbiota with brain activity to regulate sugar preference. Their results indicate an overlooked interplay between the gut microorganisms and hormone activity in the liver that modulates the brain. The strategic localization of the liver closely connected to the gut, and previous demonstration of the role of a specific liver-derived hormone in the regulation of sugar intake5, allowed them to extend the gut–brain axis into a gut–liver–brain axis involved in the regulation of sugar preferences.

Free fatty acid receptors (FFARs) are at the interface of interaction between constituents of the diet and the host metabolism. FFAR4, also known as GPR120, is a human long-chain fatty acid receptor classically associated with lipid metabolism, but its activation is also linked to sugar metabolism as it stimulates the secretion of glucagon-like peptide 1 (GLP1), which in turn increases circulating insulin.

Zhang et al. reported the downregulation of colonic and blood Ffar4 expression in different mouse models of diabetes, including genetic (NOD mice) and chemically (administration of streptozotocin) induced type 1 or type 2 diabetes models. At the same time, they also found reduced FFAR4 expression in human peripheral blood leukocytes derived from patients with diabetes.

Fig. 1: Pantothenate is a key metabolite of *B. vulgatus* that modulates sugar preference through the gut–liver–brain axis.



Intestinal FFAR4 receptor regulates the abundance of *B. vulgatus*, which produces pantothenate (1, 2). *B. vulgatus*, via pantothenate, positively regulates the secretion of GLP1 by gut endocrine cells (3). This increase in GLP1 secretion activates the secretion of hepatic hormone FGF21 (4). FGF21 acts directly in the ventromedial hypothalamus (VMH) to regulate sugar intake (5).

Source: https://www.nature.com/articles/s41564-024-01917-1

BCL6 Coordinates Muscle Mass Homeostasis with Nutritional States

Wang et.al., *PNAS*, Jan 22, 2025 (excerpt)

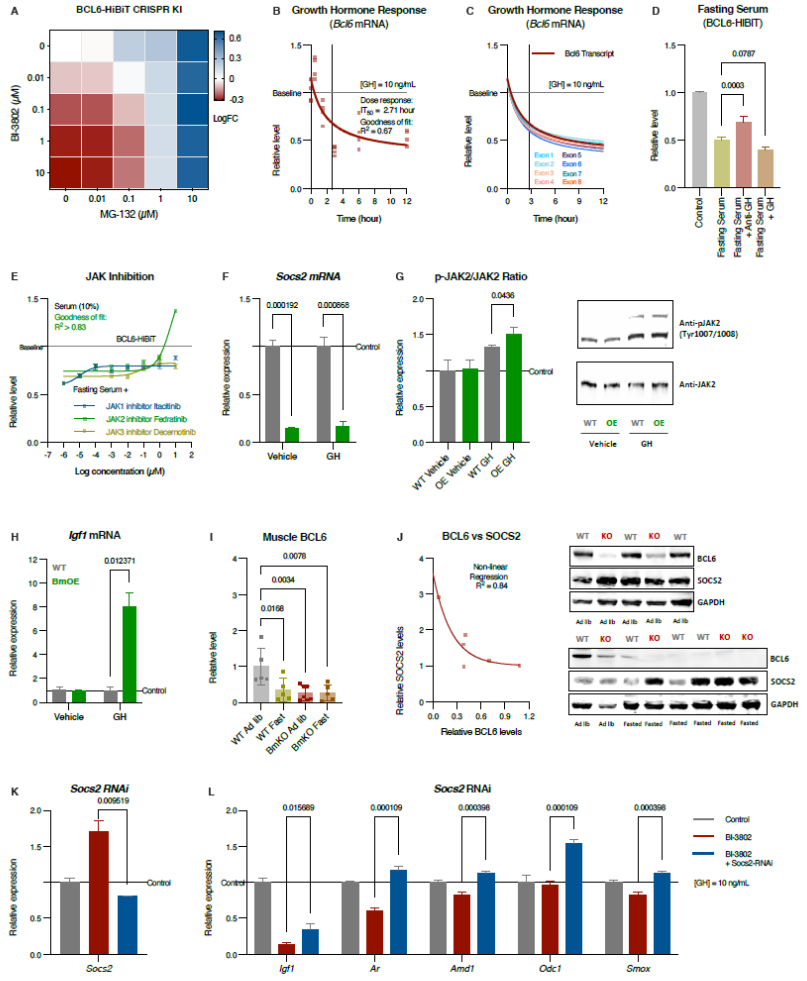
Nutritional status is a determining factor for growth during development and homeostatic maintenance in adulthood. In the context of muscle, growth hormone (GH) coordinates growth with nutritional status; however, the detailed mechanisms remain to be fully elucidated. Here, we show that the transcriptional repressor B cell lymphoma 6 (BCL6) maintains muscle mass by sustaining GH action.

Muscle-specific genetic deletion of BCL6 at either perinatal or adult stages profoundly reduces muscle mass and compromises muscle strength.

Conversely, muscle-directed viral overexpression of BCL6 significantly reverses the loss of muscle mass and strength. Mechanistically, we show that BCL6 transcriptionally represses the suppressor of cytokine signaling 2 to sustain the anabolic actions of GH in muscle.

Additionally, we find that GH itself transcriptionally inhibits BCL6 through the Janus kinase and signal transducer and activator of transcription 5 (JAK/STAT5) pathway. Supporting the physiologic relevance of this feedback regulation, we show the coordinated suppression of muscle Bcl6 expression with the induction of GH in the fasted state.

These findings reveal the complexity of the feedback controls modulating GH signaling and identify BCL6 as a key homeostatic regulator coordinating muscle mass with nutrient availability. Moreover, these studies open avenues for targeted therapeutic strategies to combat muscle-wasting conditions.



Supplementary Figure 5. BCL6 mediates growth hormone action in muscle via JAK/STAT signaling. A. Relative BCL6-HiBiT reporter signal in response to proteasome-dependent protein accumulation by MG-132 and targeted protein degradation by BI-3802 in differentiated C2C12 myoblasts compared to vehicle treated controls (n = 4 each). Color scale represents log transformed fold change of protein levels as indicated. **B.** Expression of ***Bcl6*** in differentiated C2C12 myoblasts in response to 10 ng/mL GH treatment for indicated durations assessed by real-time PCR using primers set specific to exon junctions between exon 3 and exon 4 of ***Bcl6*** mRNA (n = 4 each, R^2 value as indicated to quantify goodness-of-fit to non-linear regression). **C.** Expression of ***Bcl6*** in differentiated C2C12 myoblasts in response to 10 ng/mL GH treatment for indicated durations assessed by real-time PCR using primers set specific to each exon of ***Bcl6*** mRNA (n = 4 each). **D.** Relative BCl6-HiBIT reporter signal in response to overnight treatment of anti-GH neutralizing antibody (2 ng/mL,

Source: https://www.pnas.org/doi/10.1073/pnas.2408896122

Disclosure

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