



Biopharmaceutical Sector

Weekly Update – March 4, 2024

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STIFEL | Healthcare

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Stifel Active in Biopharma Sector Advisory and Financing Transactions

Today, biopharma companies find themselves in a fast-moving environment characterized by great opportunity. This environment calls for getting the best possible advisor by your side. Stifel's Global Healthcare Group brings senior level attention and intense focus on execution to its clients. The group has been active in 2024's dynamic financing and deal environment. Since the formation of the Global Healthcare Group in 2010, Stifel's team has helped to raise over \$115 billion in over 600 transactions and has advised on over 150 strategic transactions.

<p>\$550,000,000</p> <p>VIKING THERAPEUTICS</p> <p>Follow-On Offering</p> <p>Joint Bookrunner</p> <p>February 2024</p>	<p>\$160,125,000</p> <p>KalVista Pharmaceuticals</p> <p>Follow-On Offering</p> <p>Joint Bookrunner</p> <p>February 2024</p>	<p>UPSHER-SMITH</p> <p>Has agreed to be acquired by</p> <p>Bora Pharmaceuticals</p> <p>Advisor to Seller</p> <p>Pending</p>	<p>€50,500,000</p> <p>Sensorion</p> <p>PIPE</p> <p>Lead Placement Agent</p> <p>February 2024</p>	<p>\$147,900,000</p> <p>ALTO NEUROSCIENCE</p> <p>Initial Public Offering</p> <p>Joint Bookrunner</p> <p>February 2024</p>	<p>\$230,000,000</p> <p>DIANTHUS THERAPEUTICS</p> <p>PIPE</p> <p>Joint Placement Agent</p> <p>January 2024</p>	<p>\$345,144,000</p> <p>Dyne THERAPEUTICS</p> <p>Follow-On Offering</p> <p>Joint Bookrunner</p> <p>January 2024</p>
<p>\$175,000,000</p> <p>PROPELLA</p> <p>Has been acquired by</p> <p>astellas</p> <p>Advisor to Seller</p> <p>December 2023</p>	<p>\$230,000,000</p> <p>Syndax</p> <p>Confidentially Marketed Follow-on Offering</p> <p>Joint Bookrunner</p> <p>December 2023</p>	<p>\$180,000,000</p> <p>SPYRE THERAPEUTICS</p> <p>PIPE</p> <p>Co-Lead Placement Agent</p> <p>December 2023</p>	<p>\$100,000,000</p> <p>VANDA PHARMACEUTICALS INC.</p> <p>Has acquired U.S. and Canada rights to</p> <p>Ponvory (ponesimod) from</p> <p>Johnson & Johnson</p> <p>Advisor to Buyer</p> <p>December 2023</p>	<p>\$245,000,000+</p> <p>TEIJIN</p> <p>In-Licensing of the Japan Rights to Three Rare Endocrinology Drugs From</p> <p>ascendis pharma</p> <p>Advisor to Licensee</p> <p>November 2023</p>	<p>\$300,000,000</p> <p>XENON</p> <p>Confidentially Marketed Follow-on Offering</p> <p>Joint Bookrunner</p> <p>November 2023</p>	<p>\$185,000,000</p> <p>VIRIDIAN</p> <p>PIPE</p> <p>Co-Lead Placement Agent</p> <p>November 2023</p>

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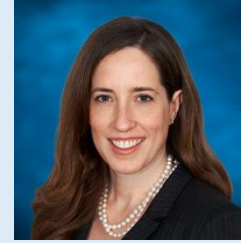
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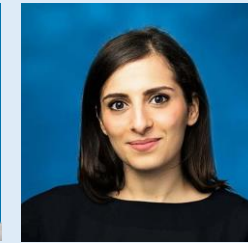
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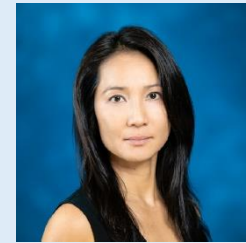
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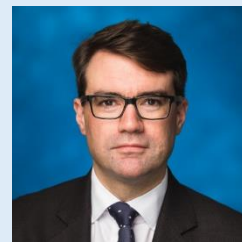
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Accessing Past Issues

If you wish to be added to mailing list for this publication, please notify Natasha Yeung (yeungn@stifel.com). Recent issues in case you missed and want to read:

[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 15, 2024](#) (FDA Commissioner Priorities)
[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](#) (Changing Pharma Strategy)
[September 11, 2023](#) (US Health System)
[September 5, 2023](#) (FTC, IRA, Depression)
[August 21, 2023](#) (Covid, China)
[August 7, 2023](#) (Employment, Summer 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)



Join Us at Biotech Hangout This Friday



Biotech Hangout held its latest event on March 1, 2024.

The next event will be on March 8, 2024.

March 1, 2024. Session: <https://twitter.com/i/spaces/1kvKpvZaddPJE>

Please join us.

To Learn More

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



The week of March 18 will feature over 5,000 biopharma professionals in Barcelona for Bio-Europe. We hope to meet you there.

To meet with Stifel @ Bio-Europe

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Macro Update



A Key U.S. Inflation Measure Moderated in January

Jeanna Smialek, *New York Times*, Feb 29, 2024 (excerpt)

A measure of inflation closely watched by the Federal Reserve continued to cool on an annual basis in January, the latest sign that price increases are coming back under control even as the economy continues to chug along.

The Personal Consumption Expenditures price index climbed 2.4 percent last month compared with a year earlier. That was in line with what economists had forecast and down from the 2.6 percent December reading.

After stripping out food and fuel costs, which can move around from month to month, a “core” price index climbed 2.8 percent from January 2023. That followed a 2.9 percent December reading.

Still, the closely watched core measure climbed more quickly on a monthly basis: It picked up by 0.4 percent, quicker than a 0.1 percent December pace. That was the fastest pace of increase since January 2023, and it came as service prices continued to climb at a rapid clip.



European Inflation Has Now Fallen From its 10.6% Peak After the Russian Invasion of Ukraine to Just 2.6%

David McHugh, *Fortune*, March 1, 2024 (excerpt)

The inflation that has ravaged the European economy eased again in February, falling to 2.6% as high interest rates, moderating oil and gas prices, and sluggish growth held back price increases in stores.

February's figure for the 20 countries that use the euro currency compares to 2.8% from January, the European Union's statistical agency Eurostat said Friday.

Inflation is now far below its peak of 10.6% in October 2022, which it hit after Russia cut off most supplies of natural gas and sent energy prices through the roof.

But the return of inflation to 2%, the goal set by the European Central Bank, is taking time. Food inflation eased to 4% from 5.6%, offering some relief to people on modest incomes who spend more of their pay on necessities than the well-off. Another factor was energy prices, which fell by 3.7%.

One key sign that inflation is losing steam was so-called core inflation, which excludes swings in food and fuel prices. The figure, closely watched by the European Central Bank as a measure of underlying inflation pressure in the economy, came in at 3.1%, down from 3.3% and the lowest since March 2022.

The drop in the inflation rate brings the European Central Bank closer to achieving its goal of 2% inflation, the rate considered best for the economy. The central bank for the eurozone swiftly raised interest rates to squeeze inflation out of the economy, taking its key rate to a record high of 4% in September.

Worries about growth and moderate inflation have shifted the focus to when the ECB might start cutting rates. The bank's rate-setting governing council meets Thursday but is not expected to change rates yet.

Source: <https://fortune.com/europe/2024/03/01/how-much-european-eu-inflation-russia-gas-energy/>



European Central Bank at Dusk

A Frothy Market Misses Vital Bubble Ingredients

James MacKintosh, *WSJ*, March 2, 2024 (excerpt)

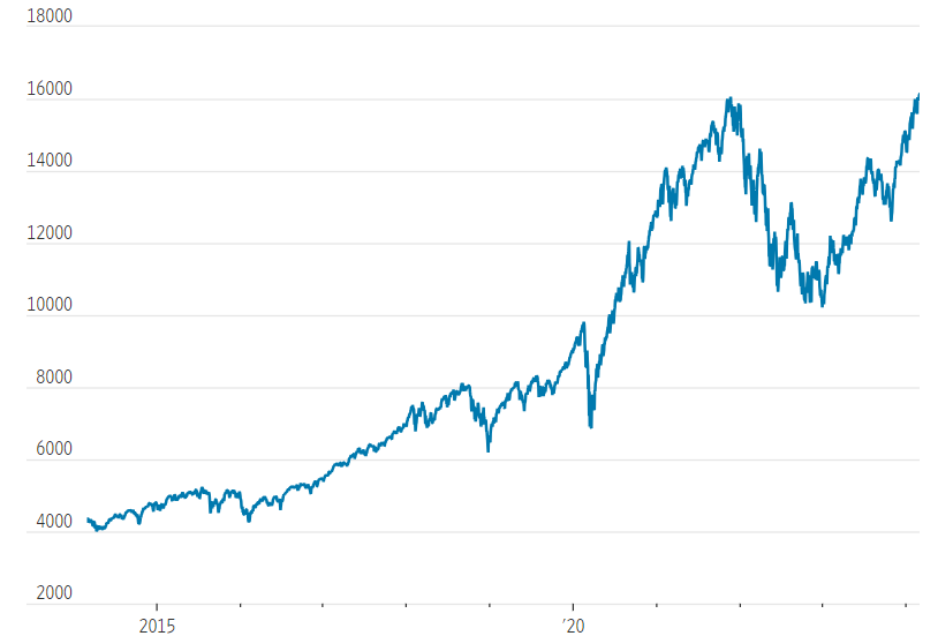
But is it a bubble? There's no single definition of a market bubble, but for me it has to involve a speculative mania. It's when buyers en masse cross the line from assessing future profit potential to buying something they know is unreasonably expensive—or just don't care about the price at all—because they think a greater fool will buy it off them at an even higher price.

This seems to be missing. Sure, there are some signs of the madness of crowds: The price of SoundHound AI more than tripled in February, mainly because investors were reminded that Nvidia, maker of the chips in demand for artificial intelligence processing, owned a tiny stake. And sure, minuscule stocks are doing phenomenally well, as they often do in a bubble, with the Russell Microcap index up almost 30% in four months, one of its best performances on record.

But compared with the postpandemic silliness in meme stocks, profitless tech, SPACs and crypto, or the dot-com bubble of the late 1990s, this pales into insignificance. Measures of investor sentiment show they are positive, but nothing like past bubbles. One example: The weekly survey by the American Association of Individual Investors shows 47% declare themselves bullish, low compared with the 75% declaring themselves bullish in 2000, or even the 60% in early 2018.

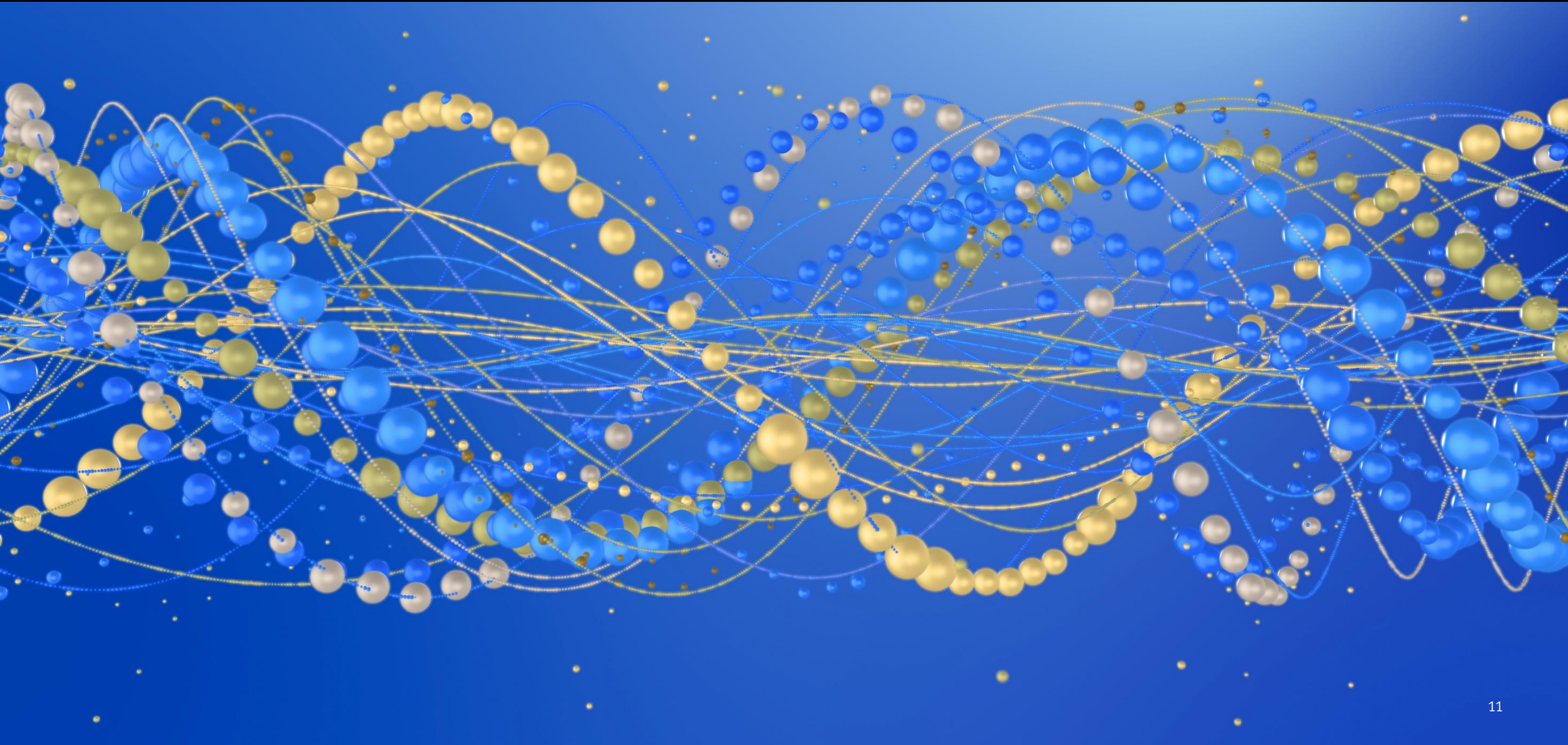
Money isn't flooding into the market, leverage isn't being used to boost investments, and so companies aren't forming especially to tap a gusher of speculative cash. Stocks might be overvalued, investors might be wearing rose-tinted spectacles, but that doesn't make it a bubble. Yet.

Nasdaq Composite hits new high



Source: FactSet

Biopharma Market Update



Biotech Market Booms Last Week

We saw the biotech go from “warming up” to “volcanic” in about two days last week.

In total over 160 biotechs in the U.S. alone gained more than 10% of their value last week (that’s 42% of the market). Over 20% of the market was up 20% or more last week.

Basically, the biotech market went nuts last Tuesday with the XBI flying past the 100-point benchmark value without a look back.

Crazy.

The data from Viking and Janux were really strong and helped to propel the XBI.

But this rally wasn’t about those companies necessarily. Their jump accounted for about a third of the biotech market’s rise last week.

The market rally also was not driven by short covering. Even little shorted names took off last week.

The story is more nuanced. Long funds are clearly moving back into the market. This was evident in the large secondaries that came into the market and the reference to “global asset managers” in accompanying press releases.

These type of “melt up” weeks are relatively rare in our industry, but we have seen them before. They occur when sentiment shifts suddenly – the negativists capitulate and realize that they are misallocated. Those who read our weekly updates carefully will recall that last week we noted that a majority of investors we spoke to were cautious but that we disagreed with them. Those cautious investors, on average, got less cautious last week as the collective will to own biotech got stronger.

Last Week Saw the Biotech Market Erupt Like a Once Dormant Volcano



Bio Boom (continued)

We had the opportunity to meet with many biotech CEO's last week as we were on a banker "road trip" talking to issuers.

Virtually every public CEO recounted the many "reverse inquiries" that were coming in from investors, eager to pick up their shares. Mostly hedge funds making the call. Groups like Avidity, Deep Track and EcoR1 are aggressively calling biotechs that they like and offering to put money to work.

Investor conversations were more positive, and we heard frequent queries as to where the ball is going next. Hot themes in the last six months have been CAR-t B-cell, I&I, late-stage neuro, radiopharma, obesity and CV.

Our data shared this week point to two strong emerging themes: (1) AI is heating up and (2) obesity is going from "red hot" to "white hot" after the Viking data last week. Obesity names like Viking and Skye have been vertical lately. On the AI side, both Absci and Recursion are up more than 100% YTD.

We'd also note that this is a "fill in" rally. That is, investors have been diversifying beyond hot or "high conviction" areas with an eye to the rest of the market. In the last five weeks for example, the average virology stock is up 138%; the average ophtha stock is up 110%; the average innate immunology stock is up 100%; and the average rare disease biotech is up 88%. ADC stories also doing better. You get the idea. Investors are filling in parts of their portfolio where they lack exposure.



Bio Boom (continued)

We at Stifel expressed the view that the market was headed up from the [depths of the market](#) last November. Before Thanksgiving we [said](#) that biotech would head up and gave seven reasons why, including that biotech would change civilization.

We said at the [start of the year](#) that the XBI would cross 100 but not get near 150.

And [last week](#) we said that the XBI will cross 120.

So, ok, now that the XBI has crossed 100, what's next?

Is it time for the market to take a breather and head south?

No. The fundamentals of this rally are just beginning to kick in.

The macro and innovation headwinds are in place and are still picking up.

There will be dozens more companies that will post 10-K's in the weeks ahead which will allow them to bring more money in via secondaries. Further, generalists are just starting to wake up and buy biotech. It won't be up every week, of course (as it has largely been for months) but this market is likely to continue to rally strongly for some time to come.

We think that last week's market boomlet is just a small foreshadowing of what lays ahead for biotech.



Biotech Stocks Are on a Tear. They Could Keep Climbing.

Josh Nathan-Kazis, *Barron's*, Feb. 28, 2024 (excerpt)

It's comeback time in biotech.

Stocks in the sector accelerated a four-month run on Tuesday as the closely watched SPDR S&P Biotech exchange-traded fund jumped 5.7%. It closed above \$100 a share for the first time in just over two years, though it has a long way to go to regain its pandemic-era highs.

The ETF, and the sector at large, are still battling back from a multiyear slump that started in early 2021. The fund, with the stock ticker XBI, fell more than 60% between early February of that year and late October 2023.

Months ago, the incipient biotech rally seemed largely based on expectations that 2024 would bring lower interest rates, and it came alongside surges in other small-cap indexes. **But in recent weeks, much of the strength appears to have been sector-specific. Investors are once again turning toward biotech, intrigued by promising medical-trial data, and anticipation that big pharmaceutical companies will snap up smaller players they think could improve their pipelines of new drugs.**

“Peak pandemic notwithstanding, we are in the midst of the most pronounced Biotech rally in over five years,” Mizuho healthcare equity strategist Jared Holz wrote in a Tuesday email to investors. “As long as market breadth allows for improved returns across small-cap equities, Biotech may move even higher especially if the M&A backdrop remains robust.”

There have been other positive signs. Investor interest in biotech initial public offerings has been nonexistent for years, after a glut of deals during the pandemic soured the market. But early 2024 has seen a handful of biotech IPOs, and the first, an offering by CG Oncology in late January, jumped 96% on the first day of trading.

Public biotechs, meanwhile, have been able to raise money, a key condition for success among companies that must spend years and billions of dollars in search of a marketable product. Companies have favored so-called PIPE deals, or private investments in public equity, which allow private investors to buy large tranches of shares without the regulatory trouble of a secondary offering. Most recently, on Tuesday, Denali Therapeutics announced a PIPE deal it expects to raise \$500 million.

The debate now among investors is whether the biotech run is played out. In a note Sunday, before Tuesday's run-up, Stifel managing director Tim Opler said that many fund managers are worrying that the XBI has “come too far too quickly.”

“A minority feel that the XBI has a long way to go still – perhaps to 120 or above this year,” Opler wrote. “We think near-term fund flows from generalists, retail and large LP's is going to work in favor of the biopharma sector this year.”

The XBI Closed at 101.5 Last Friday (Mar 1), Up 7.2% for the Week

The XBI is up 13.7% since the year began. The biotech market took off last week buoyed by a positive PPE inflation number and some important positive catalysts.

Biotech Stocks Up Big Last Week

Return: Feb 24 to Mar 1, 2024

Nasdaq Biotech Index: +0.5%

Arca XBI ETF: +7.2%

Stifel Global Biotech EV (adjusted): +10.3%*

S&P 500: 0.9%

Return: Jan 1 to Mar 1, 2024

Nasdaq Biotech Index: +3.3%

Arca XBI ETF: +13.7%

Stifel Global Biotech EV (adjusted): +32%*

S&P 500: +7.7%

VIX Down

Jan 20, 2023: 19.9%

May 26, 2023: 18.0%

July 21, 2023: 13.6%

Sep 29, 2023: 17.3%

Oct 27, 2023: 21.2%

Dec 29, 2023: 12.45%

Jan 26, 2024: 13.26%

Feb 23, 2024: 13.5%

Mar 1, 2024: 13.1%

10-Year Treasury Yield Down

Jan 20, 2023: 3.48%

May 26, 2023: 3.8%

July 21, 2023: 3.84%

Sep 29, 2023: 4.59%

Oct 27, 2023: 4.86%

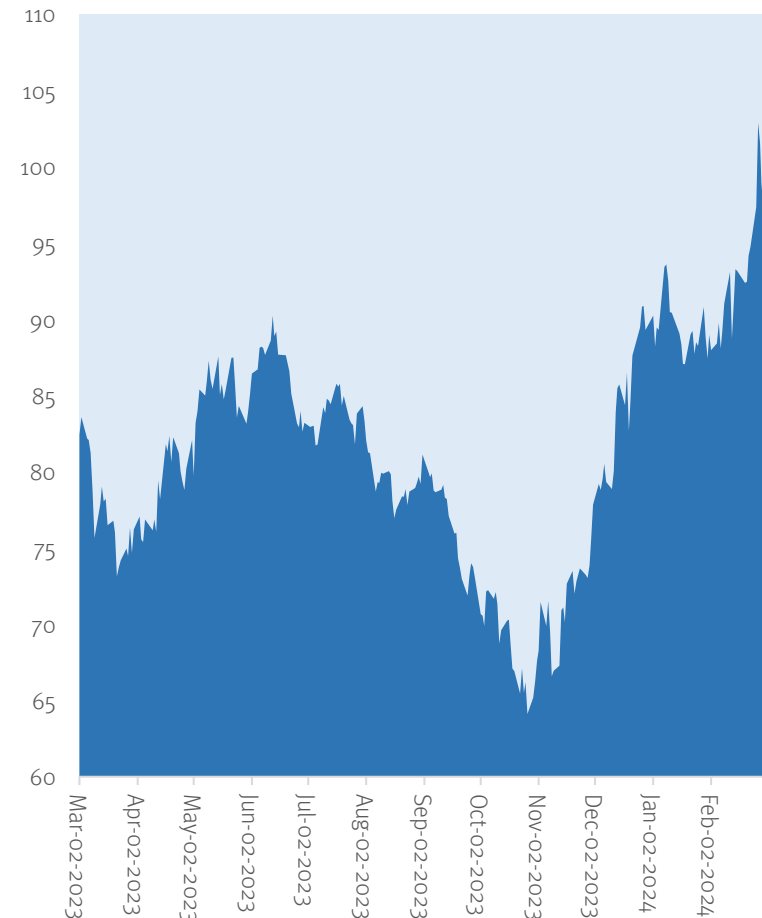
Dec 29, 2023: 3.88%

Jan 26, 2024: 4.15%

Feb 23, 2024: 4.26%

Mar 1, 2024: 4.19%

XBI, March 2, 2023 to March 1, 2024



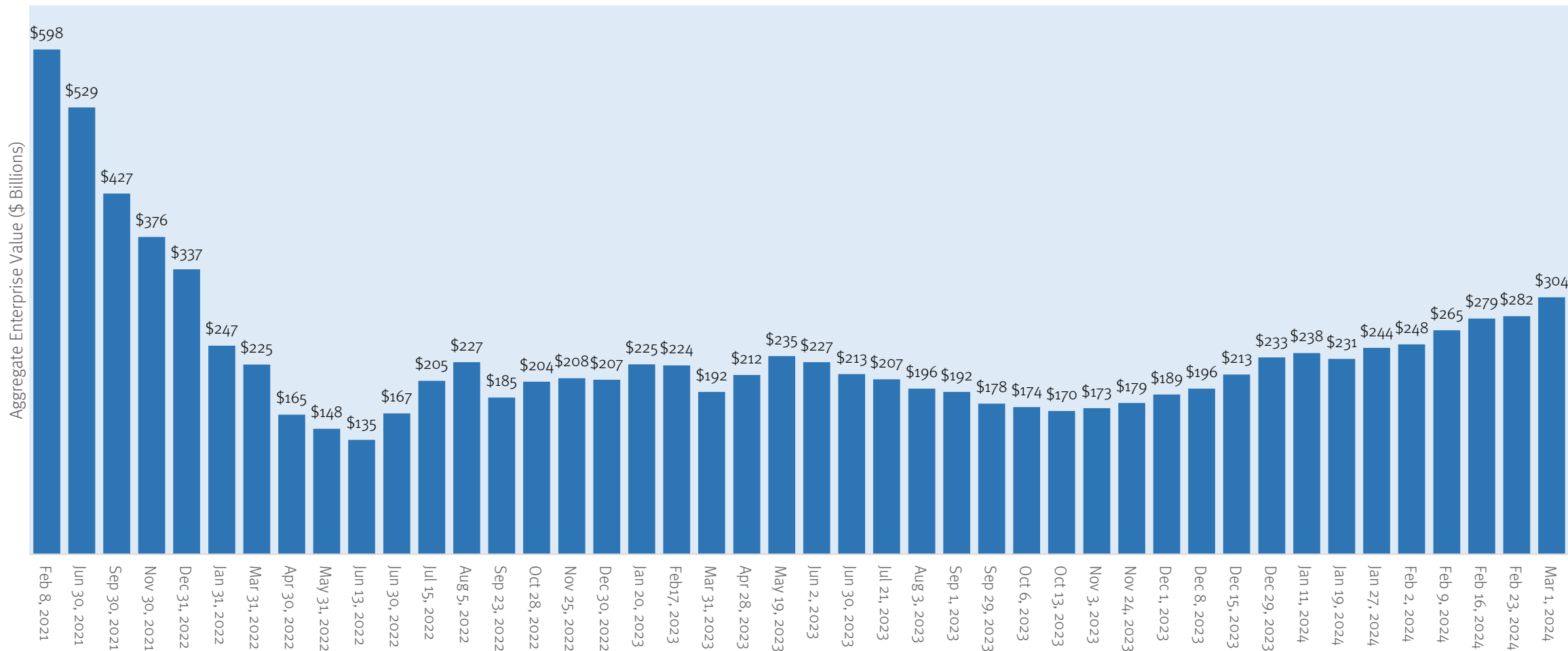
After hitting 64 on Oct 27th last year, the XBI has jumped 58.4%.

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

Total Global Biotech Sector Value Rose 10.3% Last Week

The total enterprise value of the global biotech sector is up 32% for the year to date on an addition/exit corrected basis. The rally that started last November continued in force last week. The biotech market has been up 15 of the last 17 weeks.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Mar 1, 2024 (\$ Billions)

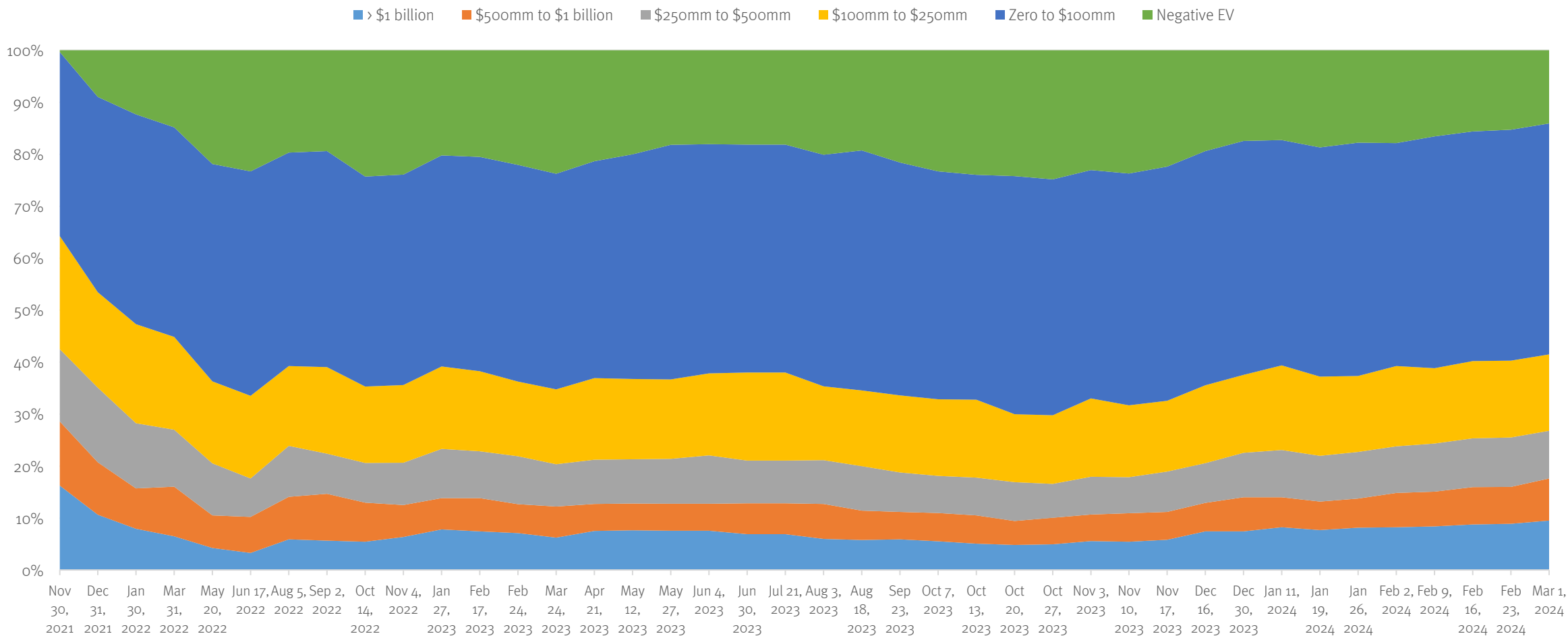


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Global Biotech Neighborhood Analysis

Last week saw continued growth in the fraction of the global biotech population with an EV over \$100 million. The population of larger biotechs (\$500mm and up EV) is also growing steadily.

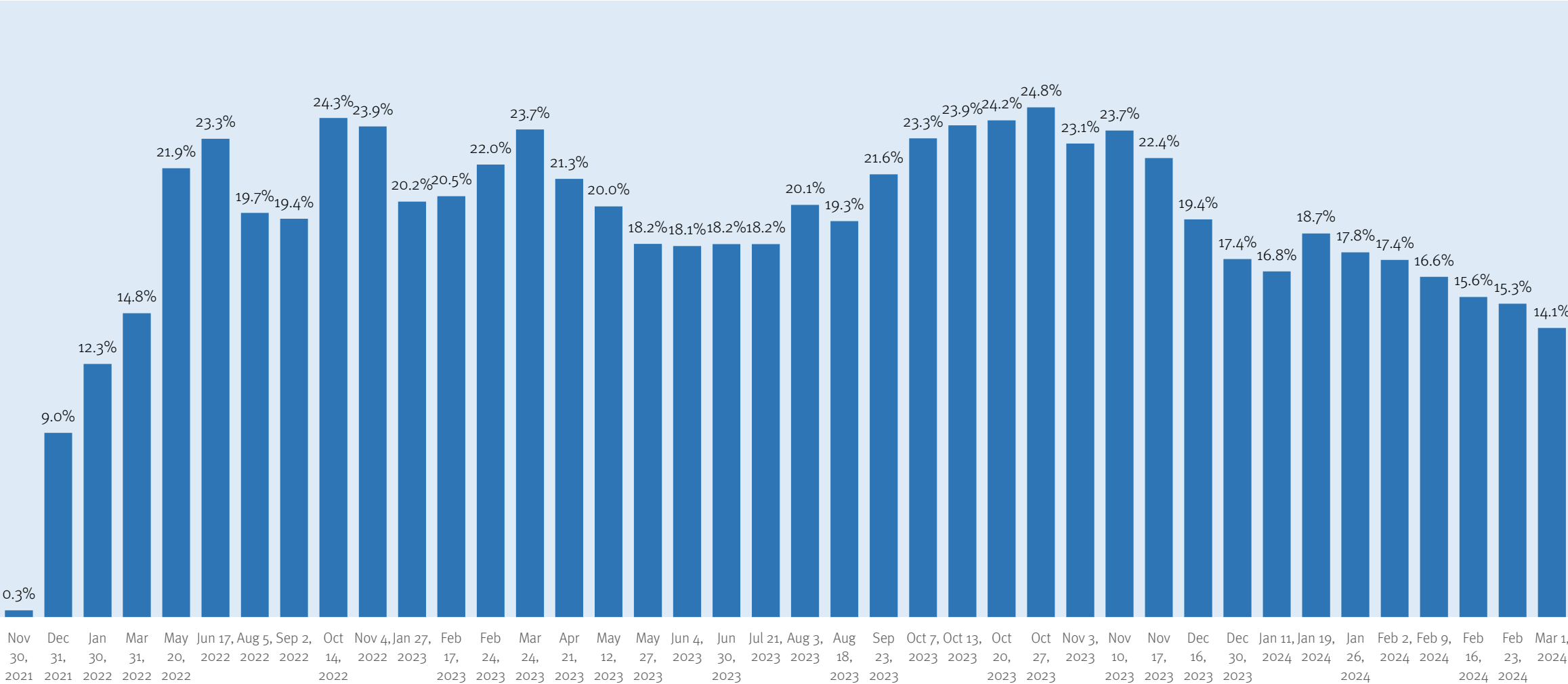
Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Mar 1, 2024



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

Continued Shrinkage in Negative EV Global Biotech Population

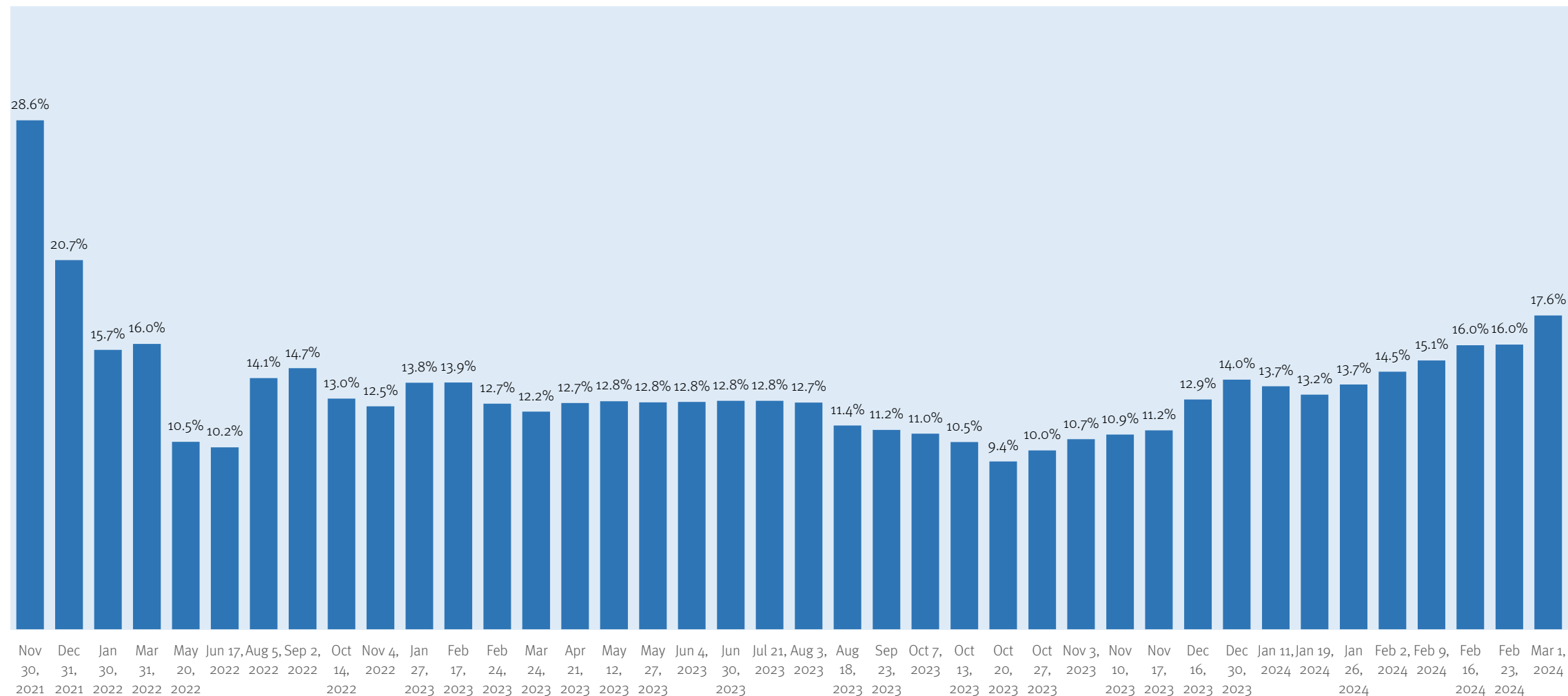
Percent of Biotechs with Negative Enterprise Value, Nov 30, 2021 to Mar 1, 2024



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

Growth in Richer Global Biotech Population

Percent of Biotechs with an Enterprise Value of \$500mm or More, Nov 30, 2021 to Mar 1, 2024

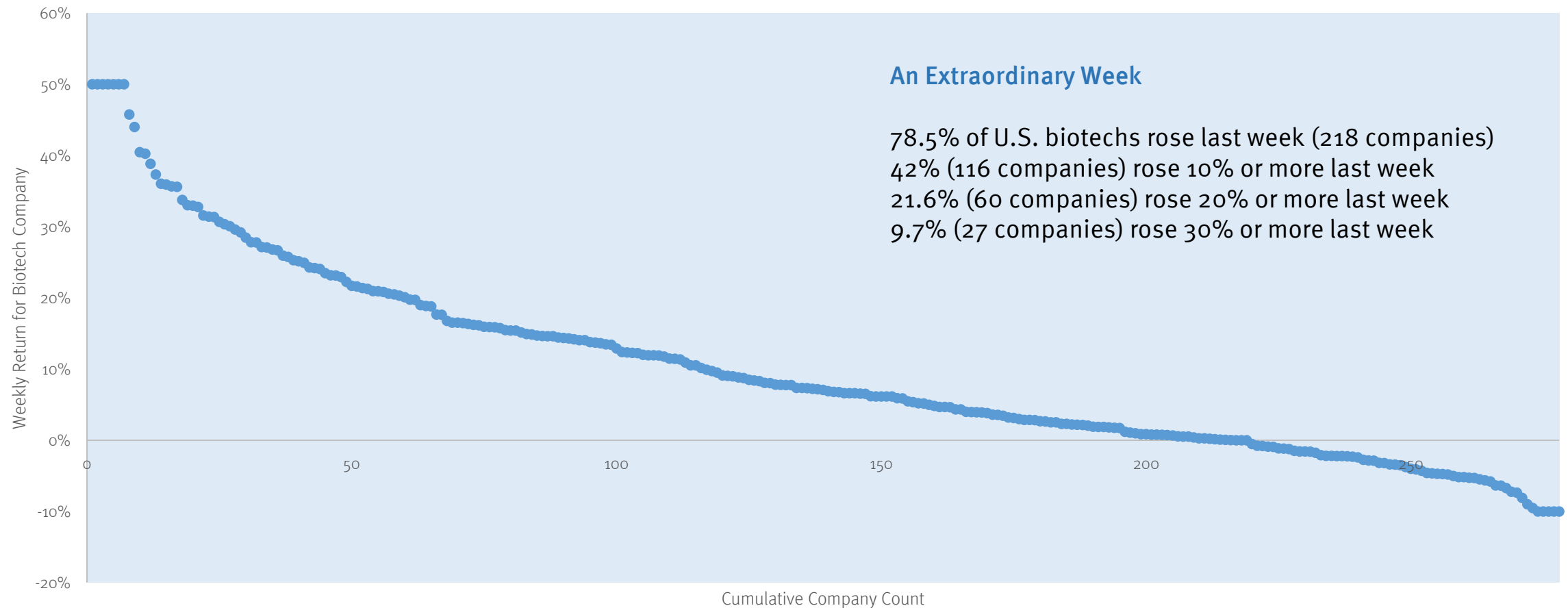


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

42% of the U.S. Biotech Market Rose At Least 10% or More Last Week

Distribution of U.S. Biotech Returns, Feb 26 to Mar 1, 2024

Market Cap of \$50mm or More on Feb 26, N=278



Source: CapitalIQ. Companies with returns over 50% or below -10% had returns truncated in this chart for visual effect.

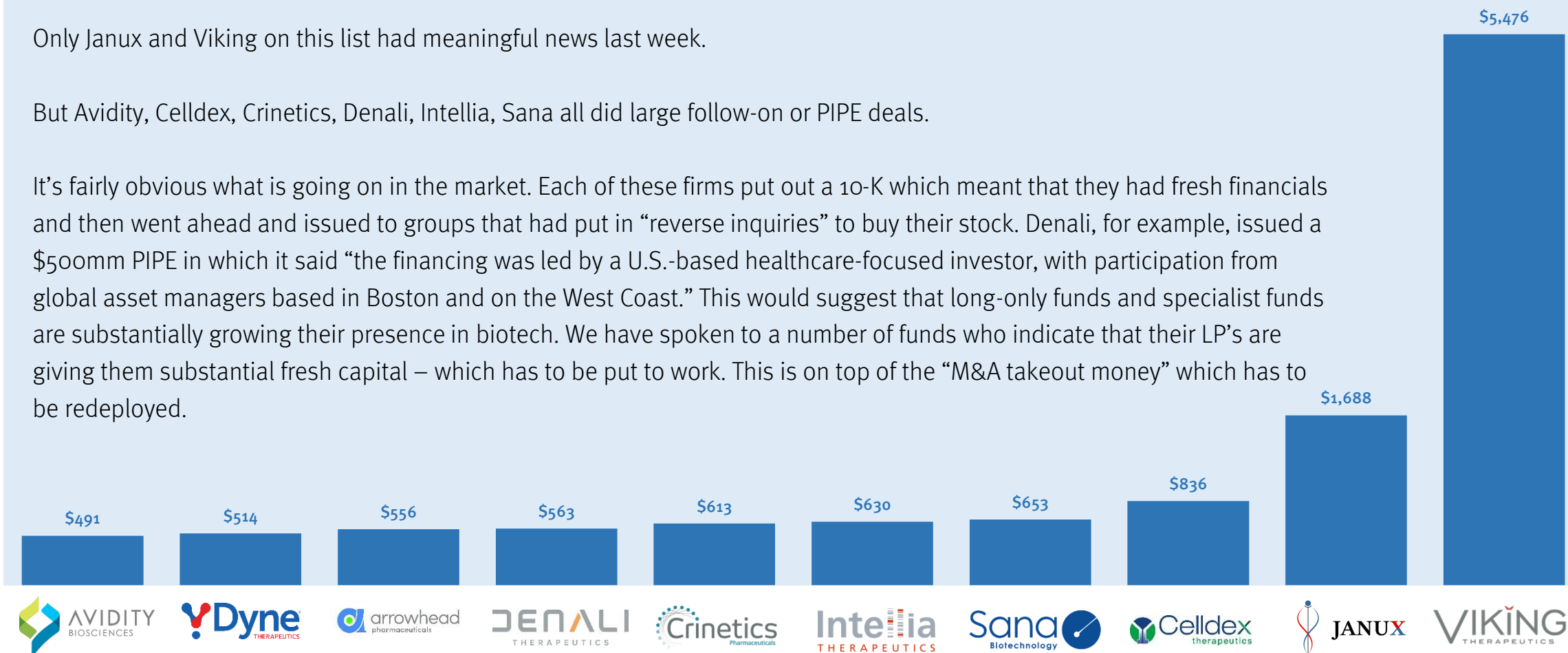
Top 10 Gainers in Biotech Picked up \$12 Billion Last Week

Top Changes in Market Cap Last Week (\$ Millions, Feb 26 to Mar 1, 2024)

Only Janux and Viking on this list had meaningful news last week.

But Avidity, Celldex, Crinetics, Denali, Intellia, Sana all did large follow-on or PIPE deals.

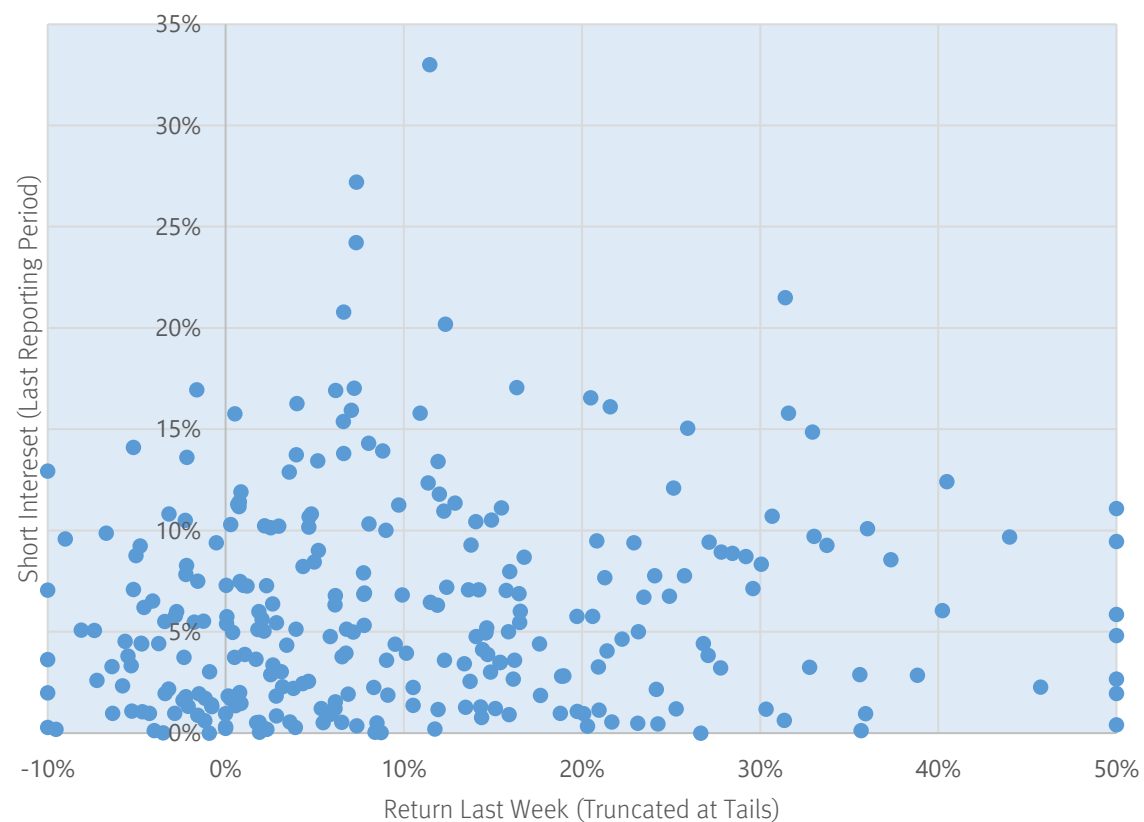
It's fairly obvious what is going on in the market. Each of these firms put out a 10-K which meant that they had fresh financials and then went ahead and issued to groups that had put in "reverse inquiries" to buy their stock. Denali, for example, issued a \$500mm PIPE in which it said "the financing was led by a U.S.-based healthcare-focused investor, with participation from global asset managers based in Boston and on the West Coast." This would suggest that long-only funds and specialist funds are substantially growing their presence in biotech. We have spoken to a number of funds who indicate that their LP's are giving them substantial fresh capital – which has to be put to work. This is on top of the "M&A takeout money" which has to be redeployed.



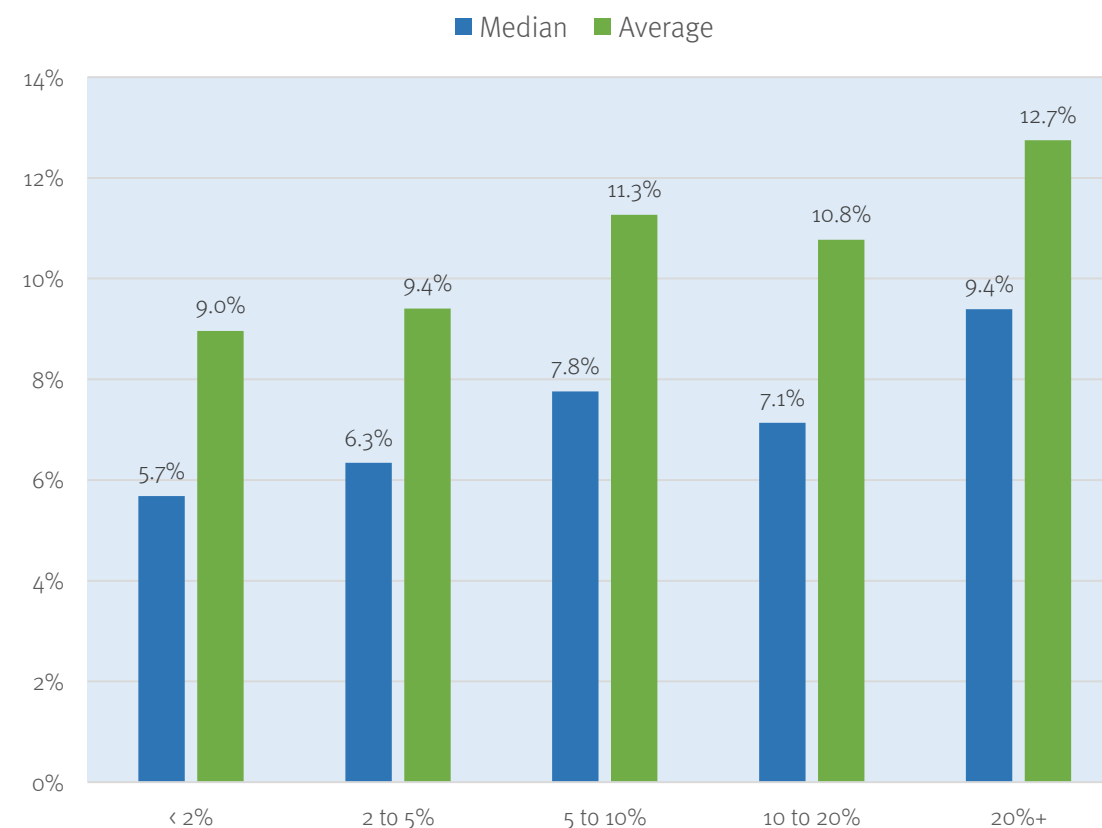
Was Last Week's Rally Caused by Short Covering?

Last week's rally was mainly *not* a short covering rally. Despite widespread comments from traders and various observers on Twitter, the average return of a little shorted stock was similar to that of a heavily shorted stock. There was, of course, some slight relationship between return and short interest levels. While not perceptible in the scatterplot at left, the Pearson correlation between baseline short interest and return last week was 0.07 (very slight positive correlation).

Relationship Between Short Interest and Return Last Week



Average Return Last Week by Baseline Short Interest

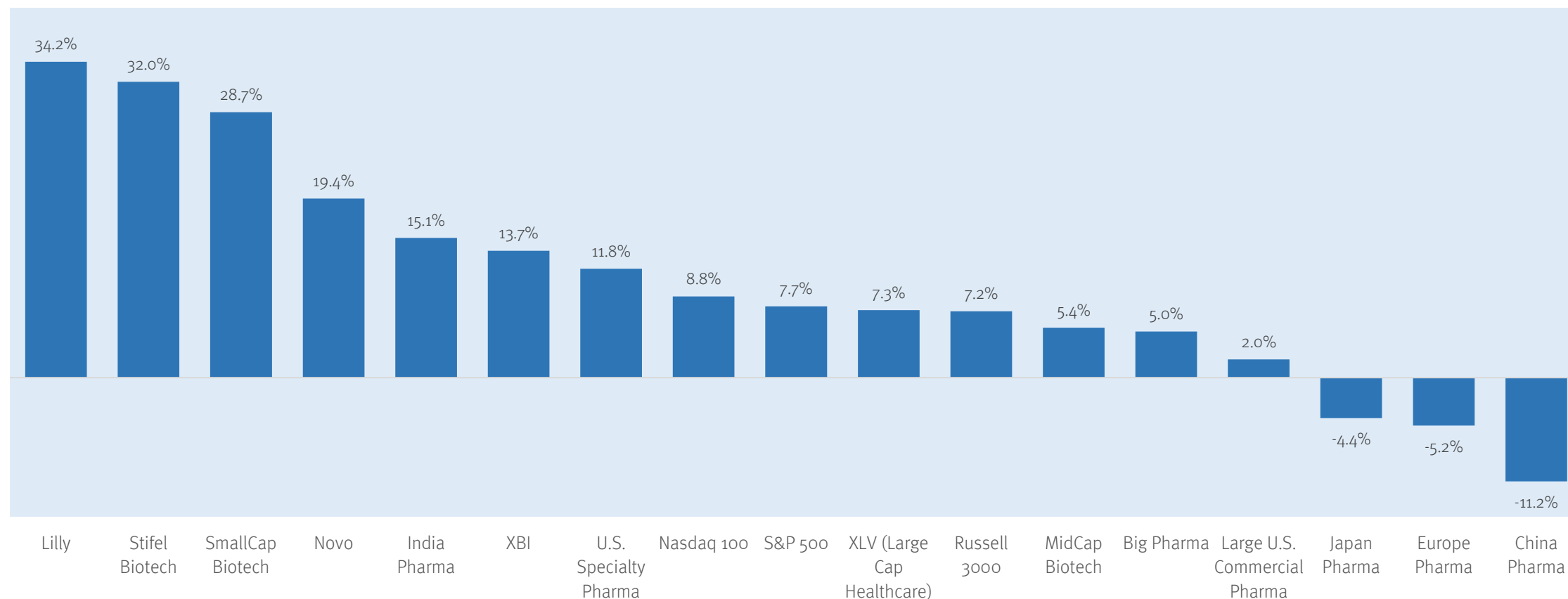


Source: CapitalIQ. Companies with returns over 50% or below -10% had returns truncated for visual effect. This analysis includes 278 U.S. biotechs with baseline market caps of \$50mm or more.

Where Has the Pharma Market Done Best?

Japan, Europe and China pharma have underperformed in 2024. Big pharma is up slightly but this is driven entirely by returns of Novo Nordisk and Eli Lilly. The XBI is up 13.7% and Stifel's biotech value tracker is up 32%. An index of small cap biotech is up 28.7% YTD. India pharma and the Nasdaq 100 have also done well thus far in 2024.

Group Share Price Return, Dec 30, 2023 to Mar 1, 2024



Notes: These data are from S&P CapitalIQ and are compiled into equal-weighted indices. Big pharma includes PFE, LLY, MRK, ABBV, NOVO B, ROG, JNJ, AMGN, AZN, NOVN and SAN. China Pharma includes 600276, 1093, 2186, BGNE, 000963, 600196, 000538, 600518, 002422, 000597, 3692 and ZLAB. India Pharma includes SUNPHARMA, 500257, AUROPHARMA, CIPLA, MANKIND, GLENMARK, 500124, ZYDUSLIFE. Europe Pharma includes Merck KGAA, IPN, HLUN A, BAYN, REC, SOBI, ALM, FRE, ORNBV, UCB, GRF. Japan Pharma includes Takeda, Daiichi-Sankyo, Chugai, Astellas, Eisai. Otsuka Holdings, Shionogi, Ono, Kyowa Kirin, Nippon Shinyaku, Santen and Sumitomo Pharma. Midcap biotech includes VRTX, ARGX, ALNY, BMRN, INCY, NBIX, OGN, IONS, EXEL, ALKS, ITCI, HRMY, INDV, BPMC, MRTX, SAGE, IDIA, APLS.

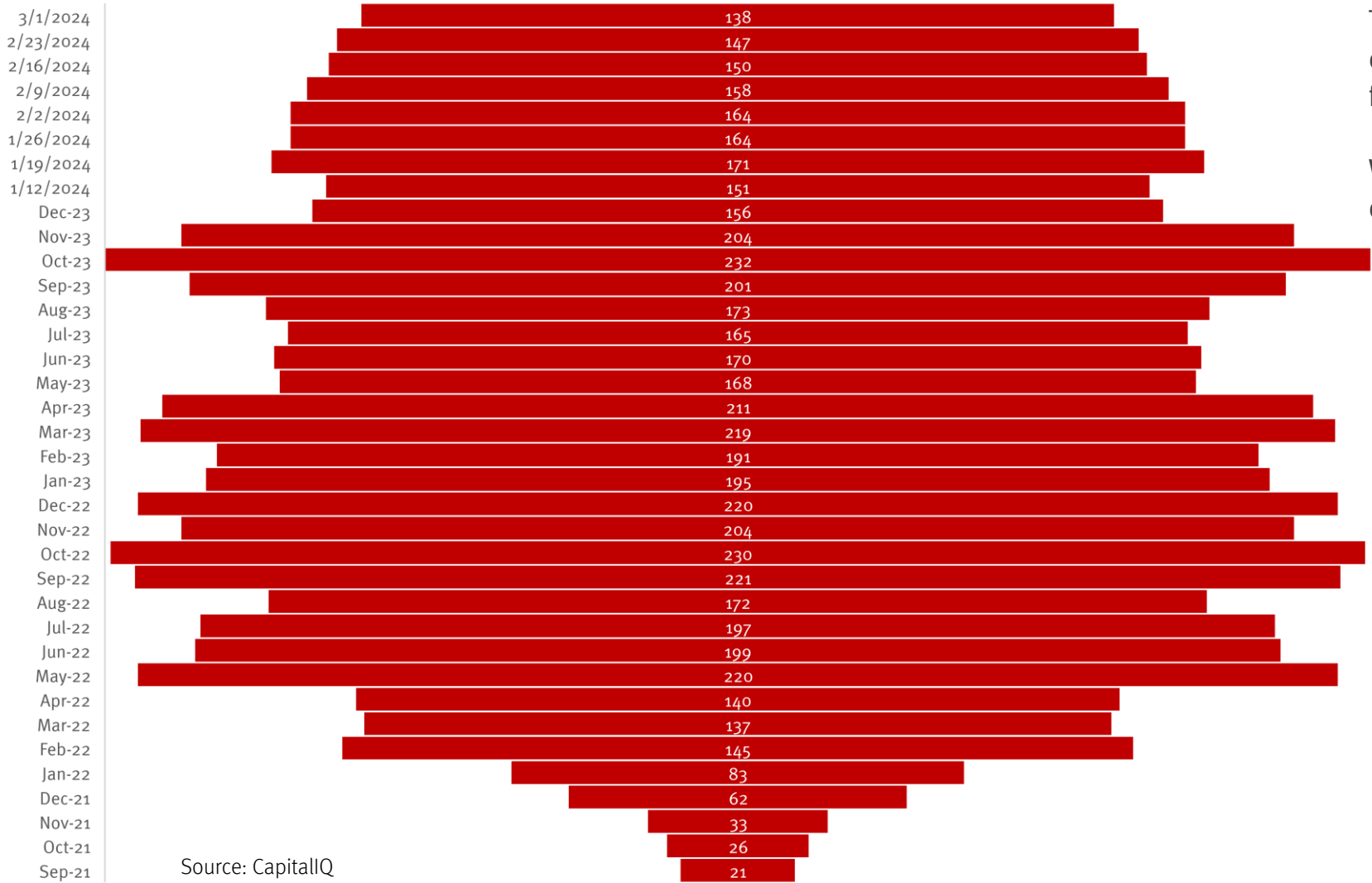
Life Sciences Sector Total Value Up Last Week by 0.2%

Last week saw the life sciences sector gain \$18 billion in value. The best performing sectors were biotech and HCIT.

Sector	Firm Count	Enterprise Value (Mar 1, 2024, \$millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	\$80,908	-0.7%	4.7%	-2.4%
Biotech	803	\$304,236	10.3%	19.1%	-5.1%
CDMO	40	\$148,016	-1.6%	1.1%	-24.3%
Diagnostics	81	\$276,522	2.7%	4.3%	1.8%
OTC	30	\$27,387	-2.7%	-1.7%	-7.7%
Commercial Pharma	719	\$6,273,012	-0.1%	4.8%	13.4%
Pharma Services	39	\$200,132	0.8%	8.4%	-6.8%
Tools	51	\$724,813	1.9%	4.2%	-3.5%
Devices	181	\$1,717,928	-0.6%	2.6%	7.5%
HCIT	10	\$21,238	3.6%	9.3%	-22.7%
Total	2035	\$9,762,251	0.2%	4.7%	9.7%

Number of Negative Enterprise Value Life Sciences Companies Declined in Last Week

Number of Negative Enterprise Value Life Sciences Companies Worldwide



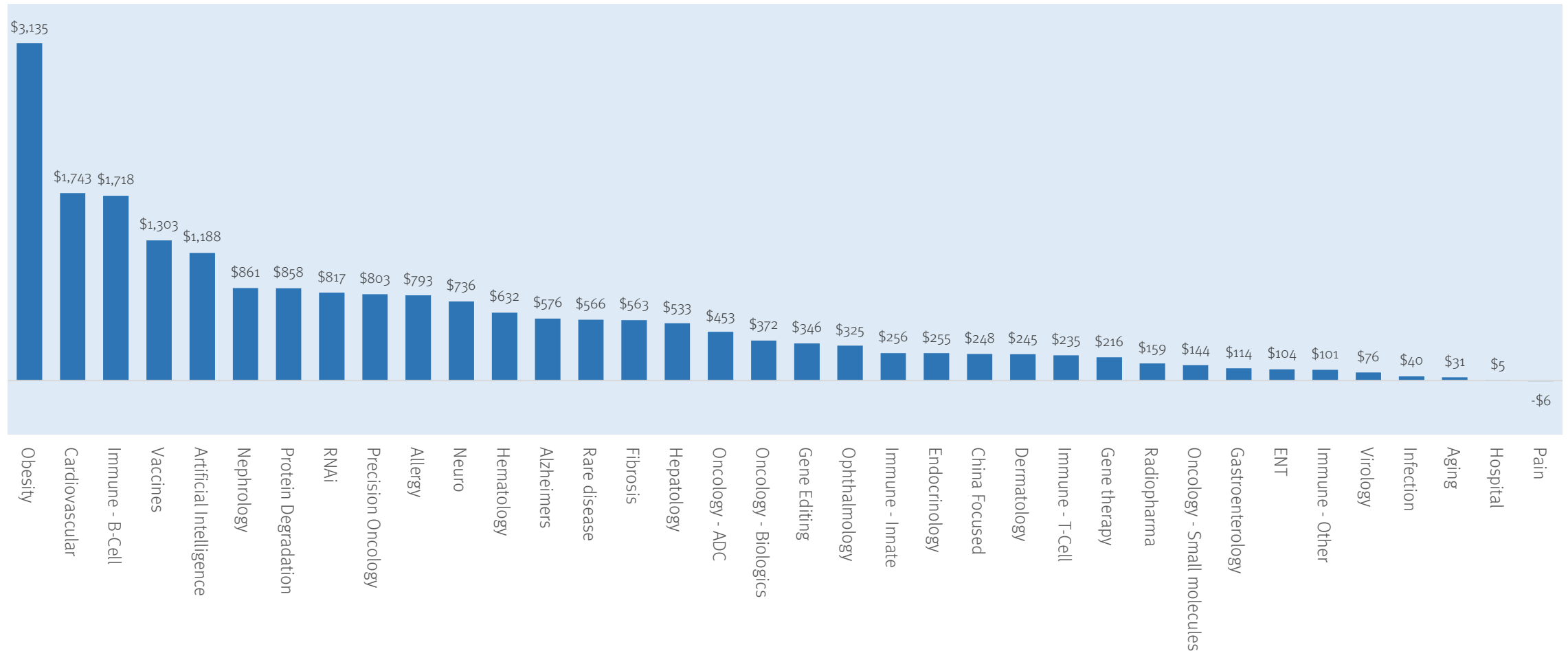
The count of negative EV life sciences companies worldwide dropped to 138 from 147 last week.

We haven't seen this few negative EV companies since March 2022.

Source: CapitalIQ

Obesity Valuations the Highest in Biotech Followed by CV, B-Cell, Vaccines and AI

Average Enterprise Value of U.S. Biotechs by Primary Field, March 1, 2024 (\$ Millions)



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

Rising Tide Lifting Many Biotech Boats: 17 of 36 Subfields of U.S. Biotech Have Gone up 40% or More in the Last Five Weeks

Field	Company Count	Dec 29, 2020	Dec 31, 2021	Dec 31, 2022	Jun 30, 2023	Dec 30, 2023	Jan 26, 2024	Mar 1, 2023	Change (Jan 26 to Mar 1, 2024)	Change (Dec 30, '23 to Mar 1, '24)	Change (Dec 30, '21 to Mar 1, '24)
Obesity	4	\$78	\$72	\$284	\$1,417	\$1,638	\$1,669	\$3,135	87.8%	91.4%	4258.4%
Cardiovascular	8	\$443	\$911	\$1,643	\$1,366	\$2,257	\$1,751	\$1,743	-0.4%	-22.8%	91.3%
Immune - B-Cell	4	\$1,077	\$198	\$741	\$830	\$1,898	\$1,792	\$1,718	-4.1%	-9.5%	769.2%
Vaccines	6	\$442	\$541	\$609	\$671	\$858	\$877	\$1,303	48.6%	51.9%	140.9%
Artificial Intelligence	3	\$0	\$1,632	\$377	\$412	\$823	\$774	\$1,188	53.4%	44.3%	-27.2%
Nephrology	7	\$49	\$157	\$297	\$508	\$407	\$545	\$861	57.9%	111.4%	448.8%
Protein Degradation	4	\$1,179	\$1,326	\$263	\$260	\$385	\$483	\$858	77.6%	123.1%	-35.3%
RNAi	4	\$344	\$235	\$362	\$168	\$209	\$505	\$817	61.8%	291.8%	248.1%
Precision Oncology	26	\$892	\$689	\$394	\$476	\$671	\$707	\$803	13.7%	19.6%	16.6%
Allergy	4	\$1,950	\$423	\$675	\$566	\$617	\$492	\$793	61.3%	28.5%	87.3%
Neuro	38	\$477	\$417	\$338	\$395	\$674	\$705	\$736	4.4%	9.2%	76.6%
Hematology	4	\$764	\$325	\$448	\$310	\$344	\$422	\$632	49.8%	83.8%	94.5%
Alzheimers	7	\$1,409	\$1,280	\$1,010	\$1,020	\$655	\$509	\$576	13.1%	-12.0%	-55.0%
Rare disease	36	\$1,498	\$1,269	\$497	\$497	\$446	\$302	\$566	87.7%	26.9%	-55.4%
Fibrosis	5	\$671	\$452	\$281	\$592	\$504	\$448	\$563	25.6%	11.7%	24.7%
Hepatology	11	\$481	\$291	\$458	\$466	\$415	\$347	\$533	53.4%	28.6%	83.4%
Oncology - ADC	5	\$698	\$319	\$121	\$22	\$130	\$343	\$453	32.1%	248.4%	41.9%
Oncology - Biologics	73	\$689	\$501	\$180	\$165	\$190	\$264	\$372	40.9%	95.7%	-25.8%
Gene Editing	5	\$107	\$572	\$200	\$131	\$241	\$219	\$346	58.0%	43.5%	-39.5%
Ophthalmology	13	\$995	\$503	\$138	\$208	\$152	\$155	\$325	109.7%	113.8%	-35.4%
Immune - Innate	5	\$111	\$507	\$468	\$397	\$24	\$129	\$256	98.4%	973.7%	-49.5%
Endocrinology	11	\$143	\$191	\$83	\$62	\$171	\$188	\$255	35.6%	48.8%	33.5%
China Focused	2	\$0	\$475	\$111	\$97	\$201	\$163	\$248	52.1%	23.2%	-47.8%
Dermatology	5	\$362	\$141	\$52	\$101	\$144	\$181	\$245	35.4%	70.6%	73.8%
Immune - T-Cell	7	\$716	\$140	\$59	\$314	\$144	\$179	\$235	31.3%	63.7%	68.3%
Gene therapy	2	\$249	\$473	\$147	\$213	\$235	\$232	\$216	-6.9%	-8.2%	-54.4%
Radiopharma*	4	\$30	\$35	\$61	\$50	\$1,116	\$896	\$159	-82.3%	-85.8%	348.2%
Oncology - Small molecules	43	\$394	\$279	\$57	\$122	\$166	\$122	\$144	18.0%	-13.4%	-48.3%
Gastroenterology	2	\$990	\$393	\$265	\$338	\$116	\$105	\$114	8.6%	-1.3%	-71.0%
ENT	2	\$34	\$15	-\$3	\$62	\$92	\$83	\$104	25.3%	13.1%	593.3%
Immune - Other	8	\$143	\$169	\$20	\$36	\$14	\$48	\$101	110.4%	614.1%	-40.3%
Virology	12	\$1,020	\$582	\$90	\$99	\$17	\$32	\$76	137.5%	340.1%	-86.9%
Infection	7	\$165	\$145	\$35	\$29	\$38	\$37	\$40	8.1%	4.0%	-72.3%
Aging	3	\$90	\$113	\$23	\$42	\$32	\$55	\$31	-43.6%	-4.2%	-72.5%
Hospital	2	\$53	\$11	\$5	\$6	\$10	\$5	\$5	0.0%	-47.4%	-53.1%
Pain	2	\$143	\$55	-\$13	-\$5	-\$6	-\$6	-\$6	0.0%	-6.0%	-110.8%

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

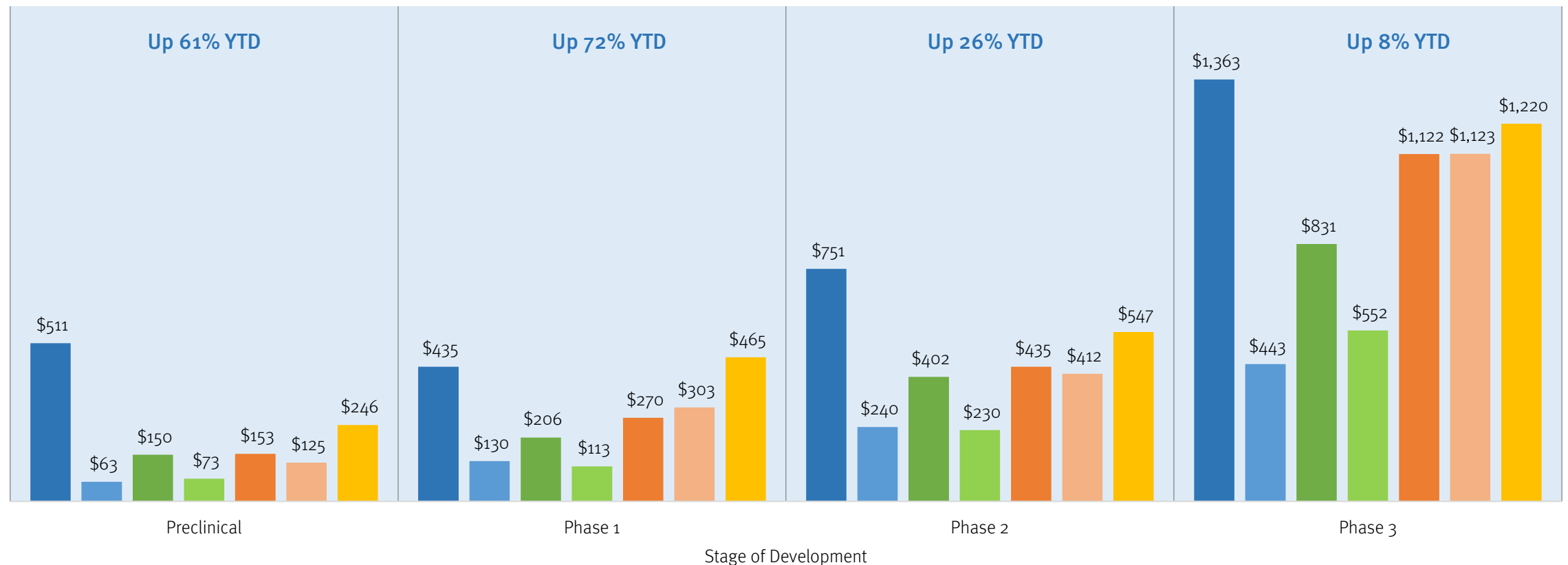
* Dropped as RayzeBio exited.

Valuations for Preclinical and Phase 1 Biotechs Up the Most In First Two Months of 2024

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development

Dec 31, 2021 to March 1, 2024 (\$ Millions)

■ Dec 31, 2021 ■ Jun 16, 2022 ■ June 30, 2023 ■ Oct 27, 2023 ■ Dec 30, 2023 ■ Jan 19, 2024 ■ Mar 1, 2024



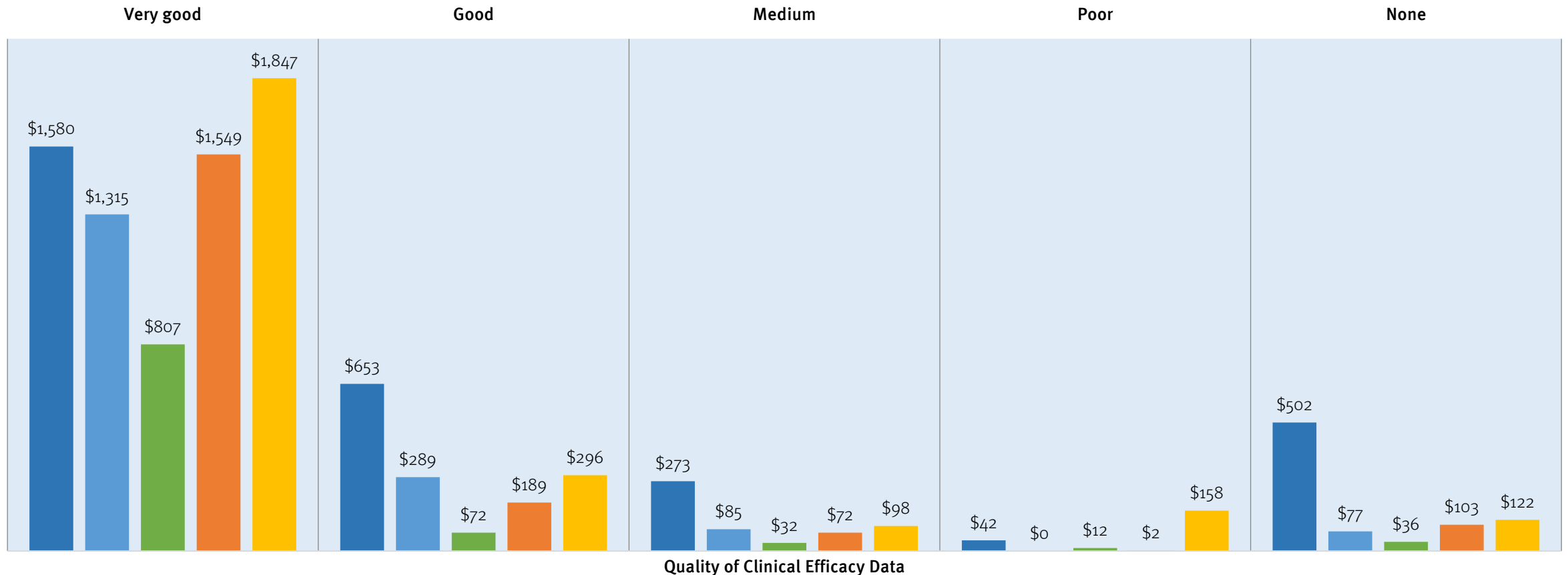
Source: CapitalIQ and Stifel analysis. Stage of development is the last completed stage of development.

Valuations Up Across the Data Quality Spectrum

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Quality of Efficacy Data

Dec 31, 2021 to March 1, 2024 (\$ Millions)

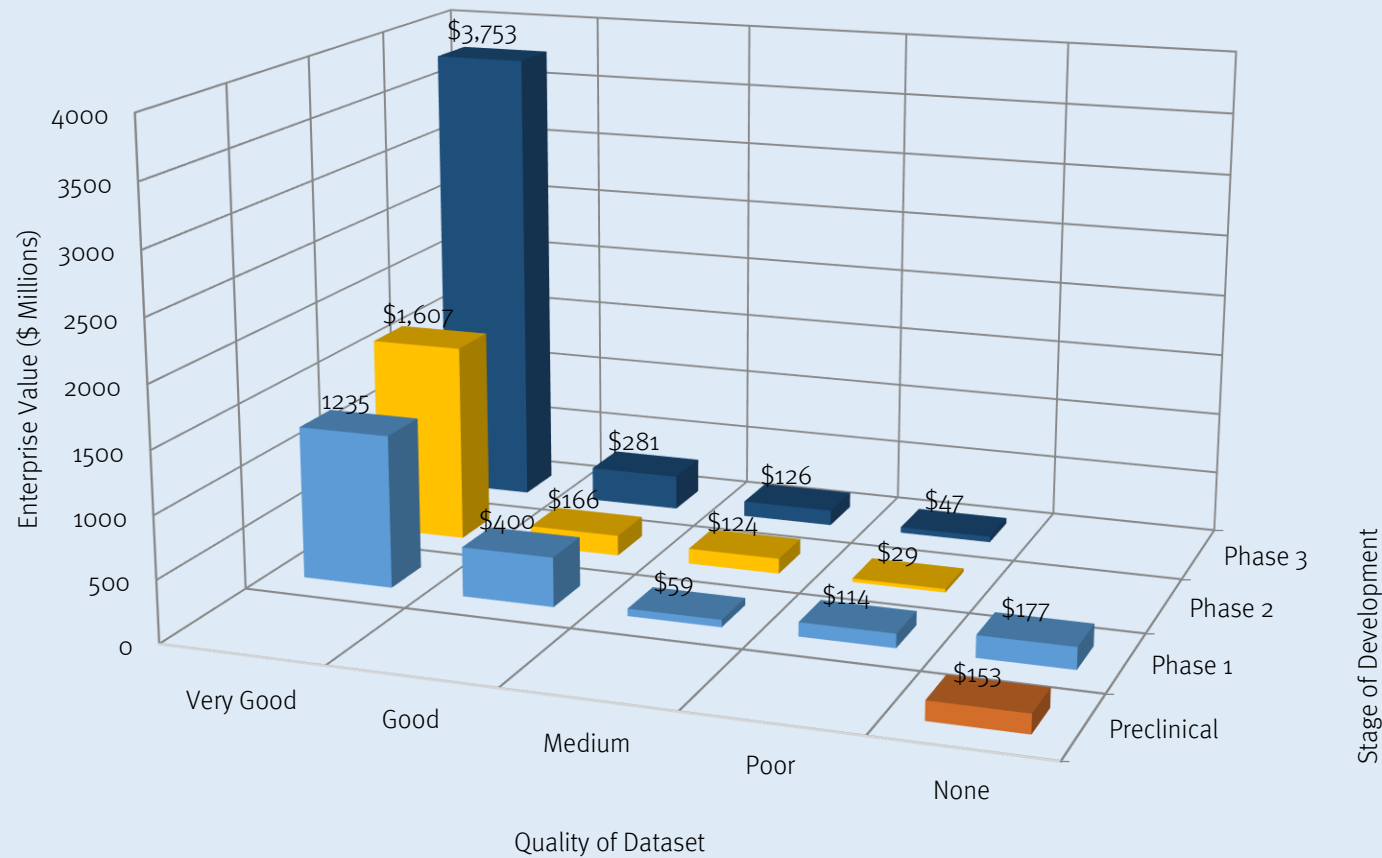
■ Dec 31, 2021 ■ Dec 31, 2022 ■ Oct 27, 2023 ■ Dec 29, 2023 ■ Mar 1, 2024



Notes: These data are sourced from CapitalIQ and based on Stifel research on the dataset quality for a company's lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as "very good". We classified "good" data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial. Stage of development refers to the stage of the last completed trial rather than the stage of ongoing clinical trials.

Market Valuing Late-Stage High Quality Datasets at \$3.75 Billion, on Average

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, March 1, 2024 (\$ millions)



Despite the strong rally in biotech, we are still seeing a quality-obsessed market.

The average valuation of a company with Phase 3 data that we rate as very good is now \$3.75 billion.

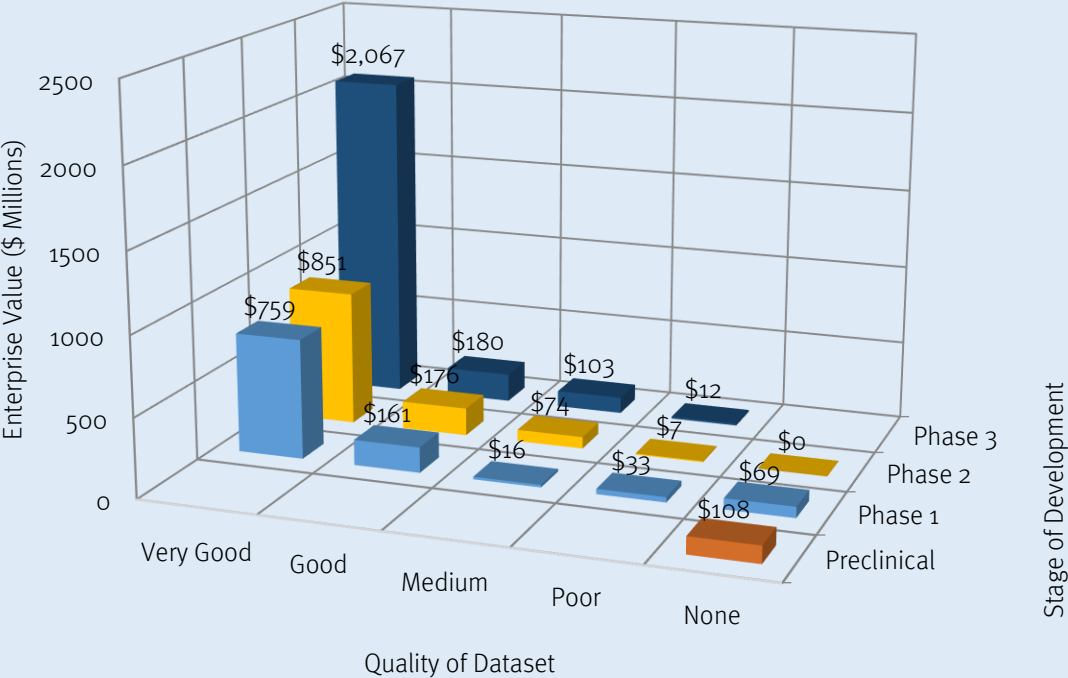
At the start of 2024 the value of the same companies averaged \$3.5 billion.

Notes: These data are sourced from CapitalIQ and based on Stifel research on the dataset quality for a company's lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as "very good". We classified "good" data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial. Stage of development refers to the stage of the last completed trial rather than the stage of ongoing clinical trials.

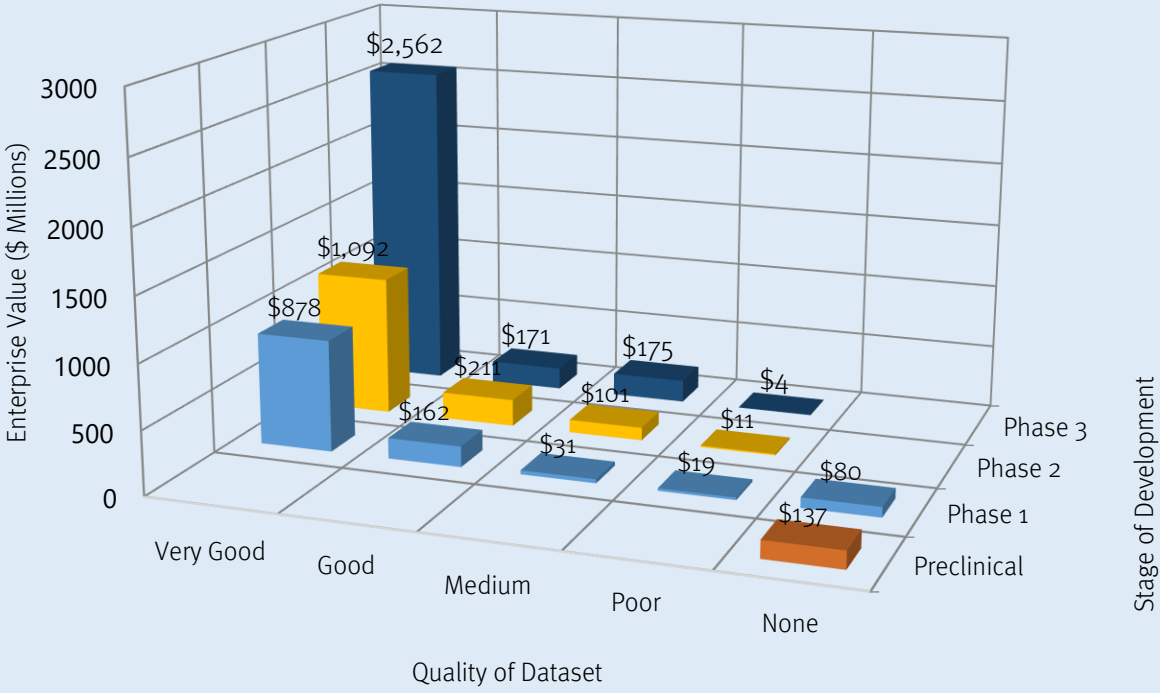
Comparison Points to 2023

In mid-2023, a company with a very good Phase 3 dataset traded at \$2.5 billion versus nearly \$4 billion today.

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Oct 20, 2023



Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Jun 30, 2023



Notes: These data are sourced from CapitalIQ and based on Stifel research on the dataset quality for a company's lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as "very good". We classified "good" data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial. Stage of development refers to the stage of the last completed trial rather than the stage of ongoing clinical trials.

Layoffs and Employment Conditions in Biopharma Sector



FierceBiotech Layoff Tracker Gives One the Impression of Catastrophic Loss of Jobs in Biopharma

**Fierce Biotech Layoff Tracker
2024: 55 job cuts tied to J&J R&D
facility closure; Gritstone lays off
40%**

By Gabrielle Masson, Max Bayer · Mar 1, 2024 2:00pm



March 1 - Moderna: The big biotech is laying off employees within its manufacturing unit, with the move tied to a resizing of its COVID production work. The Moderna rep declined to say how many employees would be affected.

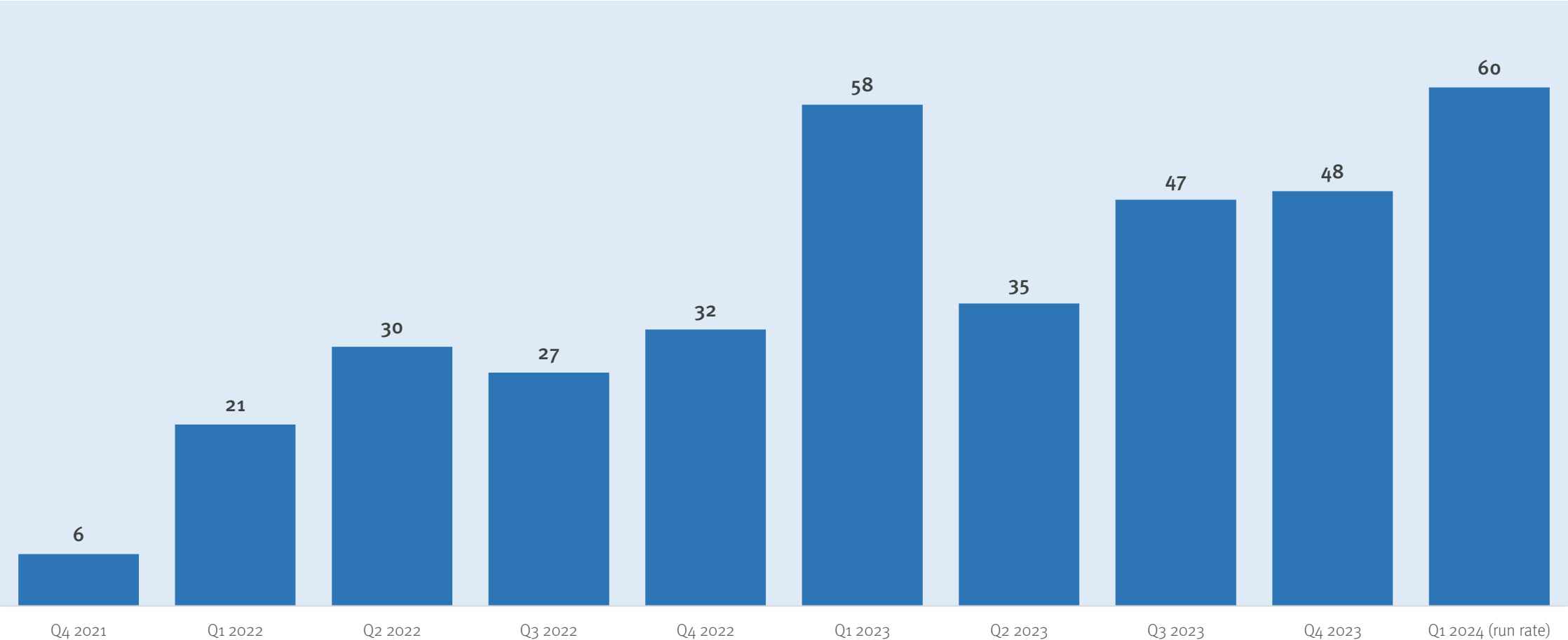
February 29 - Gritstone Bio: The biotech is laying off 40% of employees after delaying the start of a phase 2 trial testing its COVID-19 vaccine, which in turn pushed back the receipt of federal funds.

February 29 - Kineta: After a strategic review, the small oncology biotech is conducting a corporate restructuring and reducing its workforce by 64%, or seven positions, including CEO Shawn Iadonato, Ph.D.

February 28 - Johnson & Johnson: The pharma is closing a nearly 200,000 square-foot R&D outpost in Brisbane, California, less than 18 months after it opened. In conjunction with the closure, the company has implemented 55 permanent layoffs that will go into effect by April 26.

FierceBiotech's Layoff Announcement Tracker Showing Record Layoff Rate in 2024

Quarterly Count of Biopharma Industry Layoff Announcements, Q4 2021 to Q1 2024



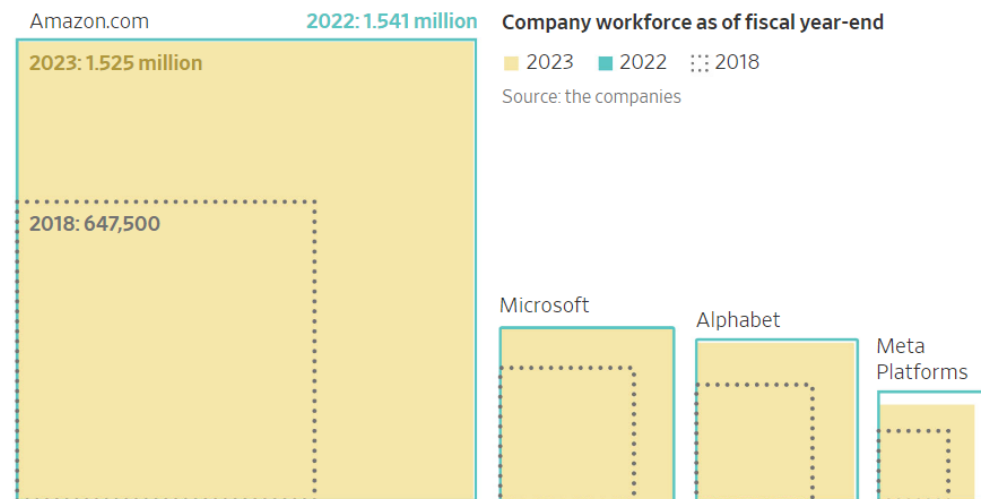
Data Source: Fierce Biotech

Tech Layoffs Not Correlated to Employment Changes

Theo Francis and Alana Pipe, *Wall Street Journal*, Feb 29, 2024

Tech Layoffs Keep Coming. Why Is Head Count Barely Budging?

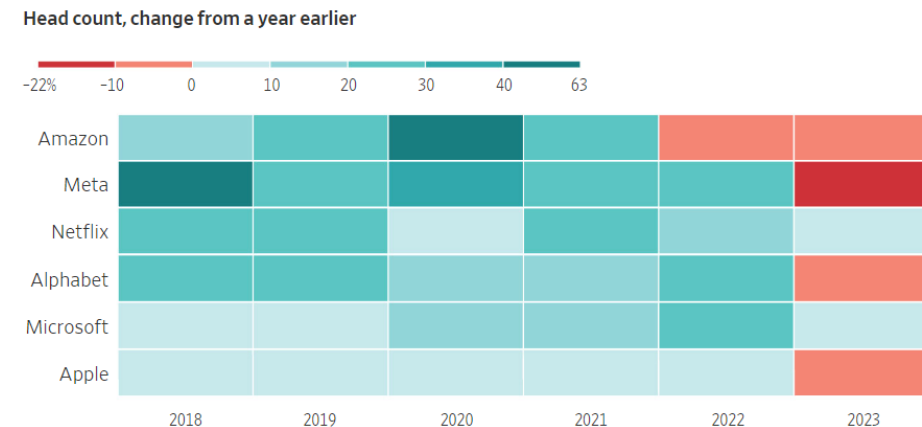
Microsoft, Meta and Amazon are among the companies dwarfing their old selves, despite announcing hefty job cuts



Never mind the layoffs: Some of the biggest U.S. tech companies have swelled their ranks much more than they have trimmed them.

Microsoft, Alphabet and Netflix each employed 50% more people than before the pandemic, year-end disclosures show. Not far behind is Meta Platforms, and Amazon.com has nearly doubled its workforce since 2019, a Wall Street Journal analysis shows.

Since late 2022, these companies have said they would cut more than 70,000 jobs combined. Continued hiring, acquisitions and past recruiting binges have more than offset the recent wave of reductions.



Source: FactSet

Source: <https://www.wsj.com/economy/jobs/tech-layoffs-keep-coming-why-is-head-count-barely-budging-760a314b>

Measuring Actual Employment Levels Using



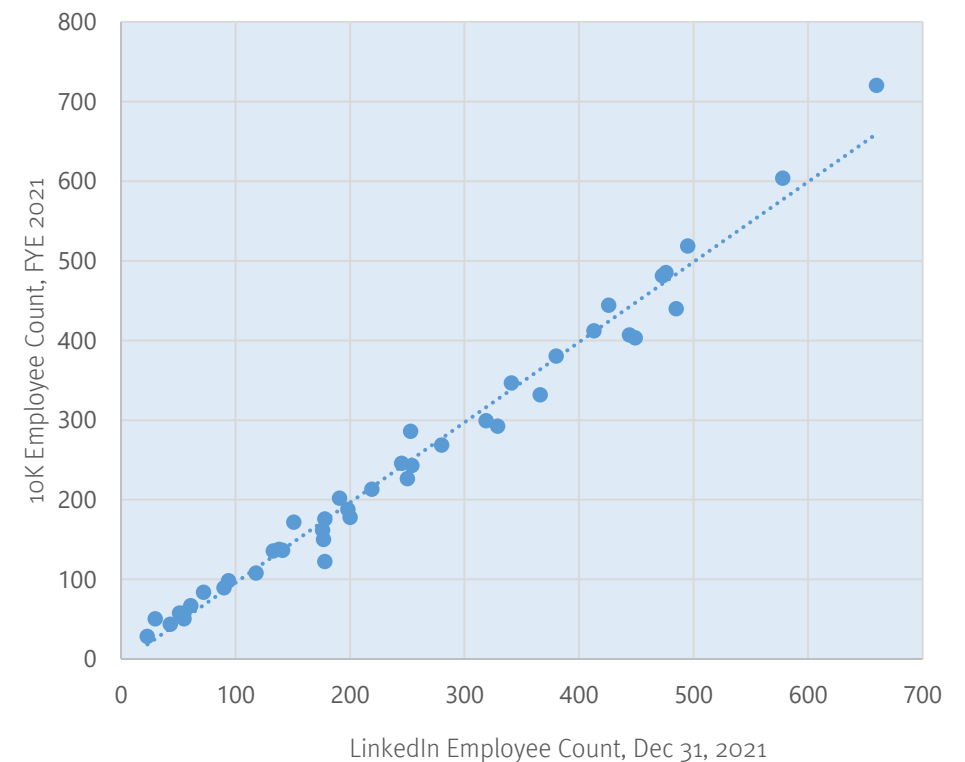
We have opted to track contemporaneous employment changes in biotech (and pharma) using LinkedIn. This business social networking site is heavily used in the U.S. as it's a good place for employees to share information and be seen by recruiters. For U.S. domiciled companies with largely domestic operations, LinkedIn gives a very good sense of employee count.

This is shown in the chart at right which compares Dec 31, 2021 employee count from LinkedIn by biotech and specialty pharma to the count provided in each company's 10K report. The correlation between the two was 0.996 and the counts were not biased.

LinkedIn is used less by employees outside the U.S. and Europe. It is also used less by blue collar employees who traditionally avoid inter-company networking and job seeking facilitated by the site. Because there is no automated method to collect LinkedIn data, we have opted to hand collect a sample of employment data on 78 biopharma companies rather than to collect data on every company. We have attempted to oversample companies that are in the news with layoffs. These data give a good picture of what is going on.

LinkedIn vs Financial Report Employee Count

(sample of 43 US based biotech and small pharma, < 700 employees, Dec 31, 2021)



Listing of 78 Companies Included in Employment Study

Big Pharma	Large Pharma	Smaller Pharma	MidCap Biotech	Small Cap Biotech
AbbVie Amgen AstraZeneca Bristol-Myers Squibb Eli Lilly GSK J&J Merck Novartis Novo Nordisk Pfizer Roche Sanofi	Biogen BioNtech Gilead Incyte Moderna Regeneron Seagen ^a Takeda Vertex	Akebia Therapeutics Athenex ^b Blueprint Chemocentryx ^a Neurocrine Optinose Otonomy ^b Puma Biotechnology Zai Lab	AkesoBio Apellis Pharma Arcus Biosciences Arrowhead Arvinas Beam Therapeutics BridgeBio Cerevel Therapeutics ^a CRISPR Therapeutics Cytokinetics Denali Therapeutics Fate Therapeutics ImmunityBio Innovent Intellia Ionis Pharma Iovance IVERIC Bio ^a Karuna Therapeutics ^a Kymera Therapeutics Mirati Therapeutics ^a Prometheus Biosciences ^a Relay Therapeutics Springworks Therapeutics Vir Biotech Xencor Xenon Pharma Zentalis Pharma	Agios Pharma Annexon Atara Biopharma Avalo Therapeutics Bluebird Bio Bone Therapeutics ^c Chinook ^a Cortexyme ^c Elevation Oncology Galapagos I-Mab Biopharma Immunic Tx Lyell Immunopharma Nektar Passage Bio Precision Biosciences Silverback ^c Taysa Gene Turning Point Therapeutics ^a

Study approach: We selected all U.S. and EU publicly listed companies in the big and large cap pharma categories. We randomly chose nine names from the small pharma list; 28 names from the midcap biotech list and 19 names from the small cap list.

This panel was selected in Feb 2021 and is carried forward even though some companies (e.g., Turning Point) have been bought and others barely remain in existence.

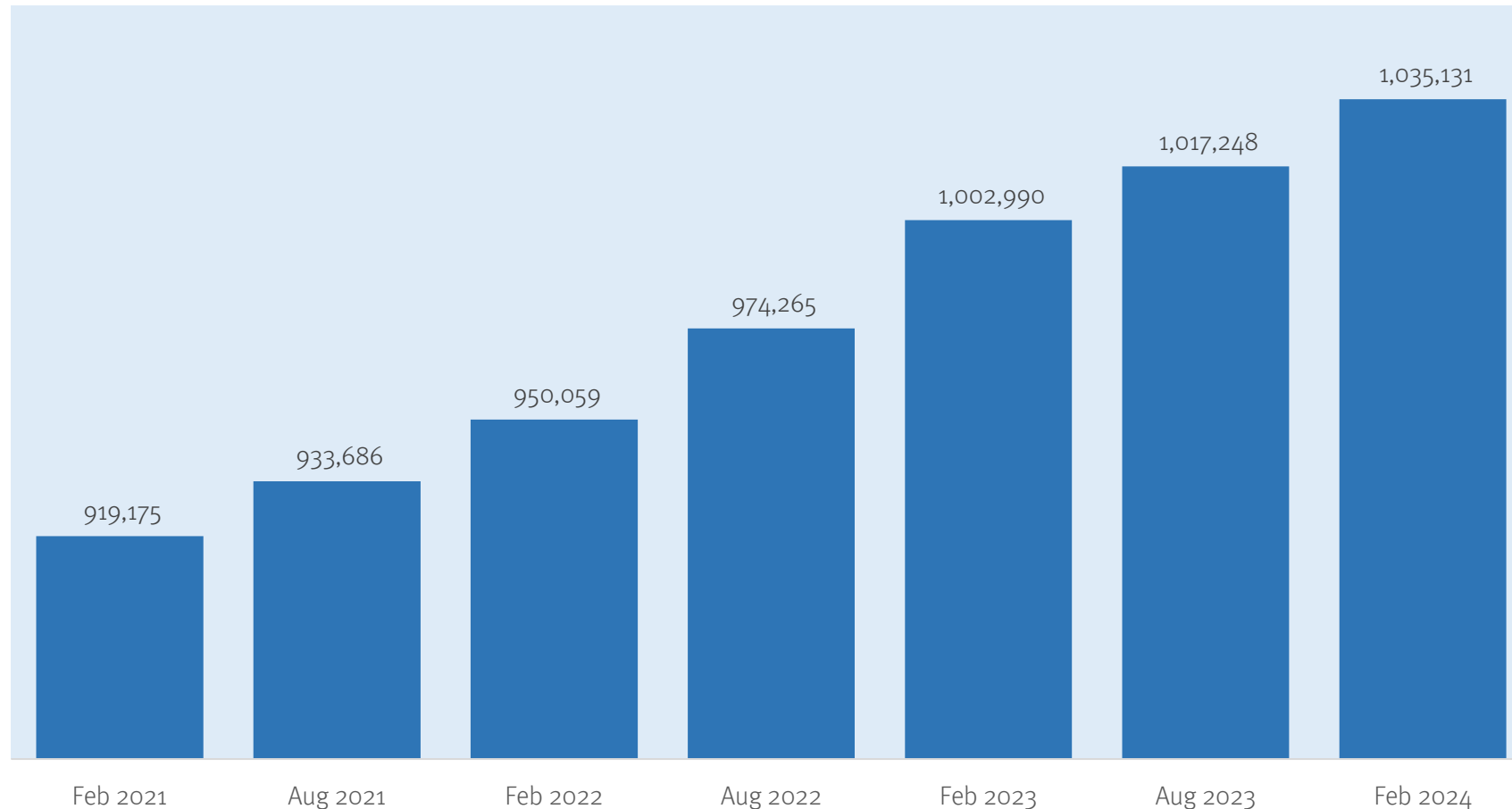
^aThis company was acquired after we put together our panel

^bThis company went bankrupt or chose to liquidate

^cThis company merged and was kept in our sample.

As a Whole, the Biopharma Sector is *Adding* Employees

Total Employee Count in Sample of 78 Public Biopharma's
Feb 2021 to Feb 2024

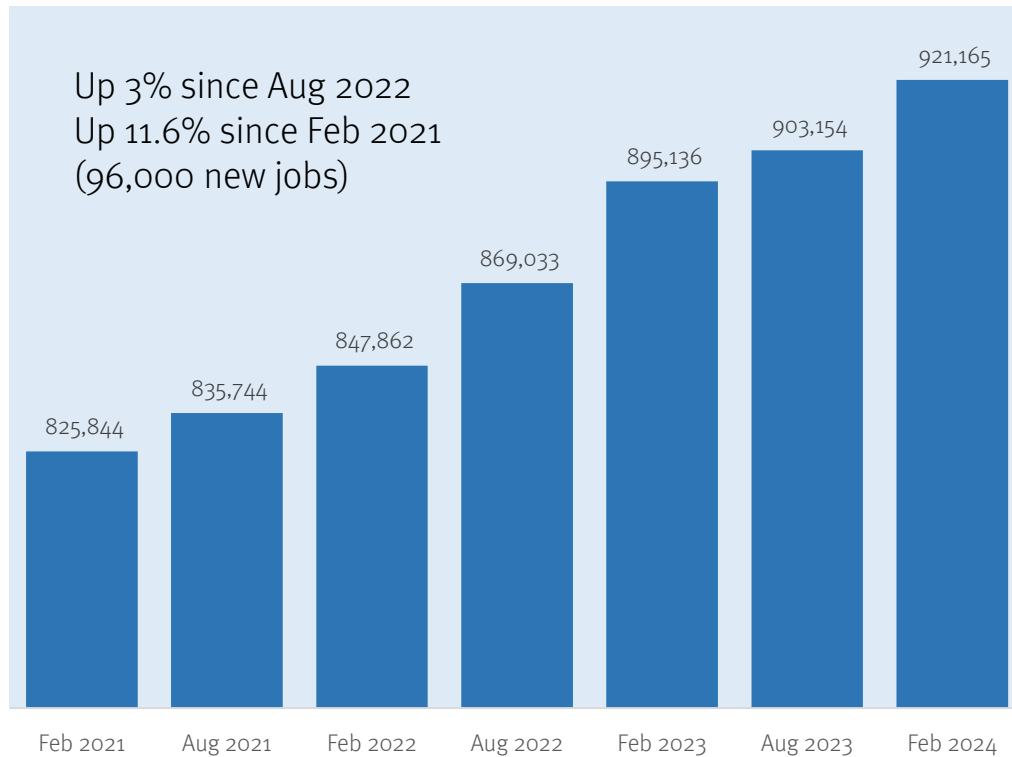


Despite the impression one might get from media stories, the biopharma sector is not shedding employees, on balance. In the year from Feb 2023 to Feb 2024 the sector added more employees than in any year period since we started tracking the statistics in 2021.

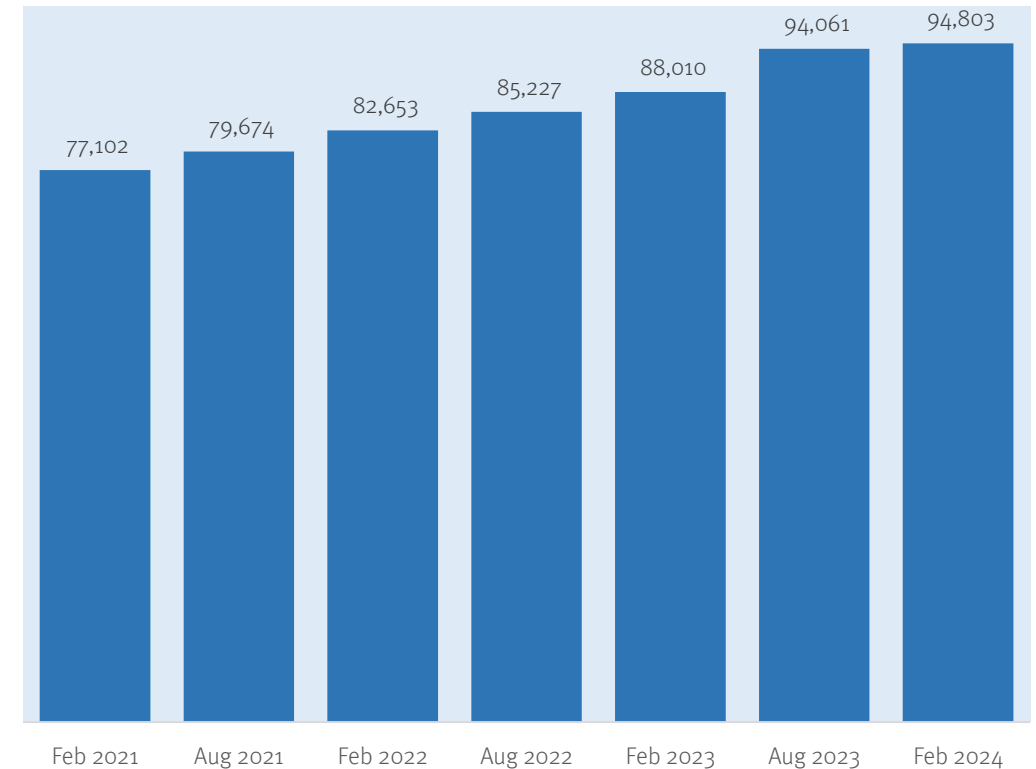
Big Pharma and Large Pharma Employment is Up

Big Pharma employment is up 3% in the Feb '23 to Feb '24 period versus 5.7% the year before. Large pharma (e.g., Vertex, Regeneron, Incyte) employment is up 7.7% in the same period versus 6.5% in the year before.

Total Employee Count in Sample of 13 Big Pharma Companies, Feb 2021 to Feb 2024



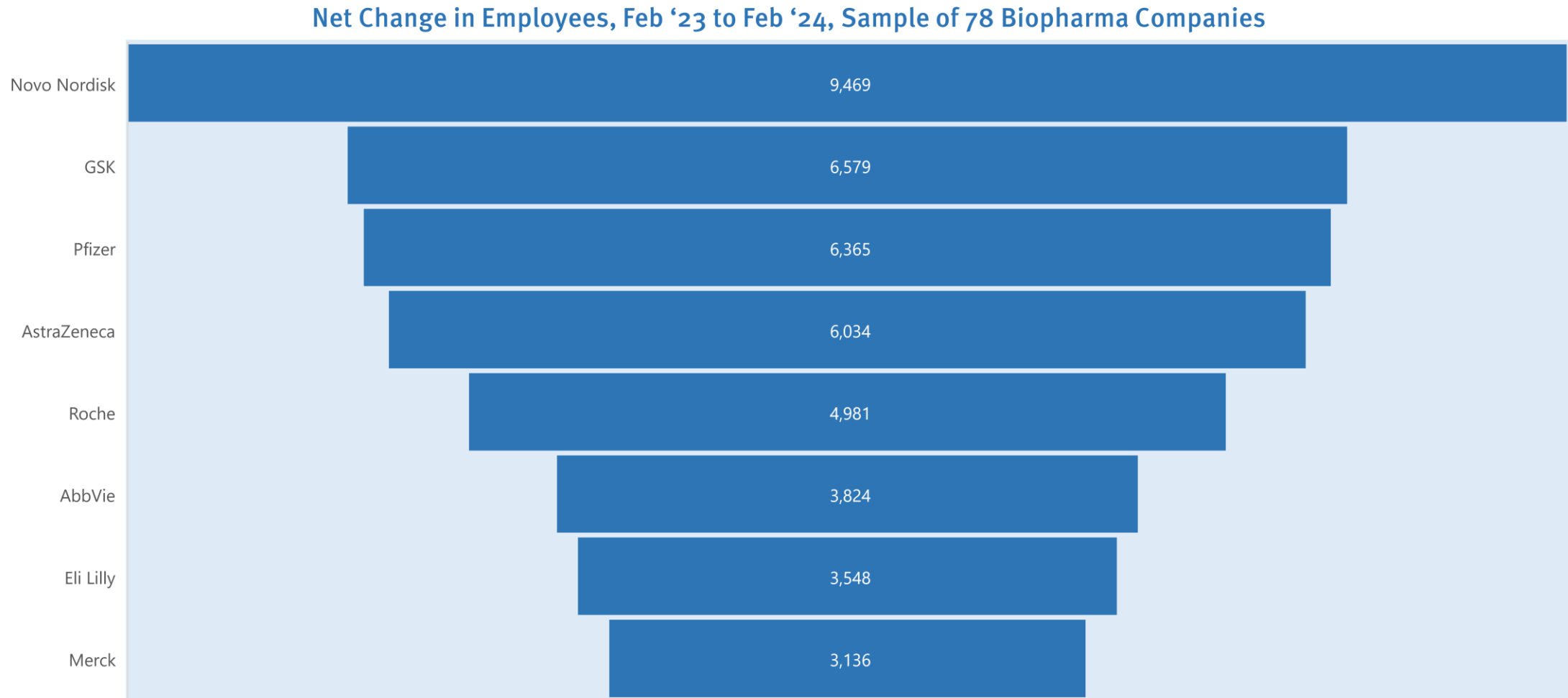
Total Employee Count in Sample of 8 Large Pharma Companies, Feb 2021 to Feb 2024



Source: Stifel Analysis of LinkedIn Employee Insight Data, Feb 2024. The “Large Pharma” group includes Takeda, Gilead, Regeneron, Biogen, Vertex, Seagen, BioNTech and Incyte.

Biggest Growth in Head Count in Last Year by Company

Big pharma has been growing quite aggressively during the biotech downturn. Novo Nordisk has added the most employees.

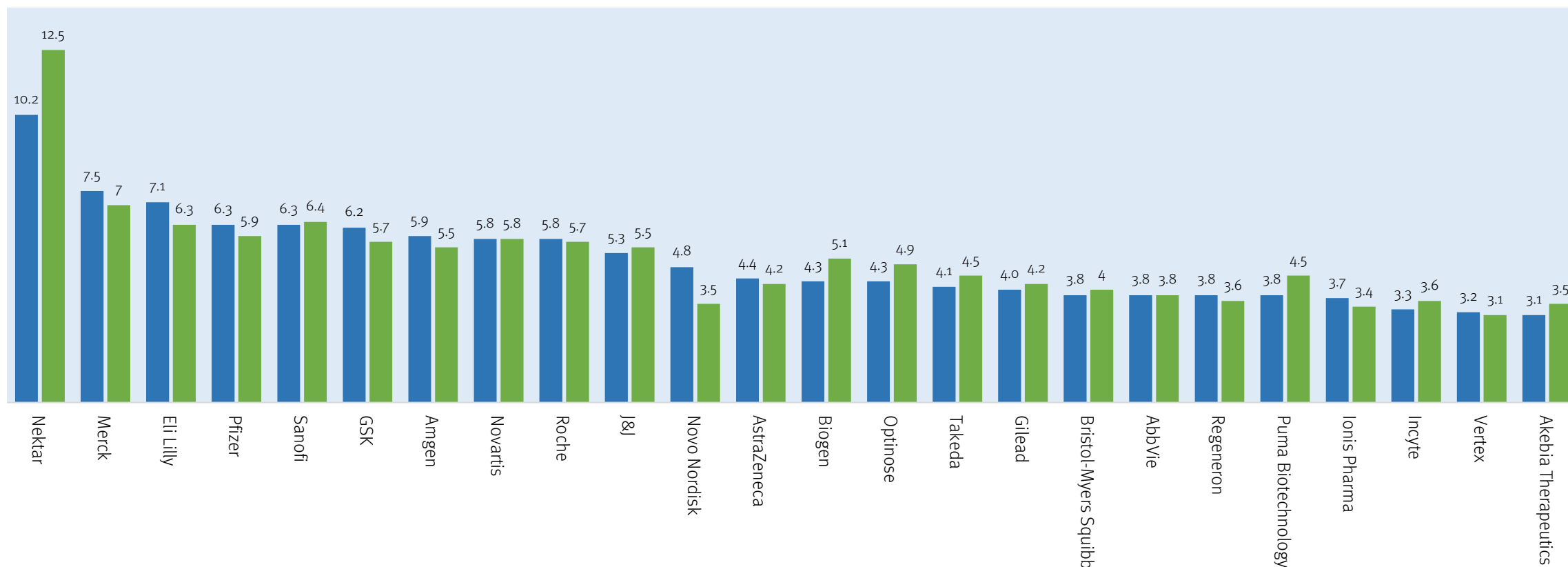


Tenure Profile Shrinking at Growing Companies Like Eli Lilly and Novo. Growing Longer at Low Growth Companies Like Nektar / Biogen

Longest Employee Tenure

(Average Years of Employment of Employees on LinkedIn, Feb 2023 and Feb 2024)

■ Feb-23 ■ Feb-24

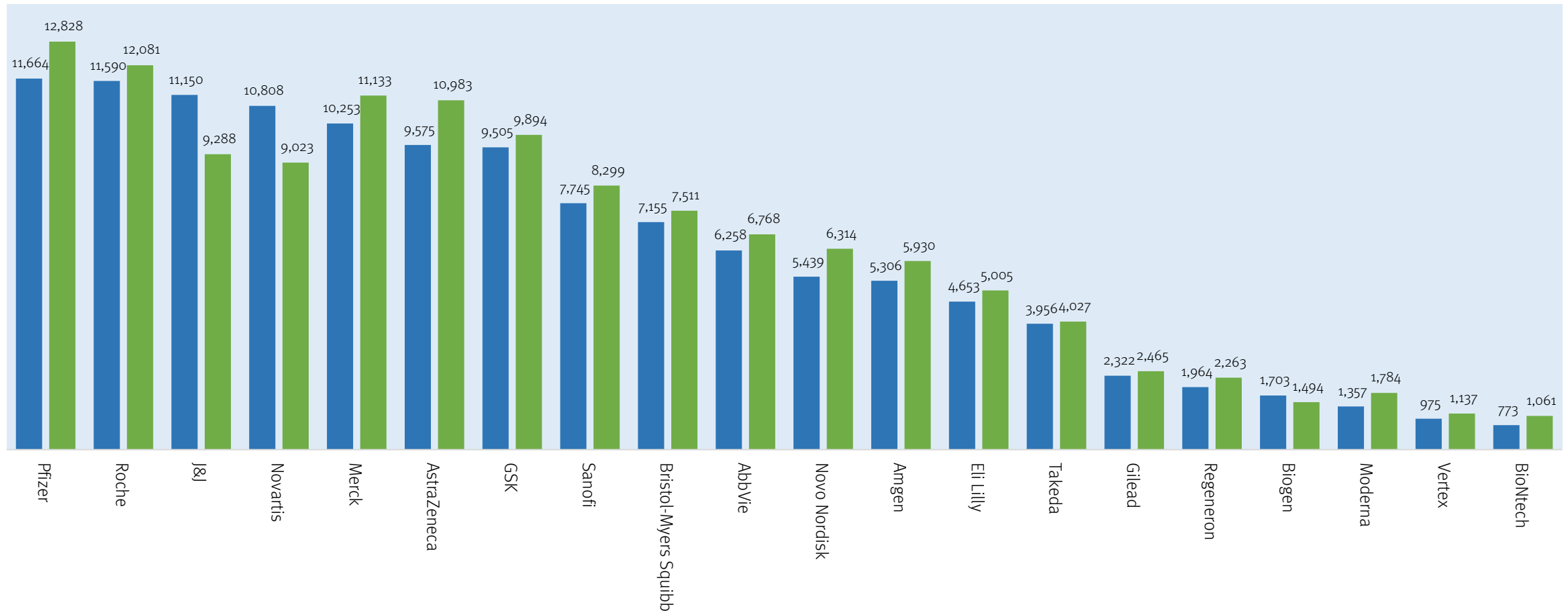


Largest R&D Teams at Pfizer and Roche

Largest R&D Teams

(Based on LinkedIn Employee Count, Titles Classified as Involving R&D Roles)

■ Feb-23 ■ Feb-24



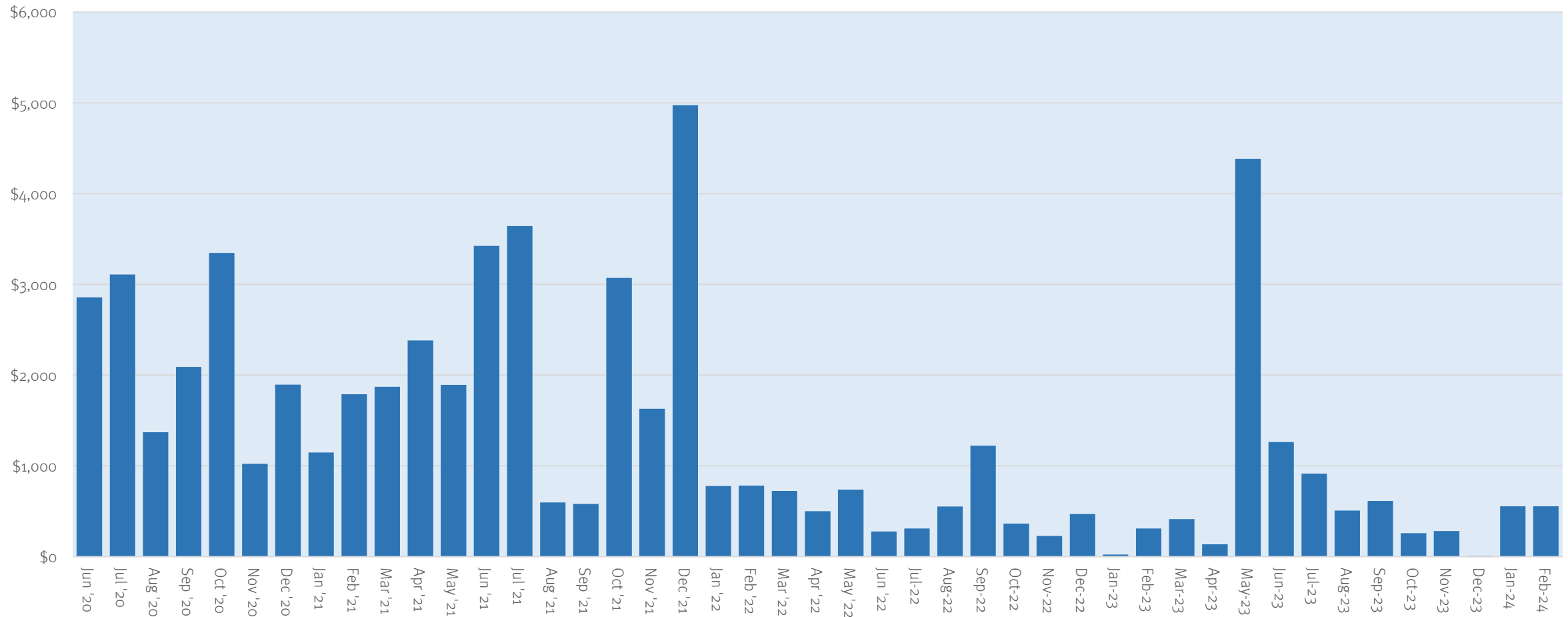
Capital Markets Update



IPO Market Did \$555 Million in Volume in February

The IPO market has been dormant for three weeks running but did a half billion in volume at the start of February.

IPO (\$volume, \$mm), Jan 2020 to Feb 2024



Source: Data from CapitalIQ and Stifel research.

Investors Flock Back to Biotech After a Long, Cold Spell

Jennifer Calfas, *Wall Street Journal*, Feb. 26, 2024 (excerpt)

The deep freeze in biotech is beginning to thaw.

About half a dozen biotechnology companies have gone public since the start of 2024, with some raising hundreds of millions of dollars. The jump-start to the new year is a welcome sign for the industry after a challenging two years fueled by layoffs, scientific hurdles and rising interest rates, investors say. Fewer than 20 companies went public in both 2022 and 2023.

Biotechs have attracted more than \$6 billion in follow-on financing since the start of the year through mid-February, which Jefferies analysts say is a record-setting pace—one that has already exceeded each quarterly amount recorded since the second quarter of 2021.

Venture capitalists have invested \$3.2 billion in biotechs this year through the middle of February, compared with about \$3 billion during the same period in 2023, according to data from research firm PitchBook.

“The healthy market is back,” said Jordan Saxe, head of healthcare listings at Nasdaq, “and it’s not just a fad.”

Among the startups drawing interest from investors are those further along in developing their drug treatments—a change from prior years when unproven drugs found success entering the market. Companies filling up with cash also include firms chasing some of the hottest areas in biotech research, such as cancer, weight loss and nonopioid pain treatment.

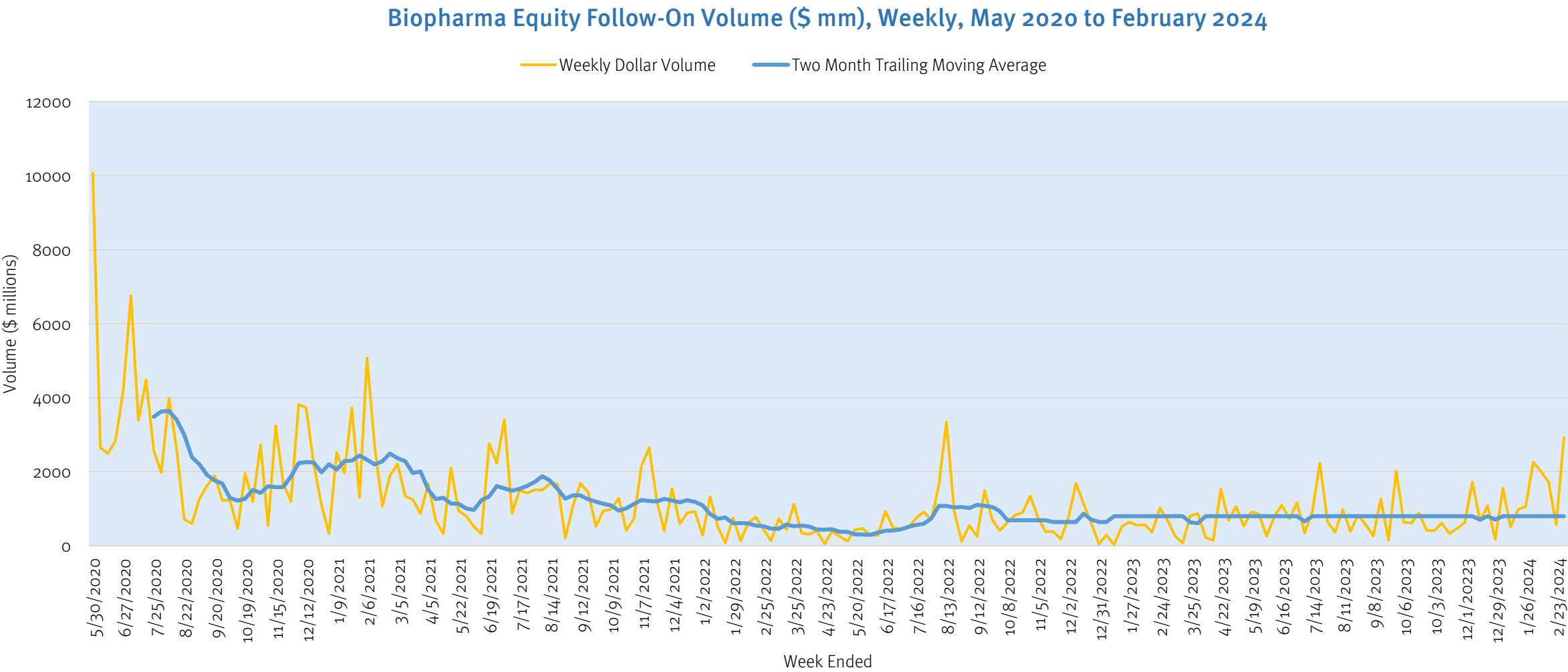
Kyverna Therapeutics raised more than \$337 million in net proceeds during its recent market debut to fund work developing the company’s autoimmune-disease drugs, Chief Executive Peter Maag said. Kyverna uses the cellular-therapy technology known as CAR-T, which has shown success in some cancers.

“It took us five years to become an overnight success,” Maag said. “The reception was phenomenal.”

High interest rates, a spotty deal market and Wall Street’s lower appetite for risk had pushed biotech into the doldrums during the past two years. Startups pulled back on seeking new funding or going public. Just 17 venture-capital-backed biotechs went public in 2022, and a further 18 made the move in 2023—a significant drop compared with the 88 companies that took the plunge in 2021 and 66 in 2020, according to PitchBook. Companies also cut back spending, leading to layoffs. Some closed.

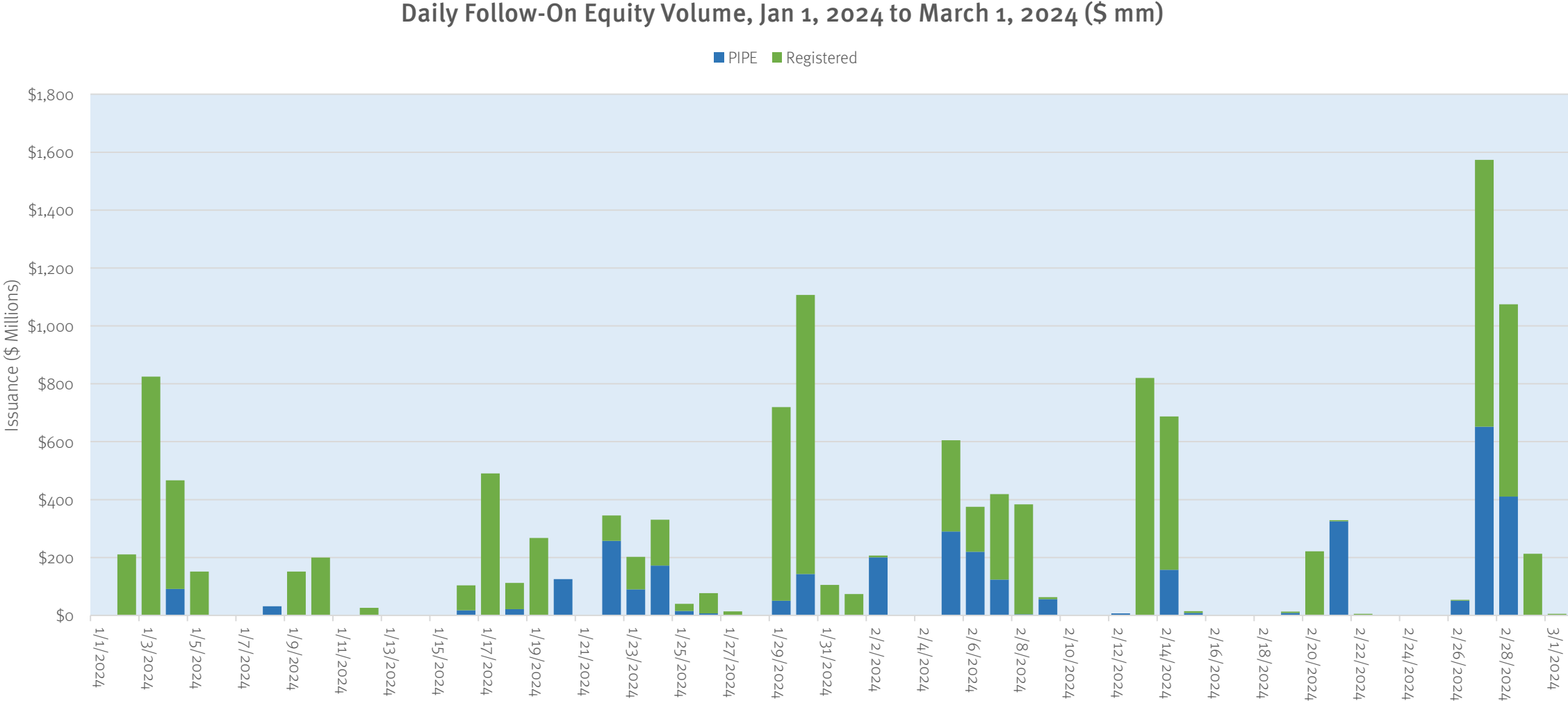
Follow-On Market Active Last Week

Last week saw the pace of follow-on issuance become the highest since August 2022. In total, 33 issuers raised \$2.9 billion in the market.



Source: Data from CapitalIQ and Stifel research.

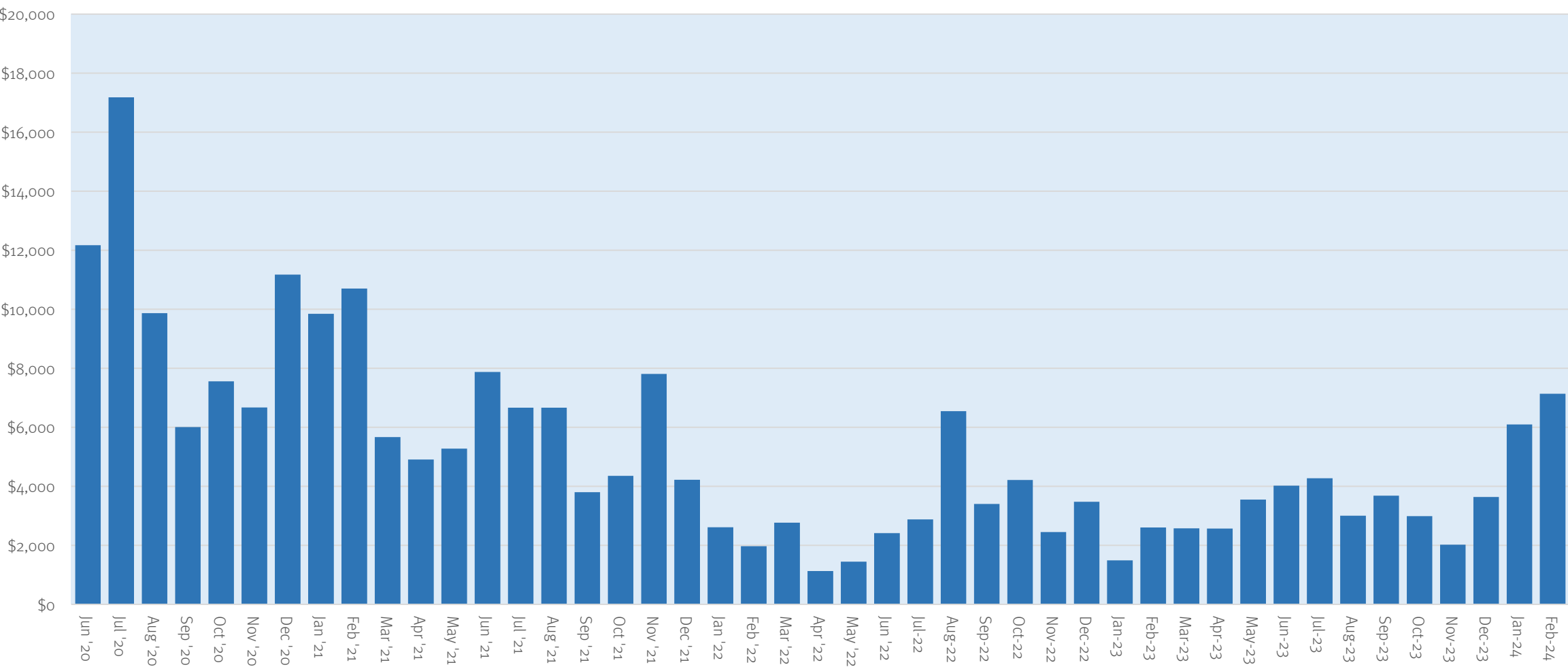
Last Week Was Busiest of the Year for Follow-On Offerings (Two Billion Dollar Issuance Days)



Source: Data from CapitalIQ and Stifel research.

Follow-On Offering Volume in February Highest Since 2021

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

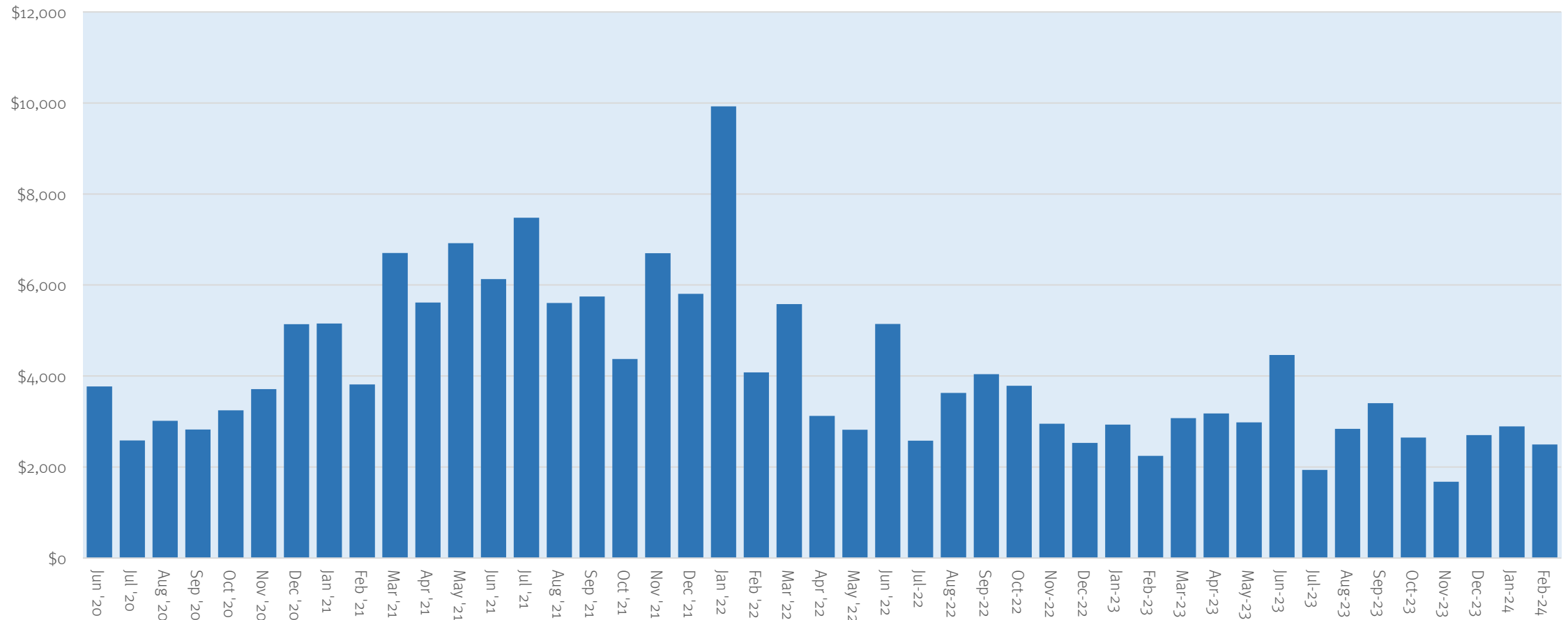


Source: Data from CapitalIQ and Stifel research.

Venture Private Volume Flat Last Week

Last week saw \$839 million in privates deal volume. It was a busier week than the week before. Venture private volume overall has been flat to down versus 2023.

Monthly Private Equity Placement (\$volume, \$mm), Jan 2020 to Feb 2024



Source: Data from CapitalIQ, Crunchbase.

FogPharma Announces \$145 Million Financing to Support Ongoing Clinical Development of FOG-001

Cambridge, MA, March 1, 2024 (BUSINESS WIRE) -- FogPharma®, a clinical-stage biopharmaceutical company dedicated to delivering a new class of therapies that go beyond the limits of currently available medicines using its Helicon™ peptide platform, today announced the successful closing of a \$145 million Series E financing round. The financing was led by Nextech Invest with participation from other new investors including RA Capital Management, Rock Springs Capital, General Catalyst, Marshall Wace, Samsara Biocapital, Foresite Capital, Symbiosis, Catalio Capital Management, Sixty Degree Capital and former chairman and CEO of Johnson & Johnson, Alex Gorsky.

There was strong support by existing investors, including ARCH Venture Partners, Fidelity Management & Research Company, GV, Cormorant Asset Management, funds and accounts advised by T. Rowe Price Associates, Inc., Farallon Capital Management, venBio Partners, Invus and Milky Way Investments. Alexis Borisy, an accomplished investor and entrepreneur, also joined the company's board of directors in the position designated to Nextech.

The financing will fund the ongoing clinical development of FOG-001, the company's first-in-class intracellular TCF-blocking β -catenin inhibitor currently being evaluated in a Phase 1/2 study in solid tumors. The round will also accelerate the development of its robust portfolio of unique discovery programs, deepen its data science capabilities and strengthen its core Helicon therapeutics platform.



"Millions of colorectal cancer patients have been told by their oncologists that no more can be done for them. We believe FOG-001 may represent the long-awaited major technological breakthrough needed to address one of the most common yet unaddressed oncogenic signaling pathways. This financing will allow us to execute on our expanded clinical development and commercialization strategy to deliver FOG-001 to patients."

Matthai Mammen, MD, Ph.D.

Chief Executive Officer
FogPharma

Kenai Therapeutics Announces \$82 Million Series A Financing to Advance Next Generation Cell Therapies for Neurological Diseases



SAN DIEGO, Calif., Feb. 29, 2024 (GLOBE NEWSWIRE) -- Kenai Therapeutics, a biotechnology company leveraging induced pluripotent stem cell (iPSC) technology to discover and develop a platform of allogeneic neuron replacement cell therapies for neurological disorders, today announced an \$82 million Series A financing co-led by Alaska Permanent Fund Corporation, Cure Ventures and The Column Group, with participation from Euclidean Capital and Saisei Ventures. Kenai Therapeutics previously raised seed funding under the name Ryne Bio.

RNDP-001 is an iPSC-derived, allogeneic dopamine progenitor cell therapy for the treatment of both idiopathic and inherited forms of Parkinson's disease, and has displayed robust survival, innervation, and behavioral rescue in preclinical models of Parkinson's disease. Proceeds from the financing will enable the Company to submit an IND for RNDP-001 and complete Phase 1 clinical trials, which will initiate within the year.

“Kenai’s proprietary platform leverages an emerging approach to treating central nervous system disorders by replacing neurons lost due to neurodegeneration,” said Jeff Jonas, M.D., chair and board member of Kenai Therapeutics and partner at Cure Ventures. “The potentially curative nature of RNDP-001 for Parkinson’s disease could dramatically alter outcomes for patients with very few treatment options.”

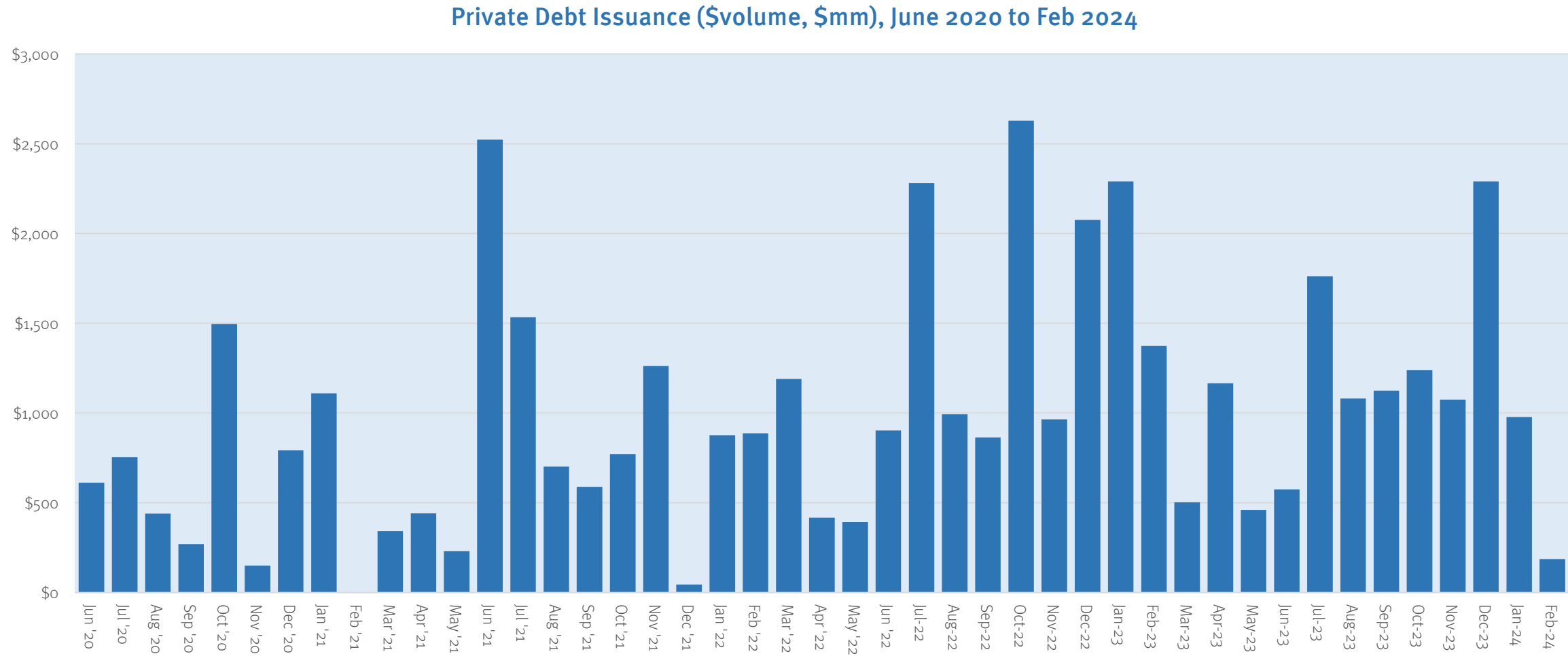


“We are grateful for the support of a syndicate of leading life science investors and a team of industry veterans, including scientific co-founders Dr. Howard Federoff and Dr. Jeffrey Kordower, who see the promise in Kenai’s approach to treating central nervous system disorders. Their guidance will be invaluable as we soon advance our lead candidate, RNDP-001, into the clinic for the treatment of Parkinson’s disease.”

Nick Manusos
Chief Executive Officer
Kenai Therapeutics

Biopharma Private Debt Placement Slowed in February 2024

The debt privates market was quiet last month with no major issuance taking place. Last week saw DNLI also do a project financing for its LRRK2 inhibitor for up to \$75m in exchange for a royalty stream. In addition, Abingworth entered into a project financing for Gilead’s Trodelvy®.



Source: Data from CapitalIQ, Crunchbase.

Abingworth Announces a Strategic Development Financing Agreement with Gilead Sciences

London, UK and New York, USA, February 29, 2024
(excerpt)

Abingworth, a leading international life sciences investment group, part of global investment firm Carlyle (NASDAQ: CG), today announced a strategic development financing agreement with Gilead Sciences. The financing agreement will provide up to \$210 million in funding to support select clinical studies of Trodelvy® (sacituzumab govitecan-hziy), within non-small cell lung cancer. As part of the agreement, Launch Therapeutics, a clinical development company backed by Abingworth and Carlyle, and Gilead have entered into a clinical collaboration agreement that establishes a Joint Steering Committee throughout development.

Gilead retains full rights to Trodelvy and, if development is successful, Abingworth would receive a fixed payment upon regulatory approval of a pre-defined label expansion, as well as royalty payments based on U.S. Trodelvy net sales within the specific tumor type.



Abingworth's Launch Therapeutics Vehicle Will Support Gilead in a Label Expansion Effort for Trodelvy®.

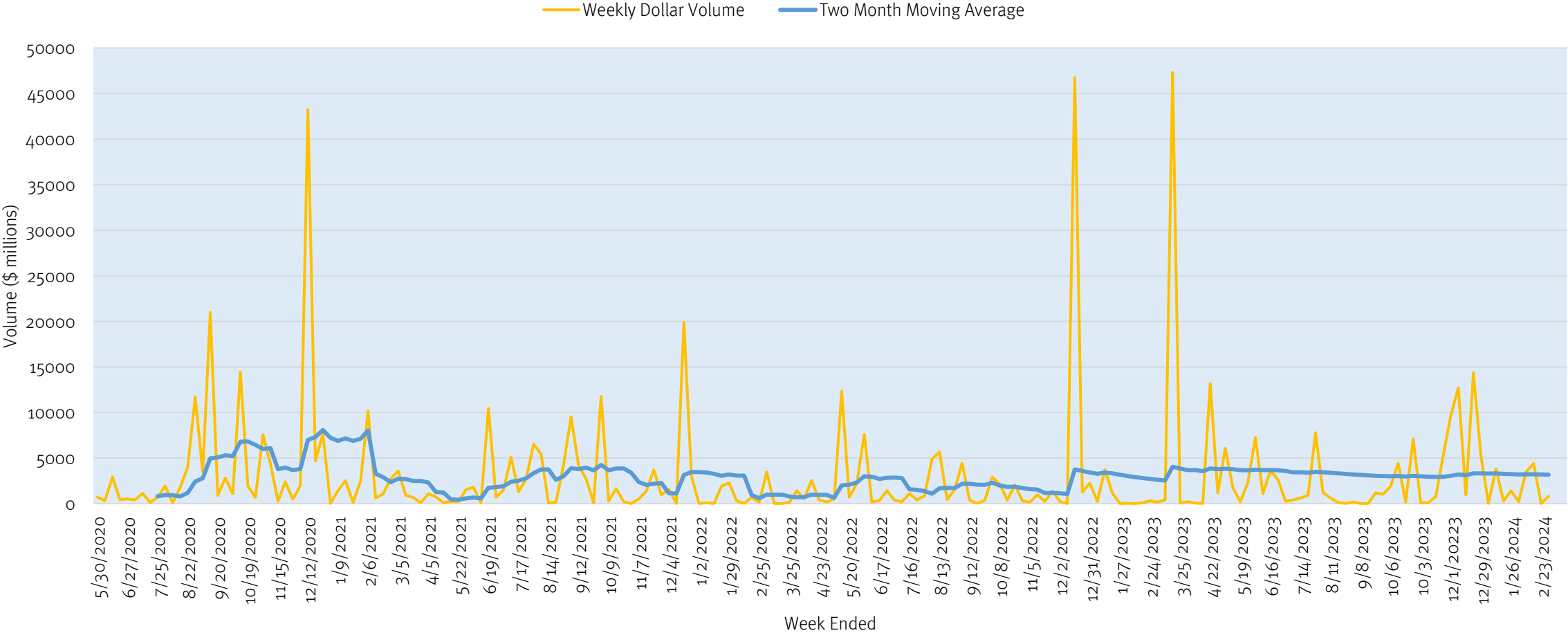
Deals Update



Last Week Saw \$880 Million in M&A Volume

Last week saw less than \$1 billion in sector M&A volume.

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

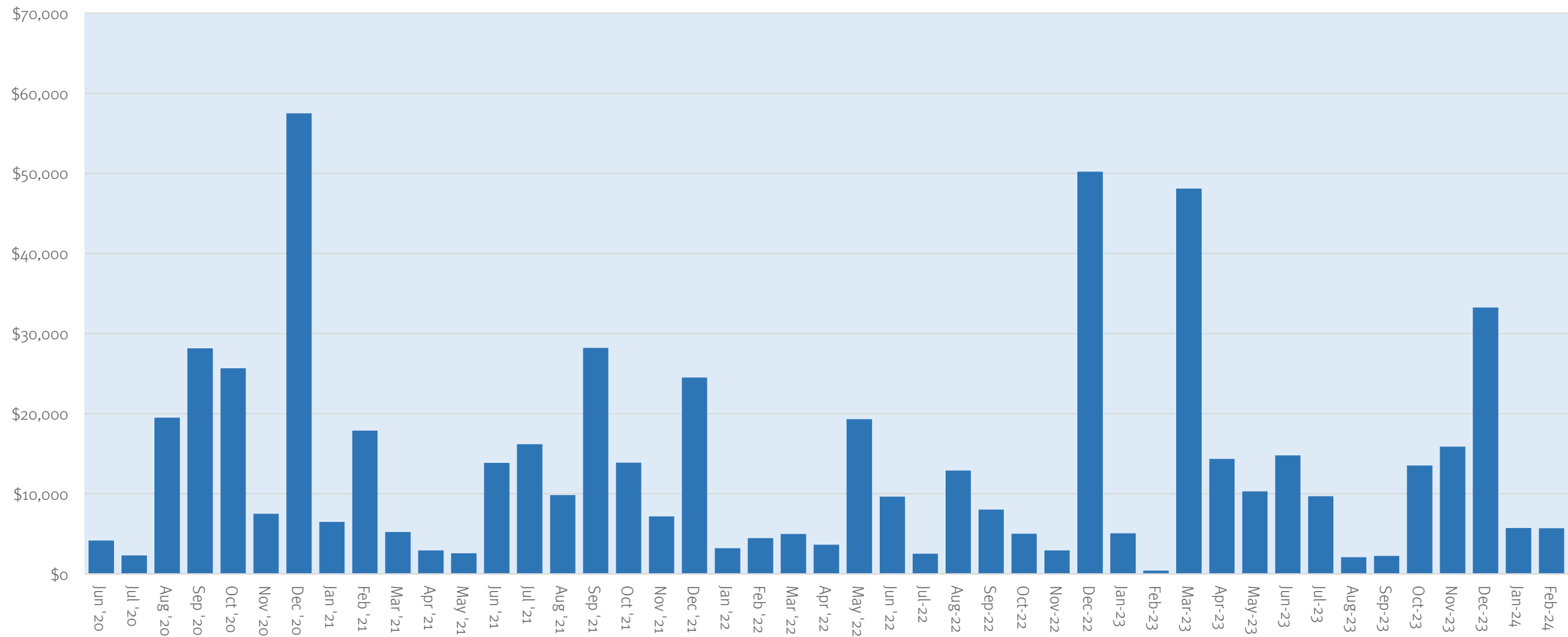


Source: S&P, CapitalIQ

M&A Dollar Volume Down Substantially in 2024

So far in 2024 we have seen \$11.4 billion in M&A volume. This puts us on a pace of less than \$70 billion in deal volume for the year – which is far less than the \$178 billion in activity in 2024. The year is only a sixth over so there is still plenty of time for the deal pace to pick up.

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



Source: S&P, CapitalIQ

Zizhu Pharma Bought for \$432 Million



華潤醫藥集團有限公司

China Resources Pharmaceutical Group Limited

(Incorporated in Hong Kong with limited liability)

(Stock Code: 3320)

INSIDE INFORMATION THE PROPOSED INTERNAL REORGANIZATION INVOLVING CR ZIZHU

This announcement is made by China Resources Pharmaceutical Group Limited (the “**Company**”, together with its subsidiaries, the “**Group**”) pursuant to the provisions of inside information under Part XIVA of the Securities and Futures Ordinance (Chapter 571 of the Laws of Hong Kong) and Rule 13.09 of the Rules Governing the Listing of Securities on The Stock Exchange of Hong Kong Limited (the “**Listing Rules**”).

THE PROPOSED INTERNAL REORGANIZATION

The board of directors (the “**Board**”) of the Company is pleased to announce that, the Board has passed a resolution and approved that China Resources Double-Crane Pharmaceutical Co., Ltd. (華潤雙鶴藥業股份有限公司) (“**CR Double-Crane**”, a non-wholly-owned subsidiary of the Company) and Beijing Pharmaceutical Group Company Limited (北京醫藥集團有限責任公司) (“**Beijing Pharmaceutical**”, a wholly-owned subsidiary) will enter into a share transfer agreement (“**Share Transfer Agreement**”), pursuant to which CR Double-Crane will agree to acquire, and Beijing Pharmaceutical will agree to sell, 100% interest in China Resources Zizhu Pharmaceutical Co., Ltd (華潤紫竹藥業有限公司) (“**CR Zizhu**”) for a total consideration of RMB3,115,453,100.00 (equivalent to approximately HK\$3,429,303,845.29) (the “**Proposed Internal Reorganization**”).

Last week’s largest M&A deal involves a \$432 million acquisition of Zizhu Pharma by CR Double Crane Pharma.

Double Crane is partially owned sub of China Resources Pharma and which is buying Zizhu from a wholly owned sub (Beijing Pharma).

Source: <https://www1.hkexnews.hk/listedco/listconews/sehk/2024/0223/2024022300808.pdf>

CoreRx to Buy Societal CDMO \$203 Million



CLEARWATER, Fla. and GAINESVILLE, Ga., Feb. 28, 2024 (GLOBE NEWSWIRE) -- Societal CDMO, Inc. (“Societal CDMO”) (Nasdaq: SCTL), a contract development and manufacturing organization (CDMO) dedicated to solving complex formulation and manufacturing challenges primarily in small molecule therapeutic development, today announced that it has entered into a definitive agreement with CoreRx, Inc. (“CoreRx”) under which CoreRx will acquire Societal CDMO. CoreRx will commence a tender offer to acquire all outstanding shares of Societal CDMO for \$1.10 per share in cash, subject to any applicable tax withholding. Societal CDMO’s board of directors unanimously approved the transaction and plans to recommend that all shareholders tender their shares in the tender offer.

“We are pleased to enter into this transaction with CoreRx, which delivers substantial value to our shareholders and is the outcome of a thorough review process overseen by the Societal CDMO board of directors,” said Wayne Weisman, executive chairman of Societal CDMO’s board of directors.

“The enhanced CDMO that will be created through this transaction will be positioned to offer both existing and new customers strength in formulation development, early-stage production, clinical trial services, commercial-scale manufacturing, and a range of packaging services. The prospects for this combined entity to establish itself as a preferred CDMO partner in the small molecule space are bright and we look forward to the opportunity to contribute to the new company’s success,” said David Enloe, chief executive officer of Societal CDMO. “We are proud to see our team’s accomplishments and are truly grateful for the contributions made by all team members to the success of the company. I am confident that this transaction will maximize value for our shareholders.”

Under terms of the merger agreement, CoreRx will promptly commence a cash tender offer to acquire all outstanding shares of Societal CDMO common stock for \$1.10 per share in cash, subject to applicable tax withholding, and Societal CDMO has agreed to file a recommendation statement containing the unanimous recommendation of its board of directors that Societal CDMO shareholders tender their shares to CoreRx. The transaction is expected to close early in the second quarter of 2024. The transaction is subject to the tender of a majority of the outstanding shares of Societal CDMO’s common stock, as well as other customary closing conditions. Following the successful closing of the tender offer, CoreRx will acquire all remaining shares of Societal CDMO that are not tendered into the tender offer through a second-step merger at the same price of \$1.10 per share, without the vote of Societal CDMO shareholders. The merger will be effected as soon as practicable after the closing of the tender offer. Until that time, Societal CDMO will continue to operate as a separate and independent company.

NGM Bio Agrees to a \$135 Buyout by The Column Group

SAN FRANCISCO, Feb. 26, 2024 (GLOBE NEWSWIRE) -- NGM Biopharmaceuticals, Inc. (“NGM Bio”) (Nasdaq: NGM), a biotechnology company focused on discovering and developing transformative therapeutics for patients, today announced that it has entered into a definitive Agreement and Plan of Merger (the “Merger Agreement”) under which Atlas Neon Parent, Inc. (“Purchaser”) and Atlas Neon Merger Sub, Inc. (“Merger Sub”) will acquire NGM Bio through a cash tender offer to be commenced by Merger Sub for all outstanding shares of NGM Bio not held by affiliates of The Column Group, LP and certain other stockholders, as described below, at a price per share of \$1.55 in cash. Purchaser and Merger Sub are affiliates of The Column Group, LP (together with certain of The Column Group, LP’s affiliates, the “TCG Stockholders”), NGM Bio’s longest and largest stockholder, holding approximately 26% of NGM Bio’s outstanding shares.

The TCG Stockholders and certain other existing stockholders of NGM Bio (the “Rollover Stockholders”) have agreed to contribute their shares of NGM Bio stock to Purchaser as a part of the transaction rather than receive the cash price per share.

This price per share corresponds to a total equity value of \$135 million on a fully diluted basis and represents an 80% premium over the last trading day closing price (December 29, 2023) prior to NGM Bio’s Form 8-K confirming receipt from the TCG Stockholders of a non-binding expression of interest in exploring and evaluating a potential acquisition of all of the outstanding shares of common stock of NGM Bio not already owned by the TCG Stockholders in a going-private transaction. NGM Bio’s cash, cash equivalents and short-term marketable securities were \$166.0 million as of September 30, 2023 and an estimated \$144.2 million as of December 31, 2023.



While this deal comes at an 80% premium to the 8K filing on the deal, the offer was, unusually, 20% less than where NGM was trading. It looks like the market got ahead of itself here. A “take under” is unusual in biotech M&A.

Viatriis Buys Two Late-Stage Idorsia Assets for \$350 Million

Allschwil, Switzerland – February 28, 2024

Idorsia Ltd (SIX: IDIA) today announced that it has entered into agreements for a significant global research and development collaboration with Viatriis Inc. (NASDAQ: VTRS), a global healthcare company, for the global development and commercialization of two Phase 3 assets – selatogrel and cenerimod – for an upfront payment of USD 350 million, potential development and regulatory milestone payments, and certain contingent payments of additional sales milestone payments and tiered royalties from mid-single- to low double-digit percentage on annual net sales.

A joint development committee will oversee the development of the ongoing Phase 3 programs for selatogrel and cenerimod through regulatory approval. Idorsia will contribute up to USD 200 million in the next 3 years and will transfer to Viatriis at closing the dedicated personnel to both programs.

Viatriis will have worldwide commercialization rights for both selatogrel and cenerimod (excluding, for cenerimod only, Japan, South Korea and certain countries in the Asia-Pacific region).

Idorsia has also granted Viatriis a Right of First Refusal and First Negotiation for certain other pipeline assets.

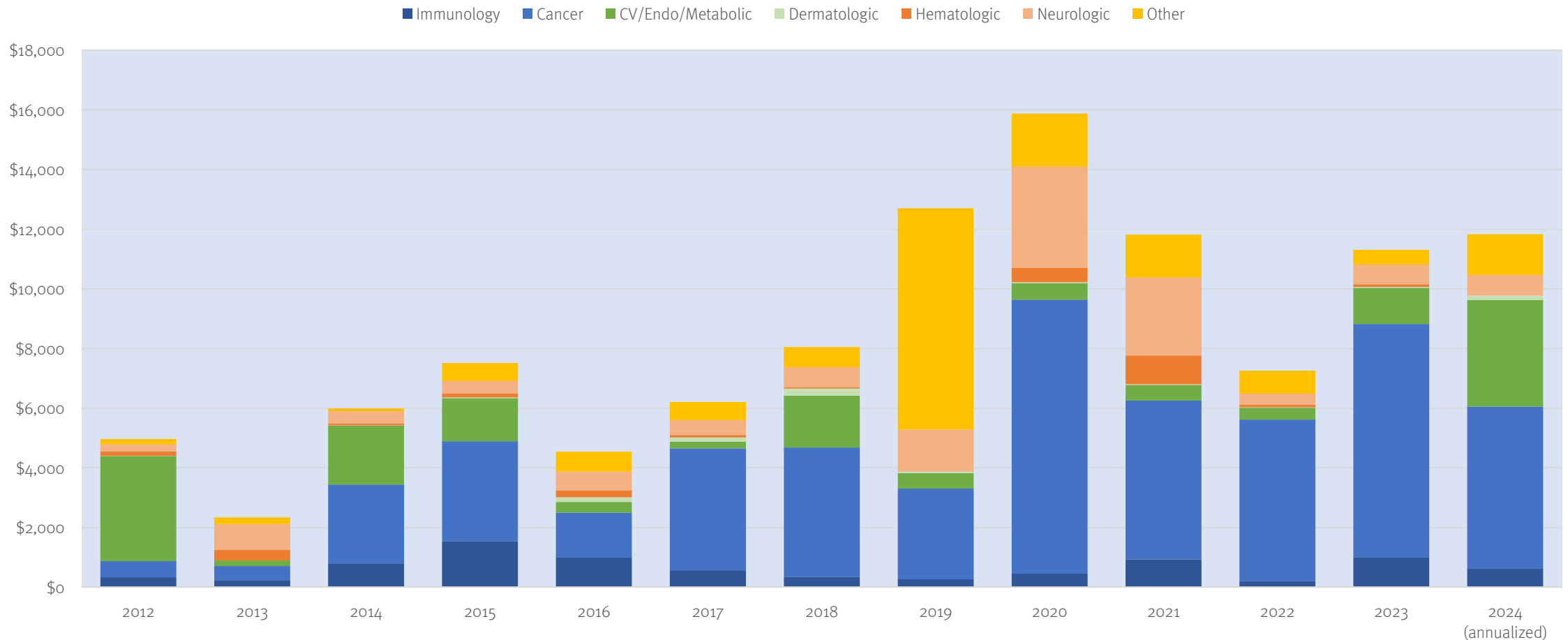
The company expects to close the transaction by the end of March, subject to customary closing conditions, but no additional regulatory or shareholder approvals are required.



Cenerimod, an S1P modulator, has shown slight efficacy in lupus so far. Viatriis gets selatogrel for myocardial infarction.

Licensing Deal Dollar Volume YTD On Track with Volume in 2023 – Big Spike in Cardiometabolic/Endocrine Deal Activity

Biopharma Global Licensing Deals (Total Upfronts \$mm) by Therapeutic Area, 2012 to 2024



Source: DealForma

Novo Nordisk Sticks Down \$1.46B in Biobucks for Molecular Glues with California Biotech

Gabrielle Masson, *FierceBiotech*, Feb 26, 2024 (excerpt)

Novo Nordisk is getting sticky, coming together with Neomorph in a new licensing pact worth up to \$1.46 billion across multiple molecular glue targets.

The Big Pharma has agreed to discover, develop and commercialize molecular glue degraders with California-based biotech Neomorph. In return for access to Neomorph's proprietary glue discovery platform, Novo is giving the biotech the chance to receive upfront and near-term milestone payments, plus R&D funding and future milestone payments for a potential total of \$1.46 billion, according to a Feb. 26 release.

Under the terms of the deal, Neomorph will lead discovery and preclinical activities against unnamed selected targets. Novo Nordisk will then have the option to exclusively pursue further clinical development and commercialization of the compounds.

While the therapeutic indications being pursued weren't specifically disclosed, Neomorph's CEO Phil Chamberlain said that the pact will expand the biotech's platform into new areas beyond oncology.

"By combining Neomorph's proprietary glue discovery platform with Novo Nordisk's vast experience in cardiometabolic and rare diseases, we are well positioned to develop transformative treatments in these areas," Chamberlain said.

Founded in 2020 and backed by investor Deerfield Management Company, the preclinical biotech's mission is to discover new therapeutics that go after 'undruggable' targets.



NEOMORPH

Cancer-Targeting Antibody–Drug Conjugates Drive Deal Frenzy

Melanie Senior, *Nature Biotechnology*, Feb 26, 2024 (excerpt)

Antibody–drug conjugates (ADCs) are driving a multi-billion-dollar dealmaking frenzy. Big pharma is snapping up ADC assets and technologies amid accelerating approvals, broadening indications and advances in ADC design. Over 20 years since the first ADC was approved, the approach — using antibodies’ specificity for targeted delivery of potent cytotoxic drugs — is coming of age.

Pfizer’s \$43-billion acquisition of Seagen and its four marketed ADCs, announced in March 2023, and AbbVie’s \$10.1-billion ImmunoGen purchase in November helped push the total value of ADC deals in 2023 to more than three times that seen in 2022. Both years eclipsed the 2021 deal tally, according to BioCentury. ADCs were also the subject of two of 2023’s biggest partnerships: Merck & Co.’s licensing of three clinical-stage ADCs from Japan’s Daiichi-Sankyo for \$4 billion up front and up to \$22 billion overall, and Bristol Myers Squibb’s \$800-million up-front deal for rights outside China to a bispecific ADC at SystImmune, in phase 1 trials for non-small-cell lung cancer (NSCLC).

Momentum continues in 2024, with Johnson & Johnson’s \$2-billion cash deal for Ambrx Biopharma and a smaller licensing deal with Suzhou, China-based MediLink Therapeutics by Roche, whose management explicitly declared ADCs a “priority area” during the annual J.P. Morgan Healthcare Conference in San Francisco in early January.

The big money reflects a growing and increasingly valuable drug class that some proponents hope may eventually replace some forms of standard chemotherapy. There are now 11 marketed ADCs in the United States, over half of which gained FDA approval in or after 2019 (Table 1). Top-selling Enhertu (trastuzumab deruxtecan) brought in \$1.6 billion last year to Daiichi Sankyo and partner AstraZeneca. By 2028, Enhertu, which links the antibody sold as Herceptin to a topoisomerase inhibitor, will generate sales of \$9 billion, with the entire ADC category predicted to be worth more than three times that, according to Evaluate Pharma. Enhertu’s approved indications have already expanded from human epidermal growth factor receptor (HER)-2-positive breast cancer into gastric cancer and NSCLC, and to breast cancers that express lower levels of HER2.

More deals and investment will likely follow, in part because ADCs offer triple innovation potential: across linker chemistry, cytotoxic payload and antibody. Buyers of ADC conjugation platforms hope to see multiple resulting products. Biotech investors like the high barriers to entry resulting from the need to master multiple skills, and ADCs’ potential to shine as monotherapies. “To have an impact in oncology today, you need a product that can show anticancer activity on its own,” thereby saving on the time, expense and complexity of combination trials, says Graziano Seghezzi, managing partner at Sofinnova, which co-led Mablink’s \$34-million series A in October 2022.

Industry News



Stakeholders Hope Bill Will Create IRA Drug Negotiation Parity Between Biologics and Small Molecules

Greg Slabodkin, *Biospace*, February 29, 2024 (excerpt)

As Medicare price negotiations continue between the Biden Administration and pharma companies for the first 10 drugs impacted by the Inflation Reduction Act, a bipartisan bill seeks to eliminate the law's "pill penalty," in which small molecules lose four years of exclusivity compared to biologics.

Under a provision of the Inflation Reduction Act (IRA), biologics are spared from price negotiations for 13 years following approval, while the grace period for small molecules is only nine years. It's a disparity that some industry stakeholders and lawmakers contend stifles investment and innovation—in the end, harming patients who depend on these medicines.

"Small molecule drugs are critical therapies that Americans with cancer, neurological conditions, and other debilitating diseases rely on every day," Rep. Greg Murphy (R-N.C.), who introduced the new bill to Congress earlier this month, said in a statement. "The IRA's price-fixing scheme shifts research and development away from these life-saving medications, ultimately leaving patients with fewer treatment options."

Called the Ensuring Pathways to Innovative Cures (EPIC) Act, the legislation is meant to "equalize" the negotiating period between biologics and small molecules under the IRA's Drug Price Negotiation Program and ensure continued R&D investments in small molecule drugs.

Incubate, a lobbying group for venture capital firms in the life sciences and critic of the IRA, supports the proposed bill, co-sponsored by Reps. Don Davis (D-N.C.) and Brett Guthrie (R-Ky.), along with Murphy.

Incubate, a lobbying group for venture capital firms in the life sciences and critic of the IRA, supports the proposed bill, co-sponsored by Reps. Don Davis (D-N.C.) and Brett Guthrie (R-Ky.), along with Murphy.

"We worked very closely with Reps. Davis, Guthrie and Murphy for the introduction of the EPIC Act," Incubate Executive Director John Stanford told BioSpace. "We may see similar legislation as well but it all amounts to fixing the small molecule penalty."

Stanford said the IRA's provision is "a real disincentive towards one type of medicine." By creating a price control mechanism after nine years, the IRA effectively "shuts off access to 50% of a drug's revenues which come in years 10 to 13," Stanford added. "That's devastating to the formulas of how we decide to allocate money as investors."

Incubate will put its legislative resources into building support within Congress for the EPIC Act, Stanford said.

Gaurav Gupta, managing partner of J.P. Morgan Life Sciences Private Capital, also sees the EPIC Act as a "hugely positive sign" that progress is being made to address the disparity between biologics and small molecules.

According to the bill's sponsors, pharma companies developing small molecule drugs have already begun pausing clinical trials and halting the pursuit of new cures of this type as a result of the reduced grace period before drug price negotiations could begin.

The EPIC Act Proposal is Simple

1 **SECTION 1. EQUALIZING THE NEGOTIATION PERIOD BE-**
2 **TWEEN SMALL-MOLECULE AND BIOLOGIC**
3 **CANDIDATES UNDER THE DRUG PRICE NEGO-**
4 **TIATION PROGRAM.**

5 (a) **IN GENERAL.**—Section 1192(e)(1)(A)(ii) of the
6 Social Security Act (42 U.S.C. 1320f–1(e)(1)(A)(ii)) is
7 amended by striking “7 years” and inserting “11 years”.

8 (b) **EFFECTIVE DATE.**—The amendment made by
9 subsection (a) shall take effect as if included in the enact-
10 ment of Public Law 117–169.

**Negotiations for small molecules
would start 11 years after market
entry rather than 7 years.**

**Implementation would start at 13
years rather than 9 years.**

Judge Rejects AstraZeneca's Challenge to Medicare Drug Price Negotiations

Annika Kim Constantino, *CNBC*, March 1, 2024 (excerpt)

A federal judge on Friday rejected AstraZeneca's legal challenge to Medicare's new power to negotiate the prices of certain costly prescription drugs with manufacturers.

The decision is another win for the Biden administration in a bitter legal fight with the pharmaceutical industry over the constitutionality of those price talks. The negotiations are a key policy under the Inflation Reduction Act that aims to make medicines more affordable for seniors and could take a bite out of the pharmaceutical industry's profits.

The legal wrangling over the policy is far from over. Manufacturers have said they intend to escalate the issue to the Supreme Court.

The judge's decision came one day before a crucial deadline in the process.

Manufacturers of the first 10 drugs selected for negotiations have until Saturday to respond to Medicare's initial price offer for their treatments. Those drugs include AstraZeneca's Farxiga, which is used to treat Type 2 diabetes, chronic kidney disease and heart failure.

In a 47-page opinion, U.S. District Judge Colm Connolly of the District of Delaware said AstraZeneca has not identified a property protected by the constitution that will be jeopardized by the price talks.

He wrote that AstraZeneca's participation in the Medicare market is voluntary, so the company's "desire" or even "expectation" to sell its drugs to the government "at the higher prices it once enjoyed does not create a protected property interest."

The opportunity to sell drugs to more than 49 million Medicare and Medicaid beneficiaries is a "powerful incentive" for manufacturers to participate in the price talks with the government, Connolly wrote. But he said that incentive is not "a gun to the head" like AstraZeneca contends in its suit.

"It is a potential economic opportunity that AstraZeneca is free to accept or reject," Connolly wrote.

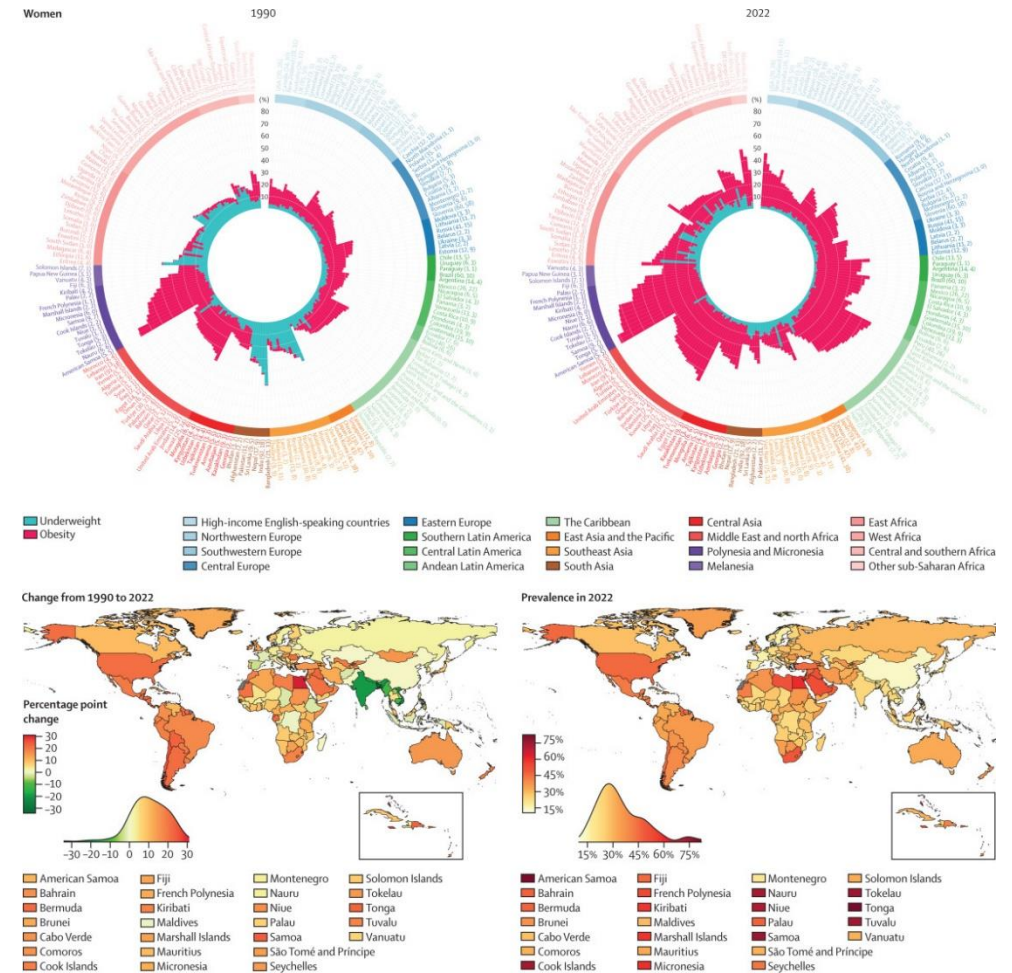


Lancet Study Finds Over A Billion People with Obesity

NCD Risk Factor Collaboration, *The Lancet*, February 29, 2024 (excerpt)

From 1990 to 2022, the combined prevalence of underweight and obesity in adults decreased in 11 countries (6%) for women and 17 (9%) for men with a posterior probability of at least 0·80 that the observed changes were true decreases. The combined prevalence increased in 162 countries (81%) for women and 140 countries (70%) for men with a posterior probability of at least 0·80. In 2022, the combined prevalence of underweight and obesity was highest in island nations in the Caribbean and Polynesia and Micronesia, and countries in the Middle East and north Africa. Obesity prevalence was higher than underweight with posterior probability of at least 0·80 in 177 countries (89%) for women and 145 (73%) for men in 2022, whereas the converse was true in 16 countries (8%) for women, and 39 (20%) for men. From 1990 to 2022, the combined prevalence of thinness and obesity decreased among girls in five countries (3%) and among boys in 15 countries (8%) with a posterior probability of at least 0·80, and increased among girls in 140 countries (70%) and boys in 137 countries (69%) with a posterior probability of at least 0·80. The countries with highest combined prevalence of thinness and obesity in school-aged children and adolescents in 2022 were in Polynesia and Micronesia and the Caribbean for both sexes, and Chile and Qatar for boys. Combined prevalence was also high in some countries in south Asia, such as India and Pakistan, where thinness remained prevalent despite having declined. In 2022, obesity in school-aged children and adolescents was more prevalent than thinness with a posterior probability of at least 0·80 among girls in 133 countries (67%) and boys in 125 countries (63%), whereas the converse was true in 35 countries (18%) and 42 countries (21%), respectively. In almost all countries for both adults and school-aged children and adolescents, the increases in double burden were driven by increases in obesity, and decreases in double burden by declining underweight or thinness.

Source: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(23\)02750-2](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)02750-2)



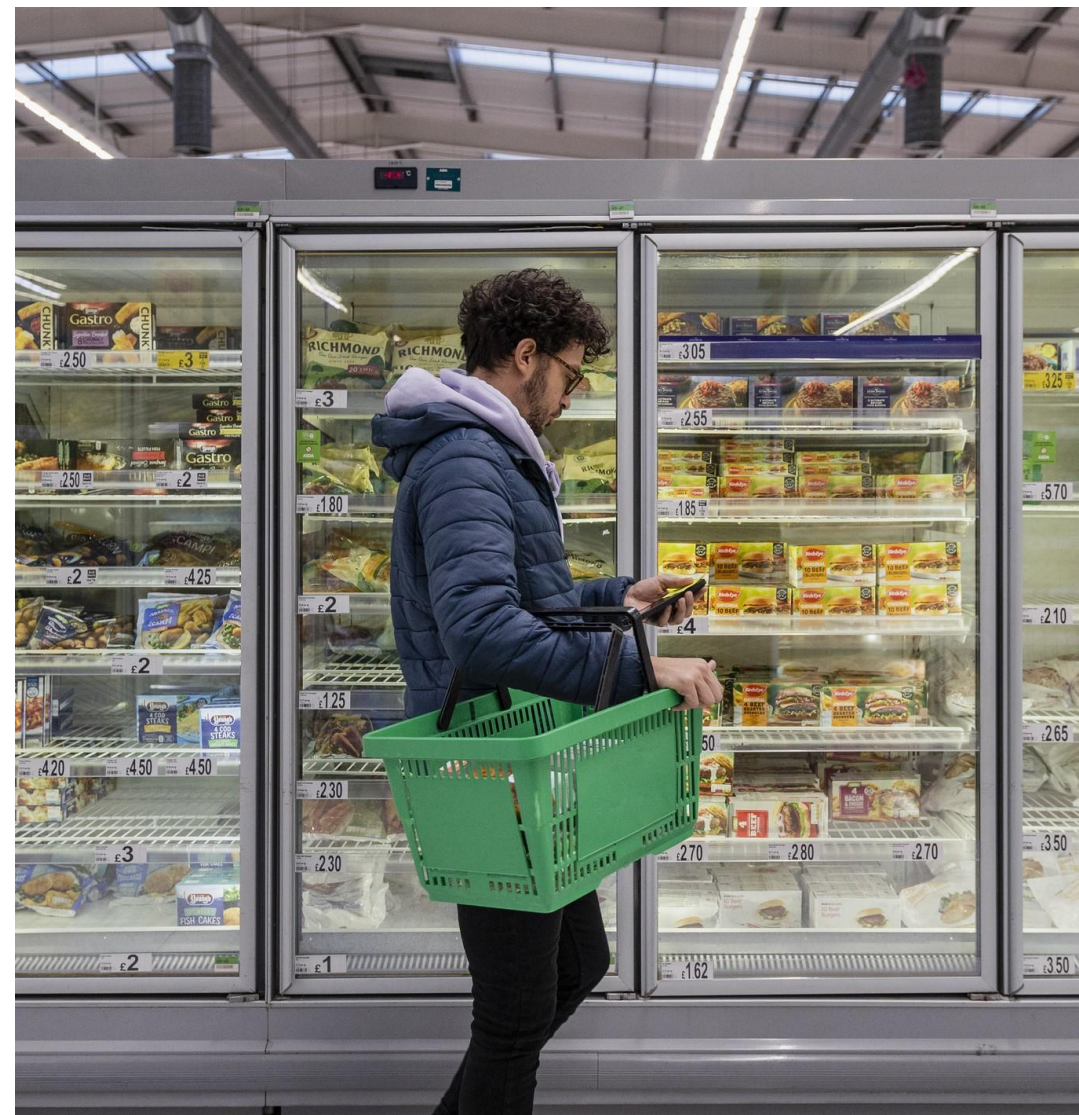
The circular bar plots show the burden of underweight and obesity in 1990 and 2022. The lengths of bars show the age-standardised prevalence of underweight (blue) and obesity (red), and their sum shows the age-standardised combined prevalence. Country names are coloured by region. The numbers in brackets after each country's name show the total number of data sources and the number of nationally representative data sources, respectively. Countries are ordered by decreasing posterior mean combined prevalence within each region. The maps show the change in combined prevalence of underweight and obesity from 1990 to 2022, and its level in 2022. The density plot alongside each map shows the smoothed distribution of estimates across countries.

Ultra-Processed Food Exposure Is Not Good for You

Lane MM et.al., *BMJ*. Feb 28, 2024, 384:e077310 (abstract)

The search identified 45 unique pooled analyses, including 13 dose-response associations and 32 non-dose-response associations (n=9 888 373). Overall, direct associations were found between exposure to ultra-processed foods and 32 (71%) health parameters spanning mortality, cancer, and mental, respiratory, cardiovascular, gastrointestinal, and metabolic health outcomes. Based on the pre-specified evidence classification criteria, convincing evidence (class I) supported direct associations between greater ultra-processed food exposure and higher risks of incident cardiovascular disease related mortality (risk ratio 1.50, 95% confidence interval 1.37 to 1.63; GRADE=very low) and type 2 diabetes (dose-response risk ratio 1.12, 1.11 to 1.13; moderate), as well as higher risks of prevalent anxiety outcomes (odds ratio 1.48, 1.37 to 1.59; low) and combined common mental disorder outcomes (odds ratio 1.53, 1.43 to 1.63; low). **Highly suggestive (class II) evidence indicated that greater exposure to ultra-processed foods was directly associated with higher risks of incident all cause mortality (risk ratio 1.21, 1.15 to 1.27; low), heart disease related mortality (hazard ratio 1.66, 1.51 to 1.84; low), type 2 diabetes (odds ratio 1.40, 1.23 to 1.59; very low), and depressive outcomes (hazard ratio 1.22, 1.16 to 1.28; low), together with higher risks of prevalent adverse sleep related outcomes (odds ratio 1.41, 1.24 to 1.61; low), wheezing (risk ratio 1.40, 1.27 to 1.55; low), and obesity (odds ratio 1.55, 1.36 to 1.77; low).** Of the remaining 34 pooled analyses, 21 were graded as suggestive or weak strength (class III-IV) and 13 were graded as no evidence (class V). Overall, using the GRADE framework, 22 pooled analyses were rated as low quality, with 19 rated as very low quality and four rated as moderate quality.

Source: <https://pubmed.ncbi.nlm.nih.gov/38418082/>

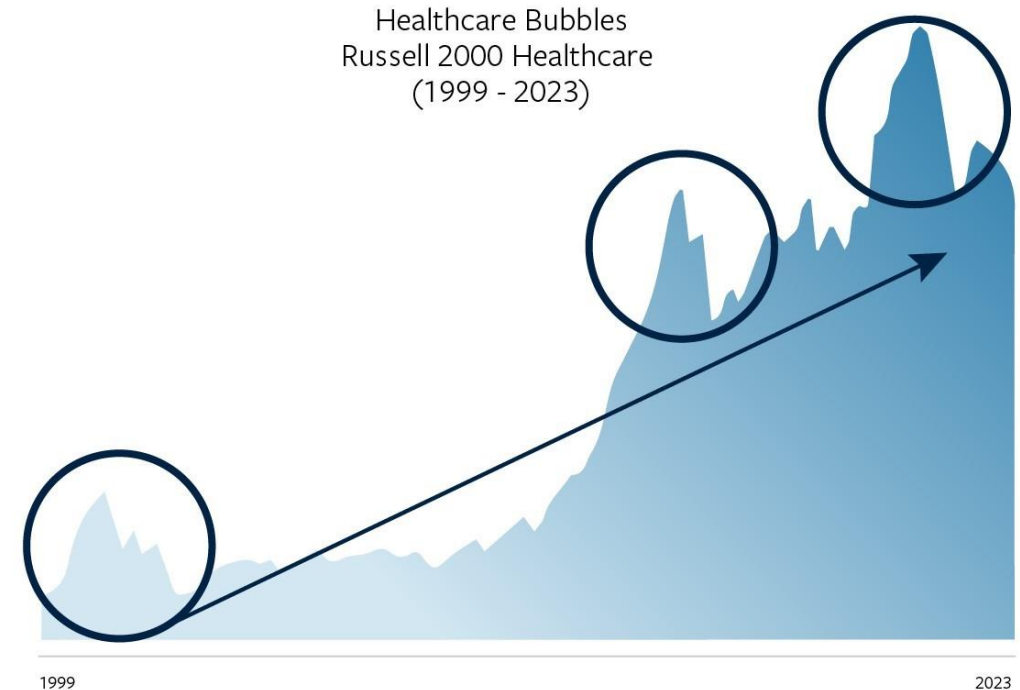


2023: Moving Past the Bubble in Lifescience

Jim Flynn, Deerfield Management, *LinkedIn*, February 16, 2024 (excerpt)

It is a unique and special time in healthcare. The intersection of meaningful data, increasingly powerful interpretive and relational software and proven platform technologies portend a cycle of innovation in therapeutics and healthcare delivery that can substantially lengthen our healthspan – the period over which we live a physically and mentally engaged life - while ultimately decreasing the total cost of care. The rate of progress across disease will vary. Drug discovery will be fastest where genetic clues point the way (for example cancers) and slowest where genetics and environment are confounded and where anatomy and biology present complexity and constraints (like in mental illness). The pace of prevention will likewise follow a path of least to most resistance. The degree of perverse reimbursement incentives, ingrained clinical habits, diagnostic certainty and ability to create low touch patient interactions to keep people on course in preventative care regimens, are all important here. But there should be little doubt that progress as a whole will be rapid and the result will be impressive advances.

There are always speedbumps along the way and about every ten years we run into a rough spot in the healthcare investment space, and biotechnology more specifically. In the rearview mirror these periods have looked awfully similar, with outrageous upmoves in public company valuations followed by less surprising compensating downward moves. The upward movement carries with it a range of predictable behaviors including investors of all types chasing performance by moving to earlier and riskier securities only to eventually find themselves in trouble. Everyone then moves back into their lane with promises to stay there this time. Depending on the magnitude of capital flows in each direction, this can entail significant damage to



capital intensive companies who have neither intact investor syndicates nor an accepting public market to fuel their burning hot engines.

This most recent bubble has been pronounced in both directions, and it has been a tough three-year digestion period. After performance hungry investors and executives with unrealistic views about the value of their technologies populated the public and private markets with dozens of high burn, long duration, low probability companies, there was a necessity to cut burn, focus on more tangible assets and demonstrate the case for realistic value creation. This is how it should be on a normal day in the market, but every decade or so healthcare investors become less discriminating. We have been cautious for some time owing to the structurally unsustainable conditions that had developed, but in the second quarter of 2023 we began to find real value in the market once again.

Pfizer Oncology Innovation Day Highlights

Extraordinary Franchise



2030 Oncology Goals



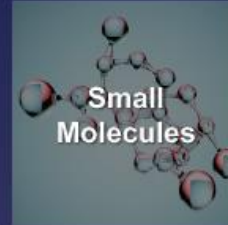
Source: https://s28.q4cdn.com/781576035/files/doc_downloads/2024/02/29/Pfizer-Oncology-Innovation-Day-Presentation_FINAL.pdf

Oncology Strategy to Drive Long-Term Sustainable Growth

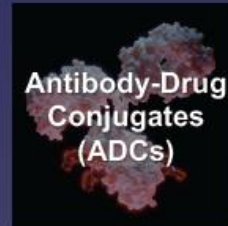
Modality Focus

Enabled by deep technical expertise

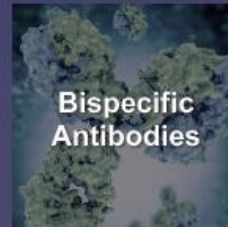
Unique ability to combine and adapt modalities to improve outcomes



World-class structure-guided drug discovery and medicinal chemistry expertise



Next-gen platform aimed at novel targets; improved and differentiated payloads



IO biologics leading with bispecific antibodies, leveraging protein engineering and antibody design

Therapeutic Area Focus

Building on established presence

Deepen our ability to address unmet medical needs across care continuum



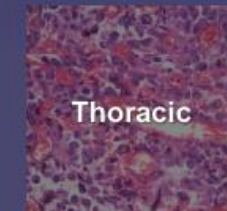
Across subtypes



Prostate Cancer
Urothelial Cancer



Multiple Myeloma
Lymphoma



Non-Small Cell Lung Cancer
Head & Neck Cancer

Accelerating New Standards of Care

Deep and Diverse Pipeline Within Focused Therapeutic Areas



	Breast	Genitourinary	Hematology-Oncology	Thoracic
Select approved products	IBRANCE palbociclib TUKYSA tucatinib 20 mg / 150 mg tablets	PADCEV enfortumab vedotin-efy enfortumab vedotin-efy Xtandi (enzalutamide) TALZENNA + Xtandi talazoparib (enzalutamide) 400 mg tablets / 150 mg tablets	ELREXFIO (elranatamab-biomim) ADCETRIS brentuximab vedotin Bosulif bosutinib tablets BESPENSA bexatazine capsules	LORBRENA lorlatinib XALKORI crizotinib BRAFTOVI + MEKTOVI (encorafenil) 450 mg capsules (dabrafenib) 75 mg tablets
Select clinical pipeline	Atirmociclib ⁵ (CDK4i) Vepdegestrant ⁵ (PROTAC ER degrader) Felmetatug vedotin ⁶ (B7H4) Disitamab vedotin ⁶ (HER2) KAT6i ⁵ CDK2i ⁵ (PF-07248144) (PF-07104091)	Sasanlimab ⁷ (PD-1) Disitamab vedotin ⁶ (HER2) Mevrometostat ⁵ (EZH2)	Maplirpacept ⁷ (CD47 SIRPα) CD70 ⁷ (PF-08046040) CD30 ⁶ (PF-08046045)	Sigvotatug vedotin ⁶ (IB6) PD-L1 ^{6,10} (PF-08046054) CEACAM5 ⁶ (PF-08046050) EGFR ^{7,10} (PF-08046052)

Selected preclinical pipeline (FIP anticipated in 2024): STING^{5,8}, LILRB1/2⁷, αLTβR^{7,9}, mesothelin-TOPO1⁶, CD30-TOPO1^{6,8}

Crym-Positive Striatal Astrocytes Gate Perseverative Behavior

Ollivier, M., Soto, J.S., Linker, K.E. et al., *Nature*, Feb 28, 2024.

Astrocytes are heterogeneous glial cells of the central nervous system. However, the physiological relevance of astrocyte diversity for neural circuits and behaviour remains unclear. Here we show that a specific population of astrocytes in the central striatum expresses μ -crystallin (encoded by *Crym* in mice and *CRYM* in humans) that is associated with several human diseases, including neuropsychiatric disorders. In adult mice, reducing the levels of μ -crystallin in striatal astrocytes through CRISPR–Cas9-mediated knockout of *Crym* resulted in perseverative behaviours, increased fast synaptic excitation in medium spiny neurons and dysfunctional excitatory–inhibitory synaptic balance. Increased perseveration stemmed from the loss of astrocyte-gated control of neurotransmitter release from presynaptic terminals of orbitofrontal cortex–striatum projections. We found that perseveration could be remedied using presynaptic inhibitory chemogenetics, and that this treatment also corrected the synaptic deficits. Together, our findings reveal converging molecular, synaptic, circuit and behavioural mechanisms by which a molecularly defined and allocated population of striatal astrocytes gates perseveration phenotypes that accompany neuropsychiatric disorders. Our data show that *Crym*-positive striatal astrocytes have key biological functions within the central nervous system, and uncover astrocyte–neuron interaction mechanisms that could be targeted in treatments for perseveration.

This article by a group of UCLA neuroscientists makes a persuasive argument that single gene changes in the astrocyte rather than the neuron can lead to repetitive behaviors in diseases like obsessive-compulsive behavior.



Baljit Khahk, UCLA Brain Research Institute

A Multi-ancestry Genetic Study of Pain Intensity in 598,339 Veterans

Toikumo, S., Vickers-Smith, R., Jinwala, Z. et al. Nat Medicine, March 1, 2024 (excerpt)

Chronic pain is a common problem, with more than one-fifth of adult Americans reporting pain daily or on most days. It adversely affects the quality of life and imposes substantial personal and economic costs. Efforts to treat chronic pain using opioids had a central role in precipitating the opioid crisis. Despite an estimated heritability of 25–50%, the genetic architecture of chronic pain is not well-characterized, in part because studies have largely been limited to samples of European ancestry. To help address this knowledge gap, we conducted a cross-ancestry meta-analysis of pain intensity in 598,339 participants in the Million Veteran Program, which identified 126 independent genetic loci, 69 of which are new. **Pain intensity was genetically correlated with other pain phenotypes, level of substance use and substance use disorders, other psychiatric traits, education level and cognitive traits.** Integration of the genome-wide association studies findings with functional genomics data shows enrichment for putatively causal genes ($n = 142$) and proteins ($n = 14$) expressed in brain tissues, specifically in GABAergic neurons. Drug repurposing analysis identified anticonvulsants, β -blockers and calcium-channel blockers, among other drug groups, as having potential analgesic effects. Our results provide insights into key molecular contributors to the experience of pain and highlight attractive drug targets.

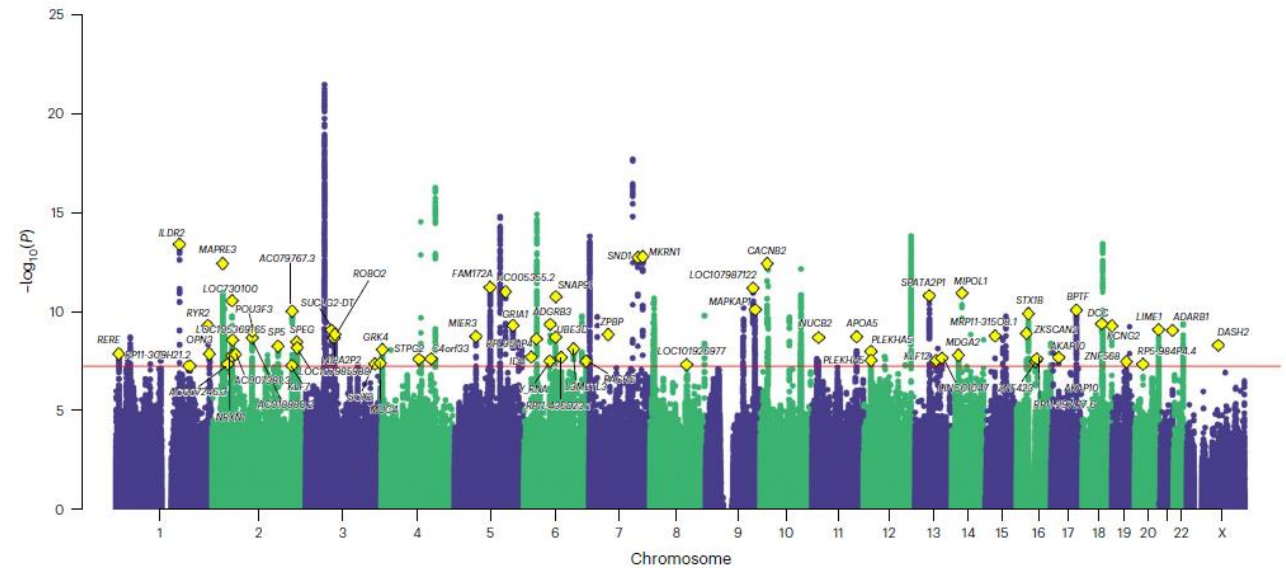


Fig. 1 | Manhattan plot for the pain intensity cross-ancestry GWAS meta-analysis ($n = 598,339$). This identified 126 independent index variants. The nearest gene to the 69 new loci (68 autosomal and 1X-chromosomal) is annotated. SNPs above the red line are GWS after correction for multiple testing ($P < 5 \times 10^{-8}$).

Endothelial Cells Drive Organ Fibrosis in Mice by Inducing Expression of the Transcription Factor SOX9

Trogisch FA, Heineke J., *Science Translational Medicine*, Feb 28 2024 (abstract)

Fibrosis is a hallmark of chronic disease. Although fibroblasts are involved, it is unclear to what extent endothelial cells also might contribute. We detected increased expression of the transcription factor Sox9 in endothelial cells in several different mouse fibrosis models. These models included systolic heart failure induced by pressure overload, diastolic heart failure induced by high-fat diet and nitric oxide synthase inhibition, pulmonary fibrosis induced by bleomycin treatment, and liver fibrosis due to a choline-deficient diet. We also observed up-regulation of endothelial SOX9 in cardiac tissue from patients with heart failure. To test whether SOX9 induction was sufficient to cause disease, we generated mice with endothelial cell-specific overexpression of Sox9, which promoted fibrosis in multiple organs and resulted in signs of heart failure. Endothelial Sox9 deletion prevented fibrosis and organ dysfunction in the two mouse models of heart failure as well as in the lung and liver fibrosis mouse models. Bulk and single-cell RNA sequencing of mouse endothelial cells across multiple vascular beds revealed that SOX9 induced extracellular matrix, growth factor, and inflammatory gene expression, leading to matrix deposition by endothelial cells. Moreover, mouse endothelial cells activated neighboring fibroblasts that then migrated and deposited matrix in response to SOX9, a process partly mediated by the secreted growth factor CCN2, a direct SOX9 target; endothelial cell-specific Sox9 deletion reversed these changes. These findings suggest a role for endothelial SOX9 as a fibrosis-promoting factor in different mouse organs during disease and imply that endothelial cells are an important regulator of fibrosis.

Source: <https://www.science.org/doi/10.1126/scitranslmed.abq4581>.

A group of researchers led by Joerg Heineke have identified a novel driver of organ fibrosis. Endothelial cells are important drivers of fibrosis in heart failure, pulmonary fibrosis, and liver fibrosis mouse models and SOX9 is a key transcription factor in this process. The contribution of endothelial cells in fibrosis has also been emphasized recently by Alentis.



Joerg Heineke (Heidelberg U)

Disclosure



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