



Biopharmaceutical Sector

Weekly Update – Feb 5, 2024

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[August 7, 2023](#) (Employment, Summer reading)
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[June 19, 2023](#) (Generative AI)
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[May 29, 2023](#) (Oncology update)
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Join Us at Biotech Hangout This Friday



Biotech Hangout held its latest event on Feb 2, 2024.

The next event will be on February 9, 2024.

Feb 2, 2024 Replay: <https://twitter.com/i/spaces/1rmGPMerXOYJN>

Feb 9, 2024 Session: <https://twitter.com/i/spaces/1YqxoDZNLyBKv>

Please join us.

To Learn More

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



Bio-Europe Spring Barcelona, Mar 18 to 20

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
yeungn@stifel.com

Macroeconomics Update



The US Didn't Just Avoid a Recession — It's Adding Hundreds of Thousands of New Jobs

Paul Wiseman, AP News, Feb 2, 2024

WASHINGTON (AP) — The nation's employers delivered a stunning burst of hiring to begin 2024, adding 353,000 jobs in January in the latest sign of the economy's continuing ability to shrug off the highest interest rates in two decades.

Friday's government report showed that last month's job gain — roughly twice what economists had predicted — topped the December gain of 333,000, a figure that was itself revised sharply higher. The unemployment rate stayed at 3.7%, just above a half-century low.

Wages rose unexpectedly fast in January, too. Average hourly pay climbed a sharp 0.6% from December, the fastest monthly gain in nearly two years, and 4.5% from January 2023. The strong hiring and wage growth could complicate or delay the Federal Reserve's intention to start cutting interest rates later this year.

The latest gains showcased employers' willingness to keep hiring to meet steady consumer spending. It comes as the intensifying presidential campaign is pivoting in no small part on views of President Joe Biden's economic stewardship. Public polls show widespread dissatisfaction largely because even though inflation has sharply slowed, most prices remain well above pre-pandemic levels. Some recent surveys, though, show public approval gradually improving.



US Payrolls and Wages Surge, Likely Keeping Fed Rates on Hold

Augusta Saraiva, *Bloomberg*, Feb 2, 2024 (excerpt)

US employers added the most workers in a year and wages jumped in a surprise reacceleration in the labor market that will likely keep the Federal Reserve from cutting interest rates soon.

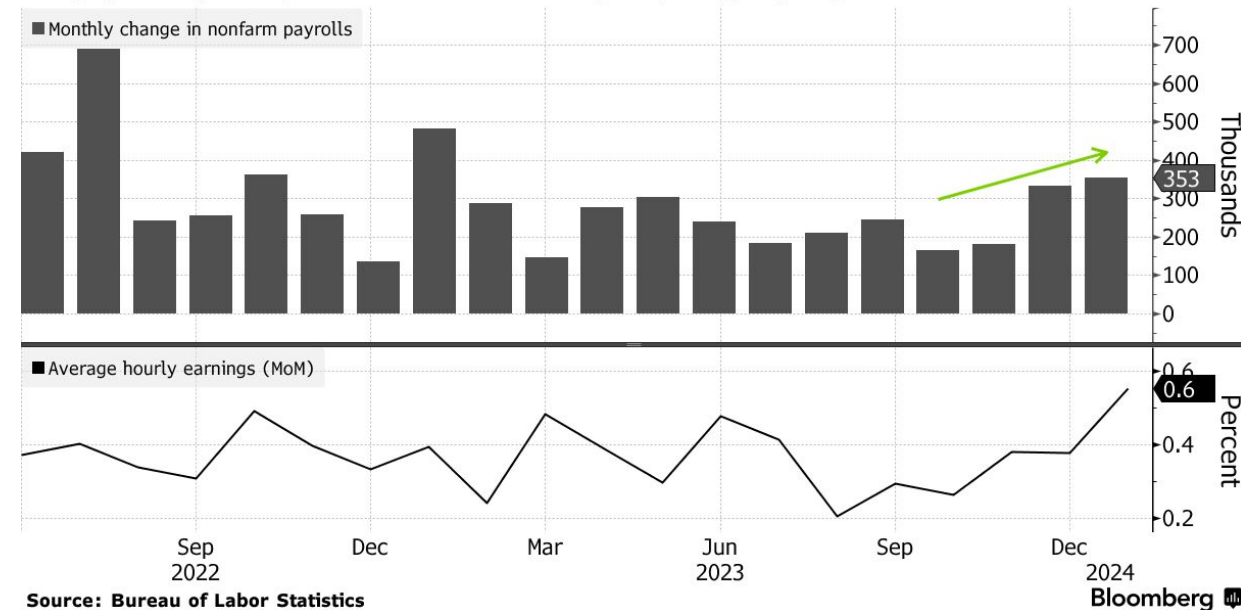
Nonfarm payrolls surged 353,000 last month following upward revisions to the prior two months, a Bureau of Labor Statistics report showed Friday. The unemployment rate held at 3.7%. Hourly wages accelerated from a month earlier, increasing by the most since March 2022.

Treasury yields, the S&P 500 Index and the dollar all rose. Swap contracts tied to Fed meeting dates further reduced the possibility of the US central bank cutting rates as soon as March. Traders also trimmed the total cuts they see for all of 2024.

“It certainly justifies the Fed staying on hold,” said Kathy Jones, Charles Schwab’s chief fixed-income strategist. “The economy is strong enough to generate a high level of jobs and hourly earnings running at 4.5% suggests potential inflation from demand to many at the Fed.”

Blockbuster Report

US payrolls pick up steam into the new year, wages jump



Biopharma Market Update



The XBI Closed at 88.0 Last Friday (Feb 2), Down 0.3% for the Week

Last week the XBI was basically flat. Our measure of total biotech market value rose by 1.7% and is now up 6.6% for the year to date.

Biotech Stocks Up Last Week

Return: Jan 20 to Feb 2, 2024

Nasdaq Biotech Index: -0.5%

Arca XBI ETF: -0.3%

Stifel Global Biotech EV (adjusted): +1.7%*

S&P 500: 1.4%

Return: Jan 1 to Feb 2, 2024

Nasdaq Biotech Index: +0.4%

Arca XBI ETF: -1.5%

Stifel Global Biotech EV (adjusted): 6.6%*

S&P 500: +4.0%

VIX Up Slightly

Jan 20: 19.9%

May 26: 18.0%

July 21: 13.6%

Sep 29: 17.3%

Oct 27: 21.2%

Dec 29: 12.45%

Jan 19, 2024: 13.3%

Jan 26, 2024: 13.26%

Feb 2, 2024: 13.8%

10-Year Treasury Yield Down

Jan 20: 3.48%

May 26: 3.8%

July 21: 3.84%

Sep 29: 4.59%

Oct 27: 4.86%

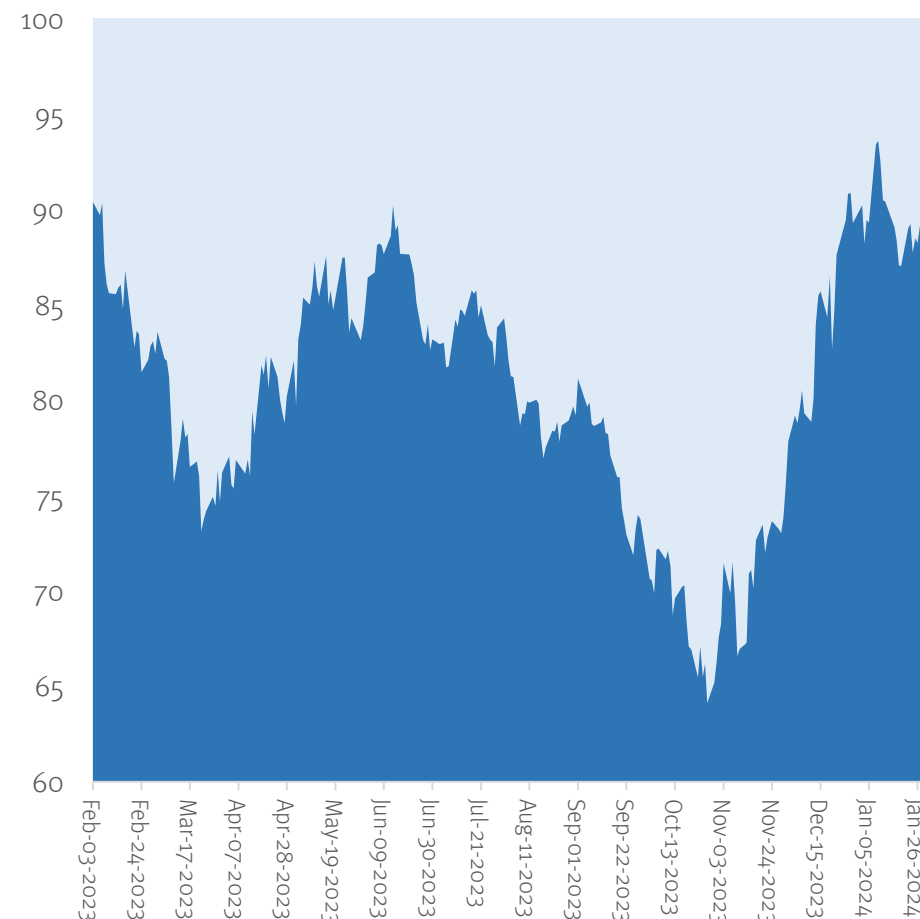
Dec 29: 3.88%

Jan 19, 2024: 4.15%

Jan 26, 2024: 4.15%

Feb 2, 2024: 4.02%

XBI, Feb 3, 2023 to Feb 2, 2024

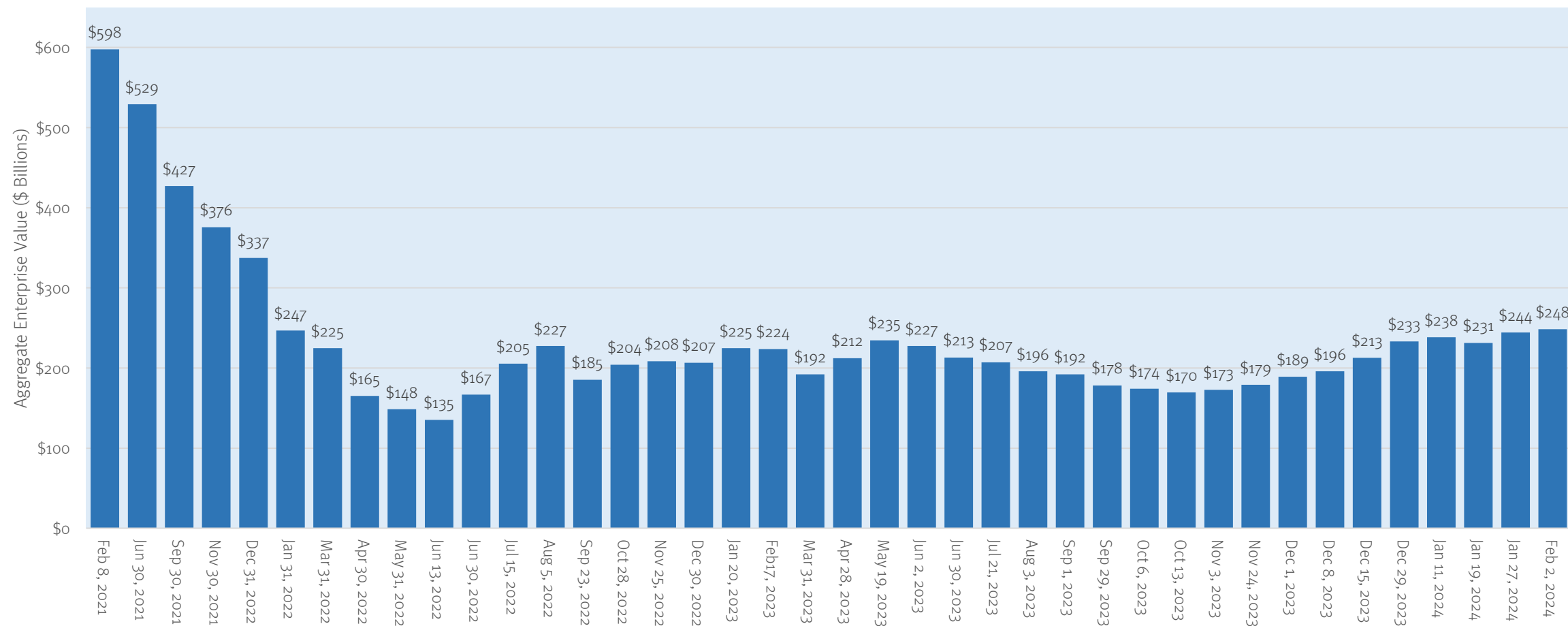


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Total Global Biotech Sector Value Rose 1.7% Last Week

The total enterprise value of the global biotech sector is up 6.6% for the year to date on an addition/exit corrected basis.* The rally that started 14 weeks ago picked up more momentum last week.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Feb 2, 2024 (\$ Billions)

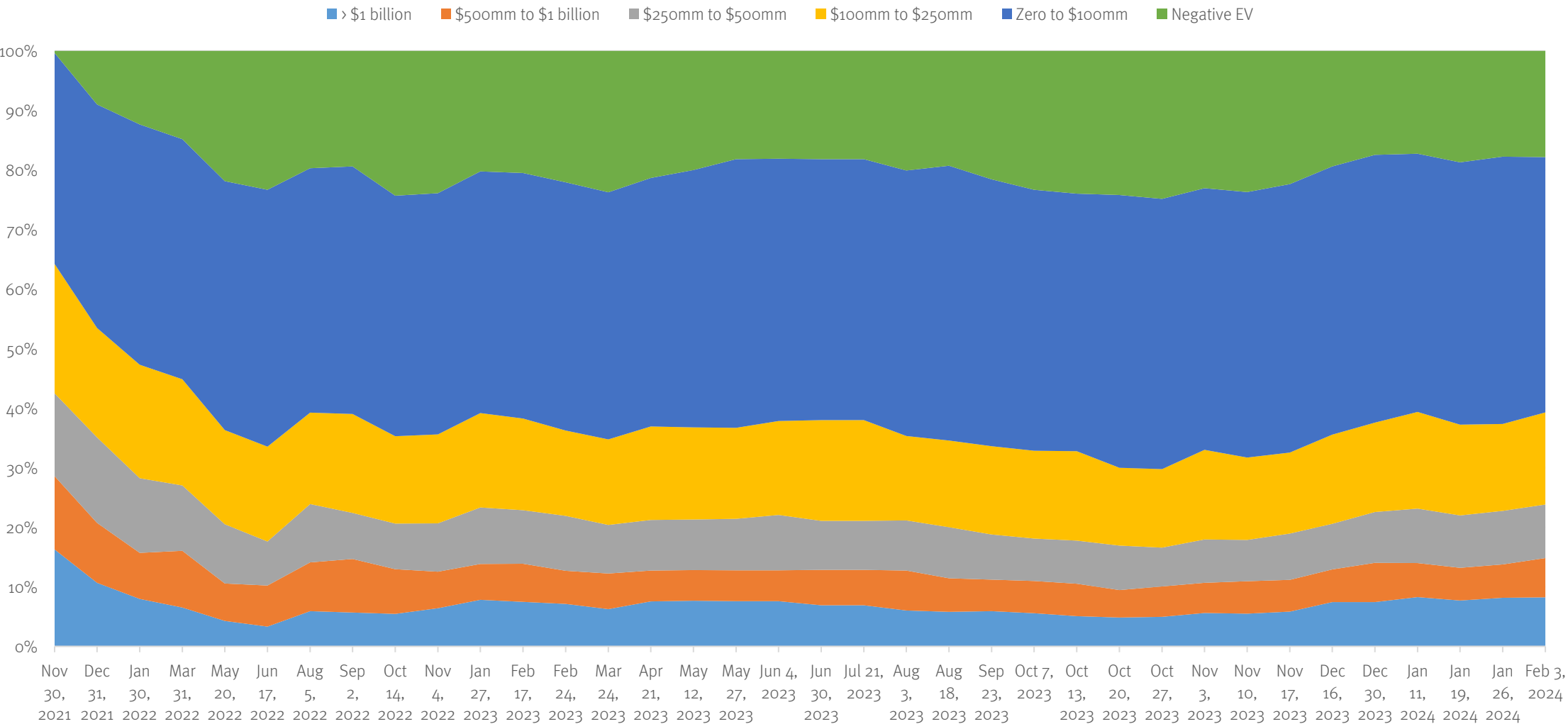


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Global Biotech Neighborhood Analysis

Last week saw continued growth in the wealthier population of the sector.

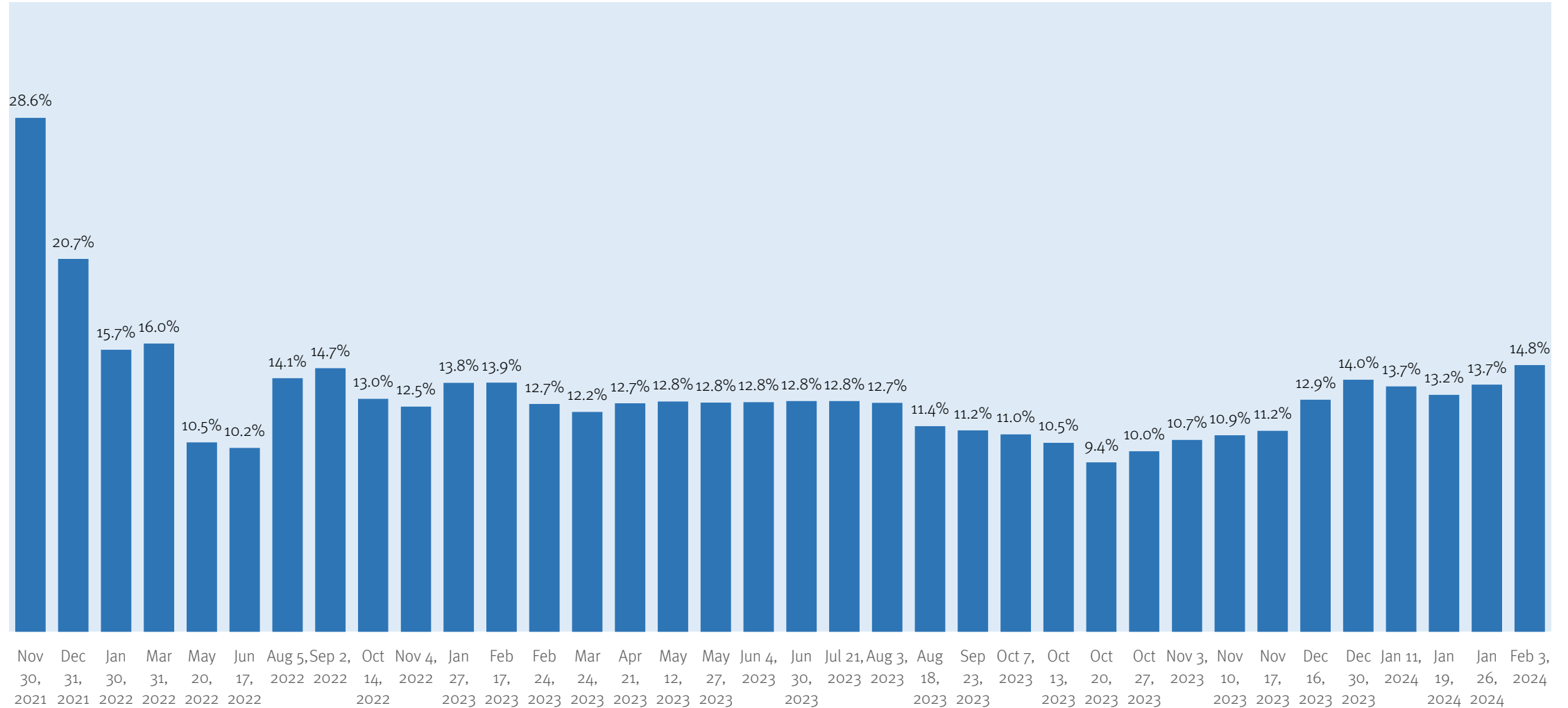
Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Feb 2, 2024



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

Fraction of Biotechs Worth over \$500 Million Rising

Percent of Biotechs with an Enterprise Value of \$500mm or More



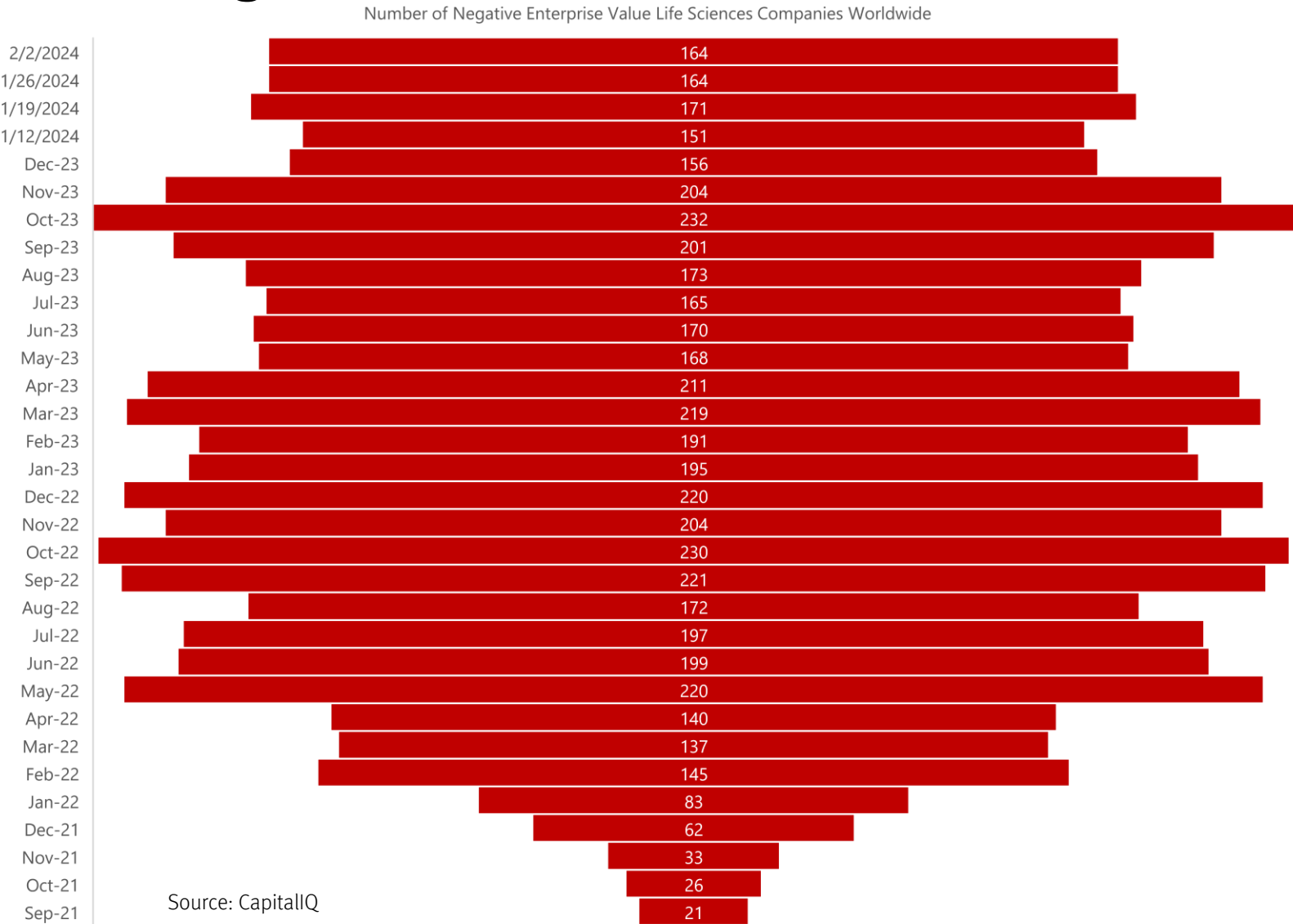
Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Life Sciences Sector Total Value Flat Last Week

Last week saw no change in overall life sciences stocks worldwide. CDMO's and biotech were up while commercial pharma was flat. Diagnostics were down 1.2% and pharma services were down 1.7%.

Sector	Firm Count	Enterprise Value (Jan 26, 2024, \$millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	\$80,158	-1.7%	-7.4%	-6.6%
Biotech	808	\$248,241	1.7%	-2.7%	-5.1%
CDMO	40	\$145,734	2.5%	0.0%	-28.0%
Diagnostics	82	\$266,213	-1.2%	-5.3%	-0.5%
OTC	30	\$27,939	0.9%	-1.2%	-8.8%
Pharma	721	\$5,981,996	0.0%	1.4%	3.6%
Pharma Services	39	\$190,457	-1.7%	-7.9%	-15.7%
Tools	51	\$684,387	1.0%	-0.6%	-12.0%
Devices	181	\$1,646,080	-0.5%	0.4%	1.6%
HCIT	11	\$21,288	-1.0%	-7.3%	-33.0%
Total	2044	\$9,280,494	0.0%	0.4%	0.6%

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



The count of negative EV life sciences companies worldwide stayed at 164 last week.

Source: CapitalIQ

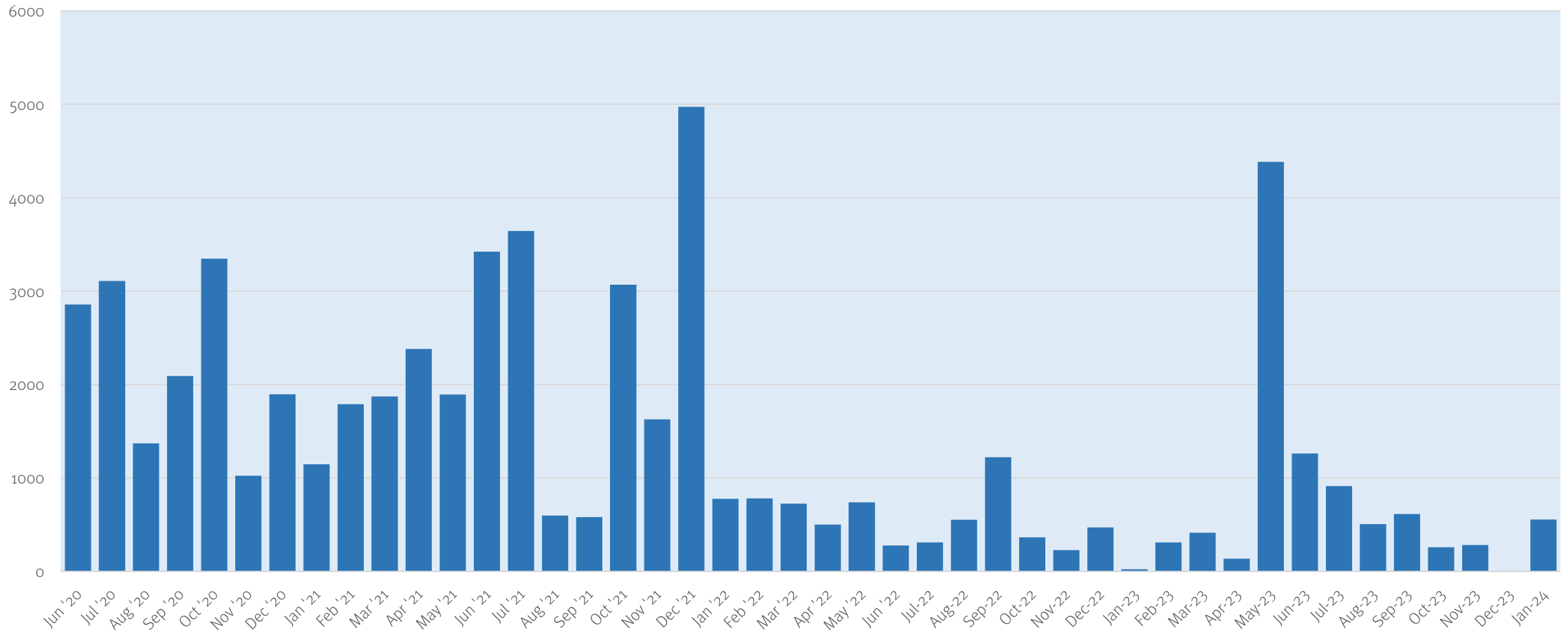
Capital Markets Update



Two More IPO's Last Week

We saw Alto Neuroscience and Fractyl Health go public last week, making four IPOs in two weeks. The market is definitely reopening. Total IPO volume for January 2024 was \$555 million.

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



Source: Data from CapitalIQ and Stifel research.



Fractyl Health Prices \$110 Million IPO in Middle of Range

Anna Brown, *Endpoints News*, Jan 22, 2024 (excerpt)

The company, backed by Investment firm Mithril Capital and venture capital firm General Catalyst, priced its offering of 7.3 million shares at \$15 per share. The company earlier expected the IPO to be priced between \$14 and \$16 per share.

Lexington, Massachusetts-based Fractyl Health develops "disease-modifying" therapies that target organ-level root causes to treat metabolic diseases like type-2 diabetes and obesity.

Source: <https://www.reuters.com/markets/deals/fractyl-health-prices-us-ipo-below-range-raise-110-mln-2024-02-02/>

PIONEERING BREAKTHROUGH THERAPIES TO TREAT TYPE 2 DIABETES (T2D) AND OBESITY

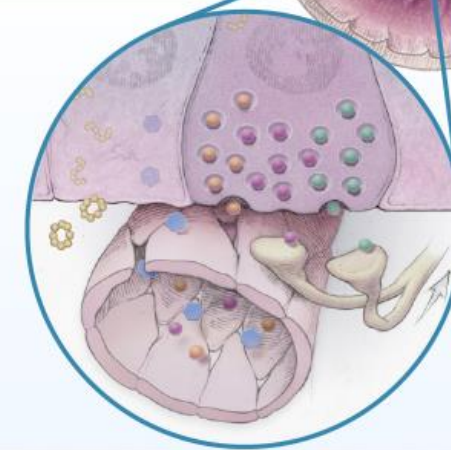
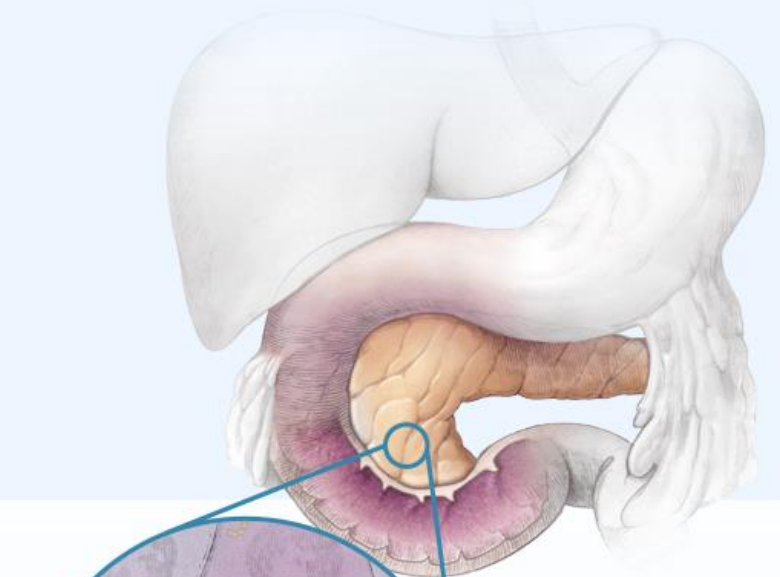
Our vision is to develop transformative therapies that have the potential to prevent and eliminate metabolic diseases. We are a mission-driven team of innovators, singularly focused on developing therapies that are designed to target root causes of T2D and obesity and delivering those therapies to patients as broadly and rapidly as possible.

OUR CLINICAL STUDIES

OUR SCIENCE

OUR PUBLICATIONS

OUR PRESENTATIONS



REVITA®

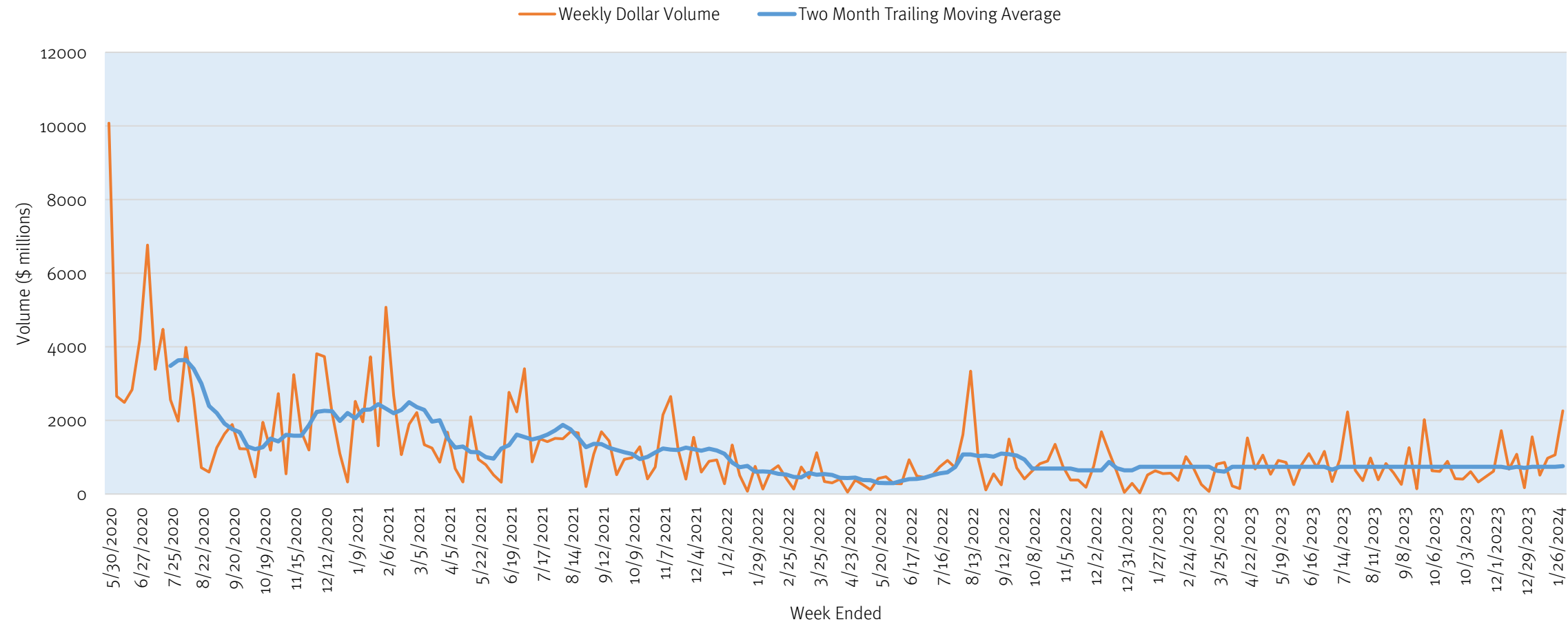
Revita is an outpatient procedural therapy designed to durably modify duodenal dysfunction via hydrothermal ablation in order to restore metabolic health.

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Follow-On Market Strong Last Week

Last week saw roughly \$2.6 billion in follow-on offerings in the market. The largest offering was a \$750mm raise by Vaxcyte. This was the biggest week since August of 2022.

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

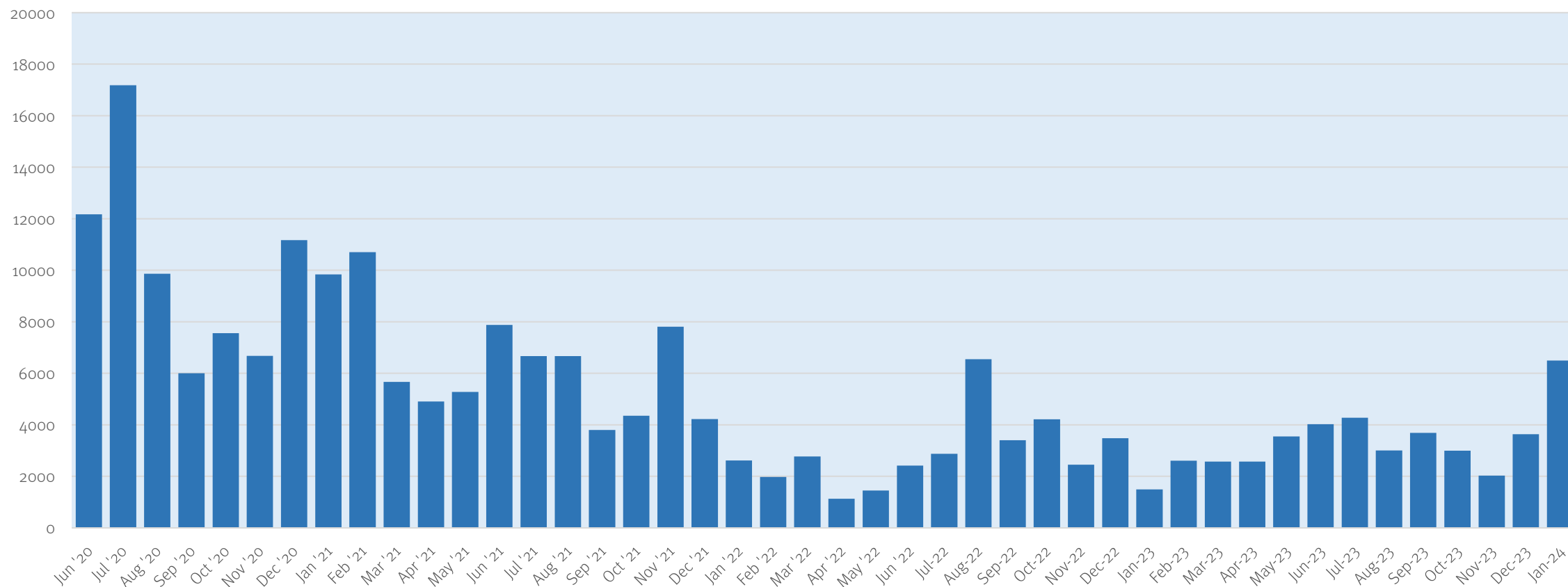


Source: Data from CapitalIQ and Stifel research.

January Was a Barnburner Month for Follow-Ons

The follow-on market saw \$6.5 billion in issuance. This matched the volume seen in August 2022 and marks a return to a normal, active follow-on market.

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



PIPEs: An Increasingly Important Source of Liquidity for Biotech

Brian Gormley, Wall Street Journal, February 1, 2024

Some venture firms are pumping money into publicly traded biotechnology companies, as falling share prices prompt these investors to expand their search for bargains to the public markets.

Private investments in public equities, or PIPEs, are financing deals publicly traded companies strike with a group of investors. Biotech companies in the U.S. raised 56 PIPEs for more than \$4.56 billion in proceeds in 2023, according to investment bank William Blair.

Both totals are the highest the firm has recorded since it began tracking these financings in 2015.

Investors in PIPEs typically focus mostly or entirely on public companies. But these deals also attract venture capitalists seeking to support newly public portfolio companies, or make initial investments in public biotechs that they see as good values.

The amount venture capitalists devote to public companies is small compared with their investment in private ones. VCs funneled nearly \$23 billion into U.S. and European biotech startups in 2023, according to HSBC Innovation Banking, which serves technology and life sciences companies and investors.

However, these investors have more opportunities to join public financing deals because many portfolio companies that went public in recent years are raising capital again, sometimes at prices well below their initial public offering. Venture firms also are joining PIPEs tied to reverse mergers, in which a startup goes public by merging with a public company.

In some cases, venture firms seek to make initial investments through PIPEs. Lightspeed Venture Partners, for example, in September became a new investor in cancer drugmaker Olema Pharmaceuticals, which does business as Olema Oncology, by participating in a \$130 million PIPE.

“I have never seen this difficult a financing market in my career,” said Lawrence Blatt, chief executive of drugmaker Aligos Therapeutics, which raised a PIPE in October from investors including Roche Venture Fund. “It isn’t going to be every biotech company that can do a PIPE.”

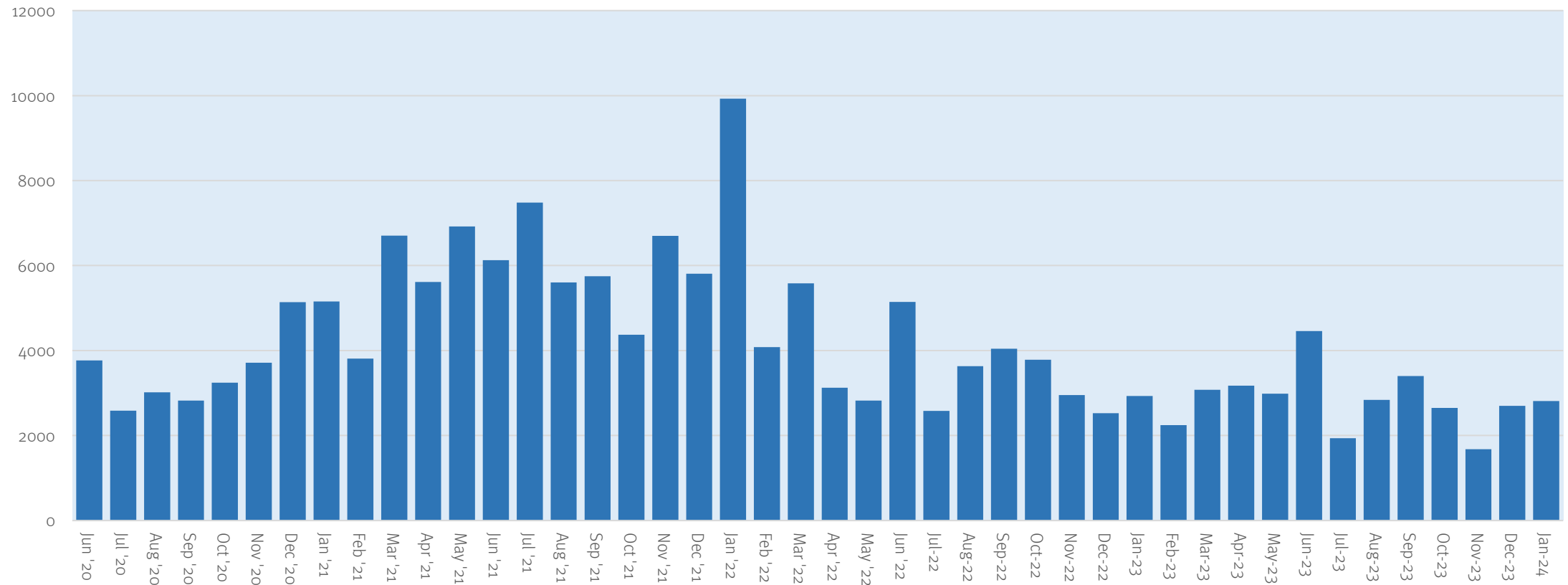
Source: <https://www.wsj.com/articles/biotech-vcs-turn-to-public-investments-in-search-of-value-e8242142>



January Equity Privates Volume Was Steady

Last month was steady in the privates market with \$2.8 billion in issues. Last week saw two \$100mm+ issues. One by Cour (\$105 million) and one by Inari (\$103 million).

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



COUR Pharmaceuticals Secures \$105 Million in Series A Financing Co-Led by Lumira Ventures and Alpha Wave Ventures

CHICAGO, Jan. 30, 2024 (GLOBE NEWSWIRE) -- COUR Pharmaceuticals, a clinical-stage biotechnology company focused on the development of first-in-class, disease modifying therapies designed to induce antigen-specific tolerance for immune-mediated diseases, today announced the closing of a Series A investment round, securing approximately \$105 million in financing. The investment was co-led by Lumira Ventures and Alpha Wave Ventures, with participation from Roche Venture Fund, Pfizer (as part of the Pfizer Breakthrough Growth Initiative), Bristol Myers Squibb, Angelini Ventures, and the JDRF T1D Fund. In connection with the financing, Benjamin “Beni” Rovinski, Ph.D., Managing Director of Lumira Ventures, and Simon Greenwood, Senior Investment Director of Roche Venture Fund, will join the COUR Board of Directors.

The proceeds will enable COUR to advance multiple, wholly owned product candidates that leverage the company’s immune tolerance platform, including Phase 2a proof-of-concept clinical studies in Myasthenia Gravis and Type 1 Diabetes, and other pipeline opportunities. These product candidates, in addition to existing Phase 2 partnered programs with Takeda Pharmaceuticals in Celiac Disease and Ironwood Pharmaceuticals in Primary Biliary Cholangitis, continue to strengthen COUR’s position as the leader in antigen-specific immune tolerance.

Benjamin “Beni” Rovinski, Ph.D., managing director of Lumira Ventures added, “There is an urgent need for innovative strategies aimed at restoring self-tolerance safely and more effectively in autoimmune disorders. We believe COUR's proprietary and strongly differentiated platform is a versatile and first-in-class approach to meet this critical medical need. We are dedicated to collaborating with COUR and its partners to help advance these potentially cutting-edge treatments for immune-related diseases.”

Source: <https://www.globenewswire.com/news-release/2024/01/30/2819700/0/en/COUR-Pharmaceuticals-Secures-105-Million-in-Series-A-Financing-Co-Led-by-Lumira-Ventures-and-Alpha-Wave-Ventures.html>



"The impressive syndicate of thought-leading investors and prominent strategic investors is a testament to COUR's platform technology and our paradigm-changing potential for patients impacted by a variety of autoimmune diseases. We are excited to have this support as we advance our pipeline and revolutionize antigen-specific immune tolerance while avoiding immune system suppression in our mission to potentially bring to market life changing therapies for patients."

John Puisis

Chief Executive Officer
Cour Pharmaceuticals

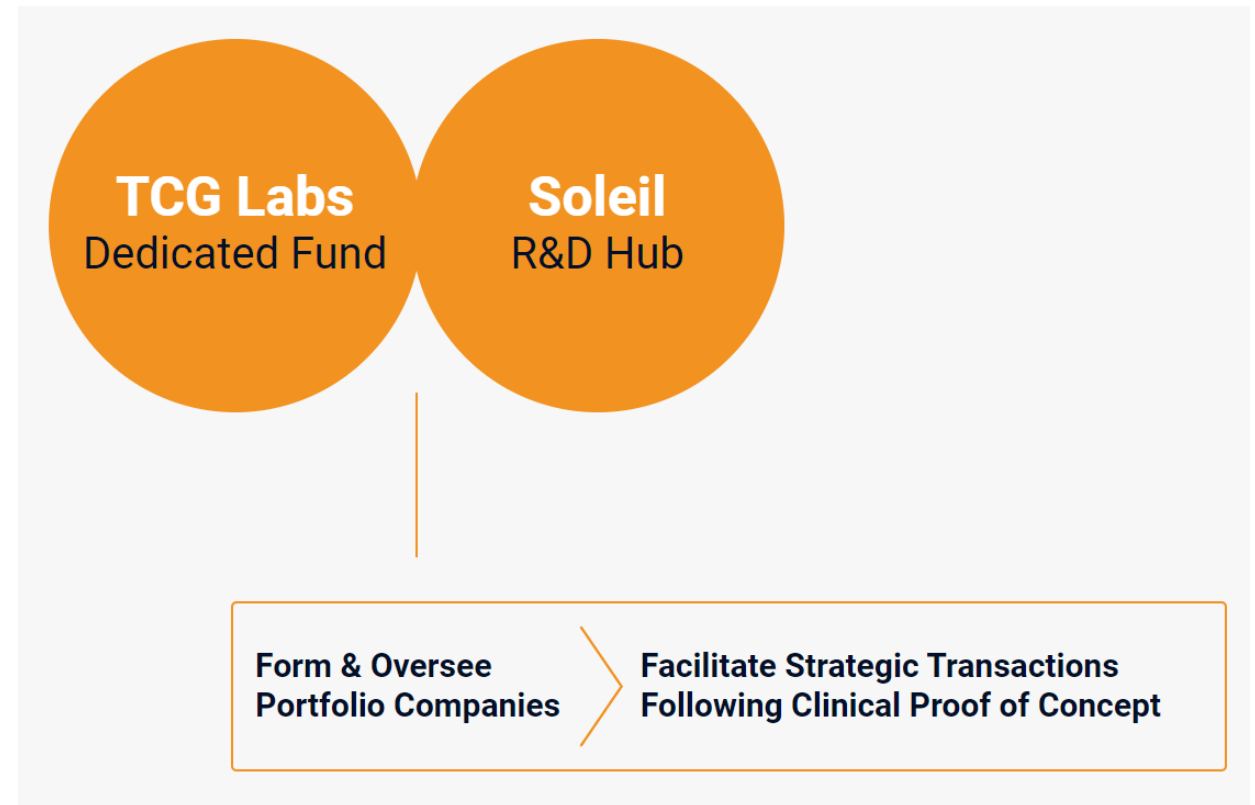
The Column Group Dedicates \$400mm to an Antibody Development Effort

Kyle LaHucik, *Endpoints News*, Feb 1, 2024 (excerpt)

As the biotech industry grapples with how to fund drug development in a world of increasing research costs, rising drug prices and government-related risk, a legacy investor is taking a different approach for its 10th fund.

The Column Group told Endpoints News exclusively on Thursday that it has raised over \$400 million for a new fund to back single-asset biologic companies derived from its extensive Rolodex of researchers and entrepreneurs. The fund will bring the group's assets under management to around \$4 billion.

Known as TCG Labs, the new fund will work with researchers and drug hunters at Soleil, a Bay Area R&D hub run by CEO Jin-Long Chen. Chen is a managing partner of TCG Labs and also the founder of NGM Biopharmaceuticals, where he worked until last spring. TCG is one of NGM's largest shareholders and told the biotech on Dec. 28 it is interested in taking it private.



Defying VC Downturn, Tiger Cub Viking Global's Hybrid and Private Funds Surge

Stephen Taub, *Institutional Investor*, Jan 29, 2024 (excerpt)

Viking Global Investors has not only survived the downturn in the venture capital business, but it's thrived.

VC fundraising is down, a growing number of private companies are raising new money at lower valuations than in earlier financing rounds, and just this past week, The Information reported that Tiger Global, which not long ago was making an average of one new investment per day, has given buyout packages to several employees responsible for fundraising.

The troubles haven't hit Viking. The Tiger Cub headed by O. Andreas Halvorsen reported to investors late last week that Viking Global Opportunities, its hybrid fund, was up 22.6 percent in 2023 and VGO Drawdown — which invests only in privates — was up 25.2 percent, according to someone who has seen the results. VGO invests in both private and public companies, but the exact mix is not known.

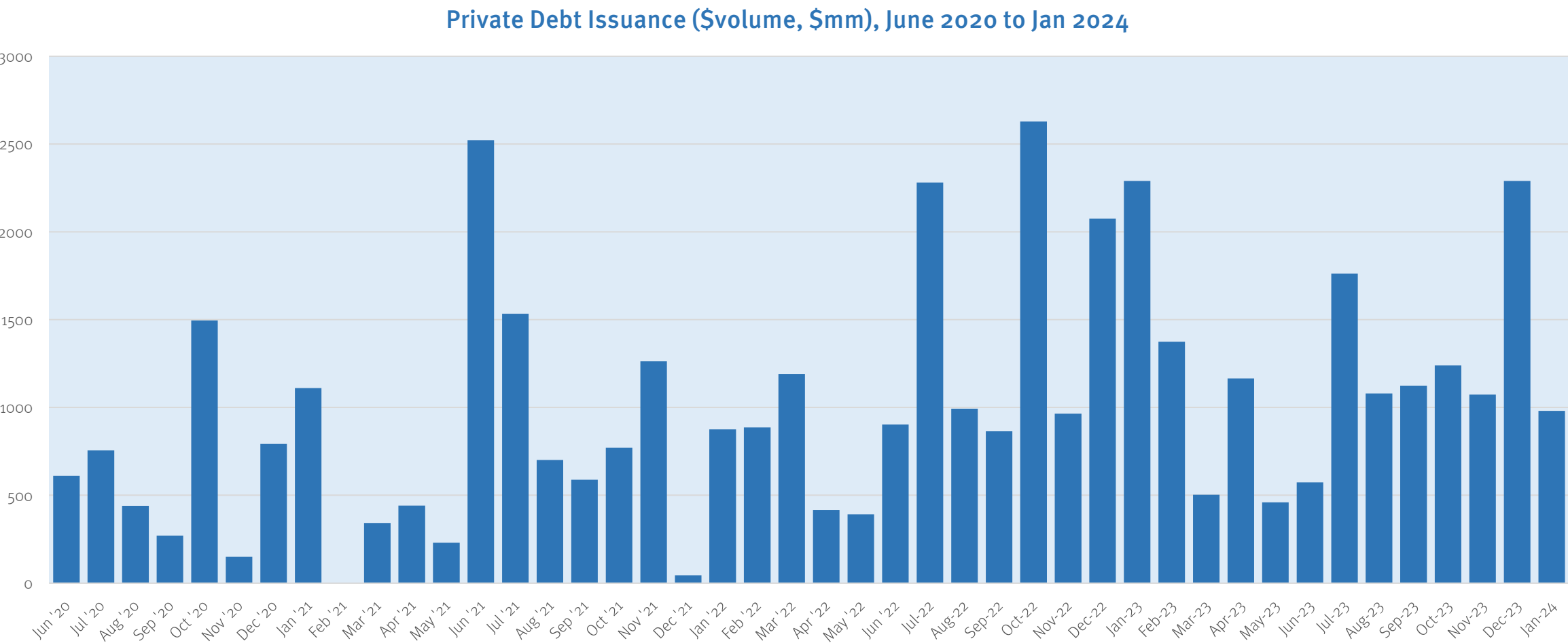
All capital not invested in private companies replicates the portfolio of the firm's hedge fund, Viking Global Equities. Viking declined to comment.

The majority of Viking's private investments over the years have been in health care, life sciences, biopharma, and other medical-related companies. In fact, in the past year, gains were driven in part by at least two health care–related companies: RayzeBio and BridgeBio.



Biopharma Private Debt Placement Market Inactive

The debt privates market was quiet last week. The largest deal was a \$37mm debt deal between Akebia and Blackstone. Total volume for the month of January was a little under \$1bn.



Source: Data from CapitalIQ, Crunchbase.

Immunocore Prices \$350mm Convertible Senior Notes Offering

(OXFORDSHIRE, England & CONSHOHOCKEN, Penn. & ROCKVILLE, Md, January 30, 2024) - Immunocore Holdings plc (Nasdaq: IMCR) today announced the pricing of \$350.0 million aggregate principal amount of 2.50% convertible senior notes due 2030 (the “notes”) in a private offering to qualified institutional buyers pursuant to Rule 144A under the Securities Act of 1933, as amended (the “Securities Act”). Immunocore also granted the initial purchasers of the notes an option to purchase, for settlement within a period of 13 days from, and including, the date the notes are first issued, up to an additional \$52.5 million aggregate principal amount of the notes. The sale of the notes is expected to close on February 2, 2024, subject to the satisfaction of customary closing conditions. The offering was upsized from the previously announced offering of \$300.0 million aggregate principal amount of convertible senior notes.

The notes will be senior, unsecured obligations of Immunocore and will accrue interest at a rate of 2.50% per annum, payable semi-annually in arrears on February 1 and August 1 of each year, beginning on August 1, 2024. The notes will mature on February 1, 2030, unless earlier converted, redeemed or repurchased.

IMMUNOCORE



Immunocore did a nice convertible deal last week.

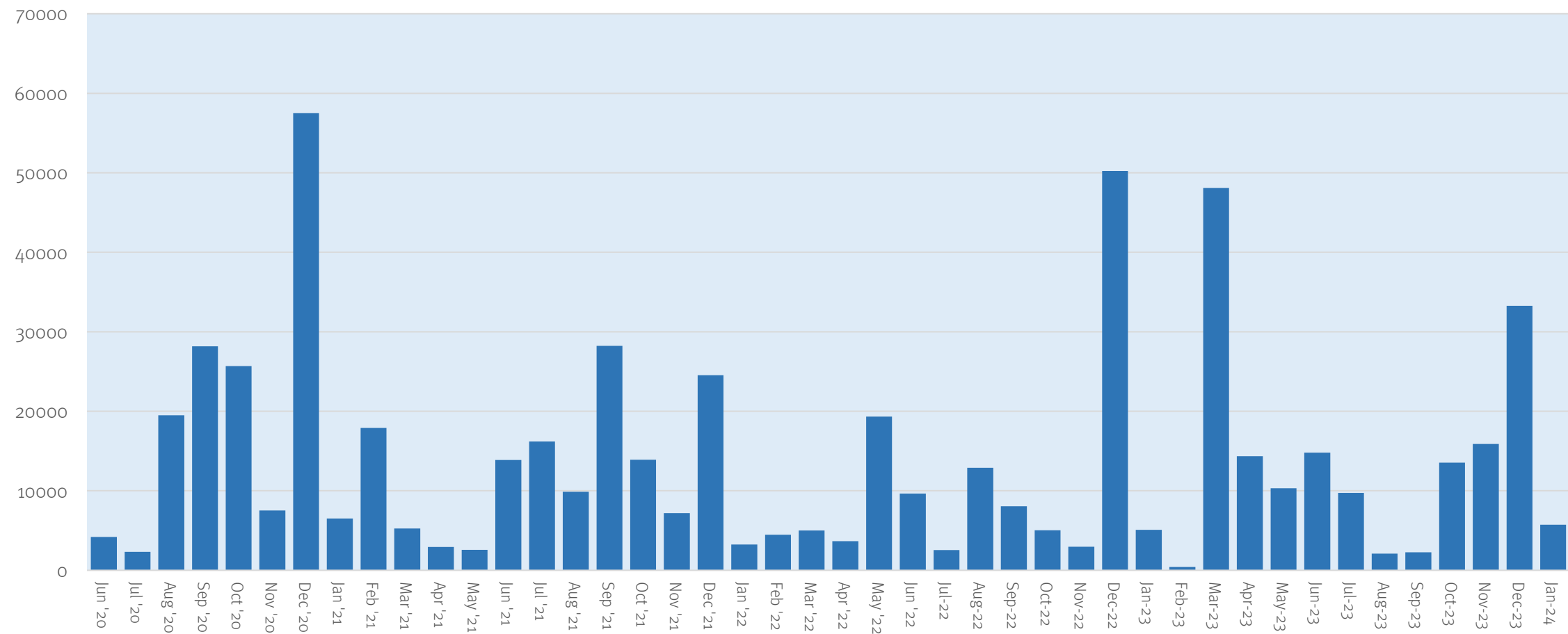
Deals Update



M&A Market Saw \$5 Billion in January Volume, Way Down from December

Last week saw AVRO merge with Tectonic. Otherwise, the market was quiet. The run rate of M&A for the year is \$60 billion. Early days but way down from 2023.

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



Source: S&P, CapitalIQ

AVROBIO and Tectonic Therapeutic Announce Merger



CAMBRIDGE, Mass. & WATERTOWN, Mass.--(BUSINESS WIRE) – Jan 30, 2024-- AVROBIO, Inc. (Nasdaq: AVRO) and Tectonic Therapeutic, Inc. (“Tectonic”), a privately-held biotechnology company developing GPCR (G-protein coupled receptor)-targeted therapeutic proteins, co-founded by Timothy A. Springer and Andrew C. Kruse of Harvard Medical School, today announced that the companies have entered into a definitive merger agreement to combine in an all-stock transaction (the “Merger”). Under the terms of the agreement, AVROBIO will acquire 100% of the outstanding equity interests of Tectonic. Upon completion of the Merger, the combined company is expected to operate under the name Tectonic Therapeutic, Inc. and trade on Nasdaq under the ticker symbol “TECX.”

In connection with the Merger, Tectonic has raised or entered into agreements for a \$130.7 million private placement with a syndicate of new and existing leading life sciences investors, led by a major mutual fund, TAS Partners, 5AM Ventures, EcoR1 Capital, Polaris Partners, funds and accounts advised by Farallon Capital Management, Vida Ventures, PagsGroup, and other investors. The combined company is expected to have approximately \$165 million of cash and cash equivalents at closing, inclusive of the proceeds to be received in the private placement. These proceeds will be used to advance Tectonic’s pipeline through multiple clinical data catalysts and are expected to fund the combined company’s operations into mid-2027. The private placement is expected to close in conjunction with the Merger in the second quarter of 2024.

“We are delighted to merge with AVROBIO at this important time for Tectonic. We are grateful to our investors for their commitment to our mission and to advancing our pipeline of uniquely differentiated molecules. Using biologics to unlock the therapeutic utility of targeting GPCRs which are not optimally drugged by small molecules could result in important advances for patients,” said Alise Reicin, M.D., Chief Executive Officer of Tectonic. “GPCRs are central to human biology and are the target of more than 30% of all currently approved drugs. However, many GPCRs remain unexplored and have proven to be challenging targets for drug development. Our GEODe™ platform makes it possible to discover a broad pipeline of biologics addressing some of the most challenging receptors in the class. This transaction enhances our ability to execute on an efficient plan to advance our clinical-stage and potential best-in-class Fc-relaxin fusion protein, TX45, as well as additional assets in our pipeline. We anticipate multiple clinical catalysts over the next three years.”

Unlike Merck, Bristol Myers to Focus on Bolt-ons After M&A Spree

Max Gelman, *Endpoints News*, Feb 2, 2024 (excerpt)

Bristol Myers Squibb likely won't be on the hunt for big M&A targets in 2024 after pulling off a \$14 billion deal for Karuna Therapeutics and its schizophrenia drug, executives said during Friday's earnings call.

This year's M&A strategy will focus more on bolt-ons and licensing opportunities instead, as new CEO Chris Boerner outlined an upcoming "transition period" starting in 2026.

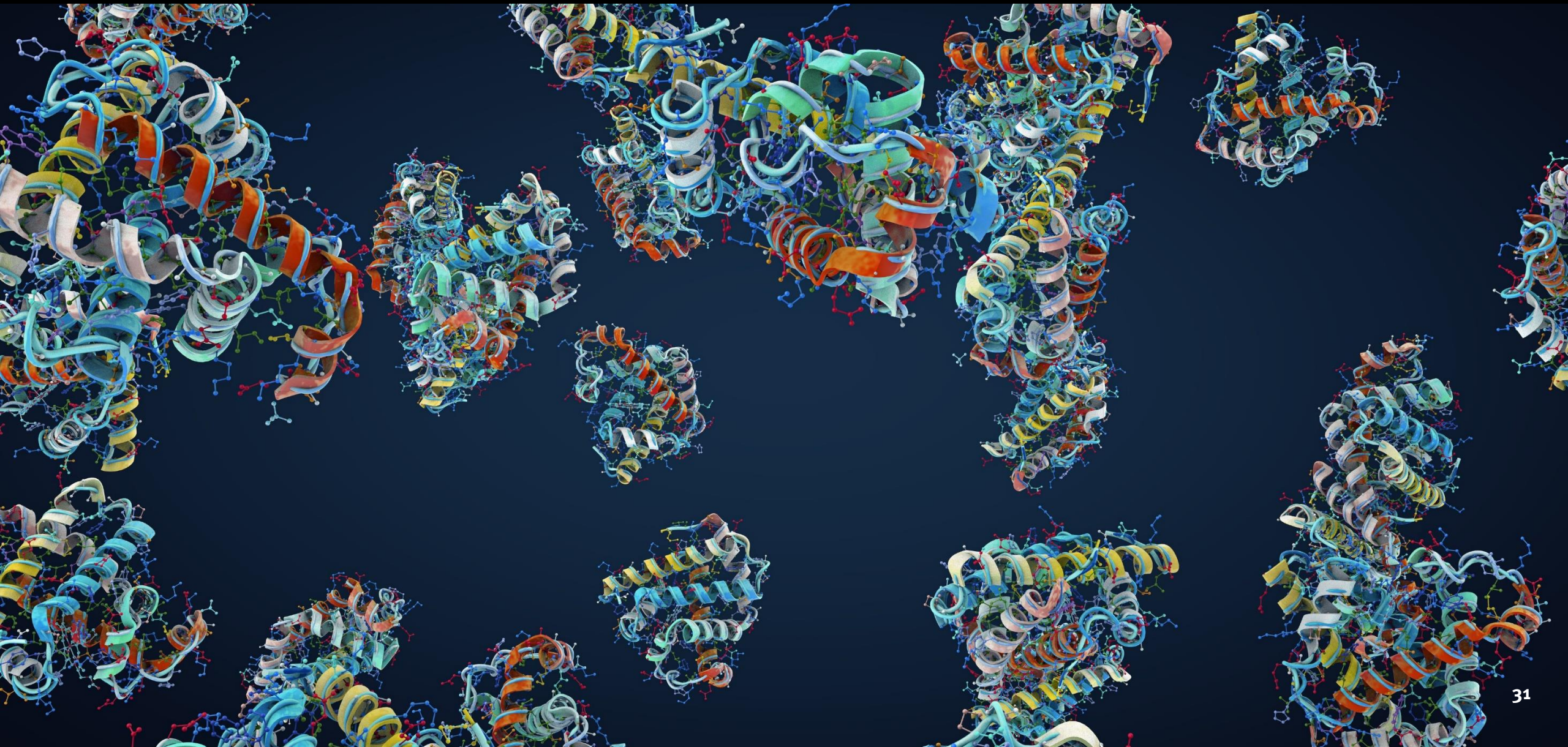
The comments come not only after the Karuna buyout, but also a smaller deal spree over the last six months: Bristol Myers also acquired Mirati (\$4.8 billion) and RayzeBio (\$4.1 billion) while partnering with SystImmune (\$800 million upfront) and Orum (\$100 million upfront). That doesn't mean BMS will rule out M&A entirely, Boerner said. But bolt-ons and partnerships will take priority.

"We certainly are going to continue to be interested in bringing innovation into the company that makes strategic and financial sense to do so," Boerner said. "I would characterize those a bit more as bolt-on opportunities at this point." Bristol Myers' plan contrasts sharply with Merck, one of BMS' Big Pharma competitors. Merck is still looking for deals similarly sized to its June acquisition of Prometheus for \$10.8 billion and its 2021 Acceleron deal for \$11.5 billion, execs said during an earnings call Thursday. Merck also pulled off a \$4 billion-upfront partnership with Daiichi Sankyo in October.



Chris Boerner, CEO, BMS

Industry News



Why Obesity Drug Coverage Doesn't Matter (Yet) for Lilly and Novo

David Wainer, *Wall Street Journal*, January 31, 2024 (excerpt)

Nearly every employer in the country is now grappling with how—and whether—to pay for new weight loss drugs. Needless to say, such decisions are highly important to patients struggling with obesity.

But for Eli Lilly and Novo Nordisk, it actually doesn't matter, for now, from a financial perspective. They are selling every injection they can make. It won't change anytime soon.

That isn't to diminish the importance of making sure patients have access to these medications. Without proper reimbursement, many are simply unable to afford them. But there isn't enough to go around: Novo Nordisk has been restricting supply of starter doses of Wegovy to new patients. On Wednesday, Novo's head of North America operations, Doug Langa, told analysts during the company's fourth quarter earnings call that the company is “doubling the amount of the lower dose strength of Wegovy compared with the previous months,” enabling more patients to start. “We will gradually be increasing the overall supply throughout the remainder of 2024,” he added.

The supply constraints of the two drugs and Lilly's Zepbound mean it could take years for there to be enough supply to meet demand around the developed world. Both companies are investing heavily to increase manufacturing. Novo in November announced that it will spend about \$2.3 billion to expand a production facility in France and more than \$6 billion to expand manufacturing capacity in Denmark.

Elon Musk's Neuralink Hype Irks Rivals Yet Shines a Light on Brain Implants

Richard Waters and James Peel, *Financial Times*, Feb 3, 2024 (excerpt)

Musk's habit of hyping a new technology, even when he is not a leader in the field, has long irked rivals.

It was on full display this week when he wrote on X that one of his companies, Neuralink, had succeeded in implanting an electrode into a human brain for the first time. The procedure is a small step towards Musk's promise of being able to wire brains directly to computers to enhance their processing powers and one day enable humans to match the capabilities of advanced artificial intelligence.

Similar implants have been a staple of science labs for years. At least three rival start-ups have succeeded in inserting electrodes and using them to collect and interpret human brain signals.

But, while Musk's claims bring a shrug of resignation from rivals, they also draw grudging acknowledgment that his attention grabbing has helped to propel the field closer to reality at a moment when it is reaching an important inflection point.

Musk has “really put a spotlight on this field and it's bringing the [venture] capital in”, said Tom Oxley, chief executive of Synchron, which carried out its first human trials in 2019 and has raised \$130mn. Creating a storm of publicity about his efforts, even when there are few details to back up his claims, “is what Elon Musk does better than anyone else”, said Anne Vanhoestenbergh, professor of active implantable medical devices at King's College London.

Are they [Neuralink] ahead? No. Is their technology unique? No, none of what I have seen is novel,” Vanhoestenbergh said — though she credited Musk's company with being “very advanced” and “state of the art” in the field.



A New Pain Mechanism Works. Pretty Much.



Derek Lowe, *Science*, Feb 2, 2024 (excerpt)

I've written here before about Vertex's long-running program(s) to get sodium channel compounds to work as analgesics, and now we have some more clinical results on their VX-548 (which is at least the third candidate in this group to reach the clinic). It targets NaV1.8, a voltage-gated ion channel that is concentrated in the dorsal root ganglions and has long been recognized as being an important player in nociception (the broad category of sensitivity to touch, pressure, pain, temperature and so on). To be accurate, the category for this post should really read "The Peripheral Nervous System", but I don't have that one!

The newest results are from two surgical-pain trials, one in patients who had bunionectomies and the other in patients who had abdominoplasties ("tummy tucks"). Both of which certainly do lead to post-operative pain! The primary endpoint in both was beating placebo at 48 hours post-surgery, and both trials succeeded there. Which is no small accomplishment - relief of pain is a therapeutic area that is absolutely littered with failures once you get out of centrally-acting mechanisms like the opioids (or the voltage-dependent calcium channels that pregabalin and gabapentin act on). The quest for a peripheral pain blocker, which you'd hope would have no addiction potential, has been long, hard, and expensive, and a lot of very plausible mechanisms have wiped out in development. So it's very good news to see VX-548 coming through like this.

On the ever-present other hand, though, both these trials had another arm to them, comparing the Vertex drug to good ol' (well, bad ol') Vicodin, which is hydrocodone and acetaminophen. That is of course a very widely used painkiller for such indications, working through the opiate pathways, and with a very long and very significant history of abuse potential. VX-548's effects did not show any statistically significant difference in the tummy-tuck patients (which is itself impressive), but the drug was significantly less effective than Vicodin in the bunion surgery ones. One of Vicodin's advantages is that it's cheap as dirt (one of its disadvantages, from another angle!), so this will make the decision to use the no-doubt-much-more-expensive VX-548 trickier in actual practice.

But the overall story is that this is really the first non-opioid non-CNS pain drug that is able to deal with these kinds of situations. Vertex has several follow-up compounds in the works, because one thing you can be sure about with ion-channel drugs is that there are going to be a lot of variations on the theme. The binding modes to these proteins are generally a very complicated story; the proteins themselves aren't too simple, either. Vertex is plowing ahead with more trials, and is planning to file for VX-548 approval this year. Let's hope this is just the beginning of a bigger story!

Autoimmunity Far More Common in Women

Autoimmune diseases impact women more than men



Systemic lupus erythematosus	6:1 (12)
Rheumatoid arthritis (adult)	3:1 (13)
Rheumatoid arthritis (juvenile)	2:1 (14)
Multiple sclerosis	2:1 (15)
Type 1 diabetes mellitus	1:1 (16) 1:2 (17)
Sjögren disease	9:1 (13)
Psoriasis	1:1.44(21)
Autoimmune hepatitis	4:1 (18) 6:1 (19)

Women constitute ~78% of those affected by autoimmune diseases, bearing a disproportionate burden of the high morbidity associated with these chronic conditions. Female sex is a risk factor for polyautoimmunity. The “gender gap” in autoimmunity has been well known for over 20 years and AI diseases are a leading cause of death among young and middle-aged women.

Why Do Women Have More Autoimmune Diseases?

Study Points to X Chromosome

Carl Zimmer, *New York Times*, Feb 1, 2024 (excerpt)

Women are much more likely than men to have their immune system turn against them, resulting in an array of so-called autoimmune diseases, like lupus and multiple sclerosis. A study published on Thursday offers an explanation rooted in the X chromosome.

The research, published in the journal *Cell*, suggests that a special set of molecules that act on the extra X chromosome carried by women can sometimes confuse the immune system. Independent experts said that the molecules are unlikely to be the sole reason autoimmune disease skews female. But if the results hold up in further experiments, it might be possible to base new treatments on these molecules, rather than on the current drugs that blunt the entire immune system. “Maybe that’s a better strategy,” said Dr. Howard Chang, a geneticist and dermatologist at Stanford who led the new study.

Male and female embryos carry 22 identical pairs of chromosomes. The 23rd pair is different: Females carry two Xs, while males carry an X and a Y, which lead to the development of male sex organs. Each chromosome holds genes that, when “switched on,” produce proteins to do work inside of cells. You might expect that women, with two copies of X, would make twice as many X proteins as men do. Instead, they produce about the same level. That’s because one of the two X chromosomes is silenced.

A molecule called Xist clings to the second X chromosome “like Velcro,” Dr. Chang said. As hundreds of Xist molecules wrap themselves around the X chromosome, they completely shut it down.

Keeping one X silent is crucial to women’s health. If a gene on the second X chromosome escapes Xist’s control, it will result in an excess supply of proteins, some of which could be toxic. The new study emerged from years of research testing his hunch that Xist molecules could cause autoimmune disease. He and his colleagues studied a strain of mice in which the females are at high risk of the autoimmune disease lupus, while the males never develop severe cases.

Article

Xist ribonucleoproteins promote female sex-biased autoimmunity

Diana R. Dou,¹ Yanding Zhao,¹ Julia A. Belk,¹ Yang Zhao,¹ Kerriann M. Casey,² Derek C. Chen,¹ Rui Li,¹ Bingfei Yu,¹ Suhas Srinivasan,¹ Brian T. Abe,¹ Katerina Kraft,¹ Ceke Hellström,³ Ronald Sjöberg,³ Sarah Chang,⁴ Allan Feng,⁴ Daniel W. Goldman,⁵ Ami A. Shah,⁵ Michelle Petri,⁵ Lorinda S. Chung,⁴ David F. Fiorentino,⁶ Emma K. Lundberg,^{7,8} Anton Wutz,⁹ Paul J. Utz,^{4,10} and Howard Y. Chang^{1,11,12,*}

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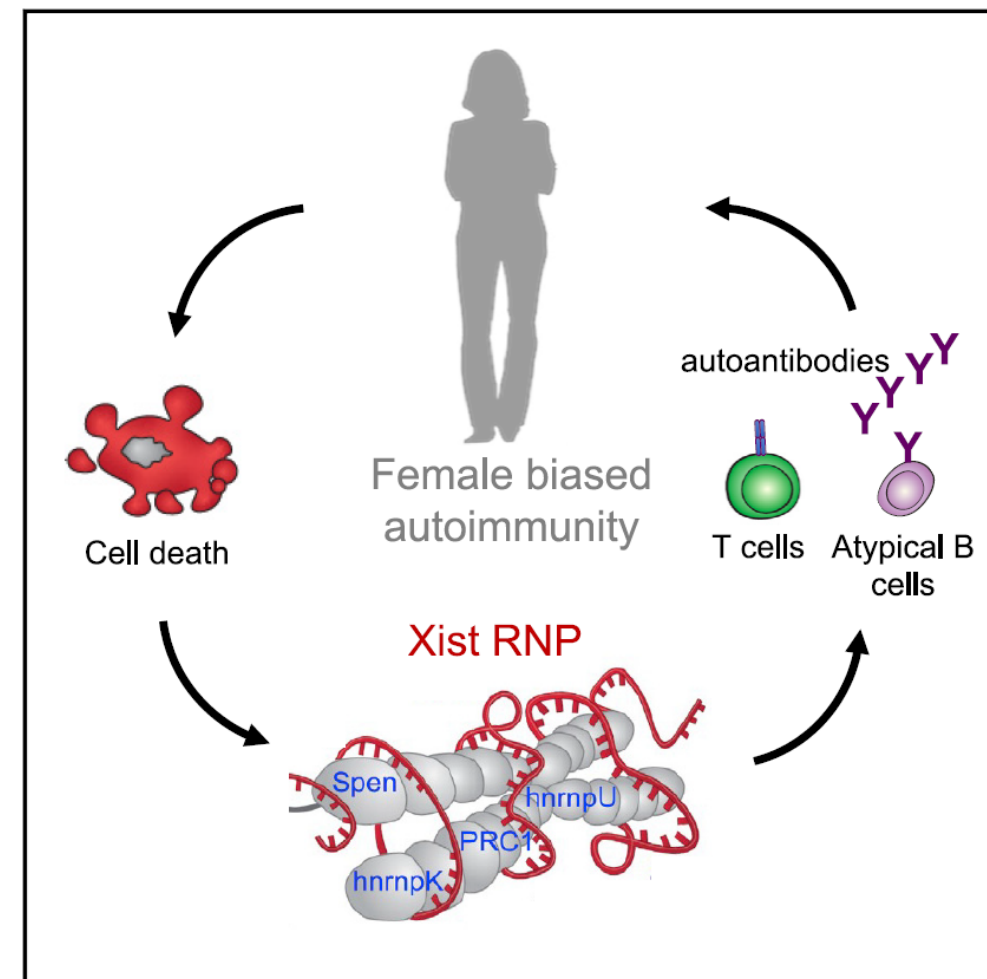
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*Correspondence: howchang@stanford.edu

<https://doi.org/10.1016/j.cell.2023.12.037>

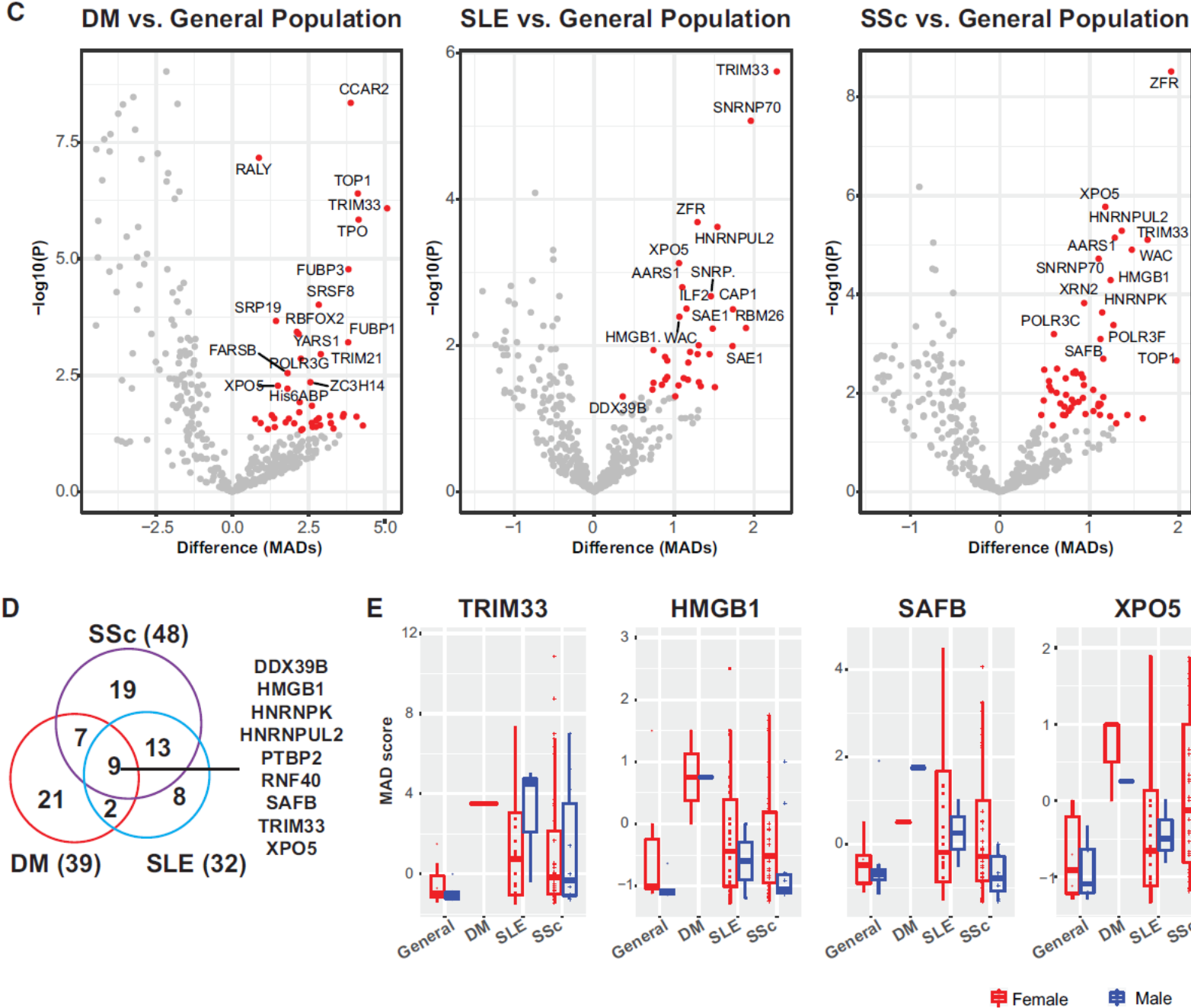
Autoimmune diseases disproportionately affect females more than males. The XX sex chromosome complement is strongly associated with susceptibility to autoimmunity. Xist long non-coding RNA (lncRNA) is expressed only in females to randomly inactivate one of the two X chromosomes to achieve gene dosage compensation. Here, we show that the Xist ribonucleoprotein (RNP) complex comprising numerous autoantigenic components is an important driver of sex-biased autoimmunity. Inducible transgenic expression of a non-silencing form of Xist in male mice introduced Xist RNP complexes and sufficed to produce autoantibodies. Male SJL/J mice expressing transgenic Xist developed more severe multi-organ pathology in a pristane-induced lupus model than wild-type males. Xist expression in males reprogrammed T and B cell populations and chromatin states to more resemble wild-type females. Human patients with autoimmune diseases displayed significant autoantibodies to multiple components of XIST RNP. Thus, a sex-specific lncRNA scaffolds ubiquitous RNP components to drive sex-biased immunity.



The Xist RNA protein complex, present only in females, is immunogenic and may underlie female-biased autoimmunity.

Blood Samples of Persons with Autoimmunity Express Much More Xist Ribonucleoproteins

(C) sera grouped by DM, SSc, and SLE patients, compared with general population baseline of serum from blood donors. Significant differentially reactive antigens, defined as $\text{padj} < 0.05$ and median absolute deviation (MAD) difference > 0 , labeled in red. Significance calculated using the Student's t test. (D) Metrics of unique antigens from the array with significant elevated serum activity in autoimmune patients, compared with the general population. (E) Serum reactivity (MAD) plots of representative antigens significantly reactive in all three autoimmune patient cohorts grouped by disease type and colored by sex (red, female; blue, male).



Precise CRISPR-Cas9 Gene Repair in Autologous Memory T Cells to Treat Familial Hemophagocytic Lymphohistiocytosis

Xun Li et.al., *Science Immunology*, Feb 2, 2024

Familial hemophagocytic lymphohistiocytosis (FHL) is an inherited, often fatal immune deficiency characterized by severe systemic hyperinflammation. Although allogeneic bone marrow transplantation can be curative, more effective therapies are urgently needed. FHL is caused by inactivating mutations in proteins that regulate cellular immunity. Here, we used an adeno-associated virus–based CRISPR-Cas9 system with an inhibitor of nonhomologous end joining to repair such mutations in potentially long-lived T cells ex vivo. Repaired CD8 memory T cells efficiently cured lethal hyperinflammation in a mouse model of Epstein-Barr virus–triggered FHL2, a subtype caused by perforin-1 (Prf1) deficiency. Furthermore, repair of PRF1 and Munc13-4 (UNC13D)—whose deficiency causes the FHL subtype FHL3—in mutant memory T cells from two critically ill patients with FHL restored T cell cytotoxicity. These results provide a starting point for the treatment of genetic T cell immune dysregulation syndromes with repaired autologous T cells.

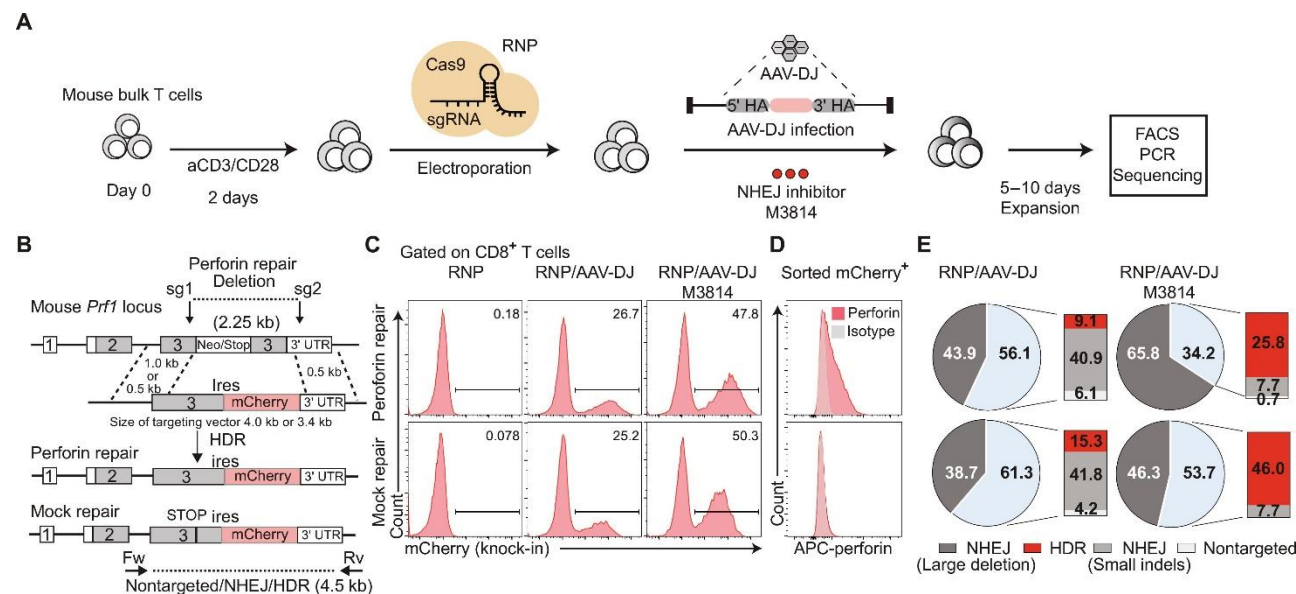


Fig. 2. Highly efficient CRISPR-Cas9 repair of the *Prf1* gene in mouse bulk T cells.

(A) Ex vivo CRISPR-Cas9 gene repair strategy for primary mouse T cells from *Prf1*^{-/-} mice, using recombinant AAV vectors to provide single-stranded DNA repair templates with homology arms. AAV-DJ was used for mouse cells. M3814—a small molecule inhibitor of NHEJ—was added to favor HDR. (B to E) Knock-in efficiency for the mouse perforin gene locus: (B) Targeting strategy. Gene locus containing a neo-stop-cassette (upper line), donor template (middle line), and targeted loci (lower two lines). (C) Percentage of targeted bulk T cells (mCherry⁺) determined by flow cytometry after the indicated treatments with Cas9–gRNA RNP complexes. Results are representative of at least four independent experiments. (D) Intracellular perforin staining of repaired sorted mCherry⁺ CD8 T cells. Results correspond to one of two independent experiments. (E) Percentage of targeted alleles determined by gel electrophoresis (pie chart) and by sequencing. Upper row: Perforin repair; lower row: Mock repair. Results correspond to one of two independent experiments each.

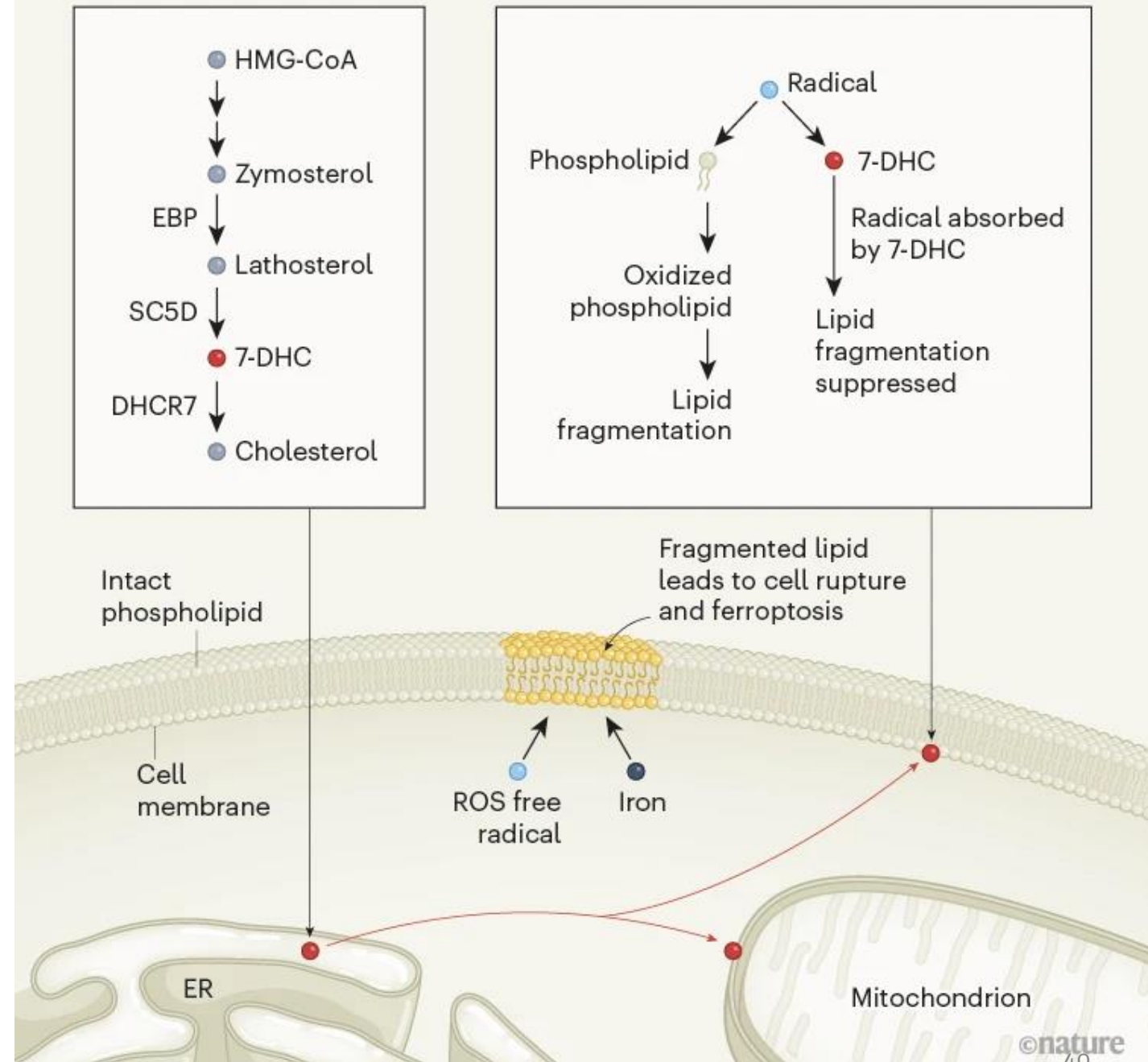
Natural Inhibitor Found for Cell Death by Ferroptosis

Dong Zhang, *Nature*, Jan 31, 2024

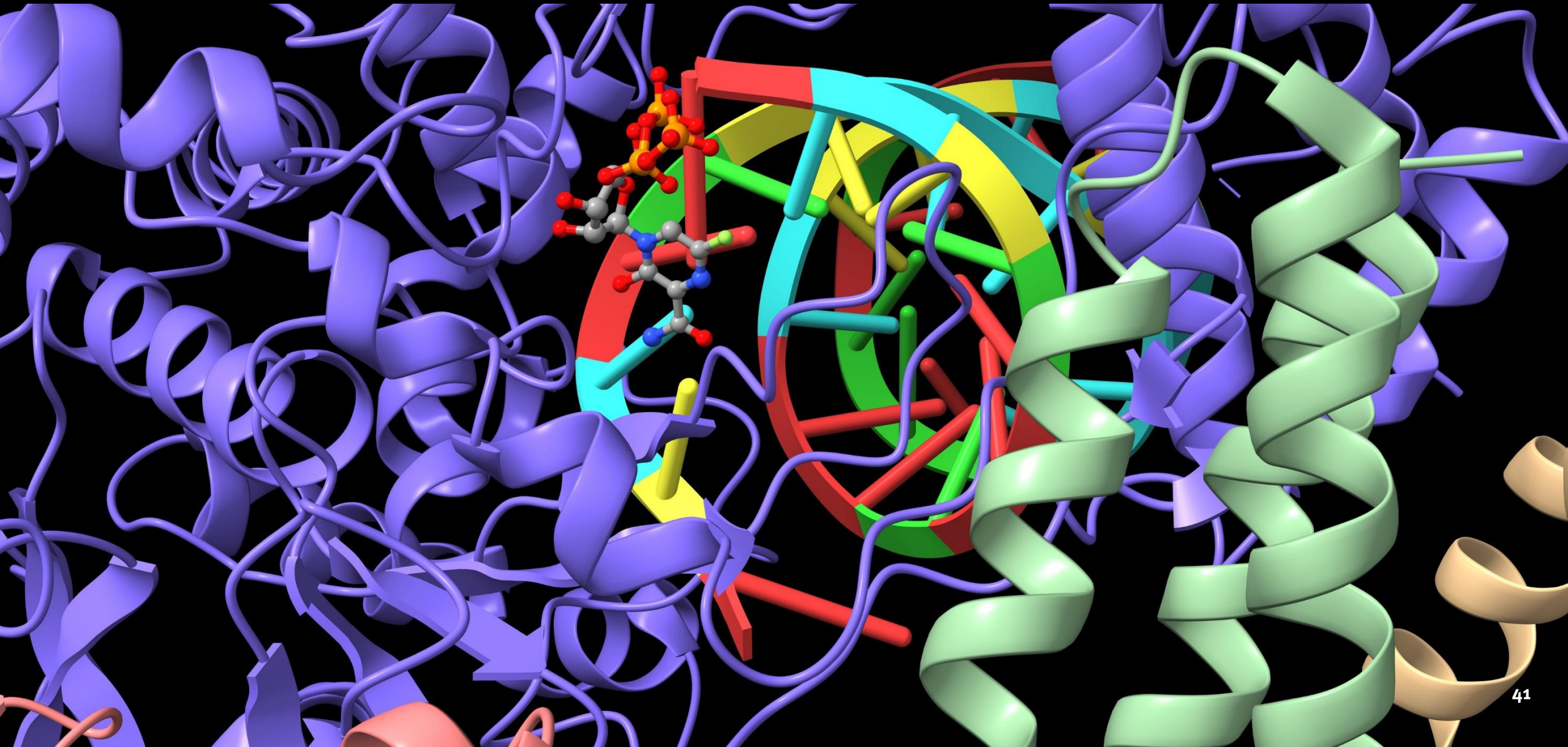
Biology remains nothing short of astonishing, as researchers unveil the underpinnings of its myriad systems, especially those that are involved in protecting against cell death. Writing in *Nature*, Freitas et al. and Li et al. shed light on a regulated form of cell death called ferroptosis, which is driven by an iron-dependent modification of lipids in cellular membranes. The results bring into sharp focus an unexpected hero, the molecule 7-dehydrocholesterol (7-DHC).

Freitas et al. and Li et al. report that 7-DHC, a molecule in the cholesterol-synthesis pathway (Fig. 1), acts to suppress ferroptosis. Both teams independently discovered the anti-ferroptotic role of the cholesterol-synthesis pathway. The authors reveal that several enzymes in this pathway function as potential suppressors of ferroptosis. However, one of the enzymes, DHCR7, which catalyses the reaction that converts 7-DHC to cholesterol, was found to promote ferroptosis. This indicates that 7-DHC, produced by the enzyme SC5D and used by DHCR7, operates as a key protection against ferroptosis.

Source: <https://www.nature.com/articles/d41586-024-00080-1>



Big Pharma Earnings



AbbVie Raises Long-Term Guidance



Expect total AbbVie sales to return to robust growth in 2025, with high-single digit CAGR through remainder of decade (2024 base year through 2029)

✓ On-Track

Skyrizi: >\$17B in 2027 (\$11.5B from PsO/PsA; \$5.5B from IBD)

↑ Raised

Rinvoq: >\$10B in 2027 (\$4.5B from Rheum; \$3.2B from IBD; \$2.3B from Derm)

↑ Raised

Oncology revenue return to growth in 2026

✓ On-Track

Vraylar: Peak sales approaching \$5B

✓ On-Track

Oral CGRPs (Ubrelevy & Qulipta): Peak sales >\$3B combined

↑ Raised

ABBV-951: Peak sales >\$1B

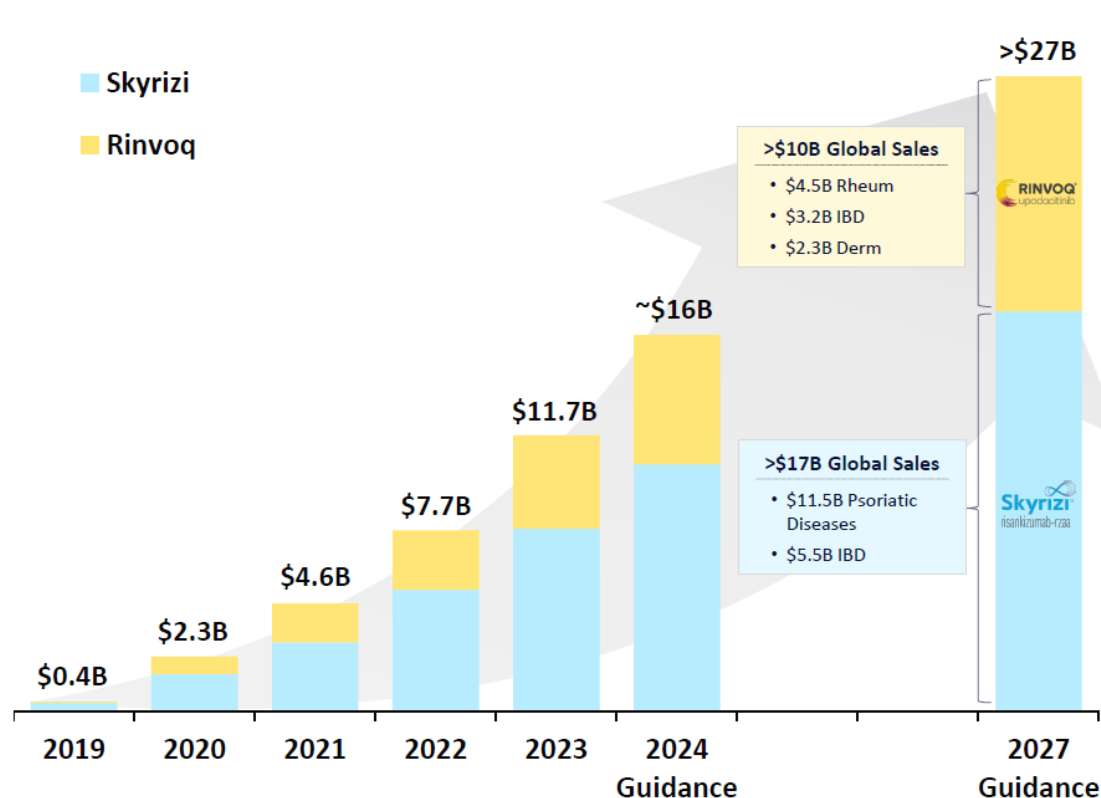
✓ On-Track

Aesthetics sales >\$9B in 2029

✓ On-Track

Skyrizi and Rinvoq Sales to be \$6Bn Above Previous Forecast

Updated Skyrizi and Rinvoq Long-Term Guidance Based on Continuing Momentum for Both Brands



- Updated 2027 guidance for combined Skyrizi and Rinvoq is \$6B above previous estimate
- Next wave of indications drive inflection for Rinvoq in 2027+
- Expect robust sales growth for Skyrizi and Rinvoq continuing into the 2030s



Rinvoq Rheum includes sales from approved rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis and ankylosing spondylitis indications, as well as modest risk-adjusted sales from additional indications in late-stage development (giant cell arteritis approval anticipated in 2025; systemic lupus erythematosus approval anticipated in 2027). Rinvoq IBD includes sales from approved ulcerative colitis and Crohn's disease indications. Rinvoq Derm includes sales from approved atopic dermatitis indication, as well as modest risk-adjusted sales from additional indications in late-stage development (vitiligo approval anticipated in 2026; hidradenitis suppurativa and alopecia areata approvals anticipated in 2027). Skyrizi Psoriatic Diseases includes sales from approved psoriasis and psoriatic arthritis indications. Skyrizi IBD includes sales from approved Crohn's disease indication and risk-adjusted sales from ulcerative colitis indication, which is under regulatory review with approval anticipated in 2024.

BMS Shows Strong Growth Portfolio

Revenue growth today supported by Legacy & Growth Portfolios

Legacy Portfolio

Generating **strong cash flow** and **flexibility** to invest in growth

~\$26B sales (2023)



Oncology Hematology Cardiovascular Immunology

Growth Portfolio

Including a more diversified and robust range of products

11 major brands across **4** TAs

+ **12** assets in/entering registrational stage

+ **30+** assets in early-stage clinical development

+ Assets from ongoing BD



Legacy: Post-LoE products or products with ≤3 years to potential impact from major LoE or IRA; Growth: >3 years until major LoE event or potential IRA impact. "Major" brands include those with \$1Bn+ risk-adjusted consensus annual sales

1. Mirati Therapeutics acquisition closed January 2024; 2. Partnered with 2SeventyBio

Q4 execution & recent business accomplishments supports momentum for 2024



Commercial

Increased investment to accelerate growth (e.g., **Sotyktu**, **Camzyos**)

Re-accelerated **Reblozyl** growth expanding label in 1L MDS (COMMANDS)

Established **Opdualag** as SOC in 1L melanoma

Increased CAR-T manufacturing capacity, especially **Breyanzi**

Research & Development

Delivered **10** INDs in 2023

U.S. approval for **Augtyro**

Achieved multiple clinical development milestones

Platform momentum for early programs

- Initiated **NEX T CD19** in MS
- **AR LDD** Ph1 data at ASCO GU

Business Development^{1,2}

MIRATI
THERAPEUTICS®

 **SYSTIMMUNE**

 **KARUNA**
THERAPEUTICS

**RayzeBio**

Not an exhaustive list of assets, programs, or indications

1. Mirati Therapeutics acquisition closed January 2024; 2. Subject to satisfaction of customary closing conditions; anticipated closing Karuna Therapeutics, RayzeBio, & Systimmune in 1H 2024

Delivering on our commitments and upgrading our outlooks

2024 Guidance

- Sales growth: 5-7%
- Adj. OP growth: 7-10%
- Adj. EPS growth: 6-9%

2021-2026 New Outlook

- >7% Sales CAGR¹
- >11% Adj. operating profit CAGR¹
- >31% Adj. operating profit margin
- >£10bn CGFO²

2026-2031 New Outlook

- >£38bn sales by 2031
- Continued focus on margin improvement, with broadly stable OP⁴ margin through dolutegravir loss of exclusivity⁵

2021-2026 Previous Outlook³

- >5% Sales CAGR
- >10% Adj. operating profit CAGR
- 30% Adj. operating profit margin
- >10bn CGFO

2031 Previous Ambition³

- >£33bn sales

Arexvy launch dynamics

Success in 2023, continued growth in 2024



US sets up success for global expansion

- 94.6% efficacy in comorbid population resonating well
- ~2/3 of healthcare professionals prefer Arexvy¹
- Strong position in all major pharmacies

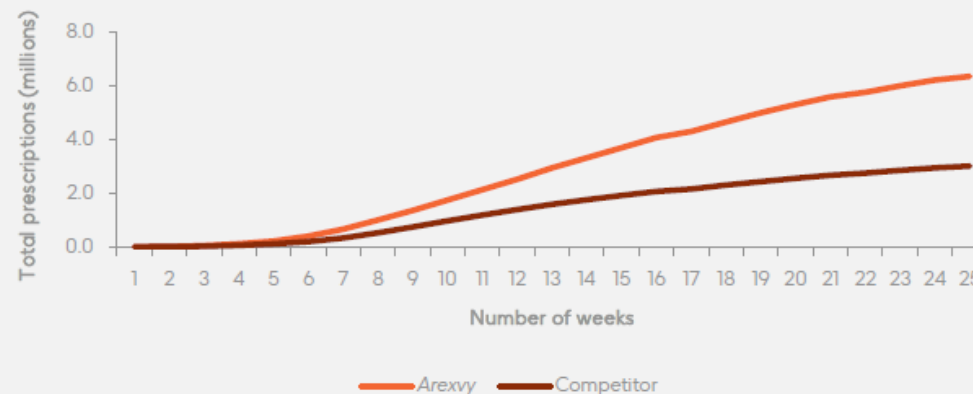
Approved in 39 countries in 2023

- 1st entrant in US, Canada, EU and Japan
- Expect additional market approvals and reimbursements in 2024

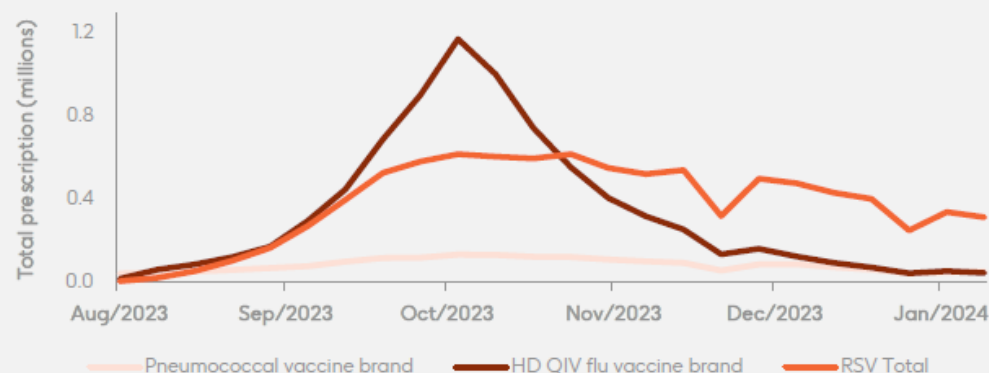
Continued evidence generation

- 3rd year efficacy data in H1 2024
- Expand the market for at risk individuals aged 50 to 59
 - 15m people 50-59 with high-risk comorbidities for more severe RSV infections in the US²

Weekly TRx since launch³



Vaccine seasonality by weekly US TRx³



1. GSK respiratory syncytial virus healthcare professional awareness trial and usage study, December 2023 2. 2023 US Census population data 3. Note: This information is an estimate derived from the use of information under license from the following IQVIA information service: IQVIA – NPA for the period August 2023 – January 2024. IQVIA expressly reserves all rights, including rights of copying, distribution and republication

Delivering profitable growth 2026-2031

Build from existing strong performance momentum



Marketed Growth Drivers ≥£2bn PYS¹

Arexvy
Shingrix
Meningococcal
vaccines²

Cabenuva/Apretude
Nucala
Benlysta
Oncology³

Sales >7% CAGR⁴

Planned launches ≥£2bn⁵ PYS¹

Meningococcal
vaccines²
mRNA influenza
HIV PrEP⁶
depemokimab
camlipixant
Anti-infectives⁷

MAPS 24v/30v+
TH HSV
bepirovirsen
HIV treatment⁶

Jemperli LCI⁸
CD226

Sales >£38bn RA⁹

Early-stage pipeline with key inflections and launches

Phase II: 30 vaccines and medicines in development¹⁰
Phase I: 23 vaccines and medicines in development¹⁰

+ targeted business development

2026

2031

Innovation-led growth

- Significant growth portfolio with increasing sales from Vaccines and Specialty medicines
- >12 major product launches from 2025

>£38 billion RA⁹

With upside opportunity from:

- Early-stage pipeline data readouts
- Targeted business development



All outlook statements are given on a constant currency basis and use 2023 average exchange rates as a base. Pipeline sales are risk-adjusted and include anticipated sales of new products and lifecycle innovation. COVID therapeutic and vaccines solutions sales and profits (2021-2023) are excluded from the above. See "Guidance and outlooks, assumptions and basis of preparation related to 2024 guidance, 2021-26 and 2031 outlooks" in Appendix of this presentation. 1. Peak year sales 2. Meningococcal vaccines (Bexsero and MenABCWY) 3. Includes Zejula, Jemperli, and Ojjaara 4. Compound annual growth rate 5. Does not include Blenrep 6. Every-four-month ultra long-acting dosing. ≥£2bn applies to the aggregation of sales of PrEP and treatment. 7. Includes gepotidacin, telipenem HBr and Brexafemme 8. Lifecycle innovation 9. Risk-adjusted sales 10. See the appendix for a full list of vaccines and medicines in clinical development.

Strong 2023 underlying performance¹ and 2024 initial guidance



Q4 Worldwide Sales

\$14.6B

+6%

+13% ex-Exchange, ex-LAGEVRIO²

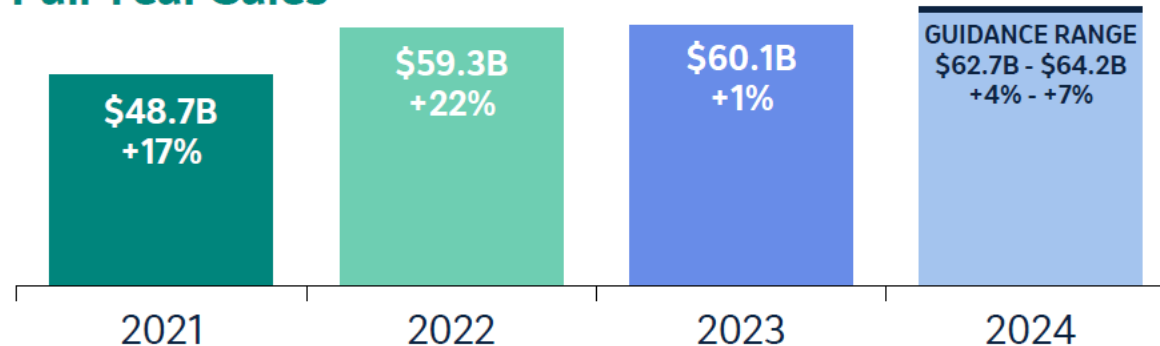


Q4 Non-GAAP EPS⁴

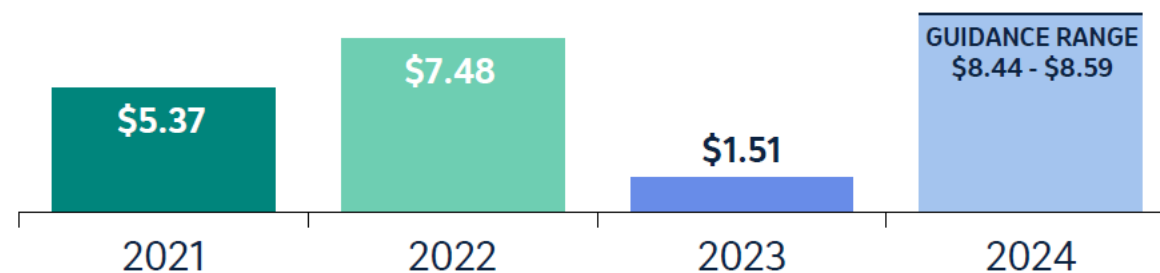
\$0.03

Includes one-time charge of \$1.69 per share from the collaboration with Daiichi Sankyo

Full Year Sales



Full Year Non-GAAP EPS³



1. Results from continuing operations attributable to Merck & Co., Inc. 2. Excludes LAGEVRIO sales of \$193 million in 4Q23 and \$825 million in 4Q22. 3. Merck does not exclude expenses for upfront and milestone payments related to certain collaborations and licensing agreements, or charges related to pre-approval assets obtained in transactions accounted for as asset acquisitions from its non-GAAP results. Full year non-GAAP results for 2023, 2022 and 2021 include \$6.21, \$0.22 and \$0.65 per share of such charges, respectively. 4. GAAP Loss per Share (\$0.48).



7

Expanding robust pipeline with opportunity for patient impact and value creation well into the next decade

Prior Outlook

Current Outlook

Oncology

(excludes innovation from marketed products)

>\$10B

Includes TROP-2¹, ROR-1, CYP11A1i², LSD-1i, KRASi, BTKi and others

>\$20B

Now includes HER3, B7H3 and CDH6 ADCs³ and V940 (INT)⁴

Cardiometabolic

>\$10B

Includes sotatercept, MK-0616, MK-2060, MK-5475 and Verquvo⁵

~\$15B

Now includes MK-6024, and reflects increased confidence supported by clinical data readouts for sotatercept and MK-0616

Immunology

Multibillion

in each indication (CD and UC) for tolosokibart

Multibillion

in each indication (CD and UC) for tolosokibart

Additional Opportunities in Late-Phase Pipeline Programs Across Vaccines, Neurosciences, HIV and Animal Health, Early-Phase Programs & Additional Potential Business Development

Note: All dollar figures above are non-risk adjusted annual sales by the mid 2030s

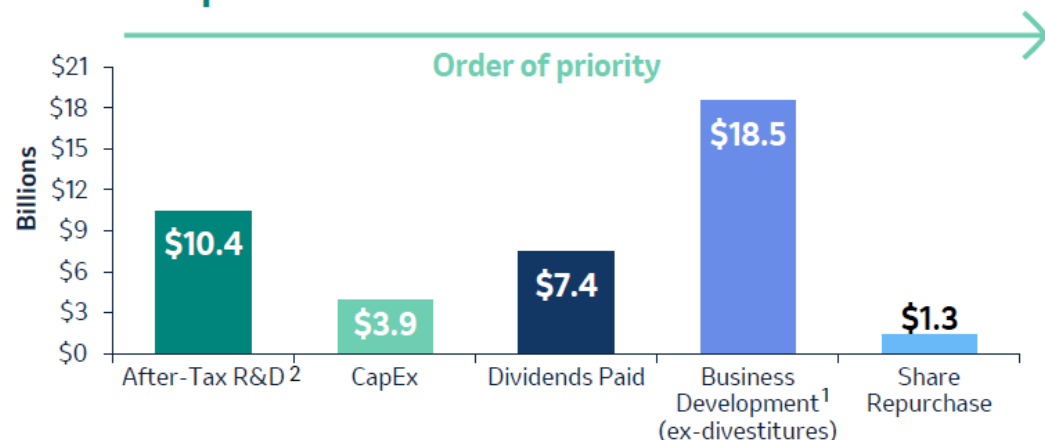
1. Collaboration with Kelun Biotech 2. Collaboration with Orion 3. Collaboration with Daiichi Sankyo 4. Collaboration with Moderna

5. Collaboration with Bayer, includes expanded indication to chronic heart failure without a worsening event for Verquvo

Capital allocation: Trailing twelve months



Over the past 12 months



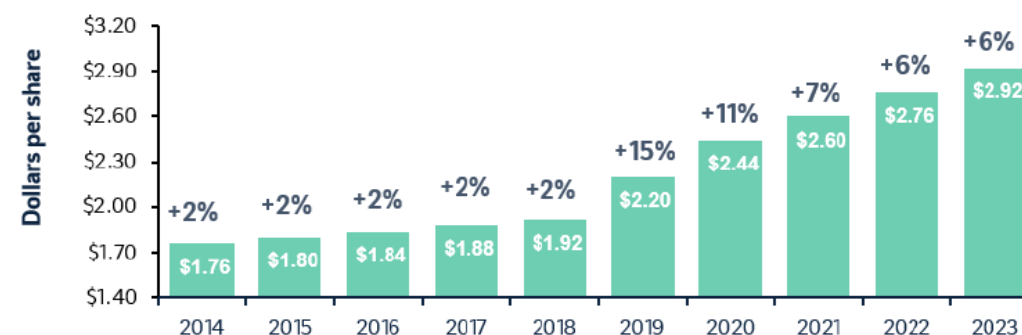
Well positioned balance sheet
with capacity to fund
**additional value-enhancing
business development
opportunities**

Capital investments 2023 to 2027

~\$18B

Over 5 years, including expanding manufacturing capacity for Oncology, Vaccines, and Animal Health. Includes >\$10B in the U.S.

Commitment to the dividend



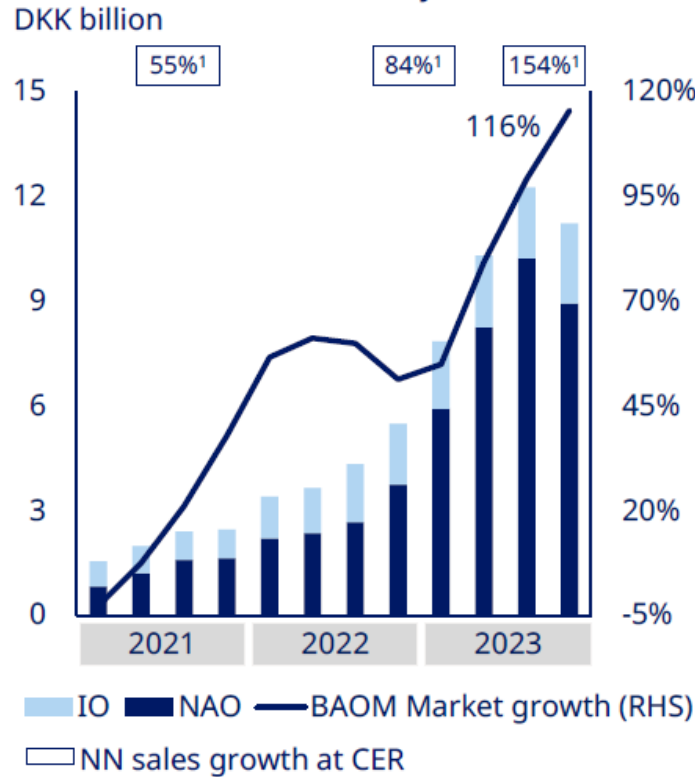
1. Includes payments reflected in operating cash flow
2. Reflects R&D excluding Business Development

Novo Results in Obesity for 2023: Holy Smokes! 154% Growth

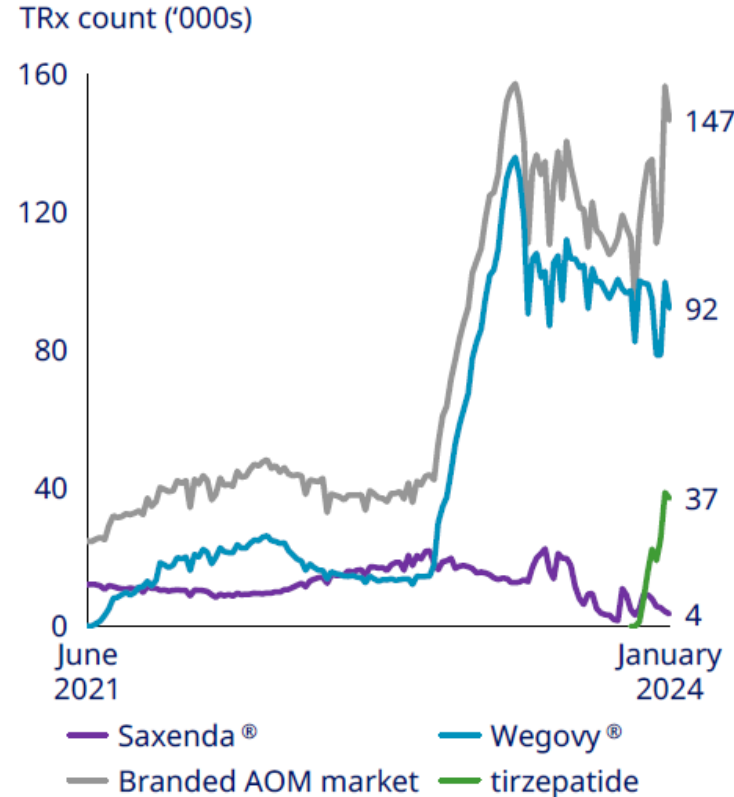


Obesity care sales grew by 154% in 2023 mainly driven by the US

NN sales and volume BAOM market growth within Obesity care



Branded AOM TRx in the US²



ONCE-WEEKLY
wegovy®
semaglutide injection 2.4 mg

The US

- The supply of the lower dose strengths has been restricted since May 2023 to safeguard continuity of care
- Novo Nordisk started gradually increasing the supply of the lower dose strengths in January 2024

International Operations

- Wegovy® launched in Denmark, Norway, Germany, UK, Switzerland Iceland and UAE
- Continued volume capped launches in IO in 2024, balancing supply and demand

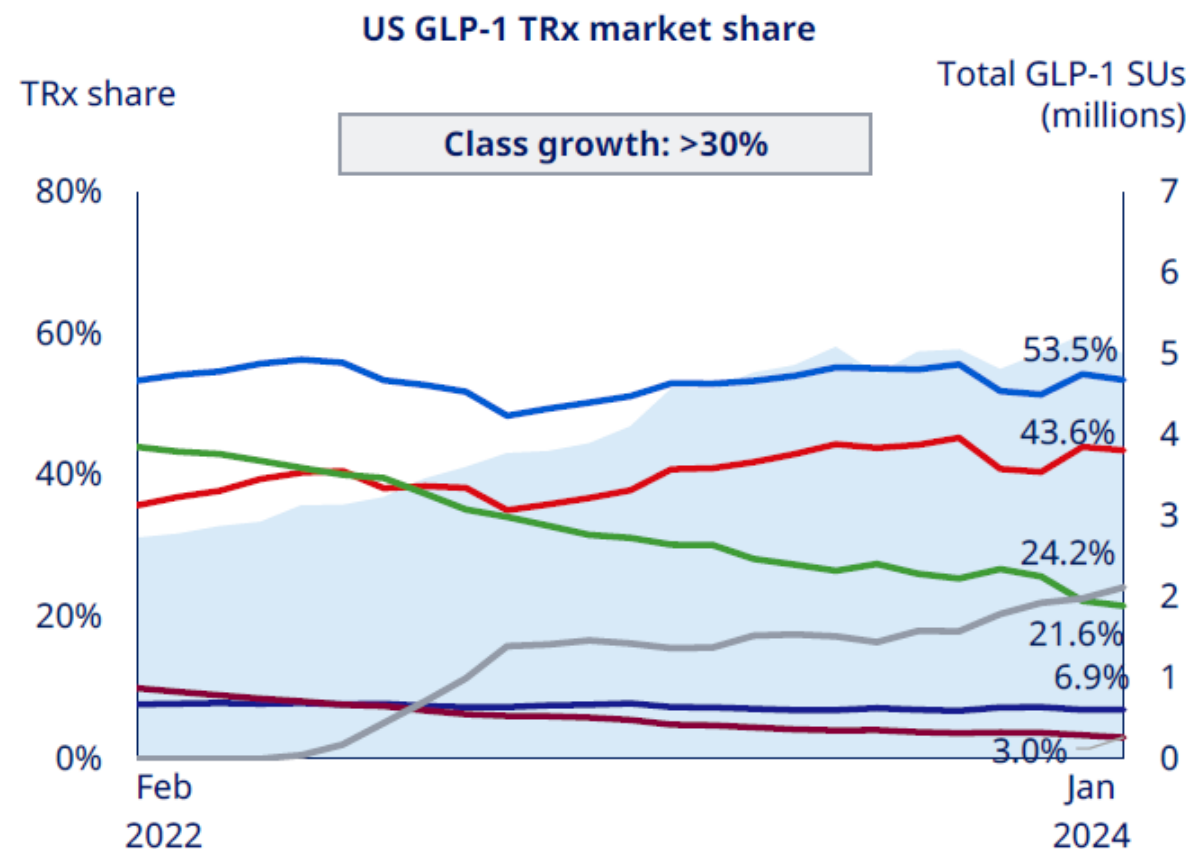
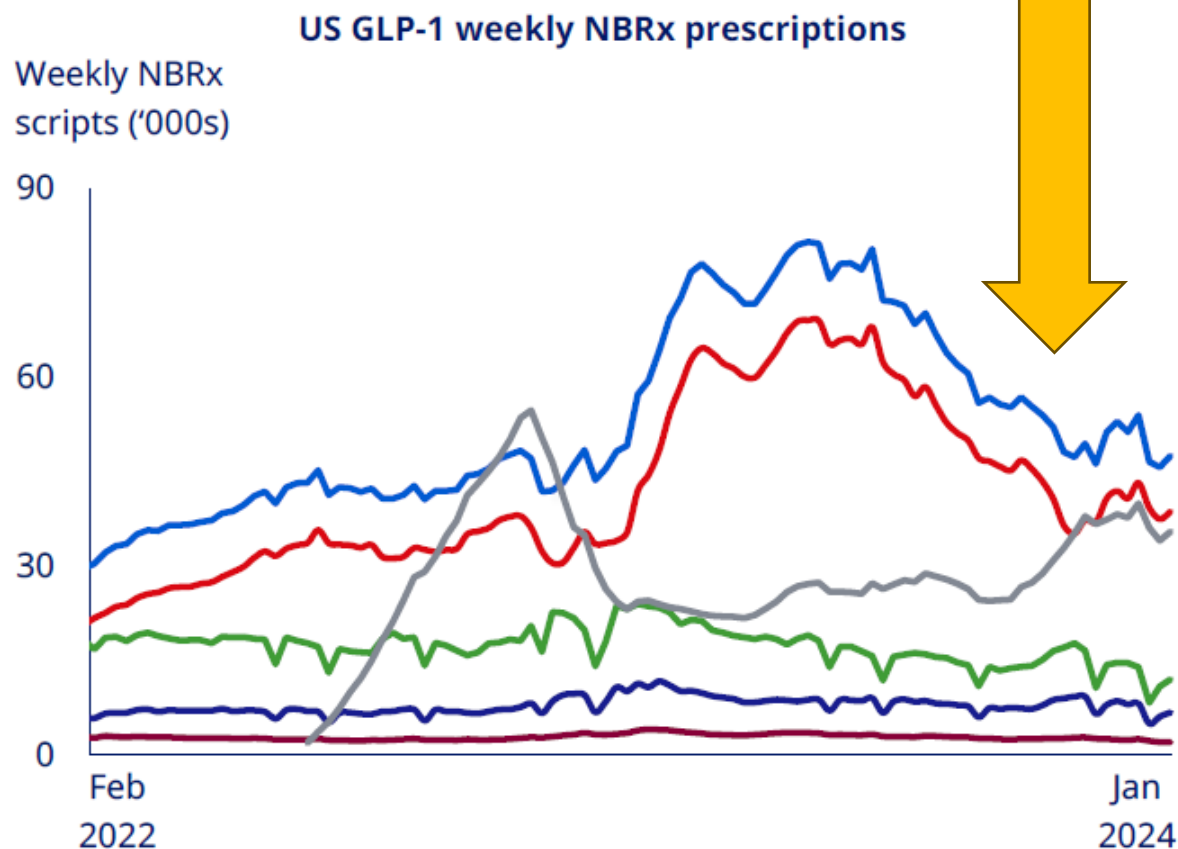
¹ Annual growth at CER. Each TRx data points represents one week of data; ² IQVIA weekly, 19 Jan 2024

CER: Constant exchange rates; NAO: North America operations; IO: International operations; RHS: Right-hand side axis; TRx: Total Prescriptions; AOM: Anti-Obesity Medications (includes Wegovy®, Saxenda®, Zepbound, Qsymia, Belviq and Contrave); BAOM: Branded AOM market; UAE: United Arab Emirates. Note: Sales growth at constant exchange rates. 116% volume growth for Global BAOM market growth refers to moving annual total.

GLP-1 class expansion in the US in 2023



Weekly scrips of semaglutide down due to supply issues.



— Ozempic® — Rybelsus® — Victoza® — NN GLP-1 — dulaglutide — tirzepatide — Total monthly GLP-1 scripts

NBRx: New-to-brand prescriptions; TRx: Total prescriptions; NN: Novo Nordisk; Scripts: Prescriptions; US: United States
 Note: Class growth calculated based on SU volume for diabetes GLP-1 as Q4 2023 vs Q4 2022
 Source: IQVIA Xponent Plantrak, NBRx/TRx data from week ending 12 Jan 2024. Each data point represents a rolling four-week average.

Maximize Performance of New Products

Key Potential Growth Drivers

Nurtec[®] ODT
(rimegepant)
orally disintegrating tablets 75 mg

Vydura[®] 75mg
oral lyophilisate
rimegepant

ELREXFIO[™]
(elranatamab-bcmm)
INJECTION FOR SUBCUTANEOUS USE | 44 mg/1.1 mL
76 mg/1.9 mL

Oxbryta[®]
(voxelotor)

Velsipity[™]
(etrasimod) tablets

ABRYSVO[™]
Respiratory Syncytial Virus Vaccine

Litfulo[™]
(ritlecitinib) capsules
50mg

Protect / Grow Core Franchises and Key Blockbusters

Prevnar family¹

Vyndaqel[®] family²
(tafamidis)

Eliquis[®]
(apixaban) tablets 5mg
2.5mg

1. Prevnar family includes revenues from Prevnar 20/Apexxnar (pediatric and adult) and Prevnar 13/Prevenar 13 (pediatric and adult).
2. Vyndaqel family includes global revenues from Vyndaqel, as well as revenues for Vyndamax in the U.S. and Vynmac in Japan.

Disclosure



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