Biopharmaceutical Sector

Weekly Update – May 6, 2024

STIFEL | Healthcare

Table of Contents

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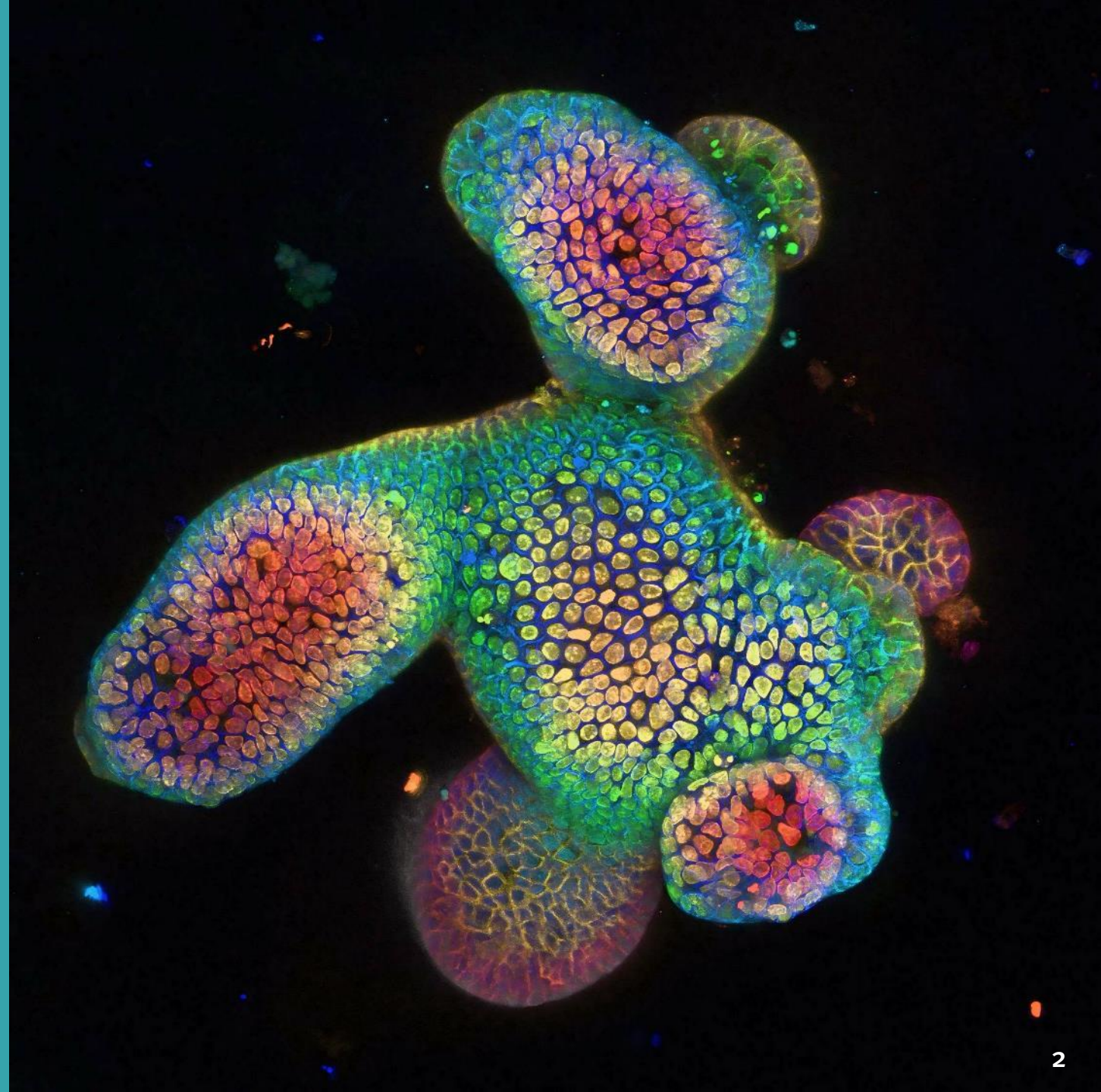
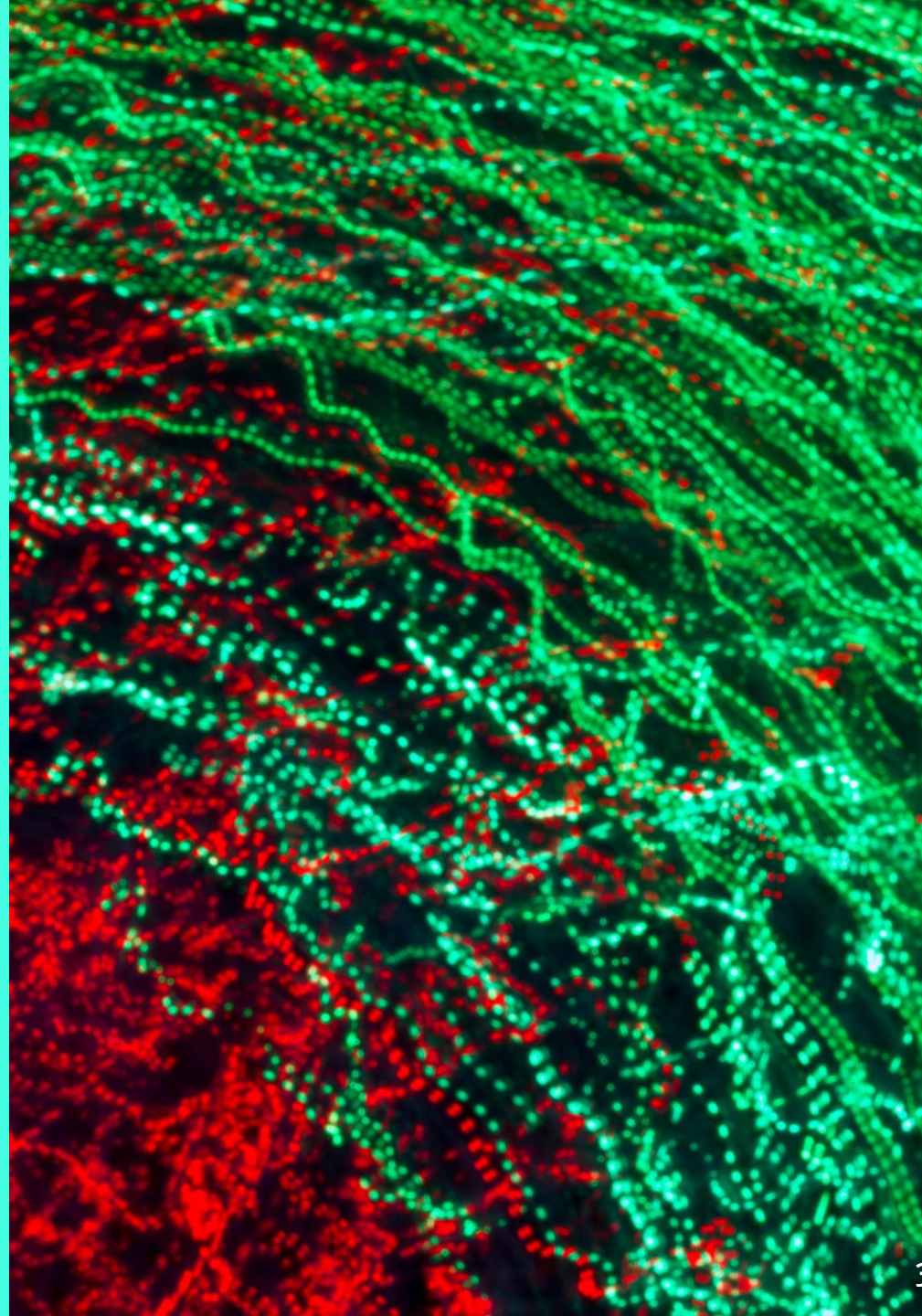


Accessing Past Issues

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

April 29, 2024 (M&A, Japan)
April 22, 2024 (Pharma Pricing)
April 15, 2024 (AI in Pharma)
April 8, 2024 (The Buyside)
April 1, 2024 (Biotech Balance Sheets)
March 25, 2024 (Women's Health)
March 18, 2024 (Inflammasome)
March 11, 2024 (IRA, Immunology)
March 4, 2024 (Biotech Employment)
Feb 26, 2024 (Biotech Strategy)
Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Jan 22, 2024 (AI in medicine)
Jan 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 (Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)



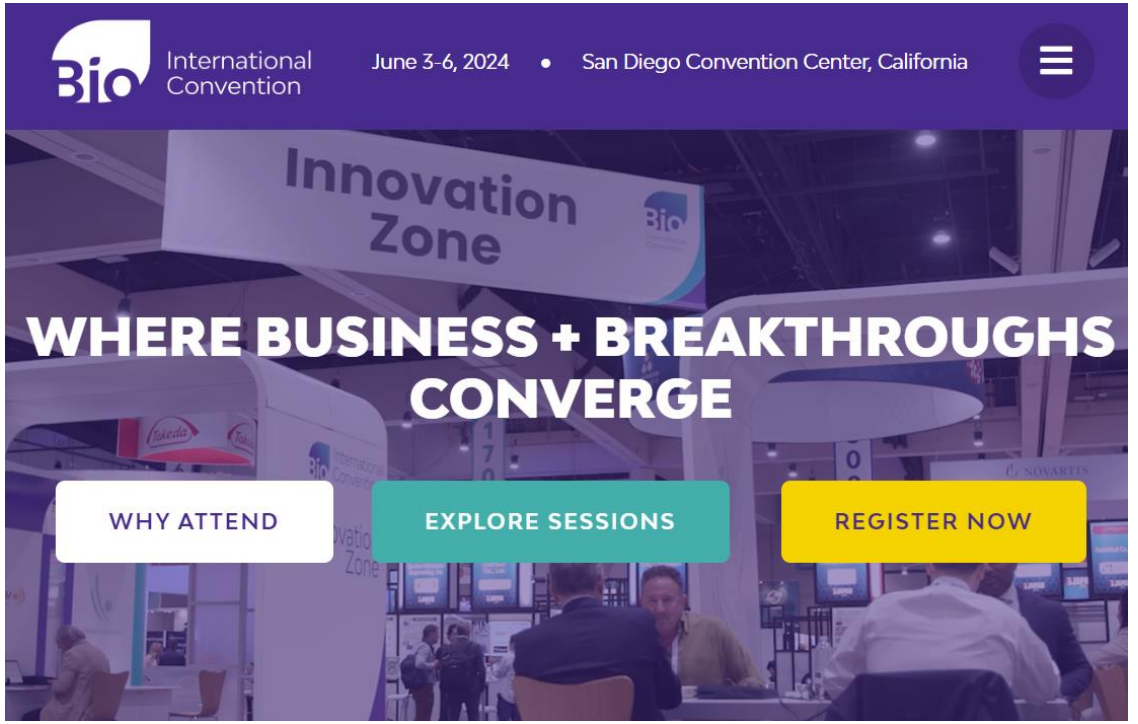
Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on May 3, 2024.

The next event will be on May 10, 2024.

Please join us.

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

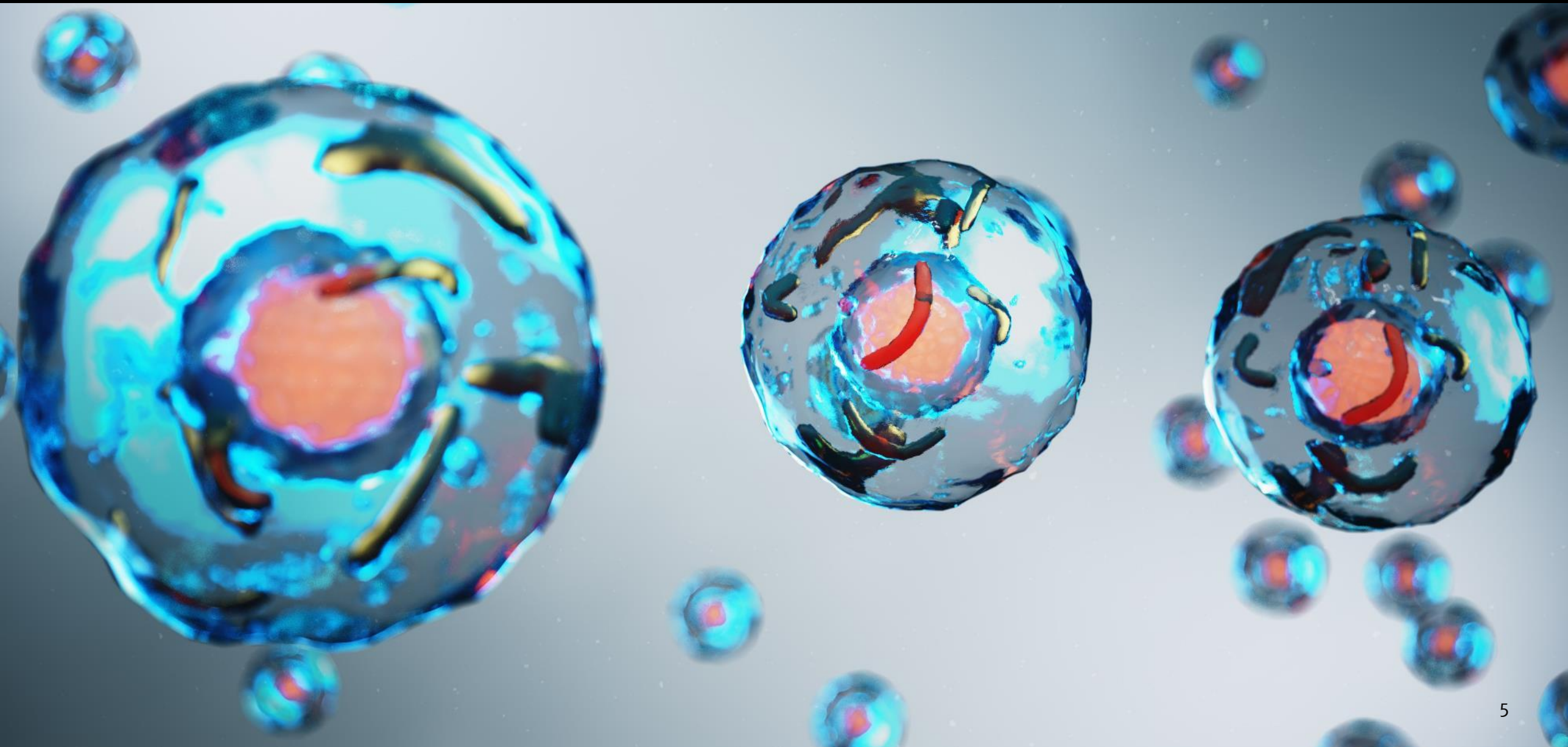


Please join us at BIO on June 3 to 6, 2024.

For details on attending please go to:
https://convention.bio.org/

We will also be at ASCO from May 31 to June 2nd. Happy to meet up there as well.

Macroeconomics Update



Fed Says Inflation Progress Stalls, Extends Cautious View

Nick Timiraos, *Wall Street Journal*, May 1, 2024 (excerpt)

The Federal Reserve held interest rates steady at their highest level in two decades and acknowledged recent inflation setbacks, extending a wait-and-see posture that could last well into the year if the economy doesn't weaken.

In their policy statement released Wednesday, officials highlighted a "lack of further progress" toward bringing inflation down in recent months. Earlier this year, officials said the risks to achieving their goals of low inflation with a healthy labor market were "moving into better balance," but officials tweaked their statement to suggest that such improvement had stalled.

Separately, the central bank approved plans to slow the ongoing reduction of its $7.4 trillion asset portfolio in a bid to extend the wind-down of emergency pandemic stimulus efforts it launched four years ago.

The Fed can reinvest the proceeds of its Treasury securities into new ones when they mature, but since 2022 it has been allowing up to $60 billion in Treasurys to roll off the portfolio every month. Starting in June, it will slow this monthly pace of decline to $25 billion.

Source: https://www.wsj.com/economy/central-banking/fed-says-inflation-progress-has-stalled-and-extends-wait-and-see-rate-stance-51b74bbf

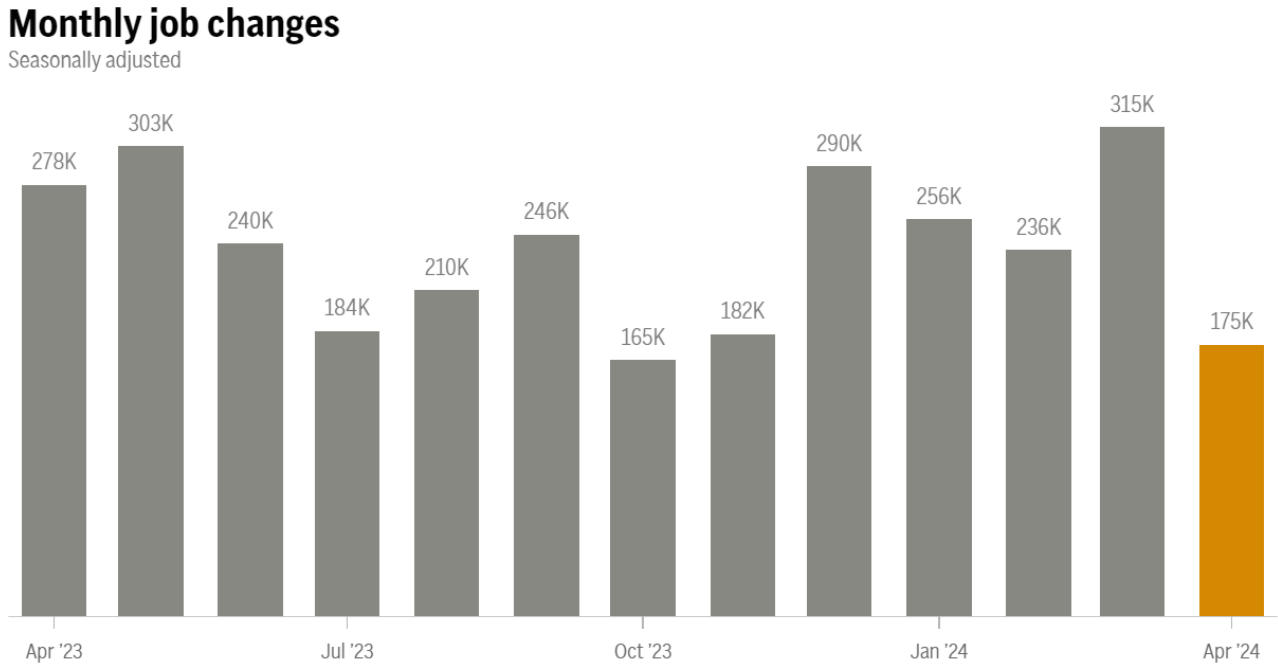
US Employers Scaled Back Hiring in April. How That Could let the Fed Cut Interest Rates

Paul Wiseman and Anne D'Innocenzio, *Associated Press*, May 3, 2024 (excerpt)

WASHINGTON (AP) — The nation's employers pulled back on their hiring in April but still added a decent 175,000 jobs in a sign that persistently high interest rates may be starting to slow the robust U.S. job market.

Friday's government report showed that last month's hiring gain was down sharply from the blockbuster increase of 315,000 in March. And it was well below the 233,000 gain that economists had predicted for April.

Yet the moderation in the pace of hiring, along with a slowdown last month in wage growth, will likely be welcomed by the Federal Reserve, which has kept interest rates at a two-decade high to fight persistently elevated inflation. Hourly wages rose a less-than-expected 0.2% from March and 3.9% from a year earlier, the smallest annual gain since June 2021.



Source: https://apnews.com/article/jobs-hiring-unemployment-economy-inflation-federal-reserve-07a3219817525o3e529988205ed36c9

S&P 500 Responded Positively to FOMC and Soft Job Number

Investors are clearly nervous people, dumping stocks ahead of the FOMC meeting. The market popped up and then went right back down on Thursday. Then, on Friday, with a positive job number, the market regained all ground lost during the week.

Source: finance.yahoo.com

Still No Stag and Not Much Flation

Paul Krugman, *New York Times*, May 3, 2024 (excerpt)

The economic news continues to be pretty good, especially compared with the dire forecasts many were making in late 2022. But you might not have gotten that message if you watch financial TV: It's hard to spend 24/7 talking about the economy while saying "not much happened this week." So commentators — and partisan media — seize on every hint of bad news.

So here's what you need to know: There's no stag out there, and not much flation.

True, G.D.P. growth came in a bit low in the first quarter. But just about every serious analyst regarded this as statistical noise. More important, as we saw in Friday morning's employment report, the U.S. economy is continuing its remarkable stretch of good job numbers and low unemployment.

What about inflation? The past few inflation reports have been a bit high, but much of that, again, is probably statistical noise. The New York Fed has a measure that tries to extract the signal from the noise; it basically says that there's nothing to see.

Inflation has clearly come way down without a recession, defying the pessimists; I can't help mentioning that Janet Yellen, the Treasury secretary, got a little snippy about Larry Summers the other day. But are we still on a glide path back to the Fed's target of 2 percent inflation, or are we stalling out around 3 percent?

The Fed seems to think that we're still on that glide path, but it left interest rates unchanged this week, and its statement was carefully hedged, noting that "there has been a lack of further progress" toward 2 percent.

Source: https://www.nytimes.com/2024/05/03/opinion/krugman-inflation-jobs-economy.html

Slower Hiring Boosts Hopes of a Late-Summer Rate Cut

Sam Goldfarb, *Wall Street Journal*, May 3, 2024 (excerpt)

Job growth slowed and unemployment ticked higher last month, marking a break from a string of data showing surprising strength in the labor market.

U.S. employers added a seasonally adjusted 175,000 jobs in April, the Labor Department reported on Friday. That was far less than in March, when gains exceeded 300,000. It was also below the 240,000 economists had expected.

Friday's report will keep hope alive for a late-summer interest-rate cut from the Federal Reserve, because it eases fears of an overheating economy. Still, it won't change much for the Fed's immediate outlook, in part because another employment report is due before officials' June 11-12 meeting.

Traders in interest-rate futures saw slightly higher probabilities of a rate cut in July after the report, though still below 50%. Expectations of a September rate cut rose to roughly 70%, up from around 60% on Thursday, according to CME Group.

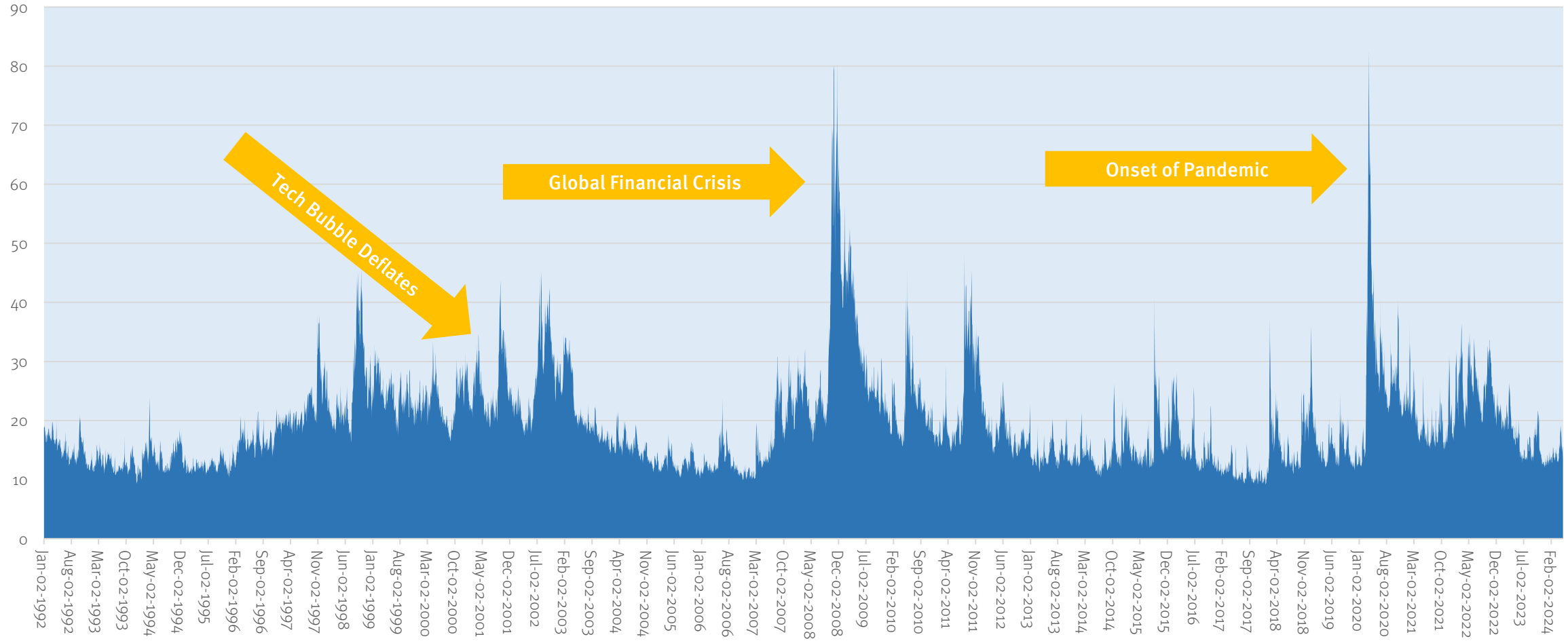
Stocks climbed. The Dow Jones Industrial Average rose 1.2%, or roughly 450 points, its best day in more than a month. The yield on the benchmark 10-year U.S. Treasury note fell to 4.498% from 4.569% Thursday.

Source: https://www.wsj.com/economy/jobs/jobs-report-april-unemployment-a8a1ac1a

Last Month's Drop in VIX Quite Meaningful

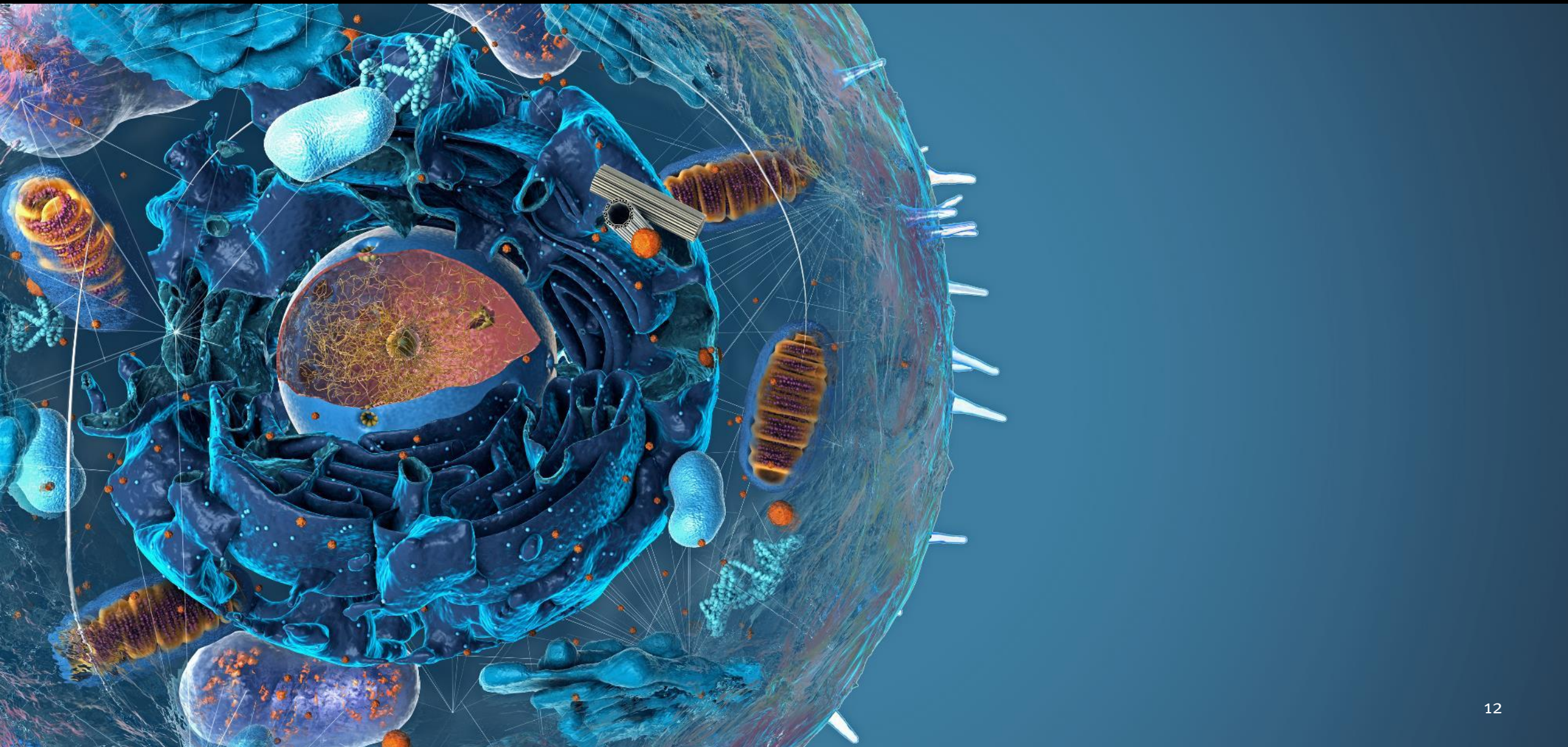
The median value of the VIX over the last 31 years has been 17.5%. A month ago, the VIX stood at 18.7%. By last Friday it had dropped to 13.5%. This represents a move from the 58th percentile of the distribution to the 24th percentile – quite a substantial change in the market's view of risk.

CBOE Volatility S&P 500 Index (VIX), 1993 to 2024



Source: CapitalIQ and Stifel analysis.

Biopharma Market Update



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

The XBI Closed at 89.98 Last Friday (May 3), Up 7.8% for the week

The XBI bounced back strong last week (up 7.8% on positive macro news). Last week saw Treasury yields improve and the VIX return to previous levels. The S&P 500 did not do nearly as well.

Biotech Stocks Up Big Last Week

Return: April 28 to May 3, 2024

Nasdaq Biotech Index: +5.6%
Arca XBI ETF: +7.2%
Stifel Global Biotech EV (adjusted): +8.9%*
S&P 500: +0.5%

Return: Dec 29, 2023 to May 3, 2024 (YTD)

Nasdaq Biotech Index: +0.2%
Arca XBI ETF: +0.8%
Stifel Global Biotech EV (adjusted): +24.1%*
S&P 500: +7.5%

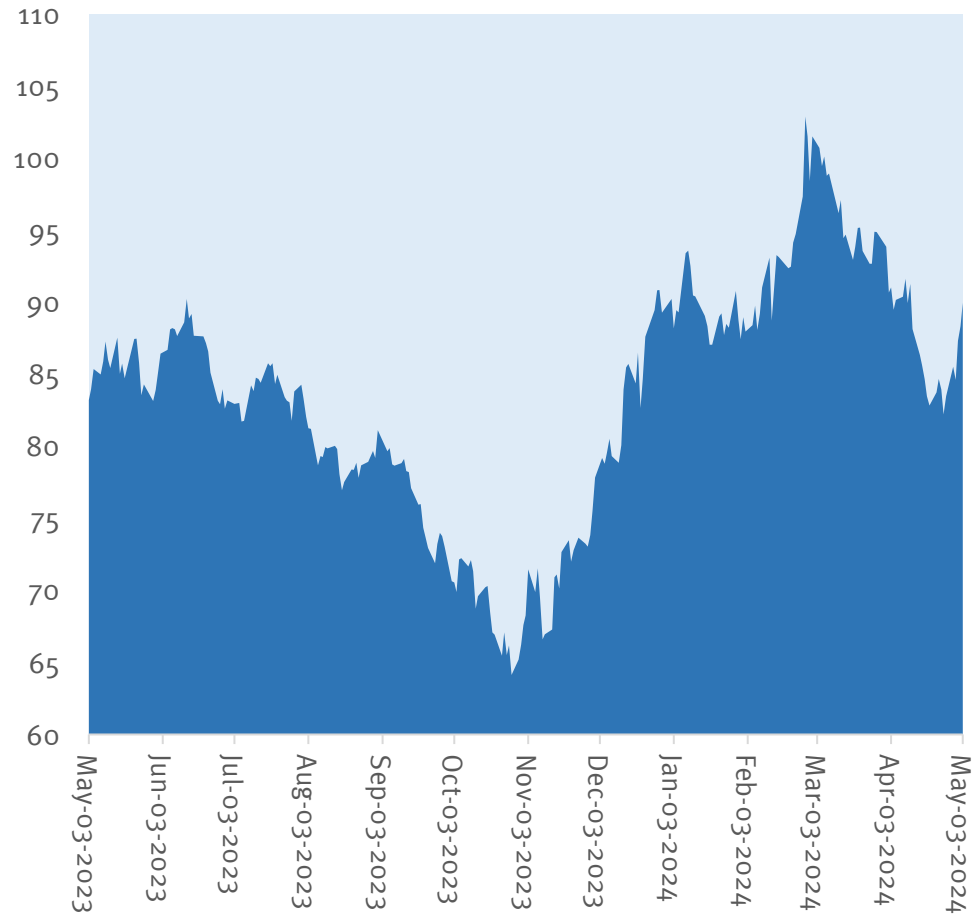
VIX Down Further

Jan 20, 2023: 19.9%
July 21, 2023: 13.6%
Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Mar 29, 2024: 13.0%
Apr 5, 2024: 18.7%
Apr 26, 2024: 15.0%
May 3, 2024: 13.5%

10-Year Treasury Yield Down

Jan 20, 2023: 3.48%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Mar 29, 2024: 4.20%
Apr 5, 2024: 4.39%
Apr 26, 2024: 4.66%
May 3, 2024: 4.5%

XBI, May 3, 2023 to May 3, 2024

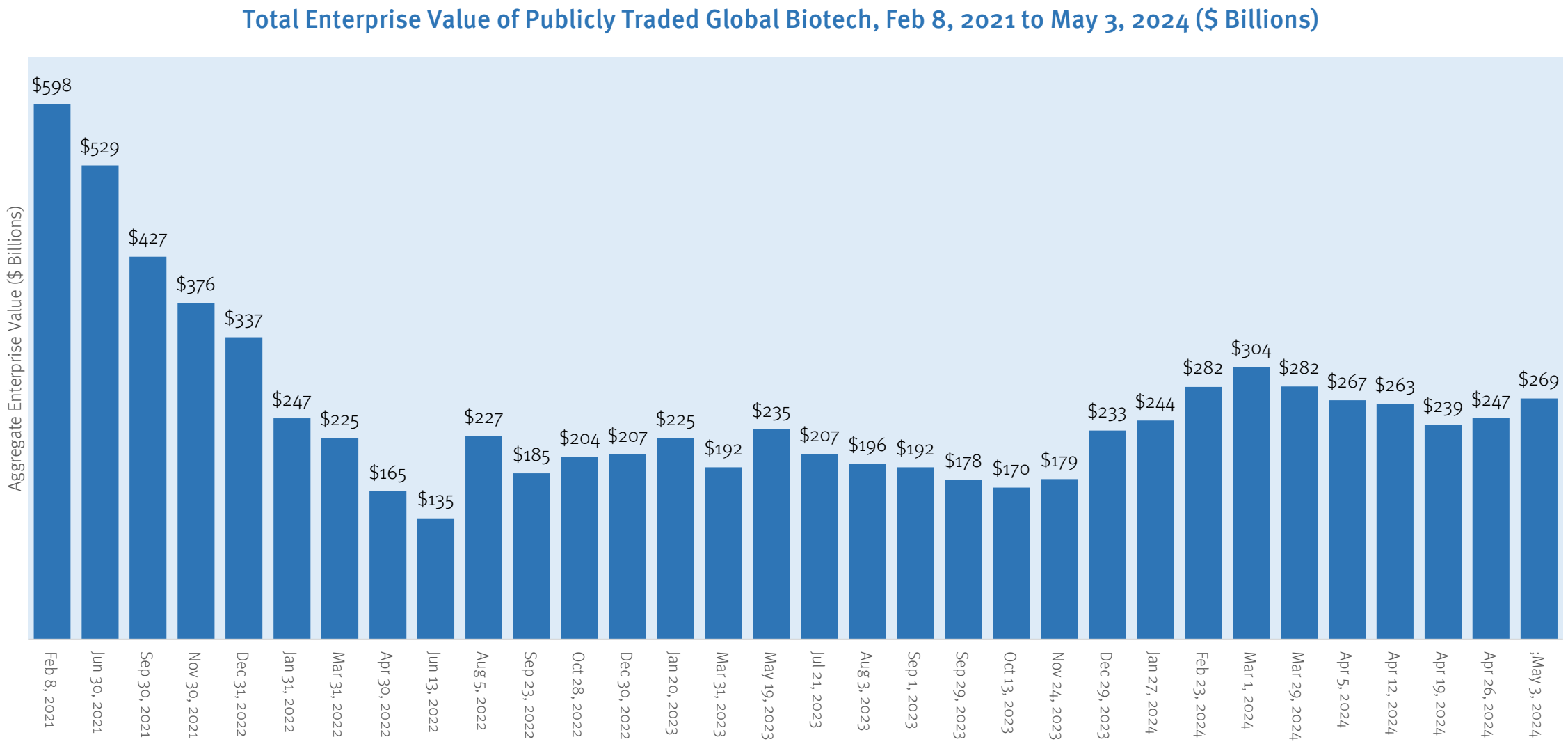


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Up 9% Last Week

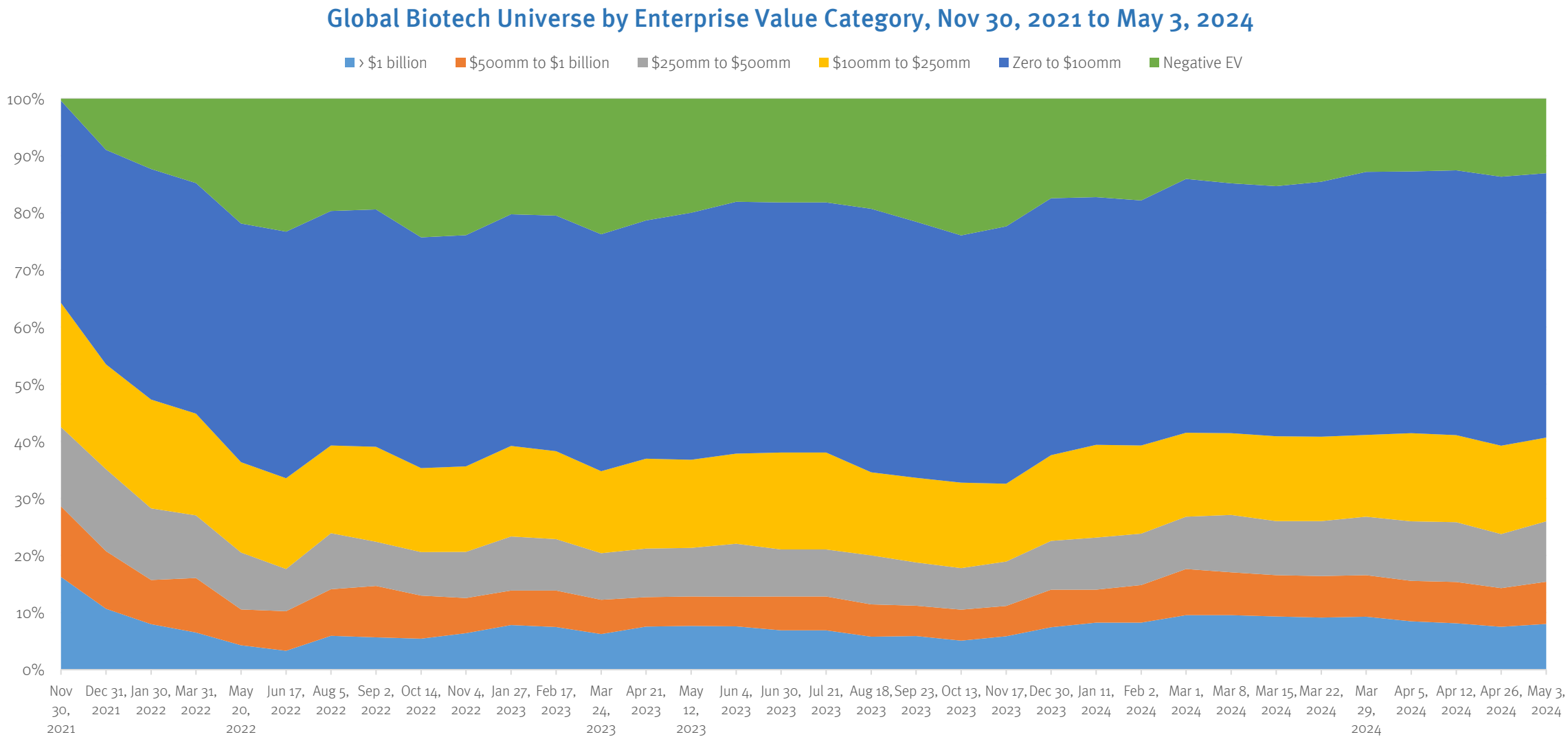
Biotech stocks bounced back last week after bottoming out last week. On an exit/addition adjusted basis biotech is up 24% for the year. While the recent downturn has taken its toll, there remains a robust rally that has unfolded in 2024.



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

Global Biotech Neighborhood Analysis

The population of companies worth over $100mm or more grew nicely last week.

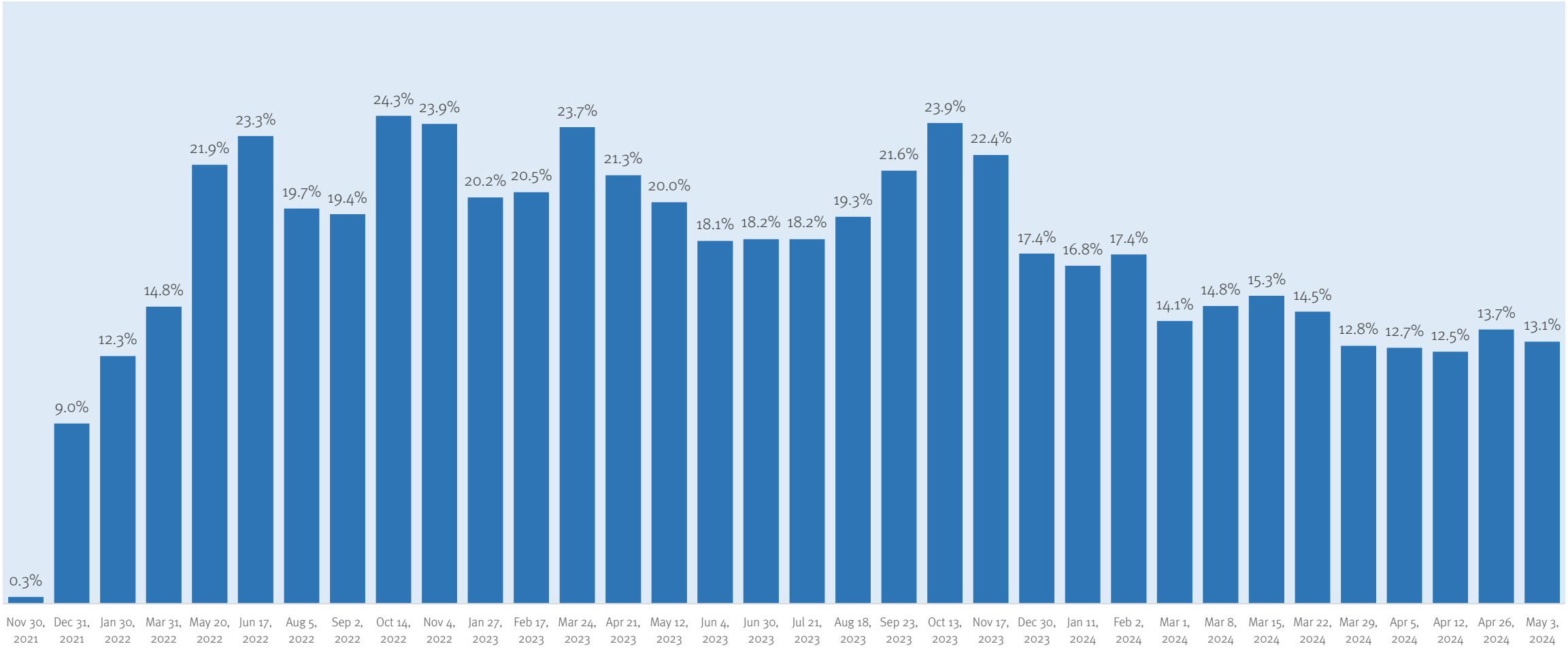


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

13% of Public Biotechs Worldwide Trading Below Cash

This figure is much improved from a year ago when 20% of biotechs were trading below cash.

Percent of Public Global Biotechs Trading Below Cash, Nov 2021 to May 2024



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

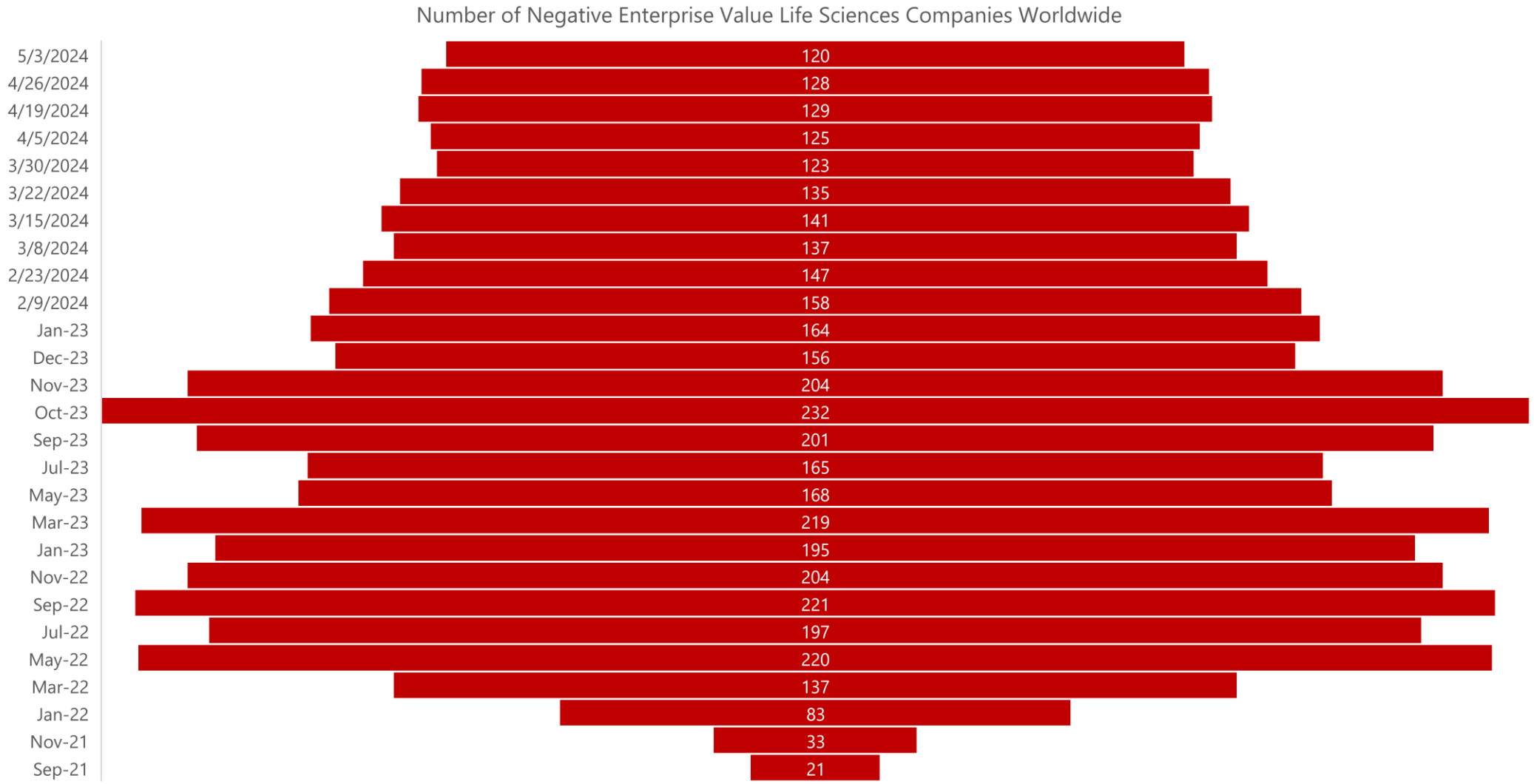
Life Sciences Sector Total Value Up 1.7% Last Week

All subsectors of the life sciences except pharma services were up last week with best relative performance from biotech, HCIT and API.

Sector	Firm Count	Enterprise Value (May 3, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$83,189	2.3%	4.8%	5.1%
Biotech	794	$269,248	8.9%	0.7%	-5.1%
CDMO	39	$145,665	1.1%	-4.1%	-21.6%
Diagnostics	81	$263,540	1.3%	-3.2%	-4.8%
OTC	30	$27,446	2.1%	-0.5%	-7.4%
Pharma	716	$6,178,636	1.9%	0.4%	4.3%
Pharma Services	38	$185,281	-0.7%	-4.3%	-4.8%
Tools	51	$695,078	0.6%	-1.6%	-3.6%
Devices	181	$1,670,937	0.9%	-1.0%	-2.7%
HCIT	10	$18,284	3.9%	-0.7%	-29.3%
Total	**2021**	**$9,527,704**	**1.7%**	**-0.2%**	**1.9%**

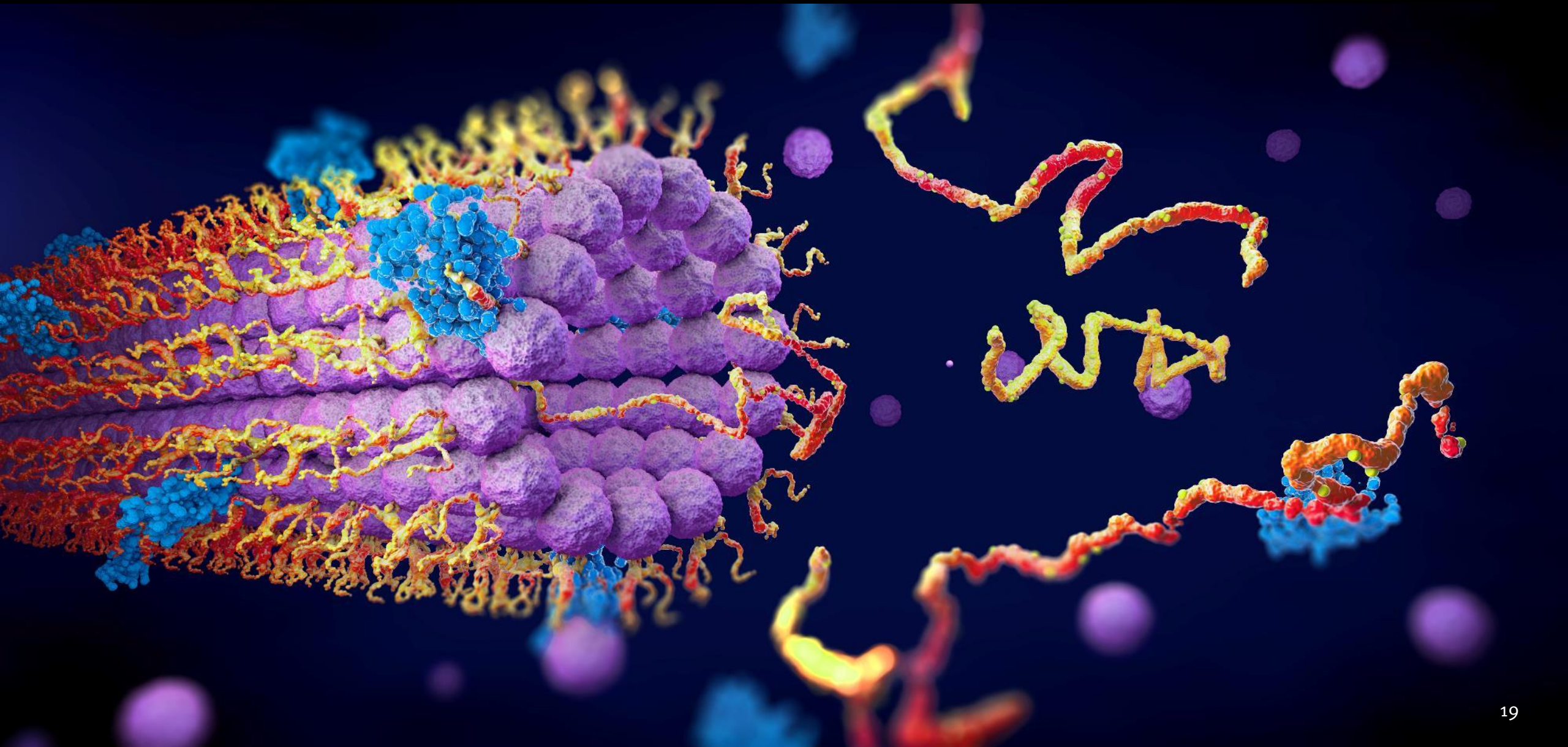
Source: CapitalIQ

Number of Negative Enterprise Value Life Sciences Companies Dropped Meaningfully Last Week



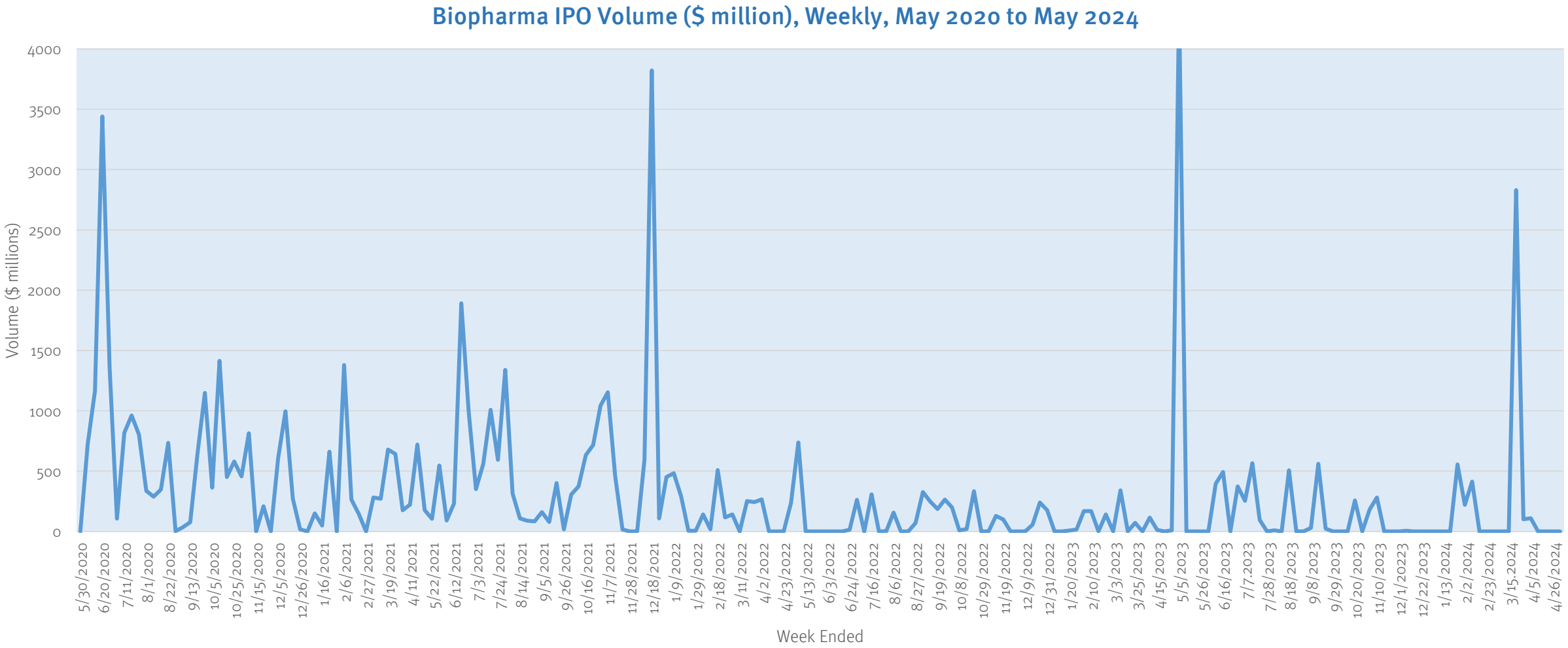
Source: CapitalIQ

Capital Markets Update



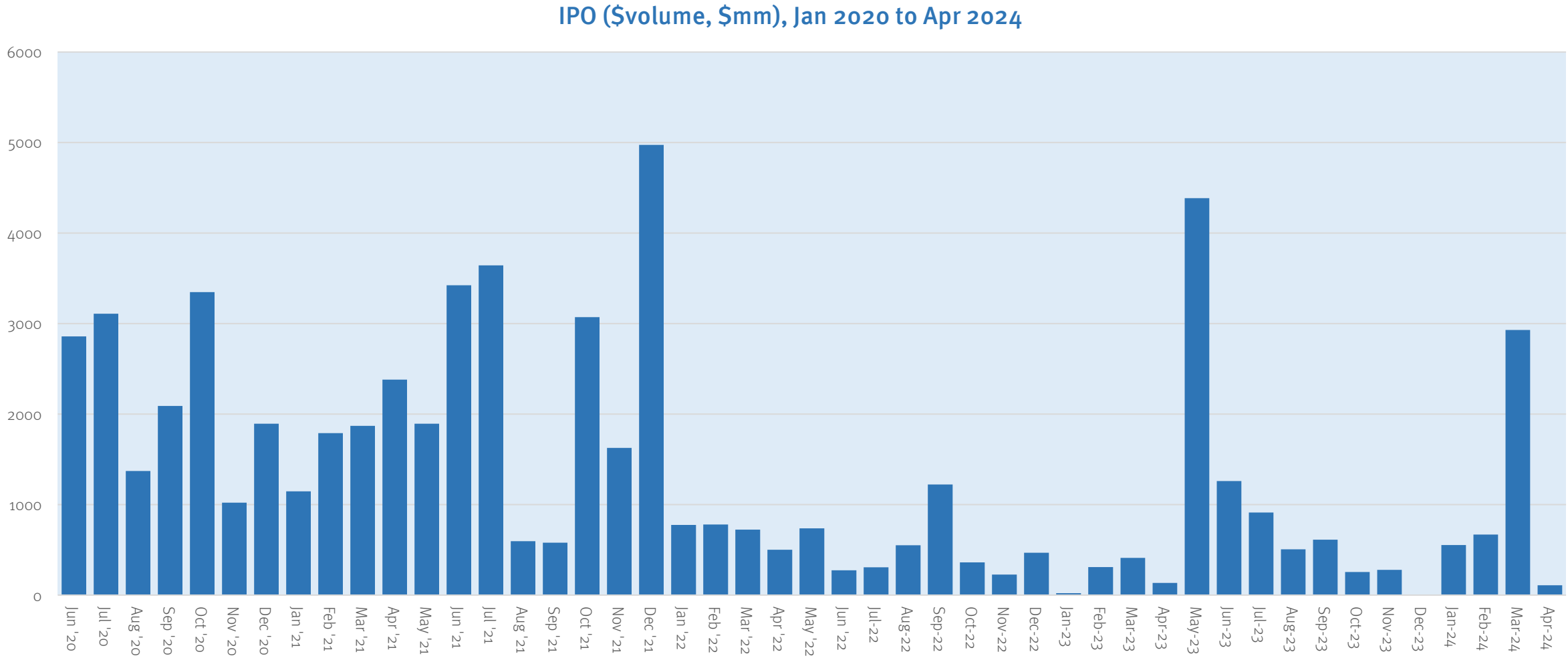
No IPO Activity Last Week

The IPO market was quiet last week. The last company to go public in the U.S. or Europe debuted a month ago.



Source: Data from CapitalIQ and Stifel research.

There Was Only One IPO in April – Contineum at the Start of April



Source: Data from CapitalIQ and Stifel research.

‘Next Wave of IPOs’ Will Arrive in Summer

James Waldron, *FierceBiotech*, May 3, 2024 (Excerpt)

Delegates at the LSX World Conference in London this week seemed to agree on one thing—the biotech IPO window finally re-opened this year. This sentiment has persisted despite the fact that the initial run of public offerings died down by the spring.

For Francesco De Rubertis, co-founder and partner of London-based life sciences investment firm Medicxi, the current lull is to be expected. What’s more, he expects “at least a number of IPOs” to arrive as soon as the summer.

“In the absence of other external [factors], the natural dynamics of markets should say that now there will be another big number of investors that will become active on the public markets, and that will translate in the next wave of IPOs,” he told Fierce in an interview on the sidelines of the LSX conference on April 30.

To back up his prediction, De Rubertis pointed to the popularity of secondary stock offerings among publicly-listed biotechs in recent months. An increase in these offerings is “already a signal of good health of the markets,” he explained, as they show that “investors are excited.”

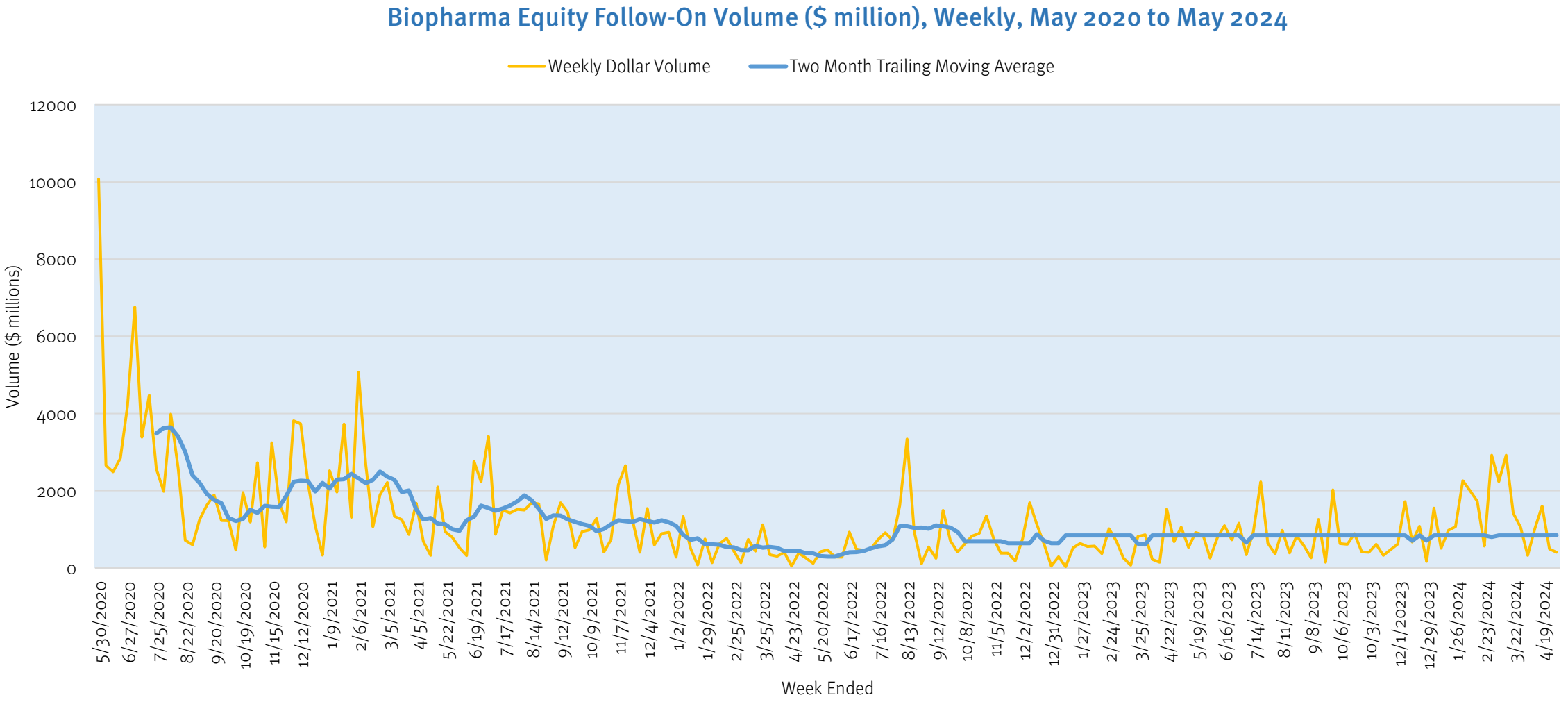
Medicxi launched its latest $400 million fund in July 2023 with the stated aim of “backing visionary biopharma entrepreneurs.” De Rubertis said he is now being “pitched a lot from bankers” who are keen for more biotech IPOs.

Francesco De Rubertis
Partner
Medicxi

Source: https://www.fiercebiotech.com/biotech/next-wave-ipos-will-arrive-summer-predicts-biotech-vc-partner

Follow-On Market Remained Quiet Last Week

The follow-on market remained quiet last week as a range of macro news hit the market. A total of $405 million was raised across 20 issues.

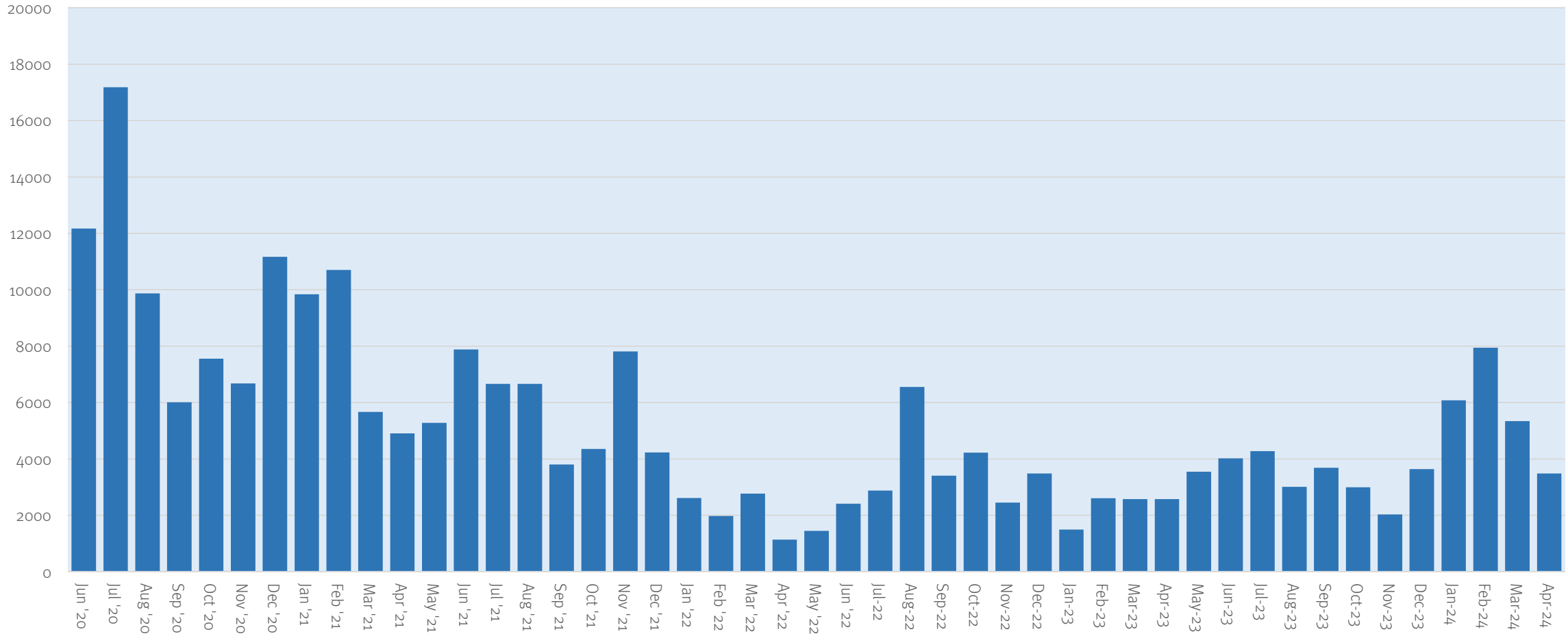


Source: Data from CapitalIQ.

Follow-on Equity Issuance Volume Down in April

The bump in follow-on equity volume seen in Q1 receded in April as the issuance volume ($3.4 billion) went back to the levels generally seen in the Sep 2022 to Dec 2023 period. We expect volumes to pick up in May in light of improved macro conditions and posting of fresh biotech financials.

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

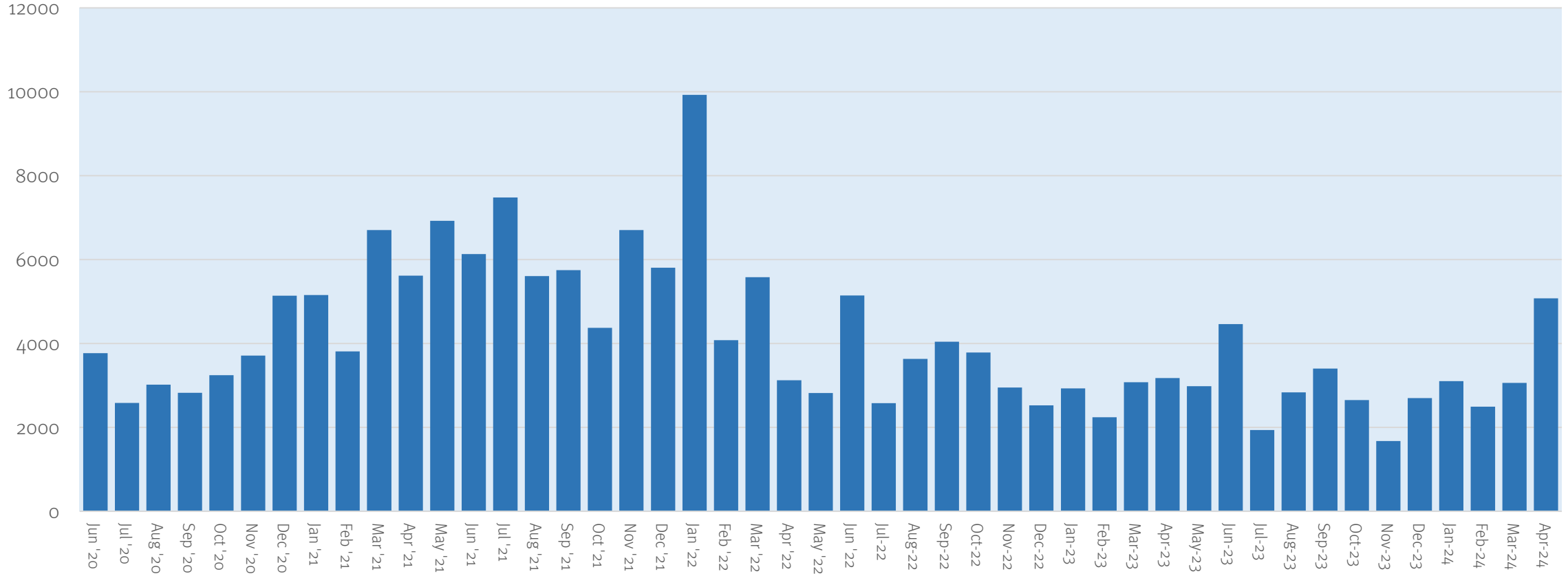


Source: Data from CapitalIQ and Stifel Research

Private Venture Equity Investment Up Big in April

The venture private market was brisk last month with $5.1 billion raised. This was the biggest month since June 2022. The Xaira deal helped to up the number but even without that financing, April would have been the strong month in ten. Last week saw BridgeBio Oncology Therapeutics raise $200 million and Enlaza raise $200 million.

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



Source: Data from CapitalIQ, Crunchbase.

BridgeBio Launches BridgeBio Oncology Therapeutics with $200M of Private Capital to Accelerate its Precision Oncology Pipeline

PALO ALTO, Calif., May 02, 2024: BridgeBio Pharma, Inc. (Nasdaq: BBIO) ("BridgeBio" or the "Company"), a commercial-stage biopharmaceutical company focused on genetic diseases and cancers, has announced the completion of a $200M private financing of its former subsidiary, TheRas, Inc. d/b/a BridgeBio Oncology Therapeutics (BBOT), to accelerate the development of its oncology portfolio. The oversubscribed financing was led by Cormorant Asset Management and co-led by Omega Funds with participation from affiliates of Deerfield Management, GV (Google Ventures), EcoR1 Capital, Wellington Management, Enavate Sciences, Surveyor Capital (a Citadel company), Aisling Capital, Casdin Capital, and Longwood Fund.

BBOT will be advancing three initial programs:

1. BBO-8520, a direct inhibitor of KRASG12C that binds to both the ON and OFF states of the protein; BBOT is currently enrolling patients in the ONKORAS-101 trial for patients with KRASG12C mutant non-small cell lung cancer
2. BBO-10203, a PI3Kα:RAS breaker that blocks the specific interaction between RAS and PI3Ka to inhibit PI3Kα / AKT effector signaling in tumors while bypassing glucose metabolic signaling to avoid hyperglycemia; BBOT expects to file an Investigational New Drug application (IND) for BBO-10203 in Q2 2024 and, subject to clearance of the IND, will begin enrolling patients later this year
3. BBO-11818, a pan-KRAS inhibitor that targets both the ON and OFF states of KRASG12X for which BBOT expects to file an IND in early 2025

In addition to these assets, BBOT will continue to undertake a robust discovery-stage research program focused on targeting additional oncogenic drivers within the RAS and PI3K pathways.

BridgeBio Oncology Therapeutics will be led by Eli Wallace, PhD, as CEO and Pedro Beltran, PhD, as CSO. "We are excited to progress our portfolio of novel small molecules to treat patients suffering from RAS pathway malignancies. In conjunction with BridgeBio and an amazing suite of investors, we look forward to seeing all three of our programs progress into the clinic over the next 12 months," said Dr. Wallace.

Source: https://www.globenewswire.com/news-release/2024/05/02/2874030/0/en/BridgeBio-launches-BridgeBio-Oncology-Therapeutics-BBOT-with-200M-of-private-external-capital-to-accelerate-the-development-of-its-novel-precision-oncology-pipeline.html

Enlaza Therapeutics Raises $100 Million Through Its Series A Financing

LA JOLLA, Calif., April 30, 2024: Enlaza Therapeutics, the first covalent biologic platform company, today announced a $100 million Series A financing. The financing will be used to further develop Enlaza's proprietary covalent protein technologies and to support advancement of wholly owned pipeline programs to the clinic.

The financing was led by the Life Sciences group of J.P. Morgan Asset Management's Private Capital division, with participation from existing investors: Frazier Life Sciences, Avalon Ventures, Lightspeed Venture Partners, and Samsara BioCapital. The financing also includes new investors: Amgen Ventures, Regeneron Ventures, Bregua Corporation, Pappas Capital, and Alexandria Venture Investments. Concurrent with the financing, Stephen Squinto, Ph.D., Chief Investment Officer (CIO) of the Life Sciences group of J.P. Morgan Private Capital, was named to the Board of Directors.

"Bringing covalency to the biologics market is an extremely valuable way to unlock the next generation of protein therapeutics that are safer and more tolerable and can be dosed more frequently with lower doses," said Stephen Squinto, CIO of Life Sciences group of J.P. Morgan Private Capital. "We believe Enlaza's platform is well positioned for many first-in-class and best-in-class opportunities and are excited to partner with this senior management team."

Enlaza's covalent biologic platform, called War-LockTM, creates highly specific therapeutic warheads that covalently bind to drug targets of interest. This white-space technology enables, for the first time, a covalent-acting protein drug that retains the selectivity of small-format biologics. These unique protein drugs enable specific covalent binding to an intended protein target, improving efficacy while simultaneously reducing toxicities related to sustained peripheral exposure.

"This financing support will enable continued expansion of our covalent protein drug platform, establishment of a diversified pipeline that demonstrates the broad potential of this approach, and advancement of our lead assets toward clinical development."

Sergio Duron
Chief Executive Officer
Enlaza Therapeutics

Source: https://enlazatx.com/press_release/enlaza-therapeutics-raises-100-million-through-its-series-a-financing-led-by-the-life-sciences-group-of-j-p-morgan-private-capital/

Bob Nelsen on ARCH-led Megarounds

May Bayer, *FierceBiotech*, May 1, 2024 (excerpt)

The three highest private biotech financings so far in 2024 totaled nearly $1.7 billion, led by Xaira Therapeutics' $1 billion unveiling last week. One constant behind all three companies: ARCH Venture Partners.

The formidable venture firm led each raise, which included Mirador Therapeutics and obesity-focused Metsera. Bob Nelsen, the lean, mean, sometimes-swearing machine at the firm's helm says a billion dollars is just the beginning for some.

"We want the IPO book in the seed round," he said in an interview. "We want to know who wants to build something big and stay with it." Nelsen added that sometimes, "It's better to get the right people in and to have people that essentially write bigger checks."

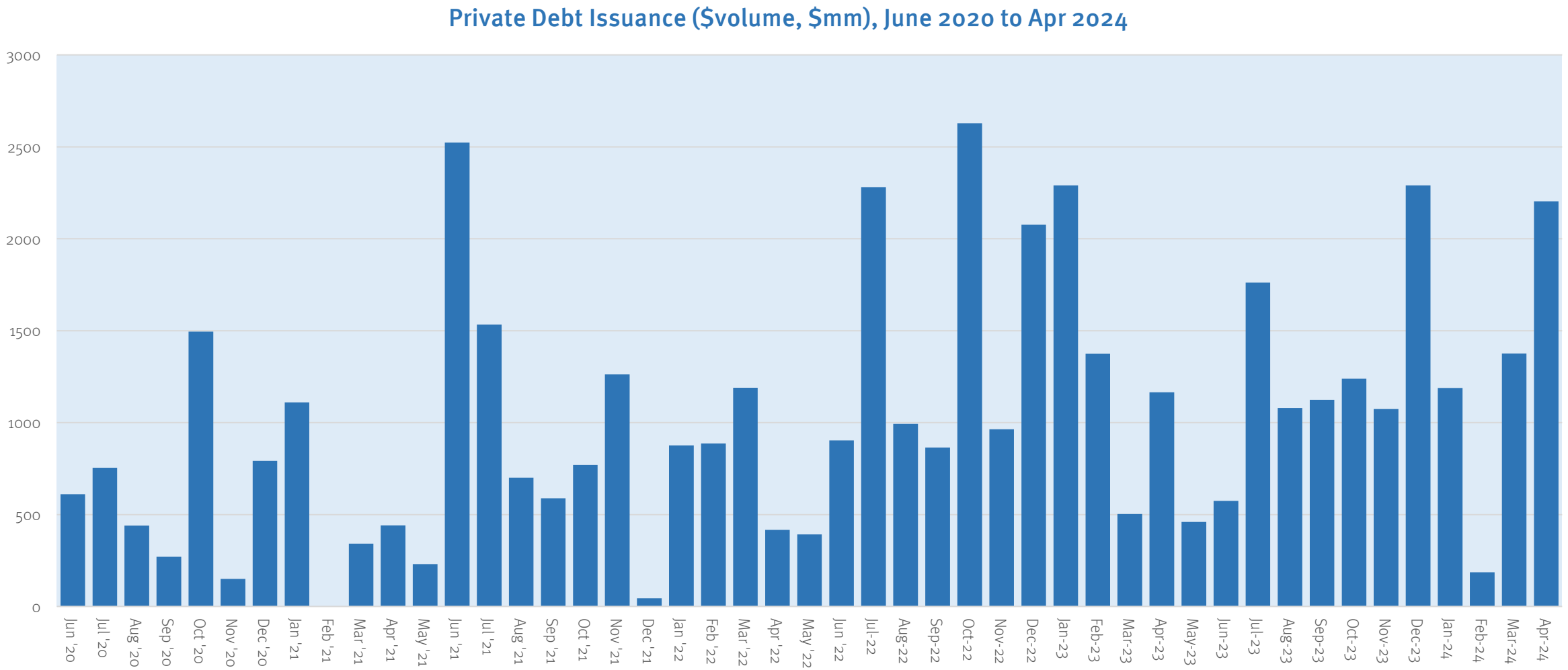
In the case of Xaira, Nelsen said investors were cognizant that $1 billion would likely be just the start if the company can realize its lofty dream of revolutionizing drug discovery. This meant building a team that could "put another billion or more in." Xaira's other backers include Forsite Labs, F-Prime Capital, Sequoia Capital and Lux Capital, among others. "It's gonna take billions, not a billion, to make the ultimate company that rethinks the system," Nelsen said, neatly summarizing his larger thesis about investing.

Bob Nelsen
General Partner
Arch Venture

Source: https://www.fiercebiotech.com/biotech/bob-nelsen-arch-led-megarounds-we-want-ipo-book-seed-round

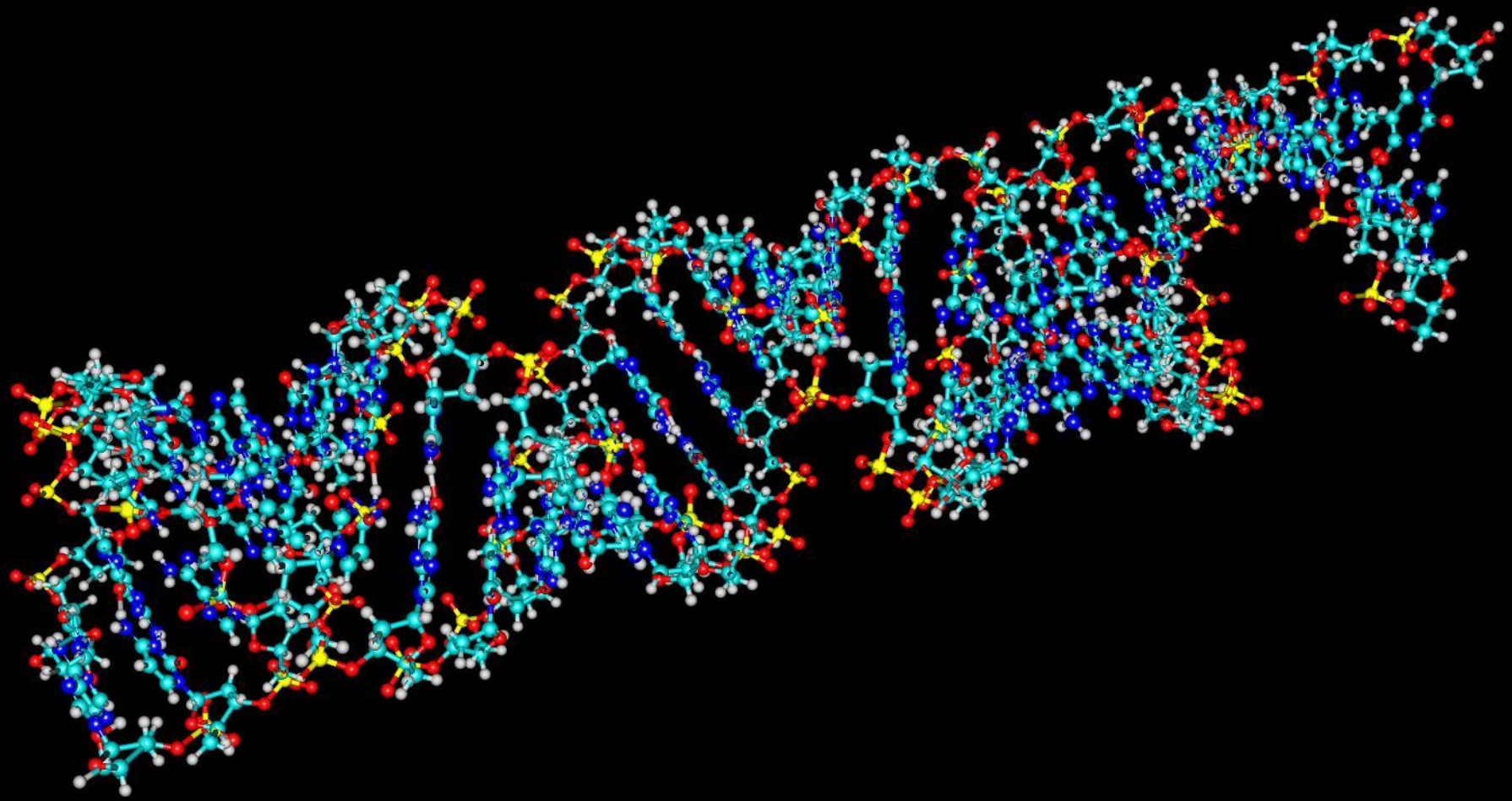
Biopharma Private Debt Market Active Last Week

Last month saw private issuers take down $2.2 billion in debt capital. This was the most active month thus far in 2024.



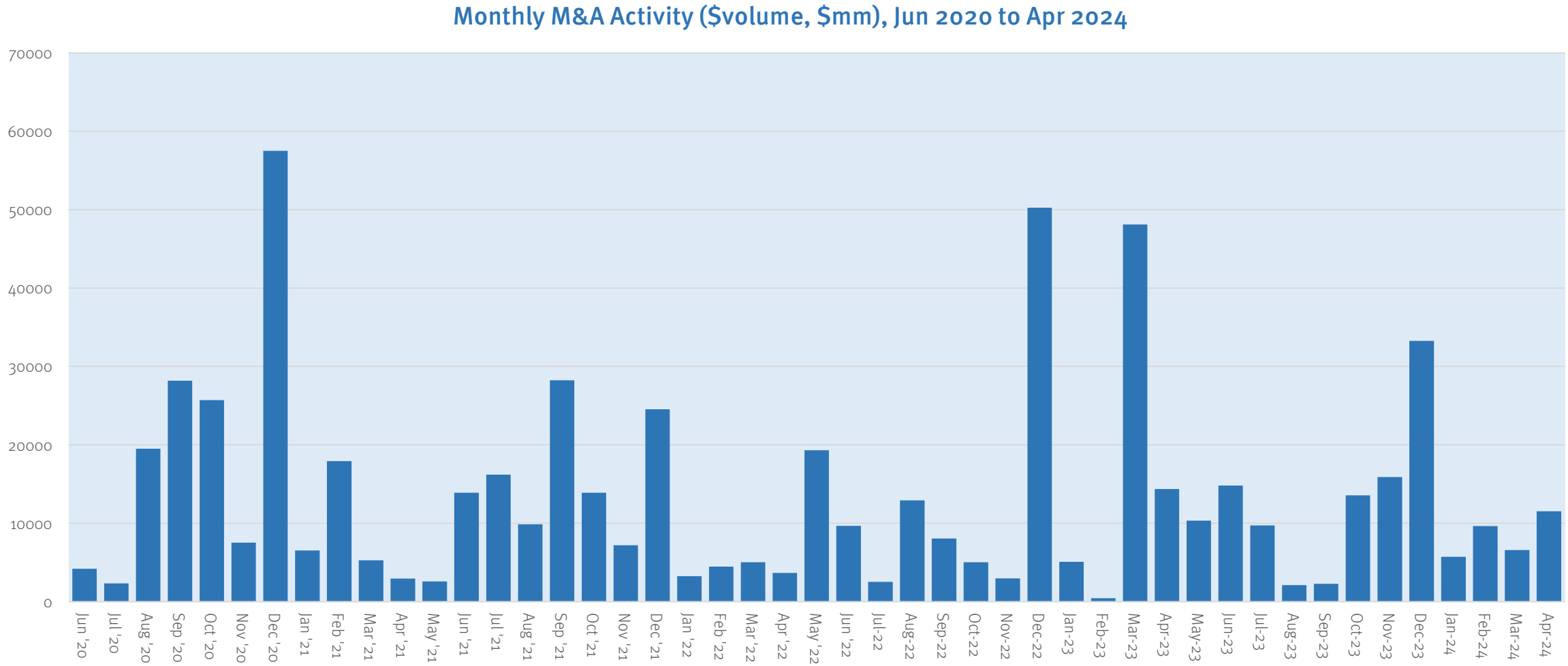
Source: Data from CapitalIQ, Crunchbase, Stifel research.

M&A News



Biopharma M&A Market Picked Up Last Month

It's been a quiet year for large M&A. Last month was the biggest of the year thus far with $11.5 billion of M&A volume. Last week saw Ono Pharma buy Deciphera for $2.4 billion and Novartis buy Mariana for $1 billion upfront (plus $750 million of potential milestones).



Source: Data from CapitalIQ, Stifel research.

Deciphera Pharmaceuticals to be Acquired by ONO Pharmaceutical For $2.4 Billion

WALTHAM, Mass – April 29, 2024 – Deciphera Pharmaceuticals, Inc. (NASDAQ: DCPH), a biopharmaceutical company focused on discovering, developing, and commercializing important new medicines to improve the lives of people with cancer, today announced that it has entered into a definitive merger agreement with ONO Pharmaceutical Co., Ltd. (ONO), under which ONO will acquire all outstanding shares of Deciphera common stock for $25.60 per share in cash through a tender offer followed by a merger of Deciphera with a wholly-owned subsidiary of ONO (the "Acquisition"), for a total equity value of $2.4 billion. The boards of directors of both companies have unanimously approved the transaction.

Together, ONO and Deciphera will accelerate their shared vision to deliver innovative new drugs and serve patients around the world. Deciphera brings specialized research and development capabilities in kinase drug discovery, well-established commercial and sales platforms in the United States and Europe, and global clinical development capabilities. In addition to QINLOCK® - Deciphera's switch-control inhibitor for the treatment of fourth-line gastrointestinal stromal tumor (GIST), which is approved in the United States and over 40 other countries, Deciphera also brings a mature, diverse pipeline of best-or-first in class potential medicines, including vimseltinib, DCC-3116 (an ULK inhibitor) and multiple additional oncology candidates. Vimseltinib is a highly selective switch-control kinase inhibitor with successful pivotal clinical data for the potential to be a best-in-class and first-in-class agent for the treatment of tenosynovial giant cell tumor (TGCT), and potentially other indications. The Acquisition is expected to enable ONO to build a robust presence in oncology, one of its key priority areas, and also support ONO's efforts to become a Global Specialty Pharma company.

Steven L. Hoerter, President and Chief Executive Officer of Deciphera, said, "Deciphera and ONO share a deep commitment to improve the lives of people living with cancer, and the transaction announced today enables us to make even greater impact for patients. Together, we expect to advance and accelerate each organization's important work through combined research and development capabilities and a global commercial footprint. Importantly, this acquisition delivers for all of Deciphera's stakeholders. It provides immediate, compelling value for our shareholders, provides greater opportunities for our world-class team, and ultimately, greater hope for patients. I am excited about the future of the combined organization, and we are honored to contribute to the continued growth of ONO in the U.S. and around the world."

Source: https://www.businesswire.com/news/home/20240429316382/en/Deciphera-Pharmaceuticals-to-be-Acquired-by-ONO-Pharmaceutical-For-2.4-Billion

Japan's Ono Pharma Says $2.4 bln Deciphera Purchase ‘First Step’ For Global Expansion

Rocky Swift, Reuters, April 30, 2024

Japan's Ono Pharmaceutical Co said on Tuesday its $2.4 billion takeover of Deciphera Pharmaceuticals, opens new tab is a "first step" in expanding in U.S. and European markets.

"We've gotten to stage 1 and 2 on a global level, but in order to start recording sales at a quicker pace, we need to obtain a pipeline from outside. This acquisition is the first step in that direction," Ono Pharma CEO Gyo Sagara said at an online briefing.

"After this first M&A, this does not mean that we will do a second or third, but we will always keep an eye on acquiring good compounds from the outside and will make sure to go in if we have a chance," he added.

Ono Pharma is best known globally for its blockbuster cancer drug Opdivo, which is sold in the U.S. by partner Bristol-Myers Squibb. The drug expected to lose patent protection in major markets from 2028.

Source: https://www.reuters.com/markets/deals/japans-ono-pharma-says-24-bln-deciphera-purchase-first-step-global-expansion-2024-04-30/

Novartis Enters Agreement to Acquire Mariana Oncology

Basel, May 2, 2024 – Novartis today announced that it has entered into an agreement to acquire Mariana Oncology, a preclinical-stage biotechnology company based in Watertown, Massachusetts focused on developing novel radioligand therapies (RLTs) to treat cancers with high unmet patient need. The transaction bolsters the Novartis RLT pipeline and expands the company's research infrastructure and clinical supply capabilities, supporting Novartis strategic priorities in oncology and RLT platform innovation.

The acquisition encompasses a robust portfolio of RLT programs spanning lead optimization to early development across a range of solid tumor indications such as breast, prostate and lung cancer – including development candidate MC-339, an actinium-based RLT being investigated in small cell lung cancer.

"The acquisition of Mariana Oncology reflects our commitment to radioligand therapy as one of our company's key technology platforms and strengthens our leadership in this field," said Fiona Marshall, President of Biomedical Research at Novartis. "We are excited to work with the Mariana team to bring forward next-generation RLTs for patients living with cancer and together shape the future of RLT as a pillar for oncology treatment."

RLTs, or radiopharmaceuticals, are a form of precision medicine that combines a tumor-targeting molecule (ligand) with a therapeutic radioisotope (a radioactive particle). RLTs bind to specific receptors expressed on the surface of certain types of tumors. Once bound to a target cell, emissions from the therapeutic radioisotope cause DNA damage that can inhibit cell growth and replication and potentially trigger cell death. This targeted approach enables the delivery of radiation to the tumor, while limiting damage to the surrounding cells.

"As pioneers in radioligand therapies, we are dedicated to building on our scientific leadership and expanding the breadth of these potentially transformative treatments to a broader range of cancer types," said Shiva Malek, Global Head of Oncology for Biomedical Research at Novartis. "This acquisition brings to Novartis phenomenal talent and new capabilities in RLT research that complement our wide-ranging internal efforts to explore novel isotopes, combinations, disease areas, and more."

As of today, Novartis has two approved RLTs for certain patients with metastatic castration-resistant prostate cancer and for certain types of gastroenteropancreatic neuroendocrine tumors. The company's early and late pipeline has several programs in or entering the clinic, including a spectrum of studies and assets for prostate cancer, as well as other preclinical and discovery programs to identify the next wave of novel RLTs. Novartis is actively exploring new isotopes and new combinations with complementary mechanisms of action, as well as looking at new disease areas for RLT.

Under the terms of the agreement, Novartis will make an upfront payment of USD 1 billion and additional USD 750 million in payments upon completion of pre-specified milestones.

Source: https://www.novartis.com/news/media-releases/novartis-enters-agreement-acquire-mariana-oncology-strengthening-radioligand-therapy-pipeline

Reflections on Mariana's Acquisition

Josh Resnick and Laura Tadvalkar, RA Capital, May 2, 2024

We are happy to announce that Novartis has acquired our portfolio company Mariana Oncology for $1B upfront and $750M in downstream milestones. Novartis has deep clinical and commercial experience with oncology and radiopharmaceuticals, and is well positioned to work with the Mariana team on advancing Mariana's portfolio of radiopharmaceuticals into the clinic to improve outcomes for cancer patients. We look forward to the R&D we worked to seed bearing fruit for patients and society someday.

This is the first acquisition of a fully-baked, "home-grown" company from RA Capital's RAVen incubator, which builds companies that our venture team funds and helps govern, so we wanted to mark the occasion by sharing a bit more about how we got here.

Our TechAtlas team has long followed the radiopharmaceutical field and noticed that these drugs are typically used in just neuroendocrine and prostate tumors (consider Endocyte and Point Therapeutics, two of RA Capital's former portfolio companies since acquired by Novartis & Eli Lilly, respectively). We wondered about all the other applications of this technology, especially after seeing that potent alpha-emitting, actinium-based agents might offer a better therapeutic index than traditional beta-emitters. To fill the radiopharmaceutical white space on the maps of other cancer types, we launched what we called "Project Activate" (activate…actinium…get it?), which eventually became Mariana Oncology.

To get there, we built a cross-functional team of RAVen Venture Partners (Alonso Ricardo, Neil Buckley, Risa Stack, Nadim Shohdy, Michael Rosenzweig) and hatched a plan to build a premier radiopharmaceutical company with a comprehensive set of capabilities that existing players hadn't fully assembled. We carefully sketched out a bundle of services spanning exceptional CMC operations, target identification capabilities, and drug discovery know-how. We even considered acquiring a radioisotope supplier and starting our own manufacturing company to achieve complete vertical integration (but our Risk Mitigation/Compliance team pointed out that LPs might not appreciate the liabilities involved in transporting radioactive isotopes from far flung corners of the globe).

After a few months, we learned that our friends at Atlas & Access were working on a similar concept, fortuitously led by Alonso's former Ra Pharma colleague, Simon Read, who we also knew well. We quickly recognized the merits of joining forces to build the best fully integrated radiopharma company, with in-house R&D and CMC capabilities and a tried and tested management team that had worked well together in the past. With a solid plan in place, RA Capital, Atlas, and Access founded the company via a three-handed $75M Series A. Alonso joined as co-founder and full time CSO and Simon joined as co-founder and full time CEO. We recruited Bernard Lambert (CTO) from Telix to level up our CMC and later recruited Linda Bain (COO/CFO) from RA Capital's CFO network to bring seriousness and professionalism to our ops and finance organization.

After investing in Mariana, we continued to support the company and help it with everything from recruiting to target prioritization. We aim to bring companies the right kind of help at the right time. For example, a 200-person public company probably doesn't need our assistance with HR & recruiting, but we've found that helping get the first few scientific hires into a brand new company can make a big difference. In 2021, we also leveraged our TechAtlas Oncology team to

Source: https://rapport.bio/all-stories/mariana-acquisition

Reflections on Mariana's Acquisition (Continued)

analyze a long list of potential targets – weighing things like market opportunity, biology risk, and technical tractability – and prioritized those we found most compelling. All of Mariana's lead targets (undisclosed, sorry!) emerged from our TechAtlas group's analysis.

As Mariana moved towards raising a Series B, RA Capital's late-stage team helped keep everyone's eyes on the ultimate prize: a compelling data package. Despite some trepidation around the size of our planned raise in a tough market, we retained conviction that the ambitious goal we set was the right size to get to undeniable value-creation milestones and trusted the quality of the company and the offering would support the raise. Our confidence paid off with an oversubscribed $175M Series B led by Deep Track & Forbion last September, amid the depths of the biotech downturn. This was an undeniably tough time in the market and the financing's size and quality was a testament to the company's strong team and the compelling data it had generated – sentiments that Novartis clearly shared! Congratulations to the Mariana team and to Novartis – we are excited to see how Mariana's radiopharmaceuticals can improve patients' lives with support from the company that brought Pluvicto to market.

Reflections on building a company builder

Most company creation firms are actually loose affiliations of solo practitioners, each with their own resources and networks. Those teams' successes and failures accrue to the track record of each individual. But when we built the machine that has become our venture team and RAVen incubator, we aimed to build a high-quality industrial process – a factory where the raw materials are knowledge and intelligence. The factory floor is RA Capital (all parts of it working together) and the outputs are companies and exits.

What makes this factory possible – above all – is a culture of transparency, generosity, and collaboration. Here at RA Capital, when we build companies, builders don't guard "their" contacts, knowledge, or time.

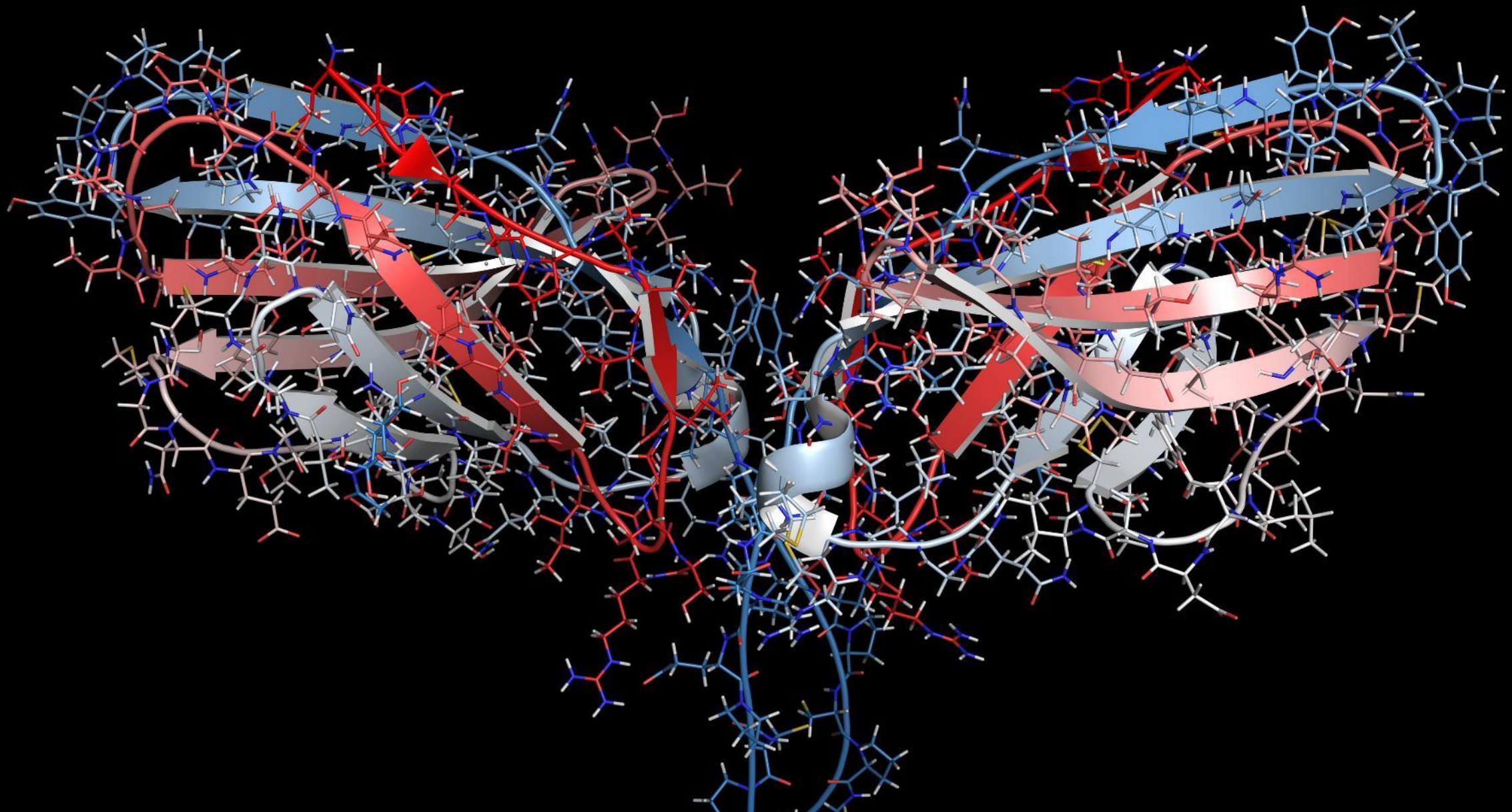
This model has helped us attract Venture Partners and Entrepreneurs in Residence who share our values and are eager to join a collaborative team. New hires are often surprised by how flat and inclusive the organization really is. (That's the idea, at least!)

To date we've shown our factory can operate smoothly and turn out companies regularly and efficiently. We've shown that our quality control mechanisms generally work and take pride in quickly reaching go/no-go inflection points to save time and money. We've shown through executive recruiting, private syndicated financings, and IPOs that other investors and experts generally like and appreciate the quality of our output, which certainly feels like a vote of confidence.

All of that is important, but with Mariana's acquisition today we've now shown that buyers also value our companies and are willing to pay a premium for them. That is the final step in our fully-integrated factory process, and we are thrilled to celebrate this milestone. This is certainly not the end of the road, though – much more to come!

Source: https://rapport.bio/all-stories/mariana-acquisition

Pharma Earnings Update



Last Week Was Second Most Important Pharma Earnings Week

Last week saw Q1 earnings announcements from Lilly, GSK, Pfizer, Amgen, Regeneron and Novo Nordisk.

It turned out the second big week for earnings was more consequential than the first. This is because the market is dominated by obesity stories and the three large companies with the most topical obesity stories reported earnings.

There was much to discuss.

Amgen announced positive news on MariTide and is executing well across all four of its major four therapeutic areas of interest. This caused Amgen shares to shoot up.

Lilly raised guidance on strong demand for Tirzepatide. Its shares took off on Monday but gave back most of the gains as the week rolled on. There was a lot to digest in Lilly's earnings. We thought Dan Skovronsky's comments on its amylin analogue were quite important as Lilly is basically setting itself up to compete against Novo's CagriSema.

GSK had quite solid numbers with particularly impressive vaccine performance.

Pfizer, for the first time in a number of quarters, didn't disappoint versus expectations on Covid drugs. Further, Pfizer is starting to report good results on some of its growth products.

Regeneron reported excellent uptake for Eylea HD and strong ongoing Dupixent growth.

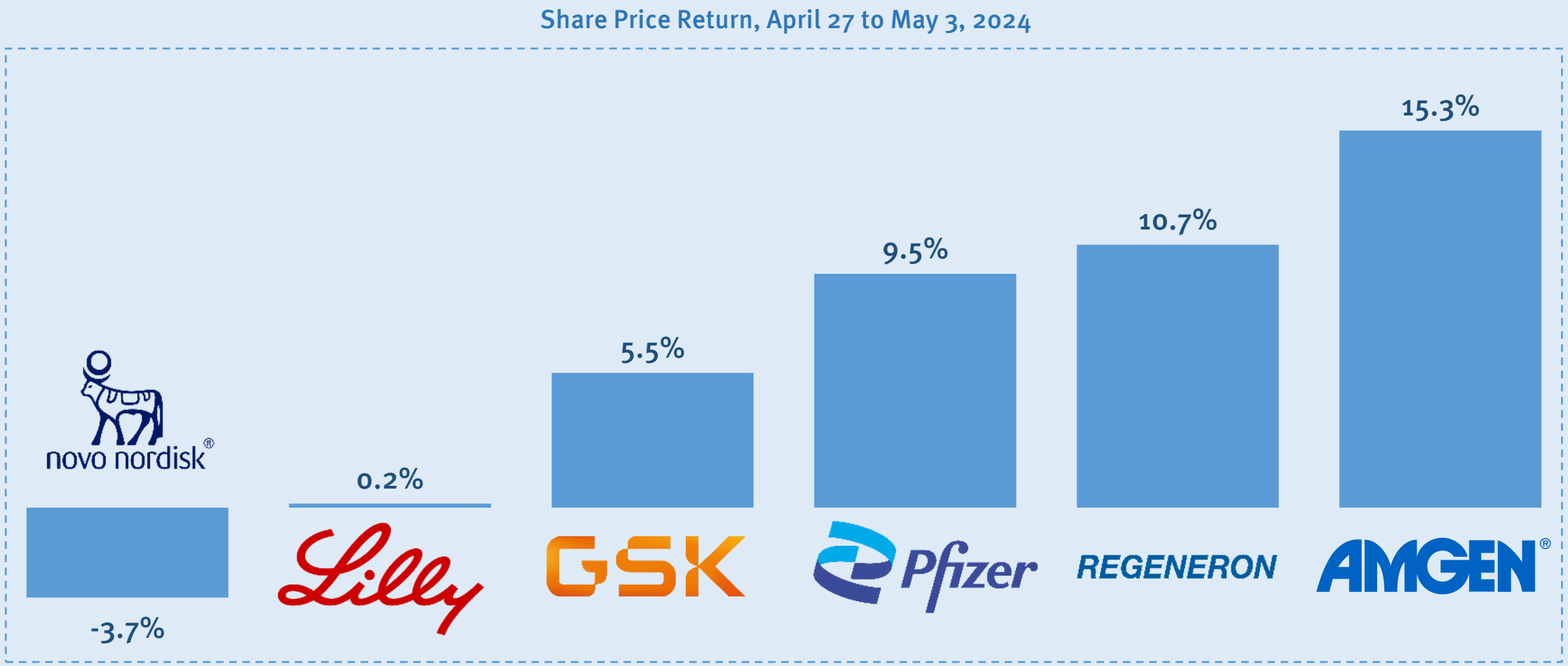
Novo Nordisk reported good GLP-1 growth but saw an earnings decline in rare disease.

Finally, J&J neared resolution of talc litigation with the effect that it's share price increased substantially, retaking the #3 position for most valuable pharma company from Merck.

Earnings Release Dates

Firm	Date
J&J	4/16/2024
Novartis	4/23/2024
Roche	4/24/2024
Biogen	4/24/2024
AstraZeneca	4/25/2024
BMS	4/25/2024
Gilead	4/25/2024
Merck	4/25/2024
Sanofi	4/25/2024
AbbVie	4/26/2024
Eli Lilly	4/30/2024
GSK	5/1/2024
Pfizer	5/1/2024
Amgen	5/2/2024
Regeneron	5/2/2024
Novo Nordisk	5/2/2024
Vertex	5/6/2024

Share Price Evolution of Firms Reporting Earnings Last Week



Source: CapitalIQ

J&J Subsidiary Floats $6.48B Settlement to Resolve Thousands of Claims That its Talc Products Caused Ovarian Cancer

Fraiser Kansteiner, *FiercePharma*, May 1, 2024 (excerpt)

Thanks to a new reorganization plan, Johnson & Johnson is on the cusp of settling more than 50,000 lawsuits linking its popular talc-based baby powder to ovarian cancer.

J&J's subsidiary LLT Management has drafted a proposed "Plan of Reorganization" that—if confirmed—would see J&J pay ovarian cancer claimants roughly $6.48 billion over 25 years to resolve 99.75% of its remaining talc lawsuits in the U.S.

The remaining personal injury lawsuits not covered in the plan are tied to claims that J&J's cosmetic talc products cause mesothelioma, an aggressive form of cancer around the lungs usually associated with asbestos exposure. J&J plans to address those claims outside of the reorganization plan and said in a press release Wednesday that it has already resolved 95% of mesothelioma lawsuits filed to date.

Now, ovarian cancer claimants have three months to vote for or against J&J's plan. The company argues that approving the plan is in the best interest of claimants, who "have not recovered and will not recover anything at trial." Aside from J&J's success rate at overcoming talc lawsuits in the past, it would take decades to litigate the remaining cases, meaning most claimants would never have their "day in court," according to J&J.

Source: https://www.fiercepharma.com/pharma/jj-subsidiary-floats-648b-settlement-resolve-thousands-claims-its-talc-products-caused


AMGEN®

Amgen Stock Rockets Up on MariTide Comments Last Week

AMGEN®

Amgen shares jumped 15.3% last week on comments that it saw good interim data for MariTide for obesity and will be going forward into Phase 3. Amgen is now the 7th most valuable pharma company in the world (up from tenth a week before).

Bob Bradway Comments on Amgen Q1 Earnings Call

Now let me just add one other important update. Whereas we don't normally comment on interim data, especially for our Phase II trial, we recognize there is significant interest in obesity in MariTide, so we'll provide additional commentary today. **The interim Phase II analysis for this study is complete, and we are very encouraged with the results that we've seen thus far** and with the conduct of the trial. Following the interim analysis, I would say we're confident in MariTide's differentiated profile and believe it will address important unmet medical needs.

We are actively planning a broad Phase III program including obesity, obesity-related conditions and diabetes. Obviously, we expect to carefully complete our ongoing Phase II trial before then moving as swiftly as appropriate to establish the safety and efficacy of this potential medicine in Phase III trials. We've initiated activities as well to further expand manufacturing capacity with both clinical and commercial supply in mind.

Bob Bradway
Chief Executive Officer
Amgen

Source: https://www.gurufocus.com/news/2426629/q1-2024-amgen-inc-earnings-call-transcript

Jay Bradner Comments on Amgen Earnings Call

Thank you, Bob, and good afternoon, everyone. Let me start with MariTide. Reiterating Bob's comments, we are very pleased with the results seen with MariTide thus far. And we're very pleased with the overall conduct of the ongoing Phase II trial. **All arms remain active, patient dropout has not been an issue, and we're fully on track for top line 52-week data from this 11-arm Phase II study in late 2024.**

We're seeing a differentiated profile of MariTide and are confident that it will address important unmet medical needs, obesity, obesity-related conditions and diabetes. We look forward to completing the ongoing Phase II study and working with regulators to move rapidly to the broad Phase III program. Later this year, we plan to initiate an additional dedicated Phase II trial investigating MariTide for the treatment of diabetes in patients with and without obesity. This new trial is not a gating step for our Phase III program in patients with obesity.

Jay Bradner
Chief Scientific Officer
Amgen

Source: https://www.gurufocus.com/news/2426629/q1-2024-amgen-inc-earnings-call-transcript

Amgen Jumps After Teasing Weight-loss Drug Data

By Manas Mishra and Christy Santhosh, *Reuters*, May 3, 2024 (excerpt)

Amgen shares headed for their best session since 2009 on Friday after the U.S. drugmaker hinted at encouraging interim trial data on its experimental obesity drug, denting rival stocks but leaving analysts frustrated with a lack of details.

Weight-loss drugmaker Eli Lilly's shares fell 1.6% while Novo Nordisk's Denmark-traded shares dropped 3.9%, on track for their biggest one-day fall since November 2022.

Smaller peer Viking Therapeutics fell 2.3%.

Amgen is conducting mid-stage studies of the injectable drug and said that, based on an interim analysis, it was "confident in MariTide's differentiated profile" and believes it will "address important unmet medical needs".

The company provided no specifics on the actual data, but said it plans to start a late-stage study later this year.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/amgen-shares-jump-after-teasing-encouraging-weight-loss-data-2024-05-03/

Amgen Shares Shoot Up After Discussion of MariTide

Naomi Kresge and Madison Muller, *Bloomberg*, May 3, 2024 (excerpt)

Insatiable demand for weight-loss drugs has made the market so feverish that any positive mention of a potential obesity therapy can send a company's stock surging — even if those treatments may still be years away.

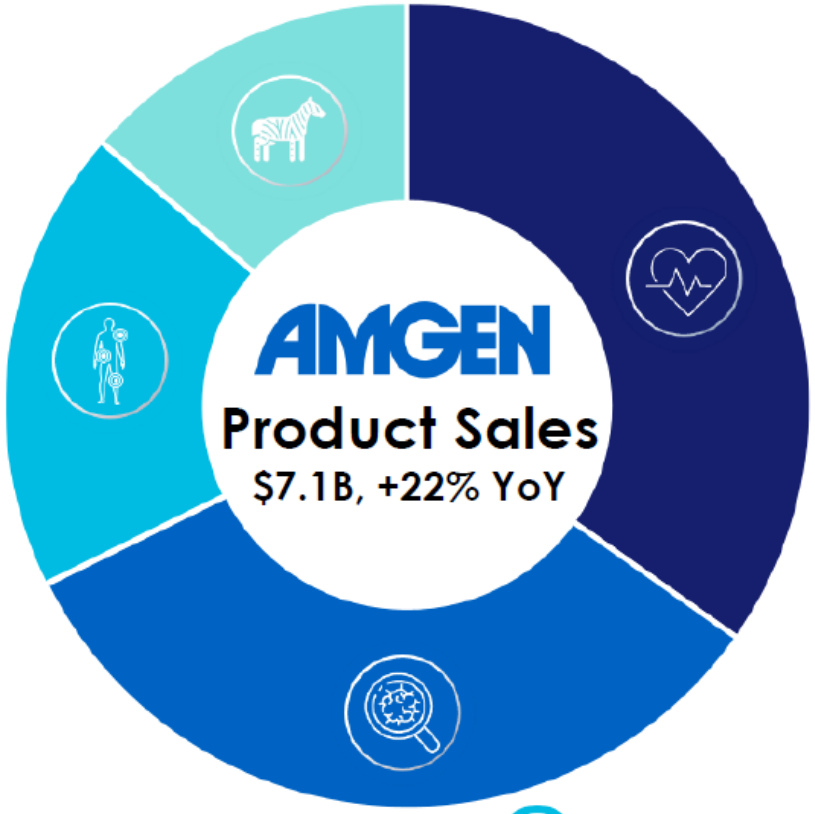
After Amgen Inc.'s chief executive officer, Robert Bradway, said he was "very encouraged" by early results of an experimental obesity shot, the stock on Friday leapt 16%, its biggest gain since 2009. That's despite no new data being released on the drug — which is in mid-stage trials — and before the approval process has even begun.

The CEO's upbeat remarks not only lifted Amgen shares, but also sent Novo Nordisk A/S, the Danish maker of hit drugs Wegovy and Ozempic, tumbling by more than 5%. Eli Lilly & Co., which makes weight-loss shot Zepbound, fell almost 3% in early trading Friday.

The potential size of the obesity drug market helps explain the excitement: Analysts at Goldman Sachs forecast it could hit $100 billion by 2030. Optimism over soaring sales has driven Novo Nordisk's market capitalization above $500 billion this year, reinforcing its position as Europe's most valuable listed company. Lilly's shares are up more than 75% in the past 12 months.

Source: https://www.bloomberg.com/news/articles/2024-05-03/here-are-the-obesity-drug-hopefuls-vying-to-unseat-lilly-novo

Product Sales Increased 22% YoY in Q1, Driven by 25% Volume Growth



General Medicine
Inflammation
Oncology
Rare Disease

Highlights

- Ten products delivered at least double-digit volume growth in Q1, including Repatha®, TEZSPIRE®, EVENITY®, BLINCYTO®, and TAVNEOS®.
- U.S. volume grew 29% and ex-U.S. volume grew 17%.

Provided May 2, 2024, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.

https://investors.amgen.com/static-files/c94912ba-7169-4c84-98b6-23a286b2f72d


Lilly

Strategic Deliverables

PROGRESS SINCE THE LAST EARNINGS CALL

Invest in Current Portfolio

- **Gross Margin**: Non-GAAP gross margin of 82.5% in Q1
- **SG&A**: 12% increase in Q1 primarily driven by promotional efforts supporting launches as well as increased compensation and benefit costs

Invest in Future Innovation

- **R&D**: 27% increase in Q1 driven by higher development expenses for late-stage assets and additional investments in early-stage research
- **Business Development**: Announced an agreement to acquire an injectable medicine manufacturing facility with production targeted to begin at the end of 2025
- **Capex:** Progressed manufacturing expansion agenda with groundbreaking at our previously announced $2.5 billion parenteral manufacturing site in Germany

Deliver Revenue Growth

- Revenue grew 26% in Q1 driven by Mounjaro®, Zepbound®, Verzenio®, and Jardiance®[1]
- New Product[2] revenue grew by $1.79 billion to $2.39 billion in Q1

Speed Life-Changing Medicines

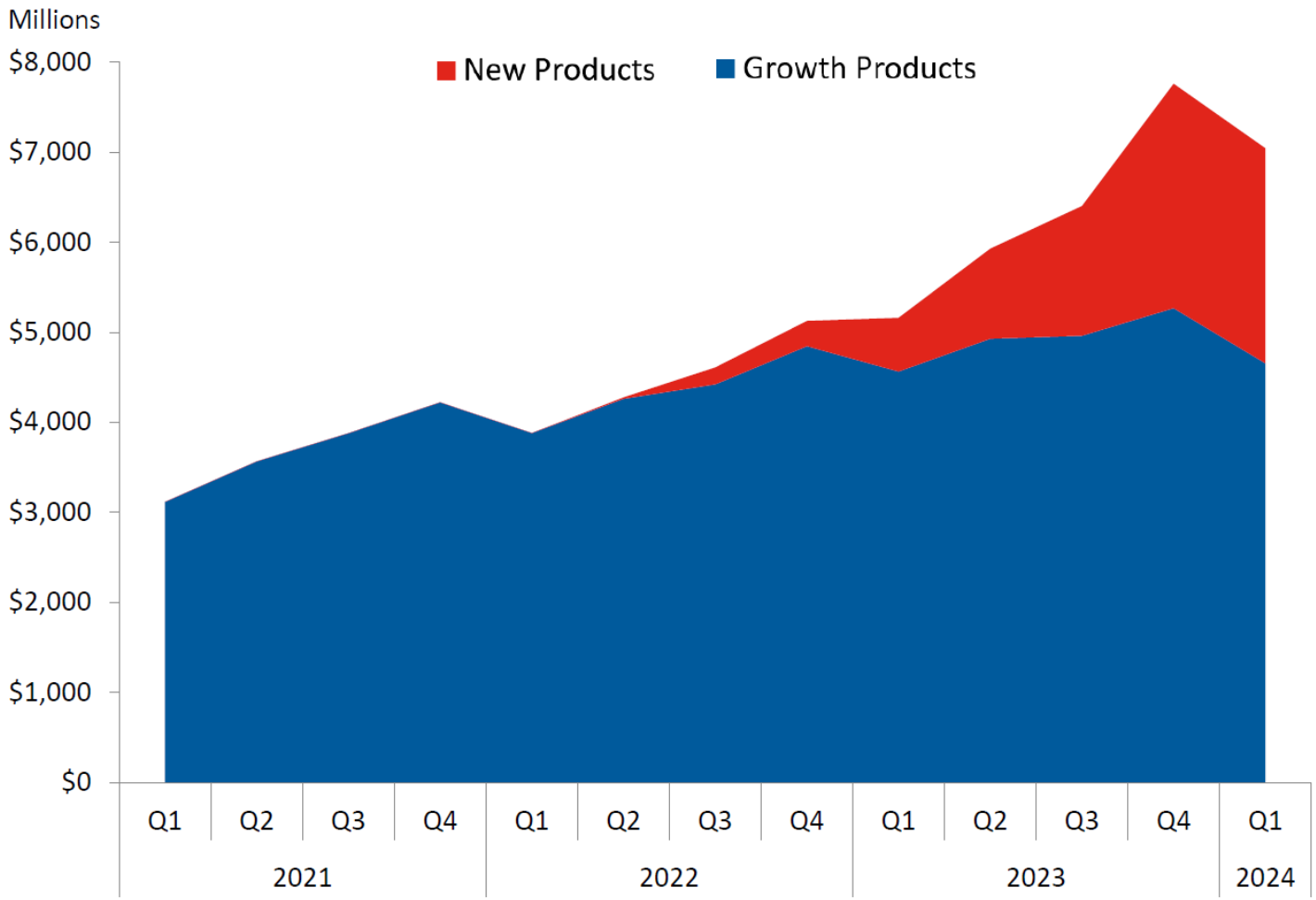
- Announced positive topline results for tirzepatide in moderate-to-severe obstructive sleep apnea and obesity
- Received approval of the multi-dose KwikPen® delivery device for Mounjaro in the EU
- Submitted mirikizumab in the U.S. and EU for moderately to severely active Crohn's disease
- Resubmitted lebrikizumab in the U.S. for moderate-to-severe atopic dermatitis
- Initiated Phase 3 program for lepodisiran in reducing cardiovascular risk

Return Capital to Shareholders: Distributed over $1 billion via **dividends** in Q1

[1] Jardiance is part of the Boehringer Ingelheim and Lilly Alliance, and Boehringer Ingelheim holds the marketing authorization for Jardiance

[2] Refer to slide 8 for a list of New Products

Q1 2024 Update on Select Products



New Products: Ebglyss®, Jaypirca®, Mounjaro, Omvoh®, and Zepbound
Growth Products: Cyramza®, Emgality®, Jardiance[1], Olumiant®, Retevmo®, Taltz®, Trulicity®, Tyvyt®, and Verzenio

[1] Jardiance is part of the company's alliance with Boehringer Ingelheim. Lilly reports as revenue royalties received on net sales of Jardiance.

NEW PRODUCTS

MOUNJARO

- U.S. T2D injectable incretins TRx SOM over 24% and NBRx SOM nearly 30% at end of Q1 2024

ZEPBOUND

- U.S. branded anti-obesity rolling 4-week TRx SOM nearly 40% and rolling 4-week NBRx SOM nearly 57% at end of Q1 2024

JAYPIRCA

- Q1 2024 sales increased to $50 million, representing an acceleration in sequential quarterly growth following the Q4 2023 approval in CLL

OMVOH

- Japan and EU approval in H1 2023; U.S. approval and launch in Q4 2023

GROWTH PRODUCTS

JARDIANCE[1]

- SGLT2 market leader in several key countries with U.S. TRx SOM over 63% at end of Q1 2024
- U.S. TRx grew over 24% vs. Q1 2023

TALTZ

- U.S. immunology TRx SOM of nearly 6% at end of Q1 2024
- U.S. TRx grew 8% vs. Q1 2023

TRULICITY

- U.S. T2D injectable incretins TRx SOM of 19% at end of Q1 2024

VERZENIO

- U.S. TRx grew over 32% vs. Q1 2023
- Strong uptake in adjuvant breast cancer indication

Zepbound U.S. Launch Progress

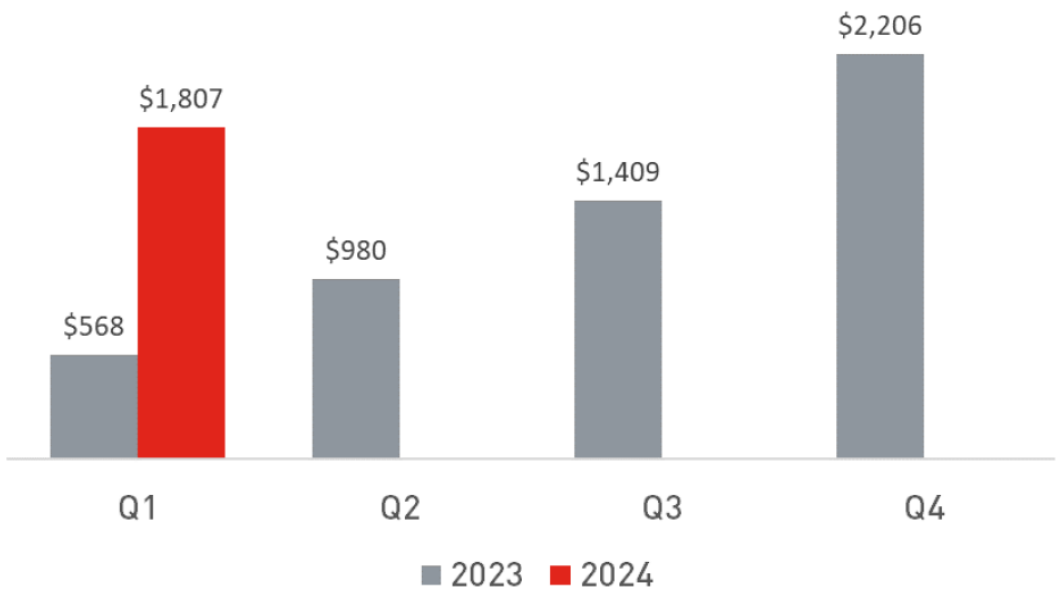
- **Exceptionally strong launch** progress since U.S. FDA approval on November 8, 2023
- We are **rapidly building access** in the U.S. and, as of April 1, we have approximately 67% access in commercial
- Continued focus on **broadening formulary access** and through **employer opt-ins**; early progress is encouraging

Source: https://investor.lilly.com/static-files/d0789b60-5579-415e-9461-8b8130413dd6

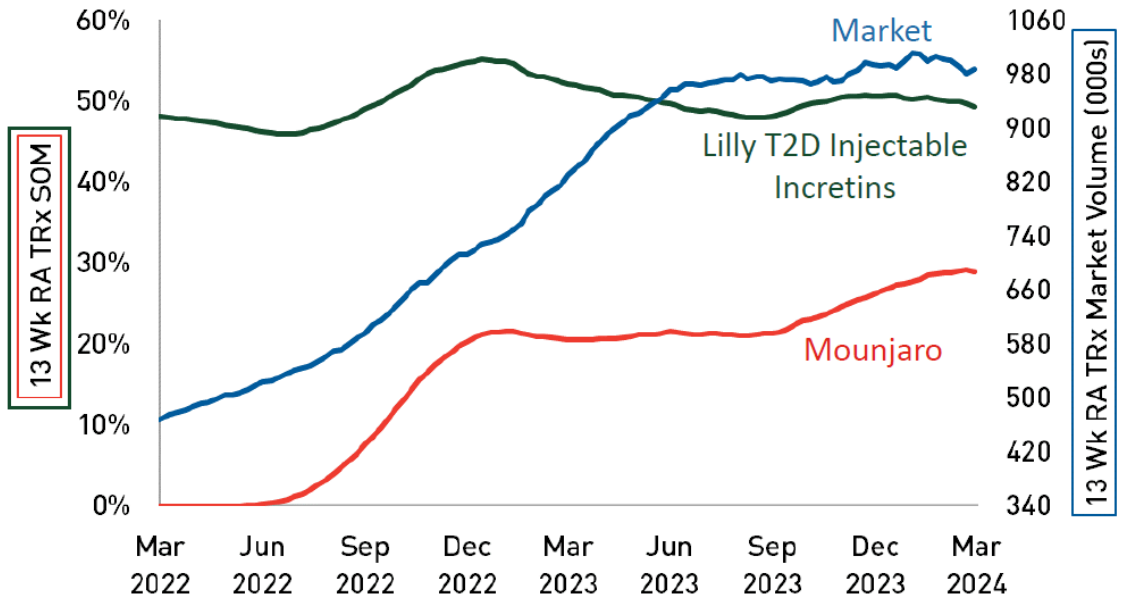
Q1 2024 Mounjaro Sales Increased $1.2B

$ in Millions

U.S. sales were $1.5 billion
International sales were $286 million



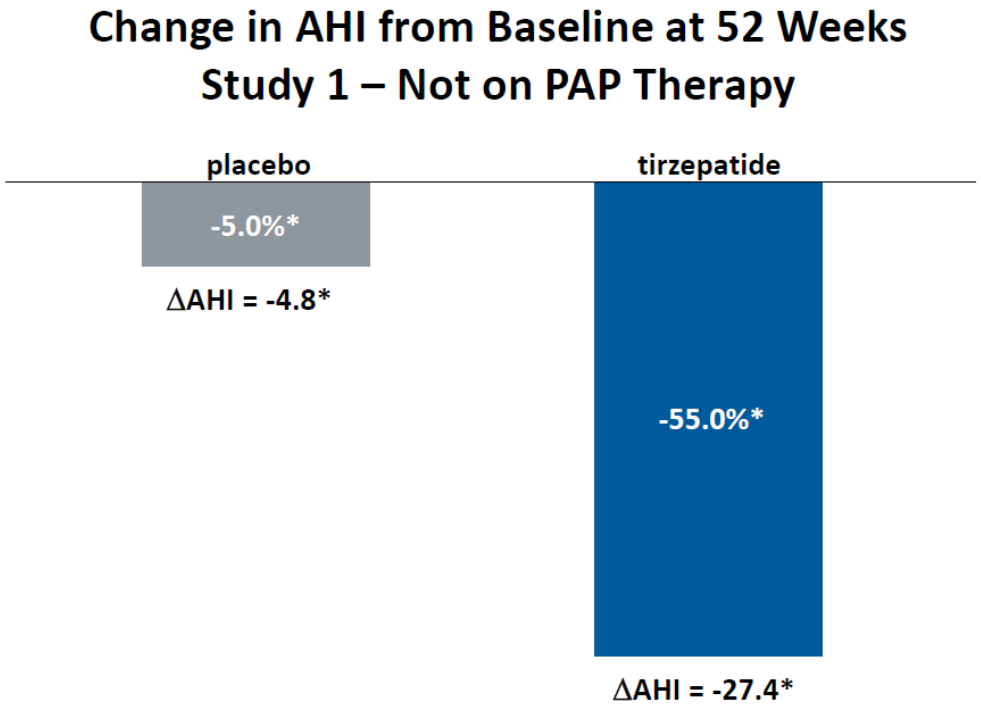
U.S. TRx SOM and Market Volume



Note: Lilly T2D Injectable Incretins consist of Mounjaro & Trulicity 13 Wk RA TRx SOM

Source: IQVIA NPA TRx 3MMA, weekly data March 29, 2024; RA = rolling average
TRx data is representative of the injectable incretin market

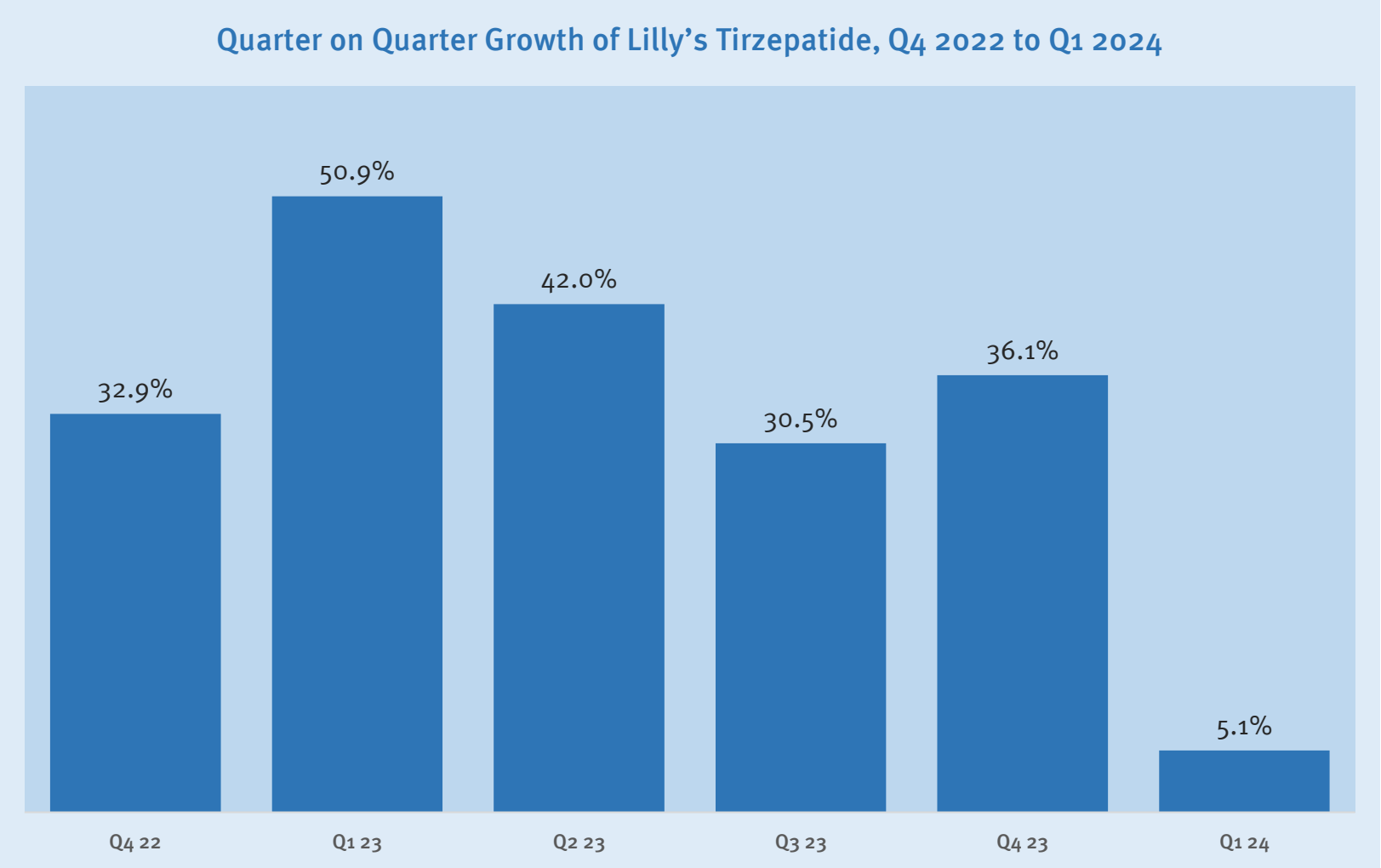
SURMOUNT-OSA Study 1 – Not on PAP Therapy



- Tirzepatide led to a mean AHI reduction of 27.4 events per hour, compared to 4.8 for placebo
- Tirzepatide led to a mean AHI reduction of 55.0% from baseline, compared to 5.0% for placebo
- Participants in the tirzepatide arm had a mean body weight reduction of 18.1%* from baseline, compared to 1.3% for placebo
- The overall safety profile of tirzepatide in Study 1 was similar to previously reported SURMOUNT and SURPASS trials

AHI = apnea-hypopnea index; ΔAHI = change from baseline in AHI (events per hour); PAP = Positive Airway Pressure
Note: Results for efficacy estimand which represents efficacy prior to discontinuation of study drug
Tirzepatide vs. placebo: *p<0.001

Supply Constraint Clearly Evident in Q1 Tirzepatide Growth Numbers



Lilly appears to have hit a capacity limit in its ability to supply Tirzepatide to the market. Lilly is guiding to substantial growth in 2024 and has indicated that more supply will come online in the second half of the year (see comments from Lilly's CFO on the next page).

Source: Eli Lilly financial workbooks (investor.lilly.com)

Anat Ashkenazi Comments on Q1 Earnings Call on Incretin Manufacturing Capacity

The demand for tirzepatide is very strong. And each week, hundreds of thousands of people fill scripts from Mounjaro and Zepbound yet we understand the frustration from those facing prescription delays or uncertainties yet in their medicine. While we are working tirelessly to ramp supply and expect meaningful increases in shipment volumes in the second half of the year, demand continues to outstrip even increased supply. We remain on track to meet expectations we set earlier this year. The production of salable doses of incretin medicine in the second half of 2024 will be at least 1.5 times the salable doses in the second half of 2023.

In the short to midterm, we expect sales growth to primarily be a function of the quantities we can produce and ship. Outside the U.S., we are delighted that the multi-dose KwikPen delivery device from Mounjaro was recently approved in the EU, adding to the UK approval earlier this year….

Now as a reminder, we do have quite a large number of nodes across our supply chain that have to come online or ramp capacity. We are, if you look at everything work we have under construction, or ramping up, we have six sites right now between the two sites in North Carolina, a site in Ireland, two sites in Indiana, a site in Germany and then the seventh one that we just purchased, they are all either ramping up or under construction. And there are multiple nodes across that supply chain that have to become operational, which requires approval, et cetera, for three products, depending on which product runs on which line, that are planned throughout the year.

Now that we're four months into the year, we have greater visibility into these nodes of capacity and feel more confident. Just as one example, the approval of the KwikPen in Europe that just came in slightly ahead of our expectation gives us additional confidence in our ability to launch KwikPen for patients in Europe. So, it is across our sites globally, as well as ramping up capacity with partners or CDMOs, as well as in existing sites where we're making investments to expand where we can, or ramp up capacity so it's across our supply chain

Source: Eli Lilly Q1 2024 Earnings Call Transcript

Dan Skovronsky Comments on Q1 Earnings Call Regarding Lilly Obesity Drugs

1. We've completed enrollment for SURMOUNT-MMO with over 15,000 participants, and for both orforglipron studies in chronic weight management, ATTAIN-1 and ATTAIN-2, which together enrolled 4,500 participants. Finally, we've now initiated the TRANSCEND Phase 3 program studying retatrutide in Type 2 diabetes.
2. Earlier in our diabetes and obesity pipeline, we've now initiated a Phase 2 monotherapy study evaluating eloralintide, our selective amylin receptor agonist in obesity.
3. … on AMG 133, we've just seen really a small amount of data. So probably anything is possible and like you will be interested to see their results. Of course, there's arguments that can be heard about GIP agonism versus antagonism. We've placed our bets, and we like the data we got with GIP agonism.
4. On CagriSema, of course, adding more agonism on different pathways on top of GLP-1 is a good idea. That's what we have with tirzepatide, as a dual agonist. So CagriSema makes sense. And you'll note that we've advanced our amylin agonist to Phase 2. Tirzepatide already is a dual agonist.

Source: Eli Lilly Q1 2024 Earnings Call Transcript


Pfizer

Pfizer: Last Hit from Covid Products

Pfizer Q1 Earnings Release, May 1, 2024

First-quarter 2024 revenues totaled $14.9 billion, a decrease of $3.6 billion, or 20%, compared to the prior-year quarter, reflecting an operational decline of $3.5 billion, or 19%, primarily due to a significant decrease in Comirnaty and Paxlovid revenues globally, as well as an unfavorable impact of foreign exchange of $107 million, or 1%. **Excluding contributions from Comirnaty and Paxlovid, revenues totaled $12.5 billion, an increase of $1.2 billion, or 11%, operationally compared with the prior-year quarter.**

First-quarter 2024 Comirnaty revenues of $354 million declined $2.7 billion, or 88%, operationally compared with the prior-year quarter, driven largely by lower contractual deliveries and demand in international markets as well as lower U.S. volumes, reflecting the anticipated seasonality of demand for vaccinations and as certain markets, including the U.S., transition to traditional commercial market sales.

First-quarter 2024 Paxlovid revenues of $2.0 billion declined $2.0 billion, or 50%, operationally compared with the prior-year quarter, driven primarily by lower contractual deliveries in most international markets and in the U.S. as a result of the transition to traditional commercial market sales, as well as lower demand in China due to the non-recurrent surge in COVID-19 infection during the first quarter of 2023, partially offset by a $771 million favorable final adjustment to the estimated non-cash revenue reversal of $3.5 billion recorded in the fourth quarter of 2023.

Source: https://investors.pfizer.com/Investors/News/news-details/2024/Pfizer-Reports-First-Quarter-2024-Results/default.aspx

Pfizer Turning the Corner on Revenue with Growth Products

Albert Bourla, CEO, Pfizer, May 1, 2024

"We delivered strong performance in our non-COVID product portfolio in the first quarter of 2024, including increased revenue from several of our recent commercial launches and acquired products, as well as robust year-over-year growth for several key in-line brands, namely the Vyndaqel family, Eliquis, and the Prevnar family. In addition, we had strong oncology revenue contributions from Ibrance, Xtandi, Padcev and Adcetris. Our Paxlovid revenues in the quarter indicate a successful transition into the commercial marketplace in the U.S. and a demonstrated trust in the brand. Overall, I am encouraged by a well-executed quarter, setting the tone for the year. Pfizer's commercial leadership is focused on data-driven opportunities across several key growth brands, both in the U.S. and internationally, and we intend to build on this positive momentum in the quarters ahead."

Source: https://investors.pfizer.com/Investors/News/news-details/2024/Pfizer-Reports-First-Quarter-2024-Results/default.aspx

Deliver Next Wave of Pipeline Innovation

Excellent Progress in Oncology

- **Three pivotal Phase 3 study starts** in Q1 2024:
  - **Atirmociclib** selective CDK4 inhibitor
  - **Sigvotatug vedotin** integrin-beta-6-directed ADC
  - **ELREXFIO** 4th Phase 3 trial in multiple myeloma
- >50 sponsored abstracts at ASCO 2024, including:
  - **5-year PFS data for LORBRENA** in 1L ALK+ metastatic NSCLC (CROWN)
  - **Phase 3 data for ADCETRIS** in DLBCL (ECHELON-3)

Sharpened Focus Across Therapeutic Areas

- **Advancing respiratory portfolio:**

ABRYSVO™
Respiratory Syncytial Virus Vaccine

- Execution across **growing hematology portfolio:**

BEQVEZ™
fidanacogene elaparvovec-dzkt
Suspension for intravenous infusion 1 × 10^{13} vg/mL

marstacimab
Potential approval before year end

osivelotor
Phase 3 study start

CDK4=Cyclin-dependent kinase 4; ADC=Antibody drug conjugates; ASCO=American Society of Clinical Oncology; PFS=Progression-free survival; ALK+=Anaplastic Lymphoma Kinase Positive; NSCLC=Non-small cell lung cancer; DLBCL=Diffuse large B-cell lymphoma; GTx=Gene Therapy; PK=Pharmacokinetics.

"I am encouraged by a well-executed quarter, setting the tone for the year. Pfizer's commercial leadership is focused on data-driven opportunities across several key growth brands, both in the U.S. and internationally, and we intend to build on this positive momentum in the quarters ahead."

Albert Bourla

Chairman and Chief Executive Officer

Source: https://investors.pfizer.com/Investors/News/news-details/2024/Pfizer-Reports-First-Quarter-2024-Results/default.aspx

2024 Key Priorities

Focused on executing with excellence against strategic goals to drive long-term growth

Achieve
world-class oncology leadership

Deliver
next wave of pipeline innovation

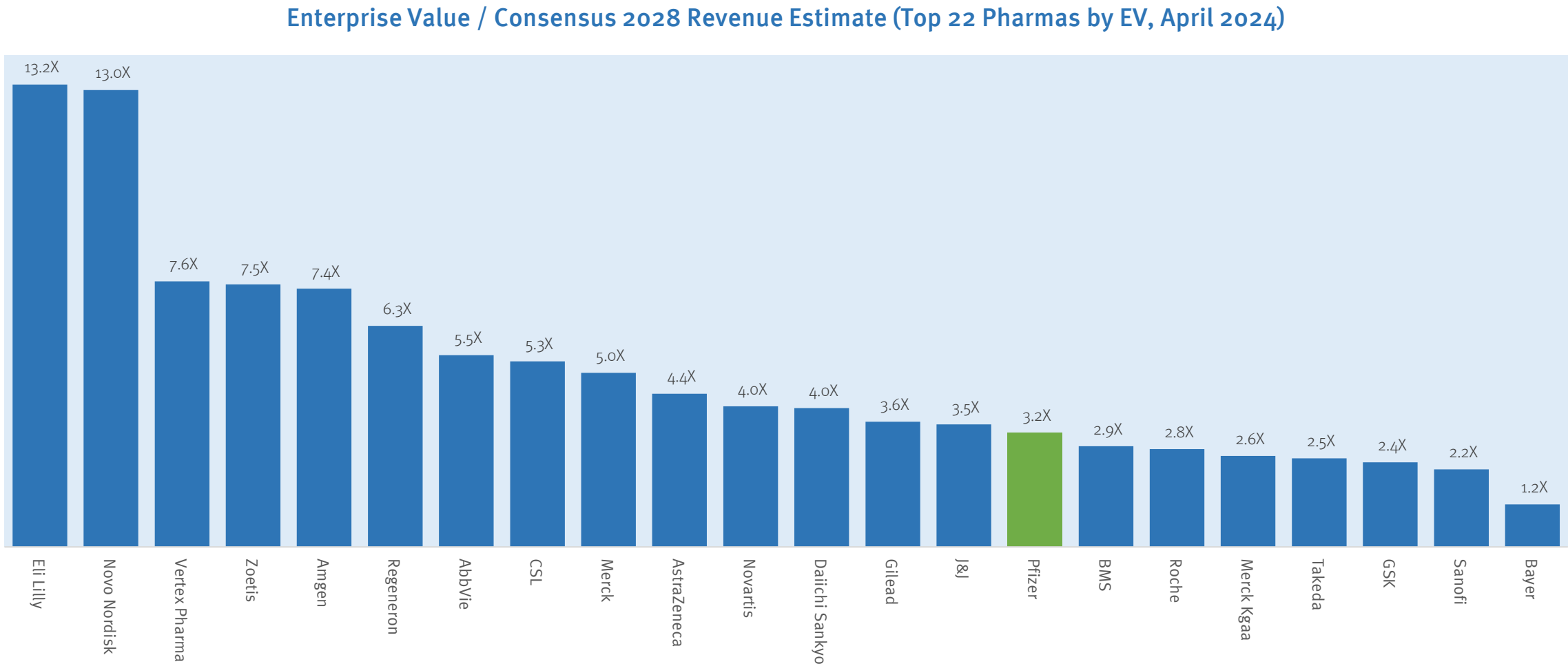
Maximize
performance of new products

Expand
margins by realigning cost base

Allocate
capital to enhance shareholder value

Source: https://investors.pfizer.com/Investors/News/news-details/2024/Pfizer-Reports-First-Quarter-2024-Results/default.aspx

Despite Improving Growth Story, Pfizer Still Trading at a Forward Multiple that Well Below Peer Average (5.0X)



Source: CapitalIQ

Issued: Wednesday, 1 May 2024, London, U.K.

Press release

First quarter 2024

GSK makes a strong start to 2024 with improving outlook for the year

Broad-based performance drives sales, profits and earnings growth:

- Total Q1 2024 sales £7.4 billion +10% and +13% ex COVID
- Vaccines sales +16%, +22% ex COVID. *Shingrix* £0.9 billion +18%, *Arexvy* £0.2 billion
- Specialty Medicines sales +17%, +19% ex COVID with HIV +14%
- General Medicines sales +1%. *Trelegy* £0.6 billion +33%
- Total operating profit and Total EPS for Q1 2024 reflected higher charges for CCL[(2)] remeasurement, partly offset by strong Core[(1)] growth
- Core operating profit +27% (with further positive impact of +8% ex COVID) and Core EPS +28% (with further positive impact of +9% ex COVID). This reflected strong sales and SG&A leverage, partly offset by increased investment in R&D and lower royalty income
- Cash generated from operations exceeded £1 billion with free cash flow of £0.3 billion

Source: https://www.gsk.com/media/11105/q1-2024-results-slides.pdf

Strong start to 2024

Delivered 13%[1] sales growth, 35%[1] core operating profit growth

Sales growth across portfolio:

- Vaccines +22%[1]
- Specialty Medicines +19%[1]
- General Medicines +1%

Cash generated from operations exceeded £1 billion, with free cash flow of £0.3 billion

GSK

Absolute values at actual exchange rates (AER); changes at CER, unless stated otherwise.
1. Excluding COVID-19 solutions

Q1 2024 performance

Sales
£7.4bn, +10%
+13%[1]

Core operating profit
£2.4bn, +27%
+35%[1]

Core EPS
43.1p, +28%
+37%[1]

Dividend per share
15p

Full-year 2024 guidance[1]: upgraded

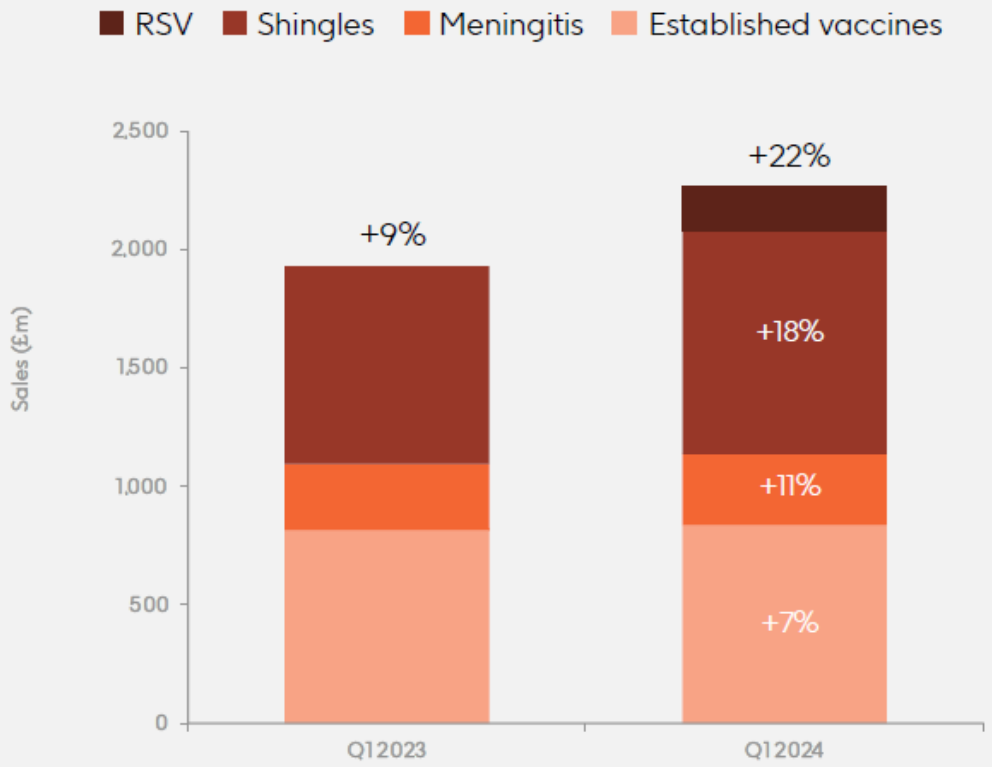
Sales growth: 5-7% (towards upper part of the range)
Core operating profit growth: 9-11%
Core EPS growth: 8-10%

Source: https://www.gsk.com/media/11105/q1-2024-results-slides.pdf

Vaccines: +22%[1] led by *Arexvy* and record sales of *Shingrix*

2024 guidance: high-single digit to low-double digit % growth[1]

Sales contribution by disease area[1]



RSV (*Arexvy*) £182m[2]

- Leading market share with 2/3 retail prescriptions

Shingles (*Shingrix*) +18%

- Growth driven by public funding expansion and early supply to Zhifei
- Launched in 39 markets ex-US, majority <5% penetration
- 37% of US adults recommended to receive *Shingrix* now vaccinated
- >£4bn in peak year sales by 2026
- 82% vaccine efficacy in adults ≥50 at year 11

Meningitis +11%

- ***Bexsero* +3%** driven by Australia performance and launch in Vietnam
- ***Menveo* +41%** driven by Brazil performance and phasing
- Combined meningitis portfolio to reach ~£2bn in peak year sales
- MenABCWY file acceptance by FDA

Influenza +8%

Established vaccines +7%

GSK

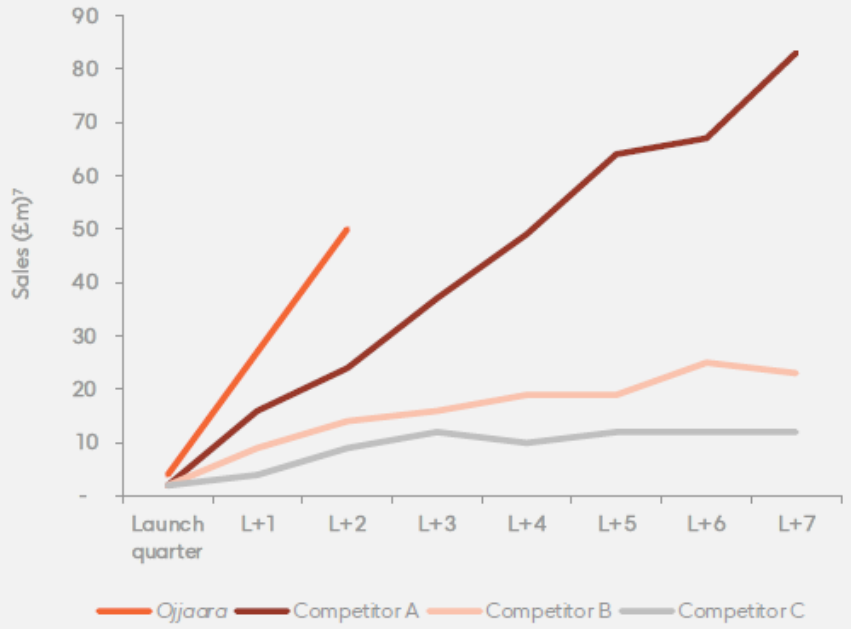
Absolute values at AER; changes at CER for full year, unless stated otherwise
1. Excluding COVID-19 solutions 2. Q1 2024 global sales

Source: https://www.gsk.com/media/11105/q1-2024-results-slides.pdf

Progress in oncology driven by *Ojjaara* launch and lifecycle innovation

Ojjaara: fastest US launch uptake in value for a JAKi[1] in MF[2]

- Driven by strong execution
- US share in patients with anaemia: 14%[3] in 1L[4] and 28%[3] in 2L[5]
- 56% of US physicians expect to increase prescribing *Ojjaara* in the next six months[6]



Jemperli: a potential backbone IO[8] therapy

- 1L[4] dMMR[9] EC[10] new patient share up to ~33%[11], nearly doubled vs Q4 2023[12]
- RUBY Part 1: only IO[8] combination to show statistically significant and clinically meaningful OS[13] in the overall EC[10] population; sBLA[14] granted priority review by FDA
- RUBY Part 2: significantly improved PFS[15] in 1L[4], OS[13] data due end of 2024

Blenrep: potential to redefine the treatment of relapsed or refractory multiple myeloma

- Encouraging DREAMM-7 and DREAMM-8 PFS[15] data
- Strong OS[13] trends, trials continue to follow up
- DREAMM-7 presented at ASCO[16] Plenary Series in February 2024
- DREAMM-8 to be presented at ASCO[16] in June
- Regulatory filing in H2 2024

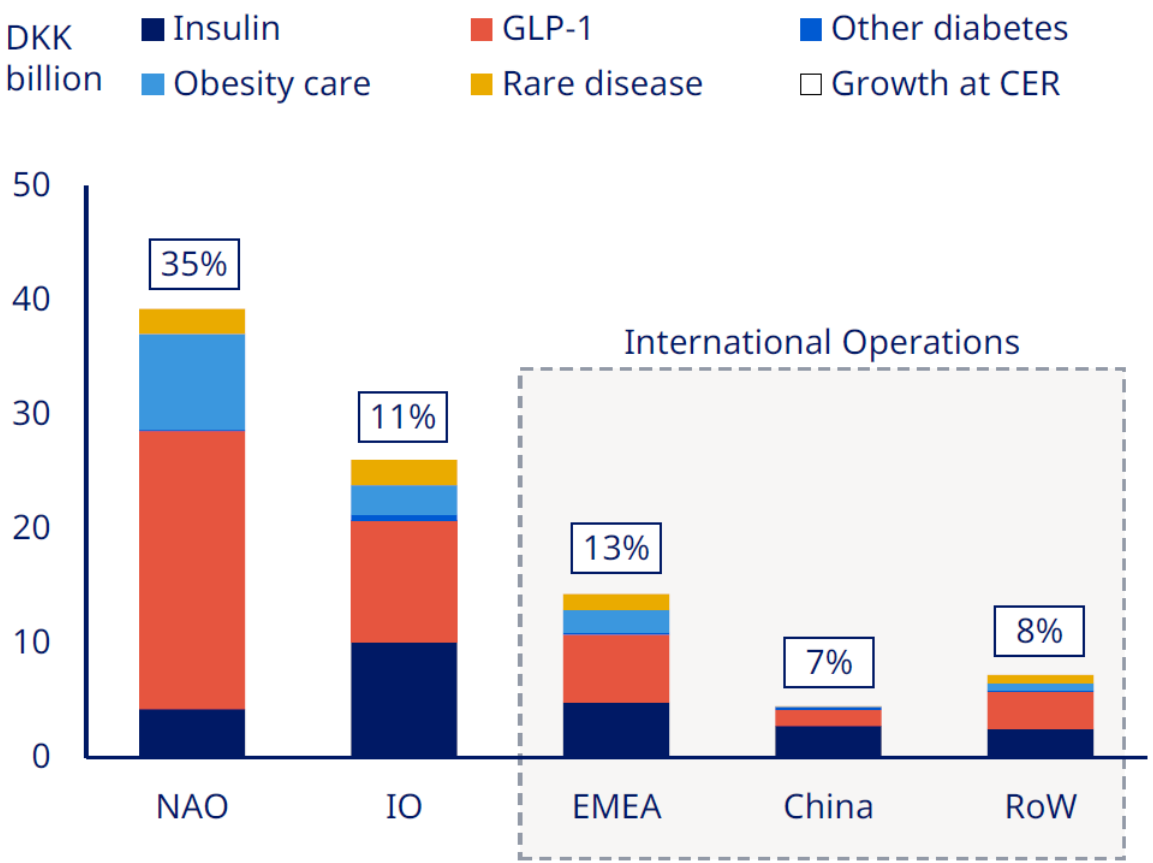
1. Janus kinase inhibitor 2. Myelofibrosis 3. Quarterly chart audits March 2024 4. First-line 5. Second-line 6. US Oncology ATU, Feb/Mar 24, n=102 7. Company quarterly financial results 8. Immuno-oncology 9. DNA mismatch repair deficiency 10. Endometrial cancer 11. US Patient Chart Study, Q1 '24, n=86 12. US ONC ATU, Nov/Dec '23, n=114 13. Overall survival 14. Supplemental Biologics License Application 15. Progression-free survival 16. American Society of Clinical Oncology

Source: https://www.gsk.com/media/11105/q1-2024-results-slides.pdf

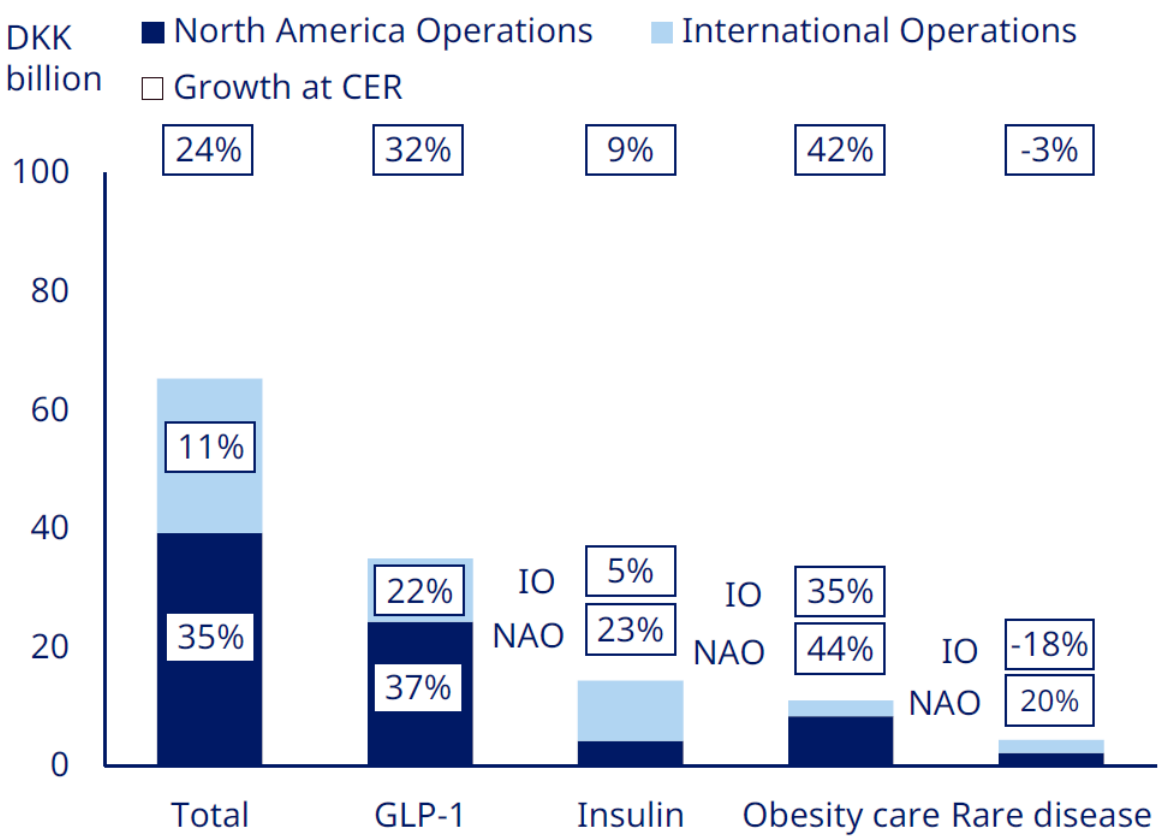

novo nordisk®

Sales growth of 24% driven by both operating units

Reported geographic sales split for first quarter of 2024



Reported therapy area sales and growth for first quarter of 2024

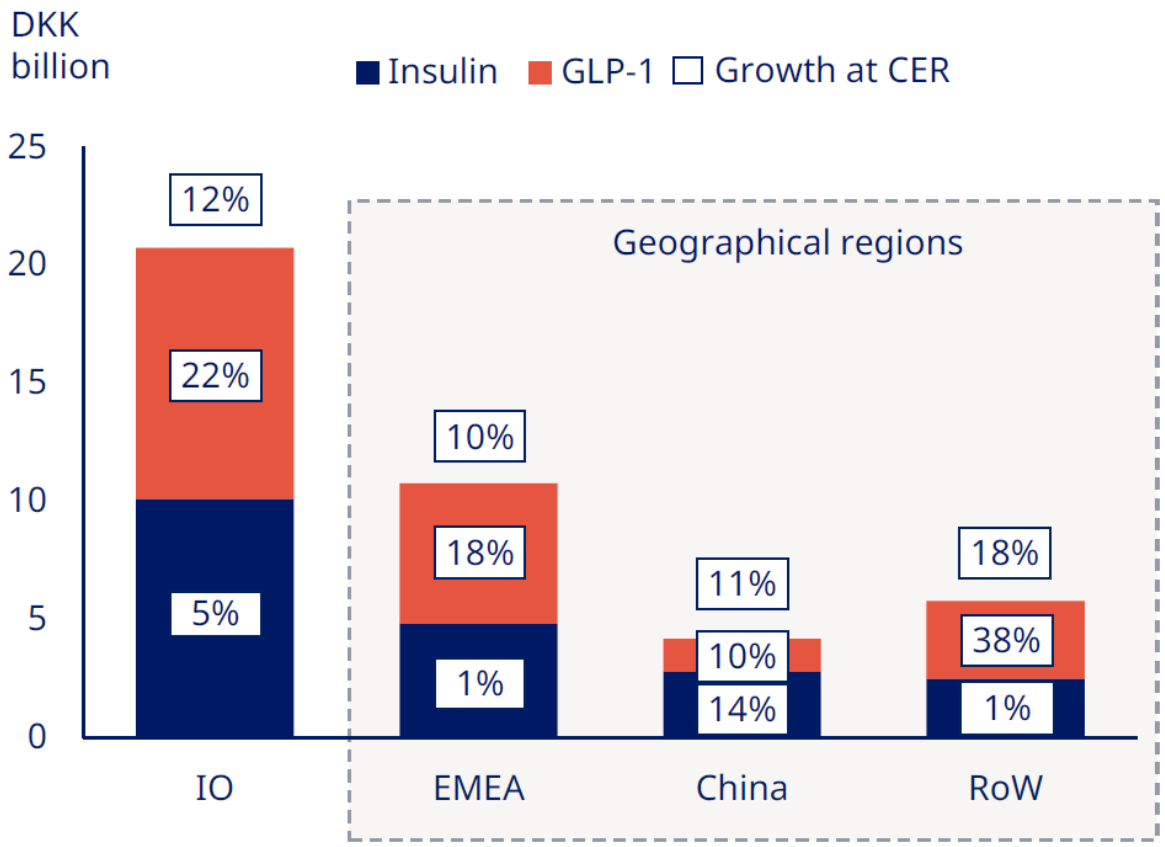


[1]'Other diabetes' is included in Total
IO: International Operations; EMEA: Europe, Middle East and Africa; China: Mainland China, Hong Kong and Taiwan; RoW: Rest of World; NAO: North America Operations; CER: Constant exchange rates
Note: Unless otherwise specified, sales growth rates are at CER

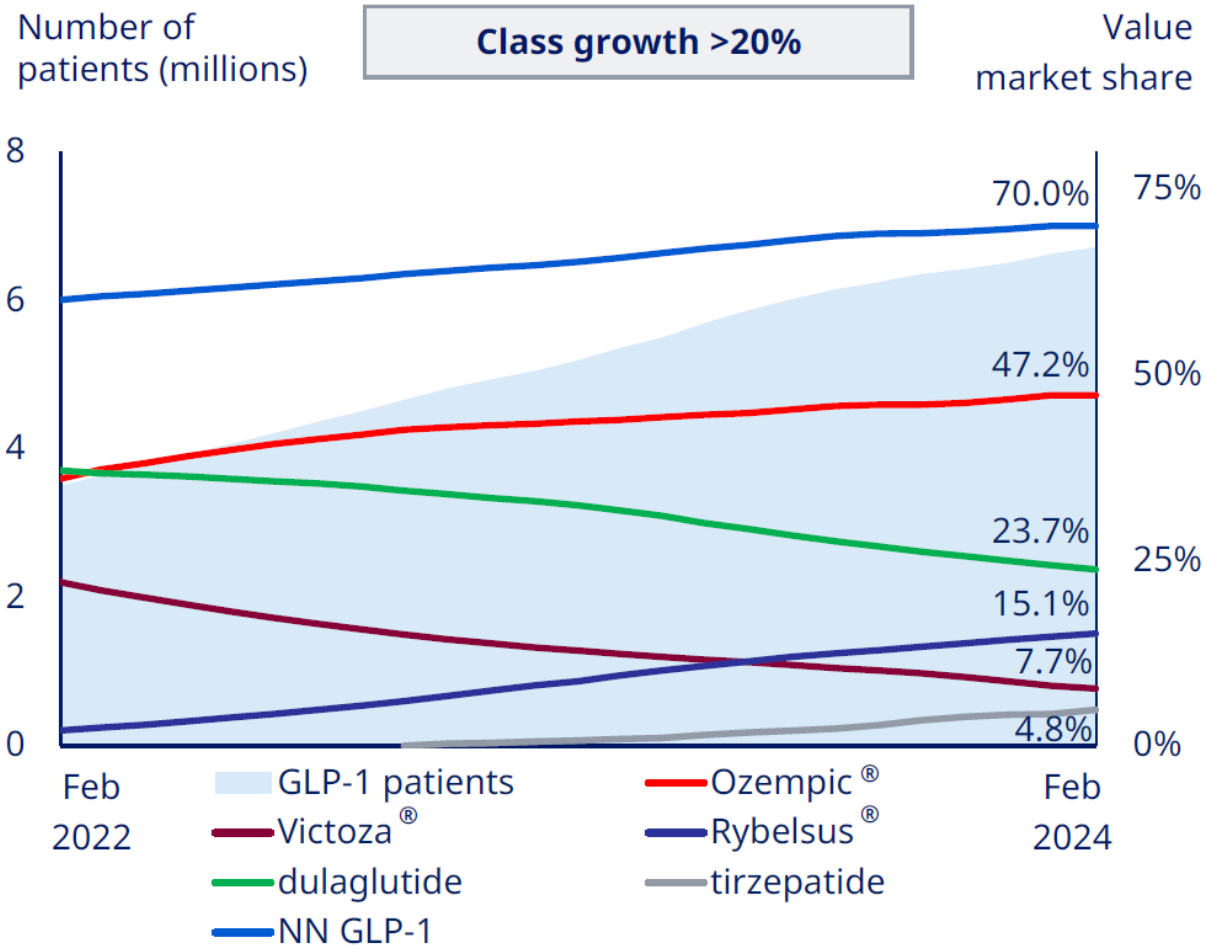
Source: https://investor.novonordisk.com/q1-2024-presentation/?page=13

International Operations diabetes care sales growth is driven by GLP-1 performance

Reported Diabetes care sales and growth per IO geography



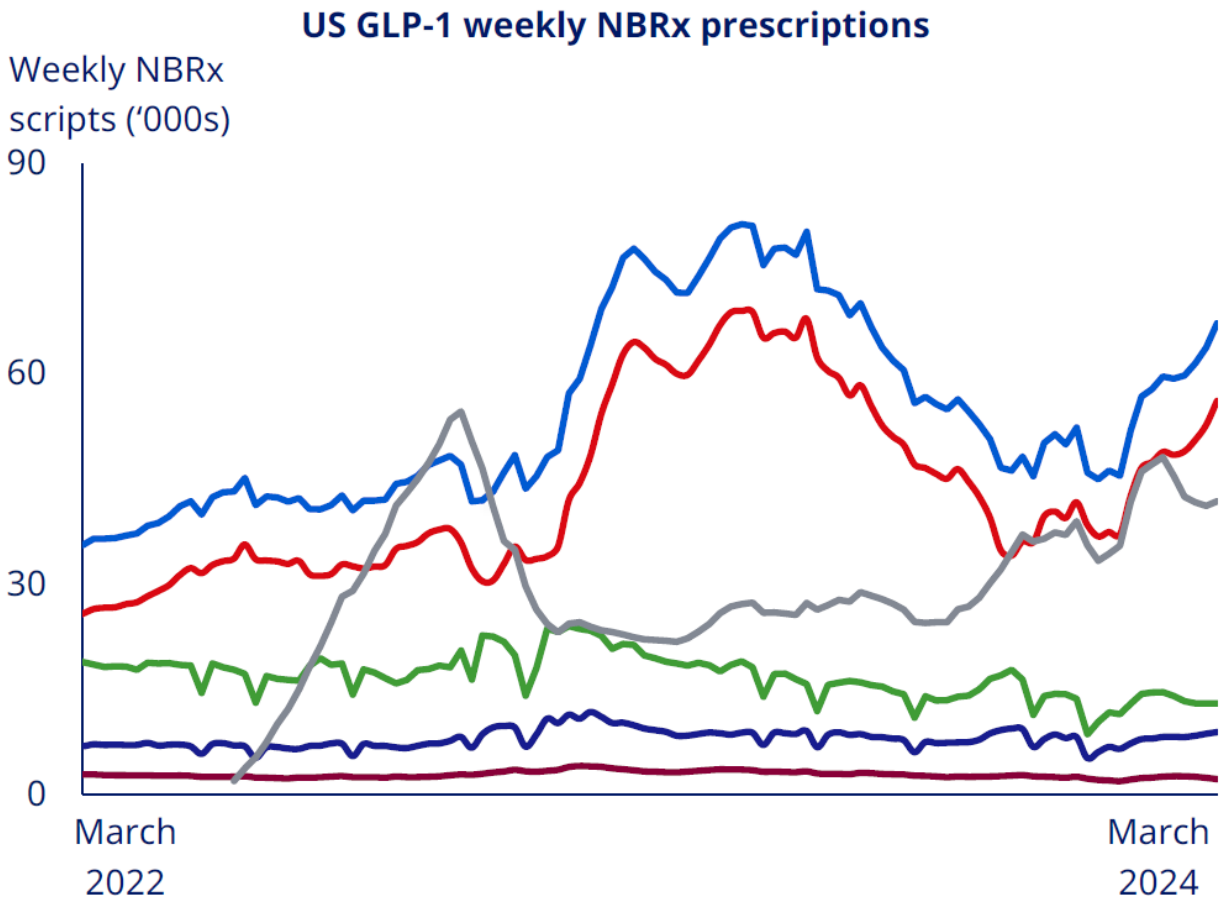
GLP-1 patients and value market share in IO

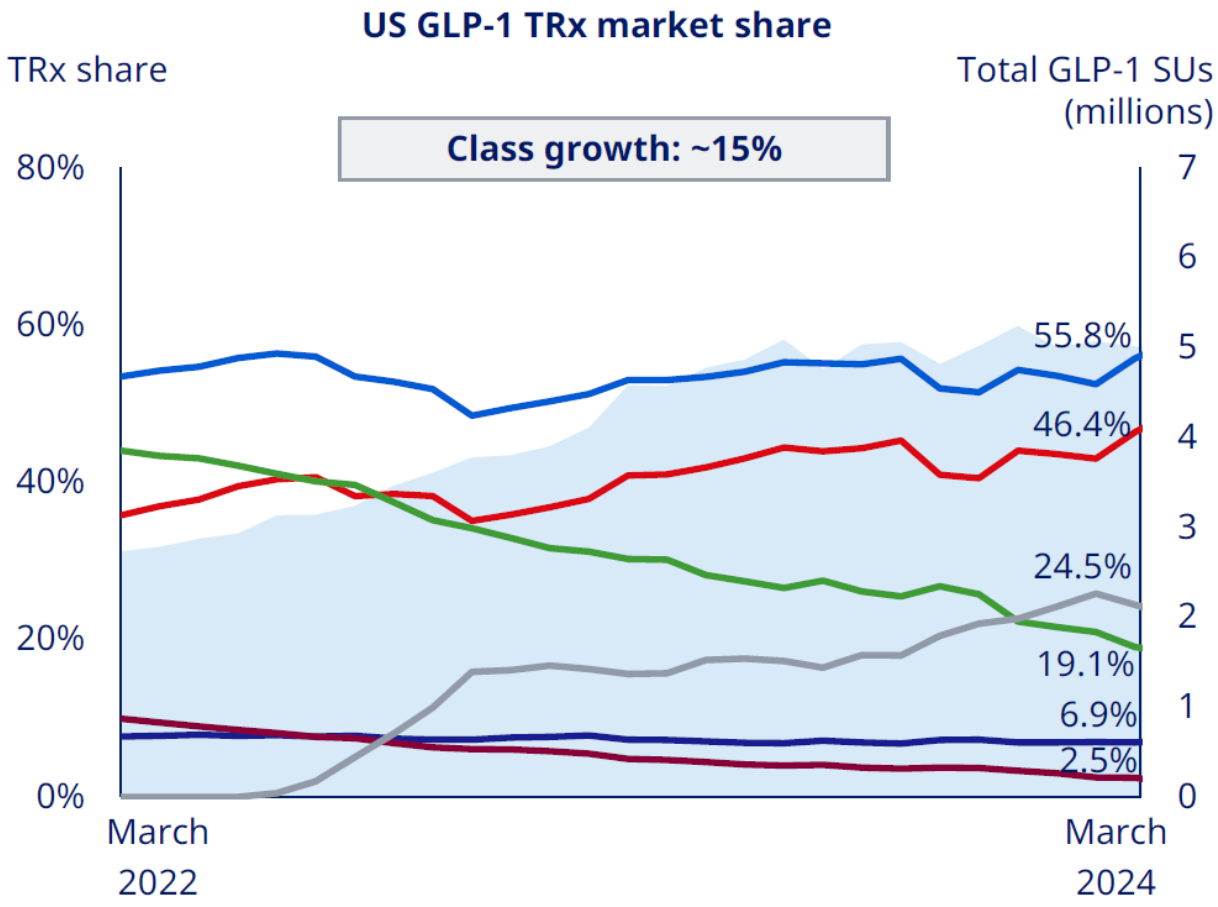


Source: https://investor.novonordisk.com/q1-2024-presentation/?page=13

IO: International Operations; NN: Novo Nordisk; EMEA: Europe, Middle East and Africa; China: Mainland China, Hong Kong and Taiwan; RoW: Rest of World; CER: Constant exchange rates
Note that the market share and patient numbers are based on countries with IQVIA coverage. GLP-1 class growth calculated as Dec'23-Feb'24 vs Dec'22-Feb'23 (Rolling 3-month average)
Source: IQVIA MAT, Feb 2024 (Spot rate). Volume packs are converted into full-year patients based on WHO assumptions for average daily doses; Market values are based on the list prices

GLP-1 class continues to grow in the US





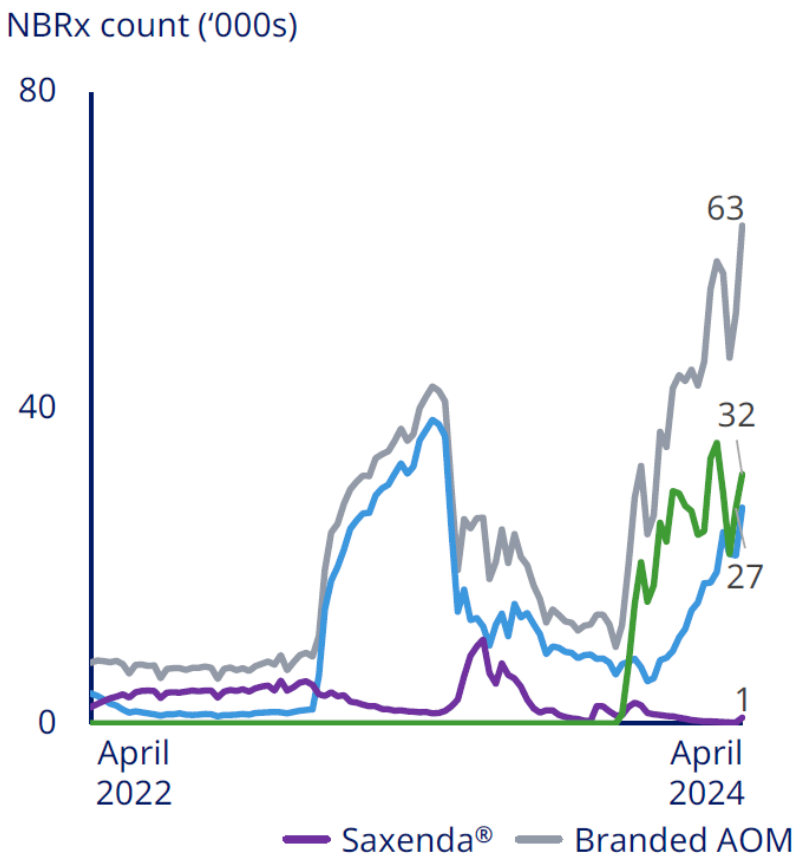
Ozempic® | Rybelsus® | Victoza® | NN GLP-1 | dulaglutide | tirzepatide | Total monthly GLP-1 scripts

NBRx: New-to-brand prescriptions; TRx: Total prescriptions; NN: Novo Nordisk; Scripts: Prescriptions; US: United States; SU: standard units
Note: Class growth calculated based on SU volume for diabetes GLP-1 as Q1 2024 vs Q1 2023
Source: IQVIA Xponent Plantrak, NBRx/TRx data from week ending 29 March 2024. Each data point represents a rolling four-week average.

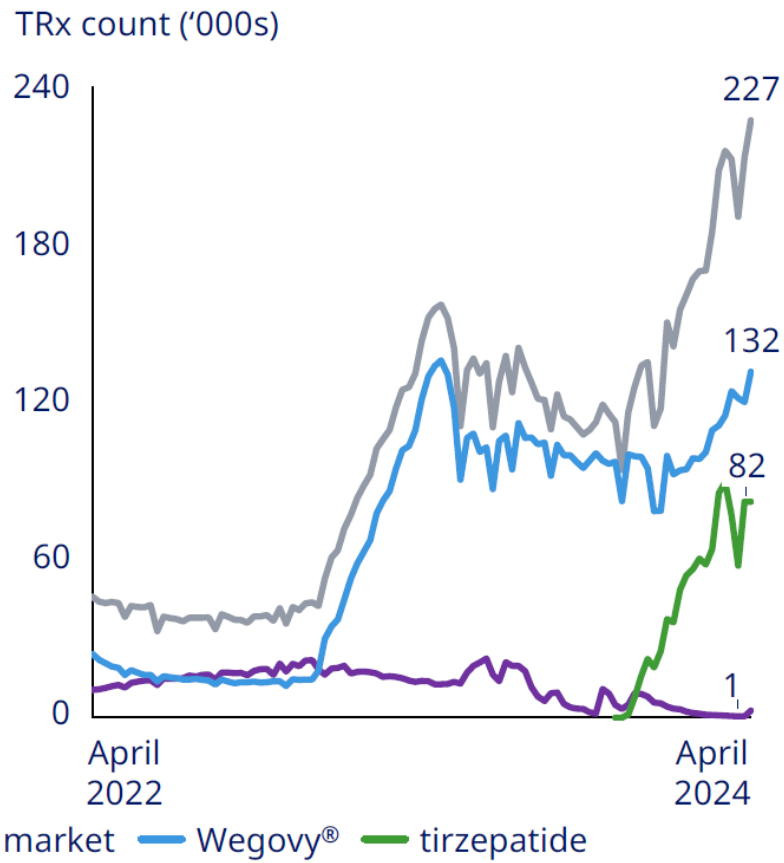
Source: https://investor.novonordisk.com/q1-2024-presentation/?page=13

Gradual increase of supply reflected in US Obesity prescription development

Branded AOM NBRx in the US[2]



Branded AOM TRx in the US[2]



Saxenda® Branded AOM market Wegovy® tirzepatide

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
- Broad commercial formulary access has been achieved for Wegovy®

[1] Annual growth at CER. Each NBRx and TRx data points represents one week of data; [2] IQVIA weekly, 12 April 2024
CER: Constant exchange rates; TRx: Total Prescriptions; AOM: Anti-Obesity Medications (includes Wegovy®, Saxenda®, Zepbound®, Qsymia® and Contrave®)
Note: Sales growth at constant exchange rates.

Source: https://investor.novonordisk.com/q1-2024-presentation/?page=13

Novo Boosts Wegovy Shipments as Lilly Rivalry Pressures Prices

Naomi Kresge, *Bloomberg*, May 2, 2024 (excerpt)

Novo Nordisk A/S is shipping more introductory doses of its blockbuster weight-loss drug Wegovy in the US as it grapples with supply constraints and competition from Eli Lilly & Co.

Wegovy sales more than doubled to 9.38 billion kroner ($1.35 billion) in the first quarter, but the number fell short of analysts' estimates due to pricing pressure. In a sign of investors' focus on the obesity medicine, the stock declined even though quarterly profit surged and the company raised its forecast.

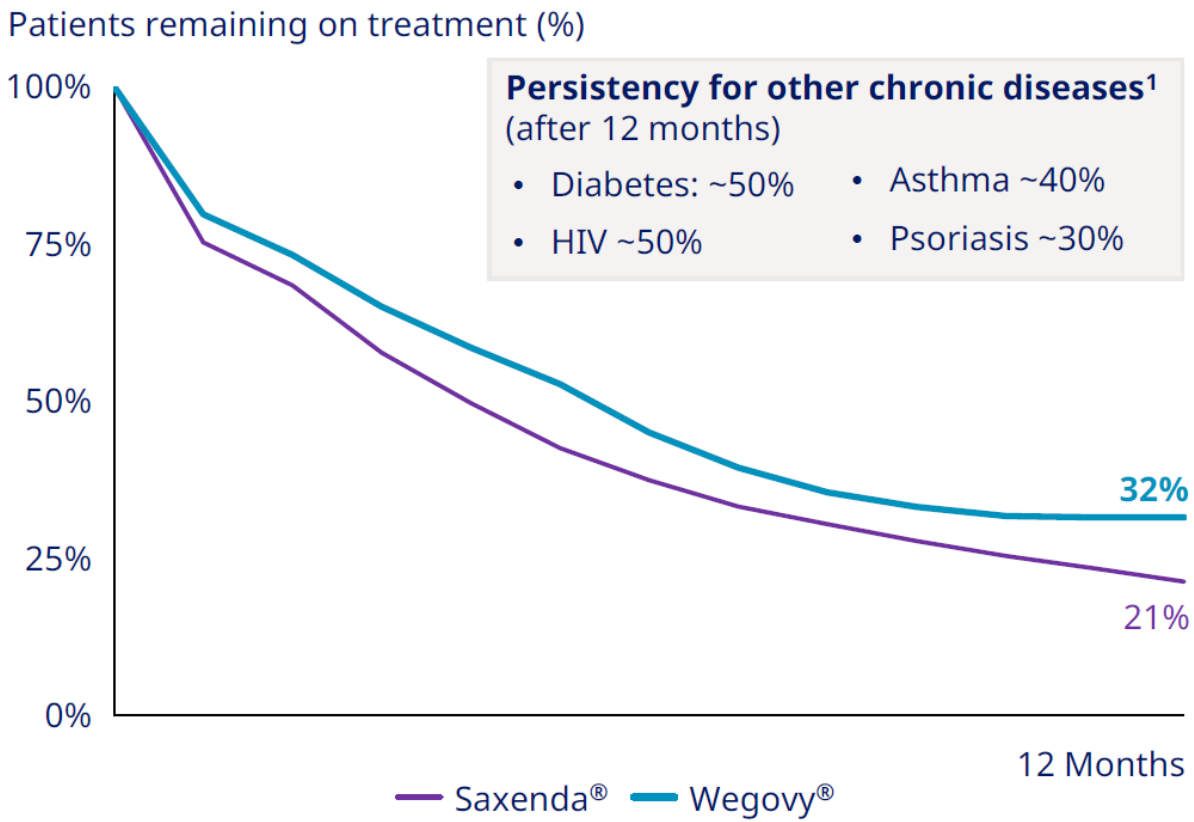
Ramping up production is a key element of Novo's strategy as it battles Lilly for supremacy in the weight-loss market. The Danish drugmaker is doubling its investment in manufacturing capacity this year to about $6.4 billion — a figure that doesn't include the planned $11 billion acquisition of three factories originally owned by contract manufacturer Catalent Inc.

More than 25,000 patients are now starting on Wegovy each week in the US, Novo Chief Executive Officer Lars Fruergaard Jorgensen said Thursday. That's up from about 5,000 in December. Another executive said earlier that the number had quadrupled to about 20,000, in a sign of how quickly Novo is moving to scale up supply for a drug that's helped carve an entirely new market.

Source: https://www.bloomberg.com/news/articles/2024-05-02/novo-quadruples-the-number-of-patients-starting-on-wegovy-in-us

Novo Nordisk is broadening focus from solely weight loss to improving health for patients with overweight or obesity

Patient persistency on anti-obesity medications after 12 months



Characteristics for patients on Wegovy® in the US

≈ 75% naïve to AOM treatment

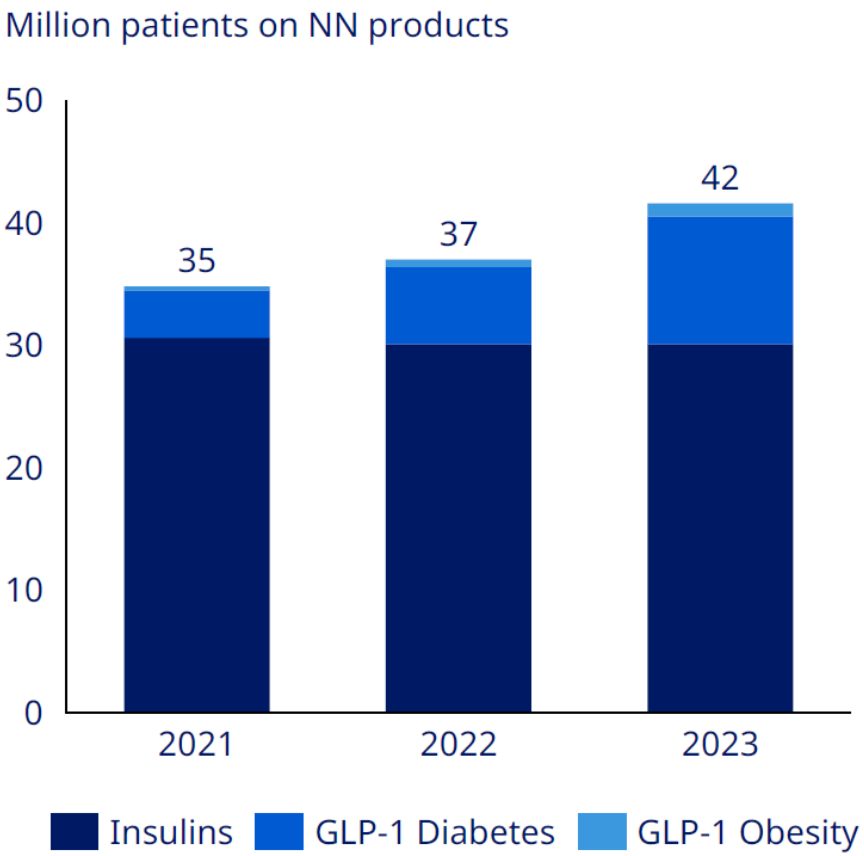
- 81% female
- Age: Average of 47 years
- Average BMI of 38
- Patients on Wegovy® with type 2 diabetes diagnosis: 8%
- With comorbidities: ≥1: 78% ≥2: 53% ≥3: 32%
- Average Wegovy® stay time >6 months despite supply constraints[2]

[1]Hichborn, et al. (2018). Improving patient adherence through data-driven insights. McKinsey & Company; [2] Based on real world data, patient cohort included those initiating therapy between Oct '21 and Mar '22, followed for 1 year;
AOM: Anti-obesity medications; BMI: Body mass index; HbA1c: Haemoglobin A1c; HIV: Human Immunodeficiency Virus; US: United States
Source: IQVIA LAAD AOM Rx August 2023; Real world evidence based on prescription data

Source: https://investor.novonordisk.com/q1-2024-presentation/?page=13

Product supply has continued step-up in investments and employees to support growth

Patient reach has accelerated since 2021



Product supply has expanded to enable the current growth

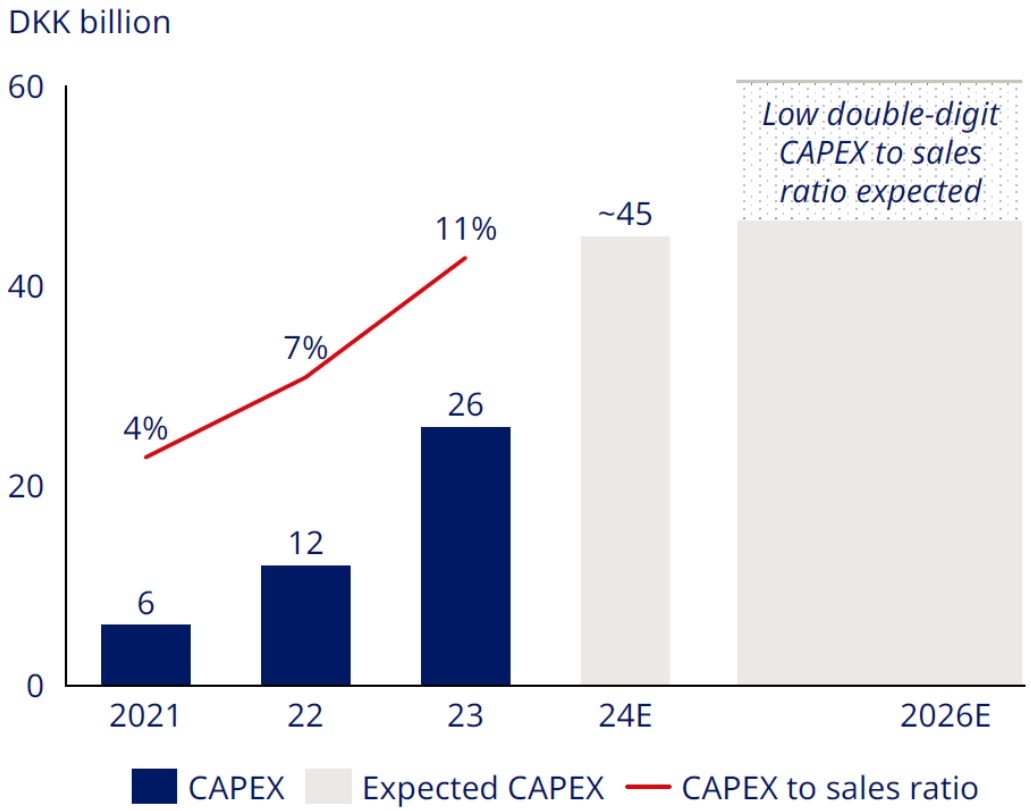
	2021	2023
Number of employees	~16,000 employees	**~25,000 employees**
CAPEX investment level CAPEX to sales ratio	6 bDKK 4%	**26 bDKK** **11%**
Ozempic® devices	Index 100	**Index ~300**
Semaglutide API	Index 100	**Index ~400**

API: Active Pharmaceutical Ingredient; CAPEX: Capital Expenditure; NN: Novo Nordisk
Note: Insulin includes new-generation insulins, modern insulins and human insulins
Sources: Novo Nordisk Annual Report 2023

Source: https://investor.novonordisk.com/q1-2024-presentation/

Significant step-up in CAPEX investments across the full value chain to enable growth for current and future products

CAPEX investments



Several large investments announced since 2021

Announced	Site	Scope	Investment
2021 December	Kalundborg Denmark	Mainly API	17 bDKK
2022 November	Bagsværd Denmark	Clinical API	5 bDKK
2023 June	Hillerød Denmark	API for CETA	16 bDKK
2023 November	Kalundborg Denmark	Mainly API	42 bDKK
2023 November	Chartres France	Fill-Finish	16 bDKK
2023 December	Athlone Ireland	Oral portfolio	1 bDKK

Typical construction timelines: API: 5+ years | Fill-finish: 3+ year

API: Active pharmaceutical ingredient; CAPEX: Capital expenditures; CETA: Cardiovascular and emerging therapy areas
Note: Investment figures have been rounded

Source: https://investor.novonordisk.com/q1-2024-presentation/

Catalent fill-finish sites are expected to start adding additional capacity from 2026

The three Catalent fill-finish sites

Bloomington site (Indiana, US)

Brussels site (Belgium)

Anagni site (Italy)

After closing, Novo Nordisk will honour all customer obligations at the three Catalent sites that Novo Nordisk is acquiring

The acquisition will help expand capacity faster

- Will help reach more patients with current and future treatments
- Enables faster expansion of manufacturing capacity at scale, while providing future optionality and flexibility
- The three sites are fully operational and employ >3,000 people
- The acquisition is expected to gradually increase Novo Nordisk's fill-finish capacity from 2026 and onwards

The acquisition is expected to be completed towards the end of 2024 upon satisfaction of various customary closing conditions

US: United States

Source: https://investor.novonordisk.com/q1-2024-presentation/

FTC Seeks More Information on $16.5 Billion Novo-Catalent Deal

Collin Kellaher, *Wall Street Journal*, May 3, 2024 (excerpt)

A $16.5 billion deal aimed at boosting Novo Nordisk's production of the weight-loss drug Wegovy is drawing extra scrutiny from U.S. antitrust regulators.

Novo Holdings, which owns a controlling stake in Novo Nordisk, in February agreed to buy contract drugmaker with plans to flip three of Catalent's most critical plants to Novo Nordisk for $11 billion to help meet demand for Wegovy and its cousin diabetes drug Ozempic.

In a filing with the Securities and Exchange Commission on Friday, Catalent said the Federal Trade Commission has asked the company and Novo for additional information and documentary materials as the antitrust enforcer reviews the deal.

The so-called second request by the FTC signals the agency is reviewing whether the deal could be anticompetitive under U.S. law.

Catalent Fill-Finish Facility in Bloomington, Indiana

Source: https://www.wsj.com/health/pharma/ftc-seeks-more-info-on-16-5-billion-novo-catalent-deal-704fb4d9

Wegovy Maker Novo Nordisk Extends Losses Following First-Quarter Results

Jenni Reid, CNBC, May 3, 2024

Shares of Danish pharmaceutical giant Novo Nordisk slid 2.5% on Friday, extending a 2.7% loss on Thursday as analysts pored over the details of the firm's first-quarter results and monitored a potential rival weight loss treatment.

The company reported that sales for its blockbuster injectable weight loss treatment Wegovy, more than doubled to 9.38 billion Danish kroner ($1.4 billion). Novo Nordisk, which also makes diabetes treatment Ozempic, said the rise in sales had offset a slight reduction in prices.

Novo Nordisk expects prices to drop further as new entrants enter the market, CFO Karsten Knudsen said on a media call, adding that the company was not seeing much evidence of Wegovy users moving to other rival treatments.

Analysts expected even higher weight loss drug sales in the quarter, and some noted that Novo Nordisk's 2024 outlook raise for both sales growth and operating profit was due to one-off accounting adjustments.

"While we continue to see Novo as a wide-moat firm, with strong intangible assets surrounding its cardiometabolic business, we think high obesity drug demand and a scarcity of supply have driven share prices above their intrinsic value," Karen Andersen, strategist at Morningstar, said in a Thursday note.

Source: https://www.cnbc.com/2024/05/03/wegovy-maker-novo-nordisk-down-4percent-heads-for-worst-day-since-october.html


REGENERON

REGENERON

Executing on our core competencies

EYLEA

#1 prescribed
FDA approved anti-VEGF treatment for retinal disease

EYLEA HD (aflibercept) Injection 8 mg

Now FDA approved
Aspire to become new standard-of-care

DUPIXENT

~$3.1B net product sales in 1Q24†

LIBTAYO

Emerging portfolio of immuno-oncology antibodies

Investing in Regeneron

- Investing **~$5B** into R&D in 2024*
- New **$3B** share repurchase program authorized in April 2024
- Repurchased **over $12B** of shares since Nov 2019§

Looking ahead to the future

- **Over 35 therapeutic candidates** in various stages of **clinical development**
- **Pioneering** novel therapeutic approaches including in genetic medicines
- **Expanding partnerships** with leading companies in new technologies

Alnylam · Intellia Therapeutics · CytomX Therapeutics · Sonoma Biotherapeutics · Mammoth Biosciences

Advancing a **best-in-class, diversified** pipeline based on innovation and strategic partnerships

RGC Regeneron Genetics Center driving new breakthroughs and target discovery

Source: https://investor.regeneron.com/static-files/d6375b15-eded-4a7f-a048-b1ec42f0d412

*Based on midpoint of most recent GAAP R&D guidance. †Sanofi records global net product sales of Dupixent. §~$1.2 billion in the aggregate remaining under the February 2023 share repurchase program as of March 31, 2024.
Note: Definitions for all abbreviations and acronyms in this presentation can be found on page 32. All trademarks mentioned are the property of their respective owners.

REGENERON®

Regeneron-discovered, approved and investigational medicines across a diverse set of diseases

Phase 1	Phase 2	Phase 3	Approved
REGN5459 (BCMAxCD3) **REGN5837** (CD22xCD28) **REGN7257** (IL-2Rγ) **REGN7508** (Factor XI) **REGN7999** (TMPRSS6)	**REGN9933** (Factor XI)	**pozelimab + cemdisiran**‡ (anti-C5 + C5 siRNA) **odronextamab** (CD20xCD3) **linvoseltamab** (BCMAxCD3) **NTLA-2001**# (TTR)	Arcalyst® (rilonacept) Injection for Subcutaneous Use † EYLEA® (aflibercept) Injection For Intravitreal Injection ° ZALTRAP® (ziv-aflibercept) Injection for Intravenous Infusion § EYLEA® HD (aflibercept) Injection 8 mg ° DUPIXENT® (dupilumab) * Praluent® (alirocumab) Injection 75mg/mL 150mg/mL LIBTAYO® (cemiplimab-rwlc) Injection 350 mg KEVZARA® (sarilumab) * Evkeeza® (evinacumab-dgnb) Injection ** Inmazeb® (atoltivimab, maftivimab, and odesivimab – ebgn) Injection Veopoz® (pozelimab-bbfg) Injection
REGN4336 (PSMAxCD3) **davutamig** (METxMET) **REGN5093-M114** (METxMET ADC) **REGN5668** (MUC16xCD28) **REGN6569** (GITR)	**vidutolimod** (TLR9) **ubamatamab** (MUC16xCD3) **nezastomig** (PSMAxCD28) **REGN7075** (EGFRxCD28)	**cemiplimab** (PD-1) **fianlimab** (LAG-3)	
ALN-PNP‡ (PNPLA3) **DB-OTO** (AAV Gene Therapy) **REGN7544** (NPR1 antagonist) **REGN13335** (PDGFβ)	**mibavademab** (LEPR) **REGN5381/REGN9035** (NPR1) **HSD siRNA** (HSD17B13) **trevogrumab** (GDF8) **ALN-APP**‡ (APP)	**garetosmab** (Activin A)	
	sarilumab* (IL-6R)	**dupilumab*** (IL-4R) **itepekimab*** (IL-33) **REGN5713-5714-5715** (Bet v 1)	
		aflibercept 8 mg° (VEGF)	

Over 35 product candidates

HEMATOLOGY | SOLID ORGAN ONCOLOGY | INTERNAL/GENETIC MEDICINES | I&I | OPHTHALMOLOGY

Collaboration with: *Sanofi; ‡Alnylam; #Intellia; °Bayer, **Ultragenyx
†Kiniksa is solely responsible for development and commercialization of ARCALYST
§Sanofi is solely responsible for development and commercialization of ZALTRAP

27 As of February 2024.

Source: https://investor.regeneron.com/static-files/d6375b15-eded-4a7f-a048-b1ec42fod412

REGENERON®

This slide contains investigational drug candidates that have not been approved by any regulatory authority.

Continued execution driving strong results

EYLEA® EYLEA® HD

LIBTAYO® DUPIXENT®

1Q 2024 Total Revenues*†

+7% YoY

1Q 2024 Non-GAAP EPS†

$9.55

Notable R&D Pipeline Advancements

EYLEA® HD

- EYLEA HD (known as EYLEA 8 mg outside of U.S.) approved in EU and Japan for wAMD and DME

DUPIXENT®

- sBLA accepted for priority review for COPD with evidence of Type 2 inflammation (PDUFA June 27, 2024)
- Approved in Japan for CSU in patients age 12+; regulatory application submitted in EU
- Approved for pediatric (1 -11 years) EoE in US; under review in EU

- BLA for linvoseltamab for MM accepted by FDA for Priority Review (PDUFA Aug 22, 2024); Phase 3 confirmatory study currently enrolling
- Positive pivotal data for linvoseltamab presented at American Association for Cancer Research (AACR)
- Praluent approved by FDA for pediatric (8+ year) HeFH
- Acquired clinical and preclinical programs from 2seventy bio
- Initiated Phase 2 study of ALN-APP in cerebral amyloid angiopathy
- Initiated Phase 2 study of itepekimab in non-cystic fibrosis bronchiectasis

*Excluding contributions from Ronapreve
†See reconciliation of non-GAAP measure on slide 31.

Source: https://investor.regeneron.com/static-files/d6375b15-eded-4a7f-a048-b1ec42f0d412

REGENERON®

This slide contains investigational drug candidates and indications that have not been approved by any regulatory authority.

EYLEA HD approved in U.S. for wAMD, DME, and DR

EYLEA® HD

has the potential to become the **next-generation standard-of-care** anti-VEGF treatment

1Q 2024 U.S. Net Product Sales:

$200 million

achieved in second full quarter following launch

EYLEA® HD (aflibercept) Injection 8 mg | EYLEA® (aflibercept) Injection For Intravitreal Injection

1Q 2024 combined EYLEA HD + EYLEA U.S. net product sales of **$1.4 billion**

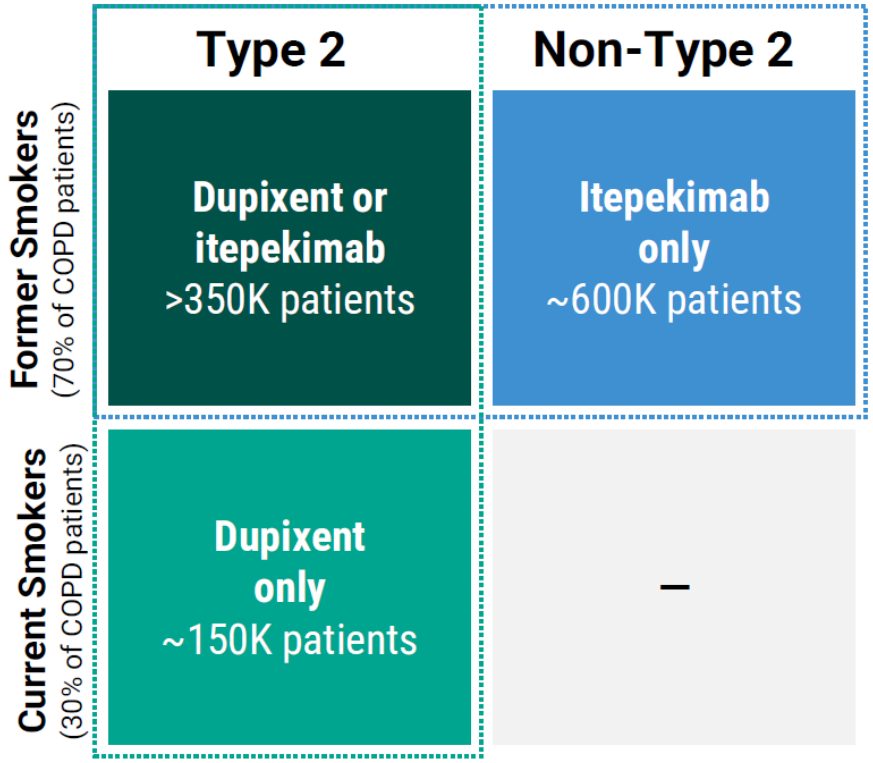
- **FDA approval** for wAMD, DME and DR received in August 2023
- Early indicators suggest **broad initial uptake** across treatment landscape
- **Strong 2-year data** from pivotal PULSAR and PHOTON studies presented in 2023, supporting **best-in-class** efficacy, safety, and durability profile
- **>80% of eligible lives have coverage**; vast majority of covered lives have **first-line or single-step-edit access** to Eylea HD
- CMS-assigned **permanent J-Code** took effect on April 1, 2024

5 Source: https://investor.regeneron.com/static-files/d6375b15-eded-4a7f-a048-b1ec42f0d412

Dupixent & itepekimab: Two opportunities to address high unmet need in COPD

DUPIXENT® (dupilumab)

- Potential to address **COPD** with a Type 2 inflammatory phenotype (eos ≥300/µl) in both **current and former smokers**
- **First and only** biologic to achieve clinically meaningful and statistically significant **reduction in COPD exacerbations** and **improvement in lung function** vs. placebo*
- sBLA **accepted** for Priority Review (PDUFA June 27, 2024)
  - ✔ Granted **Breakthrough Therapy Designation** by FDA
  - ✔ EC decision expected 2H24



Current U.S., EU and Japan addressable patient estimates

Itepekimab

(anti IL-33)

- Potential to address **COPD** in **former smokers**, regardless of eosinophilic phenotype
- Two Phase 3 studies ongoing:
  - ✔ AERIFY-1 enrolling
  - ✔ AERIFY-2 enrolling
- AERIFY studies **passed interim futility analysis** in 2023
- Enrollment nearly complete, **results expected in 2025**
- Includes patients with both high and low eosinophil counts

*Patients were randomized to receive Dupixent or placebo added to maximal standard-of-care inhaled triple therapy (LABA+LAMA+ICS)

This slide contains investigational drug candidates and indications that have not been approved by any regulatory authority.

REGENERON®

Novel treatment approach for reversing severe allergy: Linvoseltamab (BCMAxCD3) plus Dupixent (anti-IL4Rα)

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ALLERGY

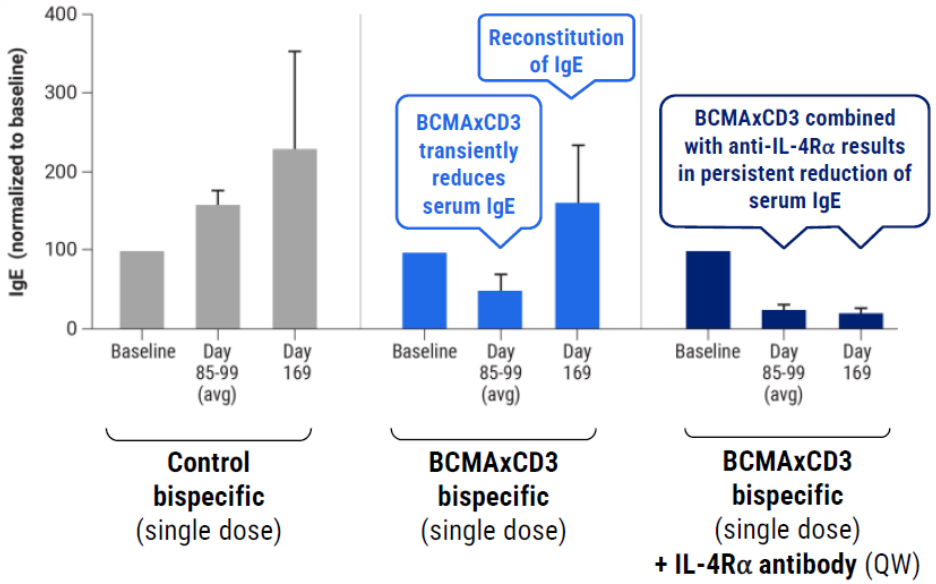
A therapeutic strategy to target distinct sources of IgE and durably reverse allergy

Andre Limnander, Navneet Kaur, Seblewongel Asrat, Carley Tasker, Anita Boyapati, Li-Hong Ben, John Janczy, Paulina Pedraza, Pablo Abreu, Wen-Chi Chen, Stephen Godin, Benjamin J. Daniel, Harvey Chin, Michelle DeVeaux, Karen Rodriguez Lorenc, Andres Sirulnik, Olivier Harari, Neil Stahl, Matthew A. Sleeman, Andrew J. Murphy, George D. Yancopoulos, Jamie M. Orengo*

Linvoseltamab and Dupixent regimen could eliminate IgE: potential groundbreaking approach for controlling severe allergy

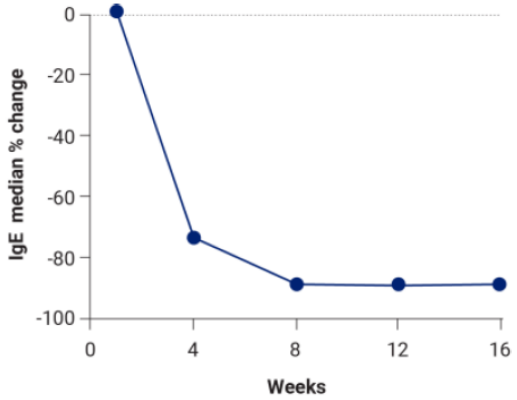
- **Immunoglobulin E (IgE)** is the key driver of allergic reactions, such as food allergies; long-lived plasma cells consistently produce IgE[2]
- In atopic patients, **transient linvoseltamab** treatment with **Dupixent maintenance** has the potential to permanently eliminate IgE and durably reverse severe allergies, while allowing the restoration of other immunoglobulins

Transient plasma cell depletion with BCMAxCD3 plus sustained IL-4Rα blockade durably eliminates IgE production in cynomolgus monkeys[1]



Myeloma patients treated with linvoseltamab rapidly reduce IgE levels[1]

Median concentrations of serum IgE over time in MM patients (n=12) receiving QW linvoseltamab*



- Linvoseltamab effectively eliminates BCMA-expressing cells, including long-lived plasma cells
- IgE reduction seen in myeloma patients supports the two-drug regimen for severe food allergies

Clinical trial with the two-drug regimen in patients with severe food allergies now underway

[1]Adapted from Limnander et al, Sci. Transl. Med. 2023.[2]Asrat et al, Sci. Immunol. 2020.
* Pooled data from n=12 multiple myeloma patients from the LINKER-MM1 Phase 1 study, treated with six different dose levels of linvoseltamab

REGENERON®

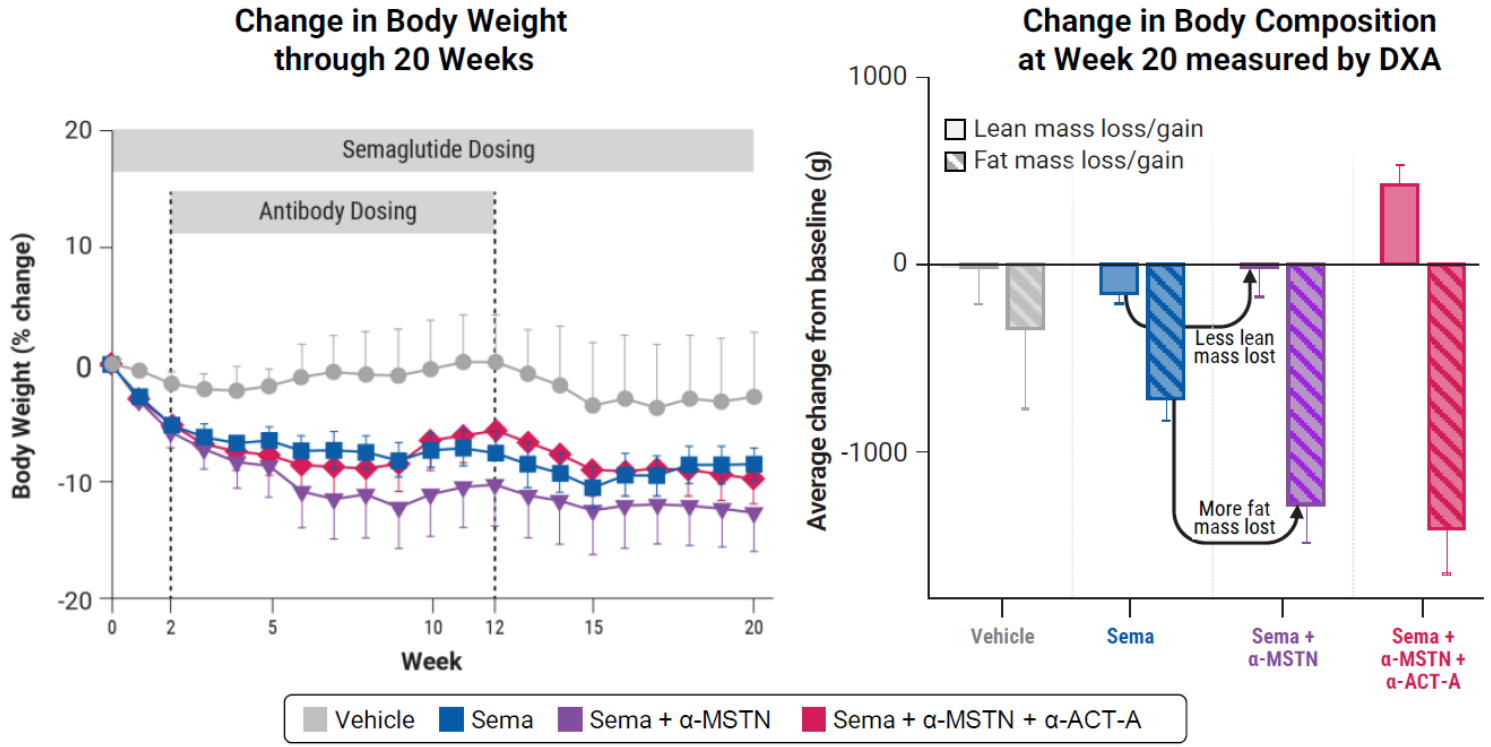
Regeneron's approach to obesity: combinations with leading medicines aim to improve quality of weight loss

Incretin-based therapies, such as semaglutide (sema) and tirzepatide, are emerging as standards of care for weight loss; However, up to 40% of weight loss from these agents is due to decreases in lean muscle mass[1]

Novel approaches for obesity

	Rationale	Program status
Incretin-based therapy + α-MSTN + α-ACT-A	Improving **quality of weight loss** by preserving lean muscle during weight loss	Mid-2024: Start Phase 2 study of semaglutide with **trevogrumab** (anti-myostatin) ± **garetosmab** (anti-activin A)
Incretin-based therapy + LEPR	Improving **maintenance of weight loss** following incretin discontinuations	Phase 2 study now underway testing combinations of tirzepatide ± **mibavademab**
GPR75	*GPR75* gene mutations are associated with **protection against obesity**	siRNA, small molecule, and antibody candidate identification and screening underway

Adding myostatin blockade to semaglutide leads to greater fat loss and less lean mass loss compared to semaglutide monotherapy in obese non-human primates[2]



[1]Wilding, Diabetes Obes Metab, 2022; PMID: 35441470, [2]from Mastaitis J, et al. Manuscript in preparation and ADA 2023 presentation, n=10 per arm; DXA: dual-energy X-ray absorptiometry measurement

REGENERON®

This slide contains investigational drug candidates that have not been approved by any regulatory authority.

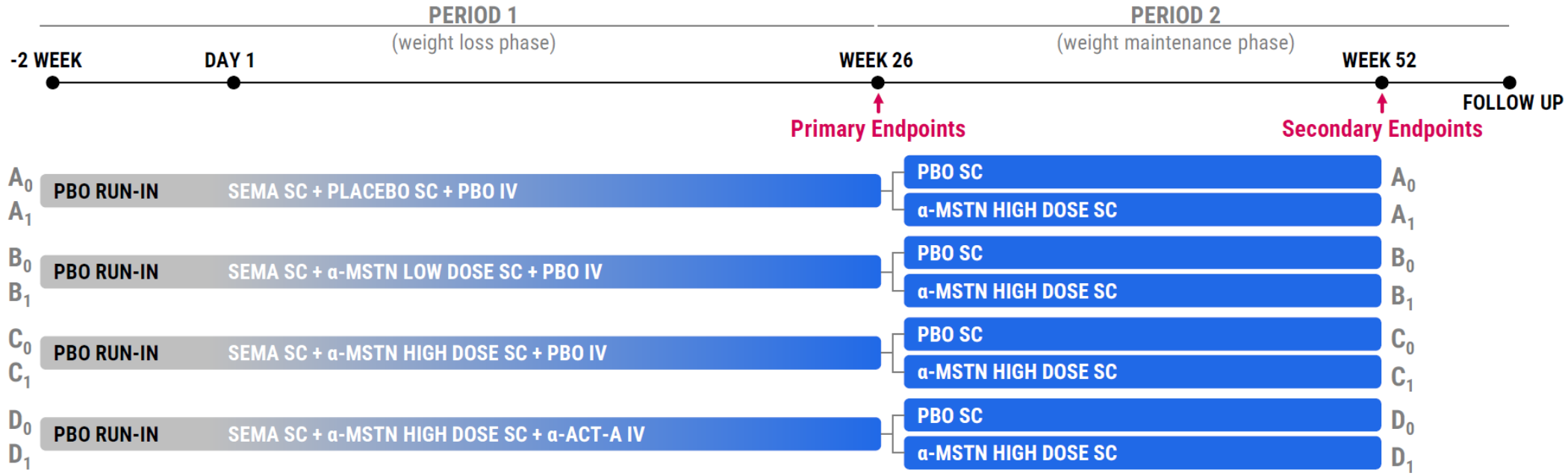
Obesity clinical program to start in mid-2024

Phase 2 study to investigate if addition of trevogrumab (anti-myostatin) to semaglutide with and without garetosmab (anti-activin A) improves the quality of weight loss and/or improves maintenance of weight loss post semaglutide discontinuation

- Enrollment of obese patients expected to begin in mid-2024; safety and tolerability trial of high-dose trevogrumab in healthy volunteers is fully enrolled

Phase 2 General Obesity Trial Design

Randomized (1:1:1:1:1:1:1:1) double-blind, active controlled trial



REGENERON®

This slide contains investigational drug candidates that have not been approved by any regulatory authority.

Regeneron restores hearing in a profoundly deaf child

DB-OTO AAV-based dual-vector gene therapy delivered to the inner ear to rescue hearing in infants

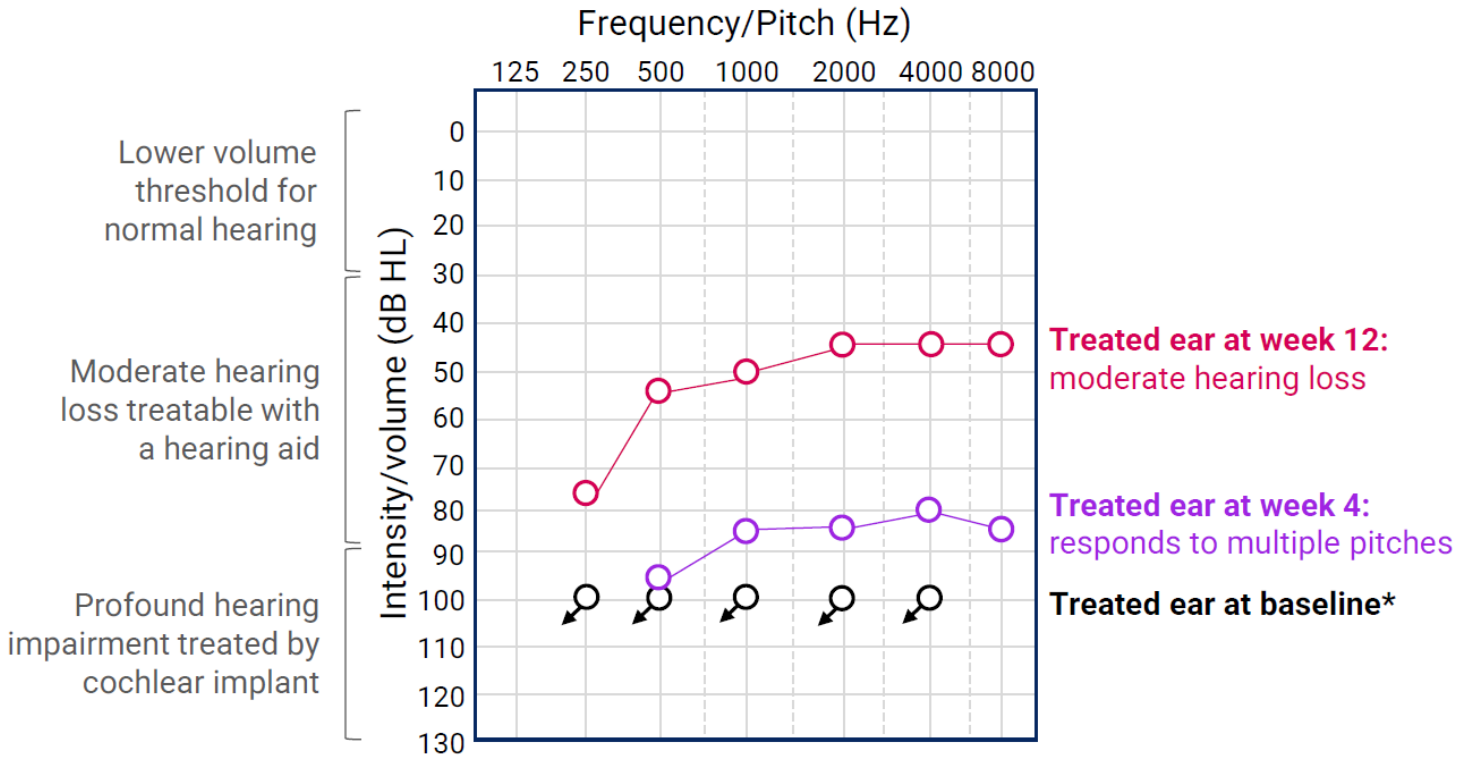
Gene therapy for genetic hearing loss

Potentially first-in-class, one-time treatment to rescue hearing in infants born with profound deafness due to biallelic OTOF mutations

- DB-OTO is a surgically delivered AAV-based dual-vector gene therapy that selectively expresses functional OTOF in the inner ear hair cells of patients, enabling the ear to transmit sound to the brain
- Preliminary, positive safety and efficacy results from the first patient (<2 years old) continue to show improvements in auditory responses, now through week 12, compared to baseline
- Paves the way for next gene therapy for genetic hearing loss – GJB2
  - Currently in IND-enabling studies

Preliminary results for first patient dosed:
Profoundly deaf child at baseline, demonstrates markedly improved hearing at 12 weeks post-treatment

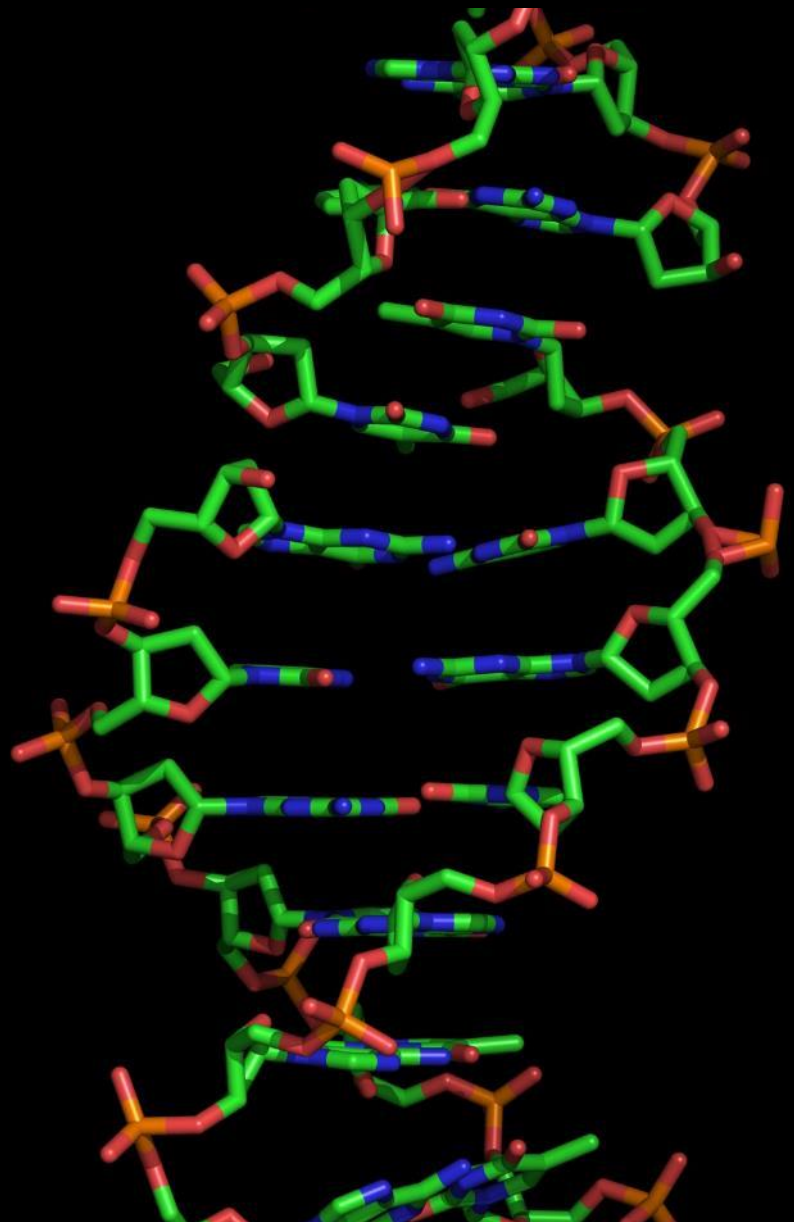
Updated data to be presented at ASGCT in May



Behavioral pure tone audiogram – a plot of softest sounds a patient can hear in an individual ear

**Arrows indicate no response at maximum level tested*

Industry News



Drug Companies, VCs Rethink R&D Strategies as IRA Stands Strong in Court

Neil Versel, *Biospace,* May 1, 2024

Big Pharma took another hit in court Monday as a federal judge in New Jersey threw out challenges by Johnson & Johnson and Bristol Myers Squibb to the drug price negotiations outlined in the Inflation Reduction Act. AstraZeneca and trade group Pharmaceutical Research and Manufacturers of America (PhRMA), along with several provider-side allies, have already lost their legal challenges to the 2022 law, and the Centers for Medicare and Medicaid Services is pushing ahead with negotiations over the first 10 drugs in the program.

Those negotiated rates will take effect in 2026, and pharma companies are now reconsidering their R&D strategies as the venture capital community ponders where to focus its investments. One big consideration is the IRA's so-called "pill penalty," which caps patent protection at 9 years for small molecules, compared with 13 years for biologics.

Drug development had already been trending toward biologics. This drug class received 30% more VC funding in 2022 than small molecule candidates, noted John Stanford, executive director of life sciences venture capital coalition Incubate—but the gap jumped to 50% in 2023, and Stanford contends that the IRA is driving much of that shift.

There will be other IRA considerations besides the pill penalty, said Christiana Bardon, co-managing partner of biotech investment firm MPM BioImpact. Because the patent protection clock starts at the first approval, "biotech and pharma companies . . . won't launch small indications first," she told BioSpace. The legal battle is far from over. BMS and AstraZeneca have appealed the judgments against them, and PhRMA said this week that it would soon do the same. With these appeals and several other IRA challenges still pending, it remains to be seen how Medicare drug price negotiations will play out, and even more uncertain are the details of shifting biopharma strategies. But what is clear is that it's complicated.

"R&D is going to be tied to not just good science, but the commercial realities associated with a product," Stanford said. Bardon said that the IRA will ultimately affect the net present value of drugs, or the total amount of money that products could make over their lifespans, and it will cause shifts in strategy to buffer against losses. For example, drugmakers will be looking for common indications with large potential markets to recoup as much of their investment as possible in a shorter timeframe, she said. In the past, biopharma firms would launch new drugs in smaller patient populations where the data might be stronger while also running trials in populations with greater market opportunity.

"Nowadays, I think that won't happen anymore," Bardon said. "We have to launch right away with the bigger indications," likely hindering development of therapeutics for rarer diseases.

Source: https://www.biospace.com/article/drug-companies-vcs-rethink-r-and-d-strategies-as-ira-stands-strong-in-court/

Senators From Both Parties Introduce Menopause Research Bill

Nicole DeFeudis, *Endpoints News*, May 4, 2024 (excerpt)

A group of Democratic and Republican senators introduced a bill on Thursday that calls for $275 million toward federal menopause research and awareness efforts over five years. The legislation would designate $25 million a year for five years to fund NIH grants, increase coordination on menopause research within the NIH and HHS, and require HHS to expand research and reporting on menopause and mid-life women's health. It would also authorize funds for education, training and promotion efforts.

"It's bigger than just menopause," Yesmean Wahdan, Bayer's VP of US medical affairs in women's healthcare, told *Endpoints News* on Friday. "Women's healthcare in general is a space that is underrepresented when it comes to research and innovation."

Women's health advocacy has gained momentum in recent months, following multiple White House initiatives to expand research. HHS' Advanced Research Projects Agency for Health committed $100 million in February for women's health R&D, and a month later, President Joe Biden signed an executive order directing agencies to expand and prioritize women's health research and data collection.

Source: https://endpts.com/senators-from-both-parties-introduce-menopause-research-bill/

CVS Shares Plummet as Health Company Slashes Profit Outlook

Annika Kim Constantino, *CNBC,* May 1, 2024

CVS Health on Wednesday reported first-quarter revenue and adjusted earnings that missed expectations and slashed its full-year profit outlook, citing higher medical costs that are dogging the U.S. insurance industry.

Shares of the company closed more than 16% lower on Wednesday, and were headed for their worst day since November 2009. The drugstore chain expects 2024 adjusted earnings of at least $7 per share, down from a previous guidance of at least $8.30 per share. Analysts surveyed by LSEG were expecting full-year adjusted profit of $8.28 per share.

CVS also cut its unadjusted earnings guidance to at least $5.64 per share, down from at least $7.06 per share. The company said its new outlook assumes that higher medical costs in its insurance business during the first quarter will persist throughout the year. CVS owns health insurer Aetna.

Insurers such as Humana and UnitedHealth Group have seen medical costs spike as more Medicare Advantage patients return to hospitals for procedures they delayed during the pandemic, such as joint and hip replacements.

Source: https://www.cnbc.com/2024/05/01/cvs-health-cvs-earnings-q1-2024.html

It's been rough sledding lately for Medicare Advantage insurers this quarter. CVS has taken a bath on medical costs in its Aetna unit.

We have also seen reversals of entry into healthcare at retail locations in the last few weeks by Walmart and Walgreen's with its VillageMD business.

UnitedHealthcare has also shut down its telehealth business.

Massive Global Benefit from WHO Vaccination Program

Andrew Shattock et.al, "Contribution of vaccination to improved survival and health: modelling 50 years of the Expanded Programme on Immunization," *Lancet*, May 2, 2024

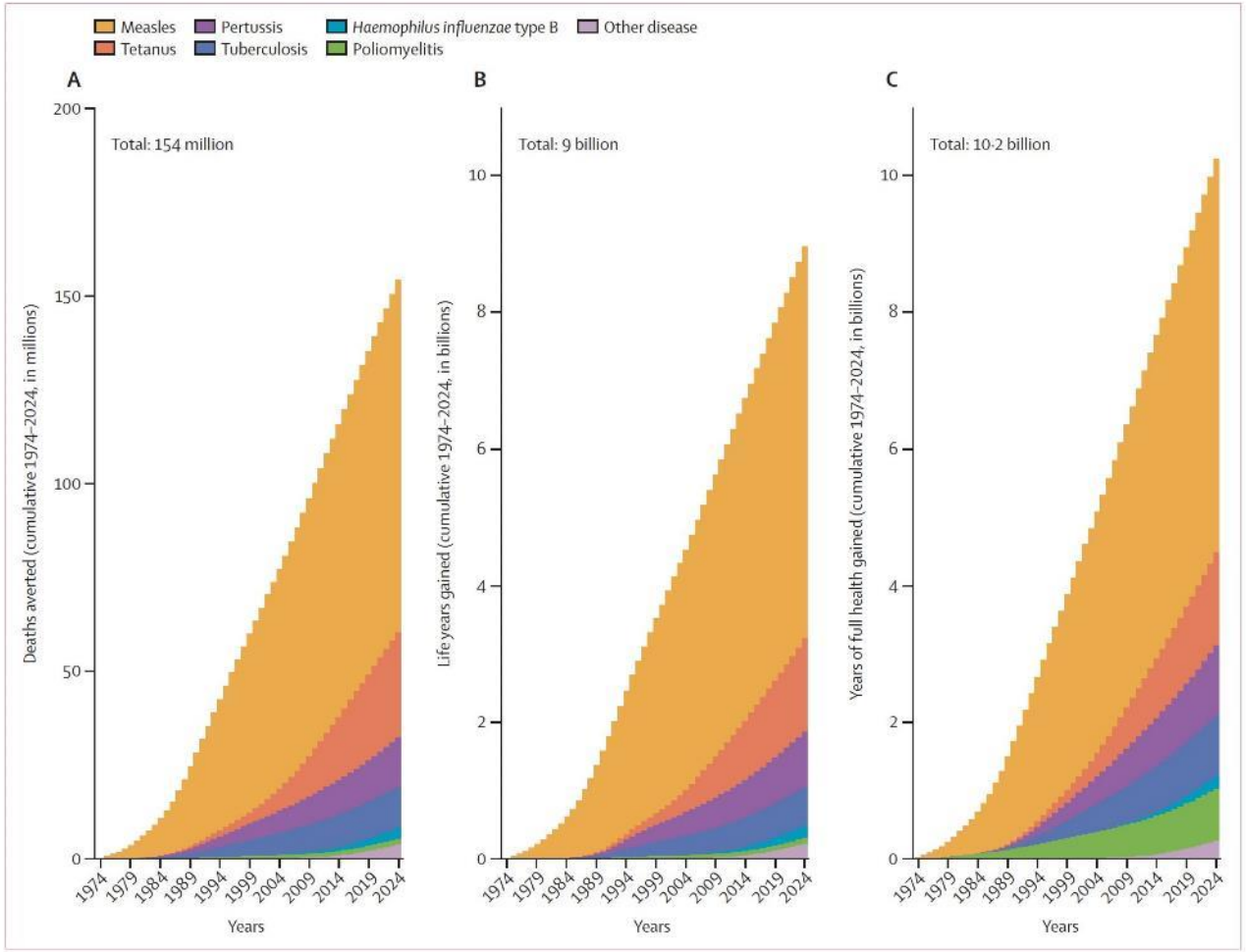


Figure 1: Deaths averted, years of life saved, and years of full health gained due to vaccination

WHO, as requested by its member states, launched the Expanded Programme on Immunization (EPI) in 1974 to make life-saving vaccines available to all globally. To mark the 50-year anniversary of EPI, we sought to quantify the public health impact of vaccination globally since the programme's inception.

Methods

In this modelling study, we used a suite of mathematical and statistical models to estimate the global and regional public health impact of 50 years of vaccination against 14 pathogens in EPI. For the modelled pathogens, we considered coverage of all routine and supplementary vaccines delivered since 1974 and estimated the mortality and morbidity averted for each age cohort relative to a hypothetical scenario of no historical vaccination. We then used these modelled outcomes to estimate the contribution of vaccination to globally declining infant and child mortality rates over this period.

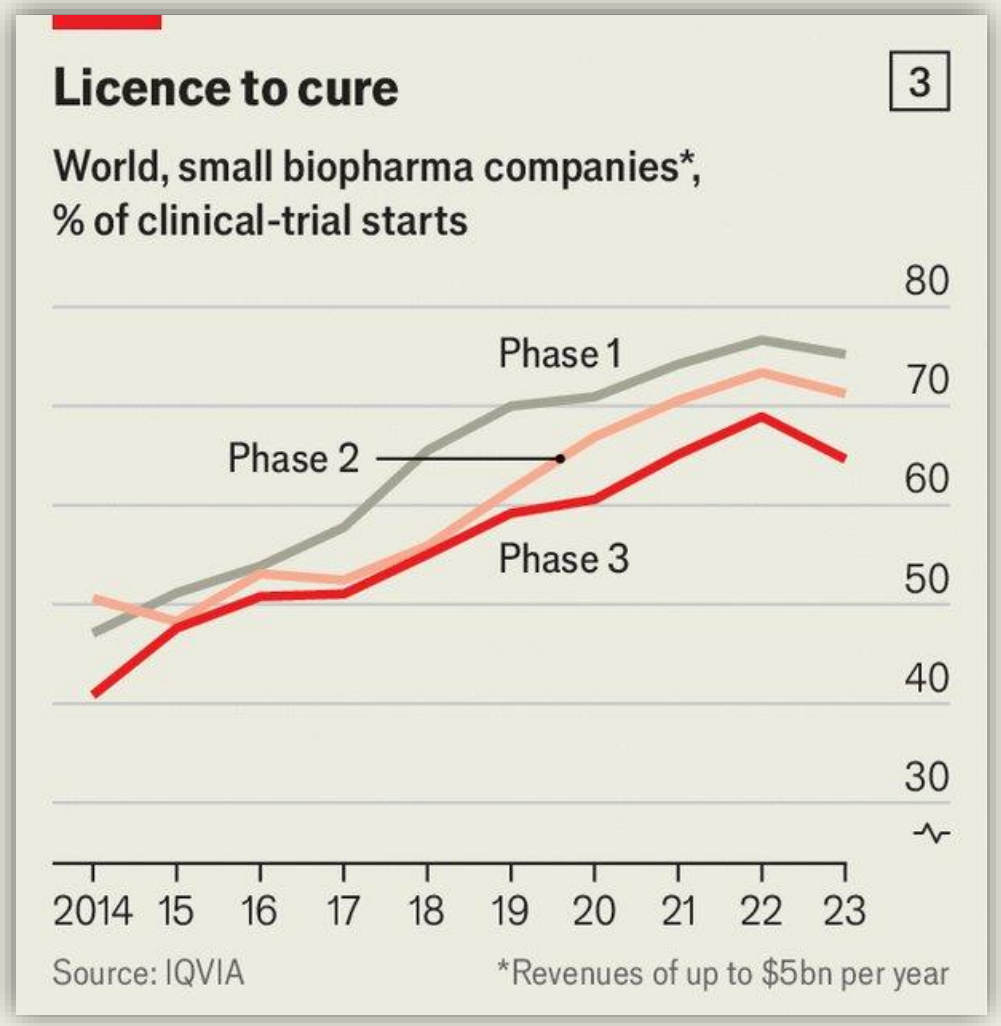
Findings

Since 1974, vaccination has averted 154 million deaths, including 146 million among children younger than 5 years of whom 101 million were infants younger than 1 year. For every death averted, 66 years of full health were gained on average, translating to 10·2 billion years of full health gained. We estimate that vaccination has accounted for 40% of the observed decline in global infant mortality, 52% in the African region. In 2024, a child younger than 10 years is 40% more likely to survive to their next birthday relative to a hypothetical scenario of no historical vaccination. Increased survival probability is observed even well into late adulthood.

Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)00850-X/fulltext

Biotechs Now Account for Over 70% of Clinical Trial Starts

Economist, May 30, 2024

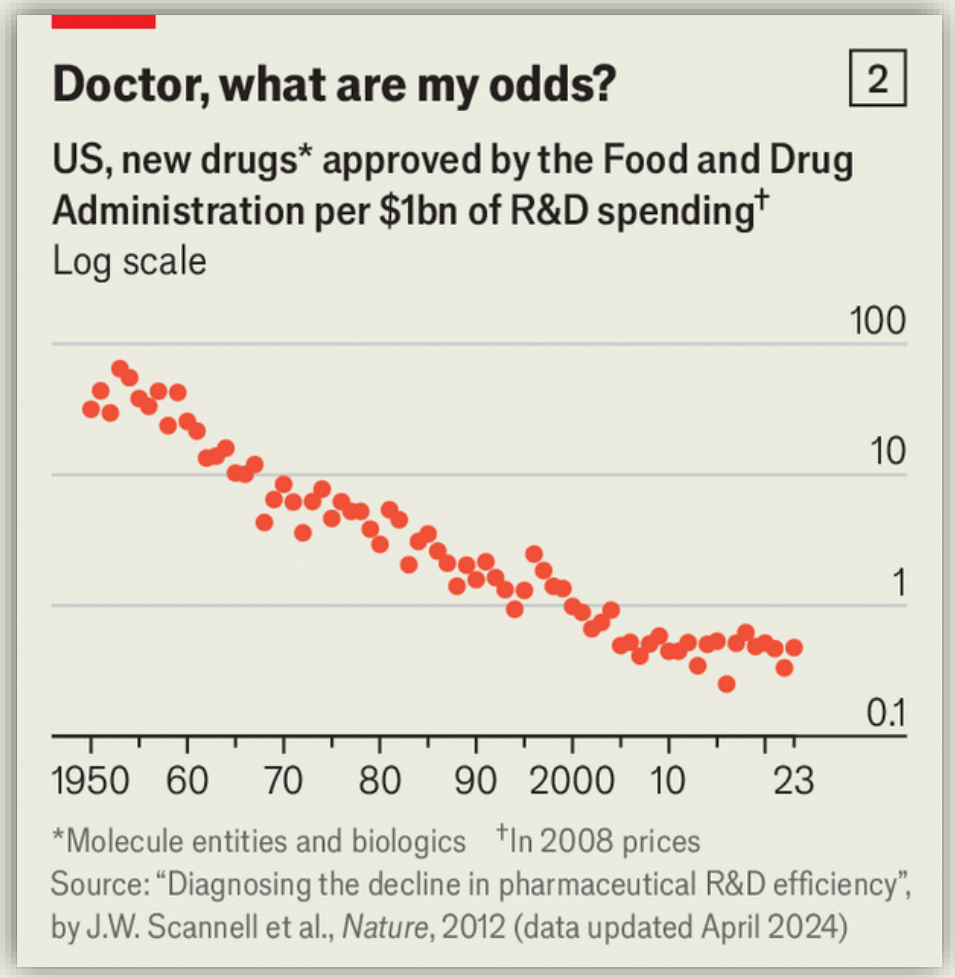


Source: https://www.economist.com/business/2024/04/30/can-biotech-startups-upstage-eli-lilly-and-novo-nordisk

Long-Term Trend: R&D Spend Per Molecule Rising Since 1950

Economist, May 30, 2024

"Jack Scannell, boss of Etheros Pharmaceuticals, a biotech firm, has analysed large drugmakers' research and development (R&D) budgets and regulatory approvals. He finds that in the 1960s $1bn in R&D (at 2008 prices) resulted in around ten new drug approvals. Nowadays that same $1bn doesn't get you even one."



Source: https://www.economist.com/business/2024/04/30/can-biotech-startups-upstage-eli-lilly-and-novo-nordisk

Recent Paper Splits R&D Productivity into Efficiency (ability to get drugs approved per R&D dollar spent) and Effectiveness (value of the R&D output)

Alexander Roland, William Fox & Ann Baker, "Efficiency, effectiveness and productivity in pharmaceutical R&D," *Nature Reviews Drug Discovery*, April 29, 2024 (excerpt)

For the purposes of the current analysis, we examined company R&D effectiveness — or the value of R&D outputs — in terms of the average net present value (NPV) of products first approved in the last five calendar years. Products originally acquired in R&D were included, but products acquired post-approval were excluded so as to eliminate any assets for which companies made no R&D contribution. The median company NPV per approval was $5.4 billion, with this figure ranging from $2.4 billion to as high as $20.4 billion in one case (Fig. 1b). Although a detailed product-by-product analysis is beyond the scope of this article, we have observed the importance of individual blockbuster products in R&D effectiveness for many of the companies in our cohort, in line with previous reports

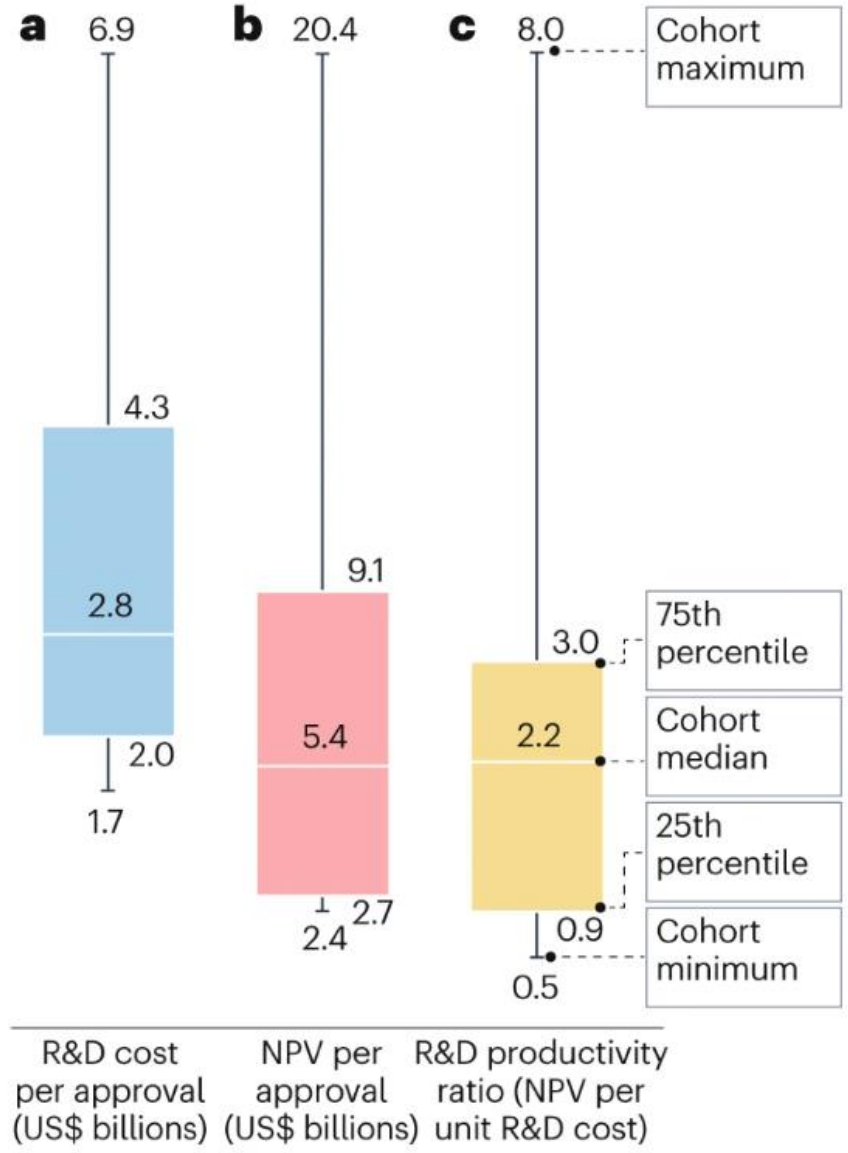


Fig. 1 | R&D efficiency, effectiveness and productivity across a cohort of fourteen leading pharmaceutical companies, 2018–2022.

Source: https://www.nature.com/articles/d41573-024-00068-6

Cancer Vaccine Renaissance

Cassandra Willyard, *MIT Technology Review*, May 3, 2024 (excerpt)

Last week, Moderna and Merck launched a large clinical trial in the UK of a promising new cancer therapy: a personalized vaccine that targets a specific set of mutations found in each individual's tumor. This study is enrolling patients with melanoma. But the companies have also launched a phase III trial for lung cancer. And earlier this month BioNTech and Genentech announced that a personalized vaccine they developed in collaboration shows promise in pancreatic cancer, which has a notoriously poor survival rate.

Drug developers have been working for decades on vaccines to help the body's immune system fight cancer, without much success. But promising results in the past year suggest that the strategy may be reaching a turning point. Will these therapies finally live up to their promise?

Long before companies leveraged mRNA to fight covid, they were developing mRNA vaccines to combat cancer. BioNTech delivered its first mRNA vaccines to people with treatment-resistant melanoma nearly a decade ago. But when the pandemic hit, development of mRNA vaccines jumped into warp drive. Now dozens of trials are underway to test whether these shots can transform cancer the way they did covid.

Source: https://www.technologyreview.com/2024/05/03/1092026/cancer-vaccines-are-having-a-renaissance/

Recent news has some experts cautiously optimistic. In December, Merck and Moderna announced results from an earlier trial that included 150 people with melanoma who had undergone surgery to have their cancer removed. Doctors administered nine doses of the vaccine over about six months, as well as what's known as an immune checkpoint inhibitor. After three years of follow-up, the combination had cut the risk of recurrence or death by almost half compared with the checkpoint inhibitor alone.

The new results reported by BioNTech and Genentech, from a small trial of 16 patients with pancreatic cancer, are equally exciting. After surgery to remove the cancer, the participants received immunotherapy, followed by the cancer vaccine and a standard chemotherapy regimen. Half of them responded to the vaccine, and three years after treatment, six of those people still had not had a recurrence of their cancer. How many neoantigens do you need to create that sketch? "We don't really know what the magical number is," says Michelle Brown, vice president of individualized neoantigen therapy at Moderna. Moderna's vaccine has 34. "It comes down to what we could fit on the mRNA strand, and it gives us multiple shots to ensure that the immune system is stimulated in the right way," she says. BioNTech is using 20.

There's no guarantee any of these strategies will pan out. Even if they do, success in one type of cancer doesn't automatically mean success against all. Plenty of cancer therapies have shown enormous promise initially, only to fail when they're moved into large clinical trials.

But the burst of renewed interest and activity around cancer vaccines is encouraging. And personalized vaccines might have a shot at succeeding where others have failed. The strategy makes sense for "a lot of different tumor types and a lot of different settings," Brown says. "With this technology, we really have a lot of aspirations."

ADC's Drawing Venture Capital

Brian Gormley, *WSJ*, May 2, 2024 (excerpt)

Biotechnology startups are seeking to improve a type of guided-missile treatment for cancer attracting increased interest from top pharmaceutical companies.

Conventional chemotherapy affects healthy as well as cancerous cells. Antibody-drug conjugates, or ADCs, use antibodies to guide chemotherapy drugs to cancers. The goal is to expose more of the medicine to tumors and less to healthy tissue.

The idea of linking an antibody to a chemotherapy drug is decades old. But improvements in areas such as linker technology have led to greater success in clinical trials and regulatory approvals of several new ADCs recently.

They include Enhertu, sold by drugmakers AstraZeneca and Daiichi Sankyo, which has emerged as a blockbuster treatment for breast and other cancers since its initial U.S. approval in 2019.

Scientific and commercial success has spurred mergers and acquisitions. Pfizer, for example, completed a $43 billion purchase of ADC pioneer Seagen in December.

Last year, the global total value of ADC-focused M&A and partnership activity neared $100 billion, nine times the deal tally in 2019, research and analytics firm Evaluate Pharma, a Norstella company, said in February.

Though the field is beginning to mature, it is still in an exploratory phase as drugmakers test new approaches to building ADCs. Many great ideas are emerging, but uncertainty remains about which will prove most effective, said Mark Lansdell, director of Evaluate consulting and analytics.

ADCs consist of an antibody, a linker and a drug payload. Once in the body, they are designed to bind to antigen markers on tumors, enter cancer cells and release their drug.

Araris Biotech, seeks to soup up ADCs by equipping them with multiple drug payloads. Its initial ADC will carry chemotherapy compounds that work in different ways to hit tumors from different angles, said co-founder and acting CEO Dragan Grabulovski.

One way to extend ADCs' use to more cancers is to identify new antigen markers that distinguish cancer cells from healthy ones. This would give researchers new targets for their ADCs.

San Diego-based MBrace Therapeutics tackles this problem with technology to search for targets that allow ADCs to zero in on tumors, exit the bloodstream and enter cancer cells, according to the company.

Its initial ADC, which entered clinical trials last year, binds to a target antigen called EphA5.

To be sure its treatment is specific for this target, MBrace screened its antibody against more than 6,000 other membrane-associated proteins to be sure it wouldn't bind to them, said CEO Dr. Isan Chen.

Source: https://www.wsj.com/articles/emerging-form-of-targeted-cancer-therapy-draws-venture-capital-29036475

Found: The Dial in The Brain That Controls The Immune System

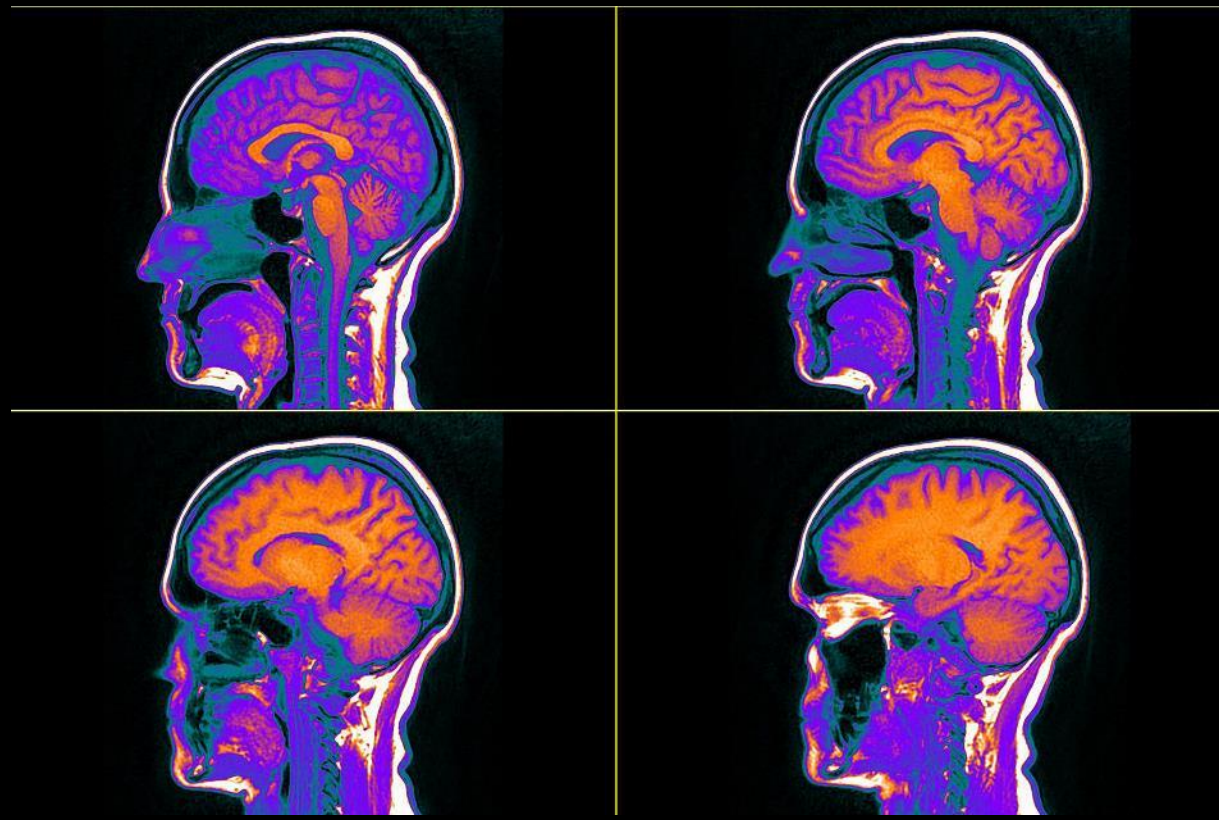
Jin, H., Li, M., Jeong, E. et al., "A body–brain circuit that regulates body inflammatory responses," *Nature*, May 1, 2024

The body-brain axis is emerging as a principal conductor of organismal physiology. It senses and controls organ function, metabolism and nutritional state.

Here, we show that a peripheral immune insult powerfully activates the body-brain axis to regulate immune responses.

We demonstrate that pro- and anti-inflammatory cytokines communicate with distinct populations of vagal neurons to inform the brain of an emerging inflammatory response.

In turn, the brain tightly modulates the course of the peripheral immune response. Genetic silencing of this body-to-brain circuit produced unregulated and out-of-control inflammatory responses. By contrast, activating, rather than silencing, this circuit affords exceptional neural control of immune responses. We used single-cell RNA sequencing, combined with functional imaging, to identify the circuit components of this neuro-immune axis, and showed that its selective manipulation can effectively suppress the pro-inflammatory response while enhancing an anti-inflammatory state. The brain-evoked transformation of the course of an immune response offers new possibilities in the modulation of a wide range of immune disorders, from autoimmune diseases to cytokine storm and shock.



Source https://www.nature.com/articles/s41586-024-07469-y

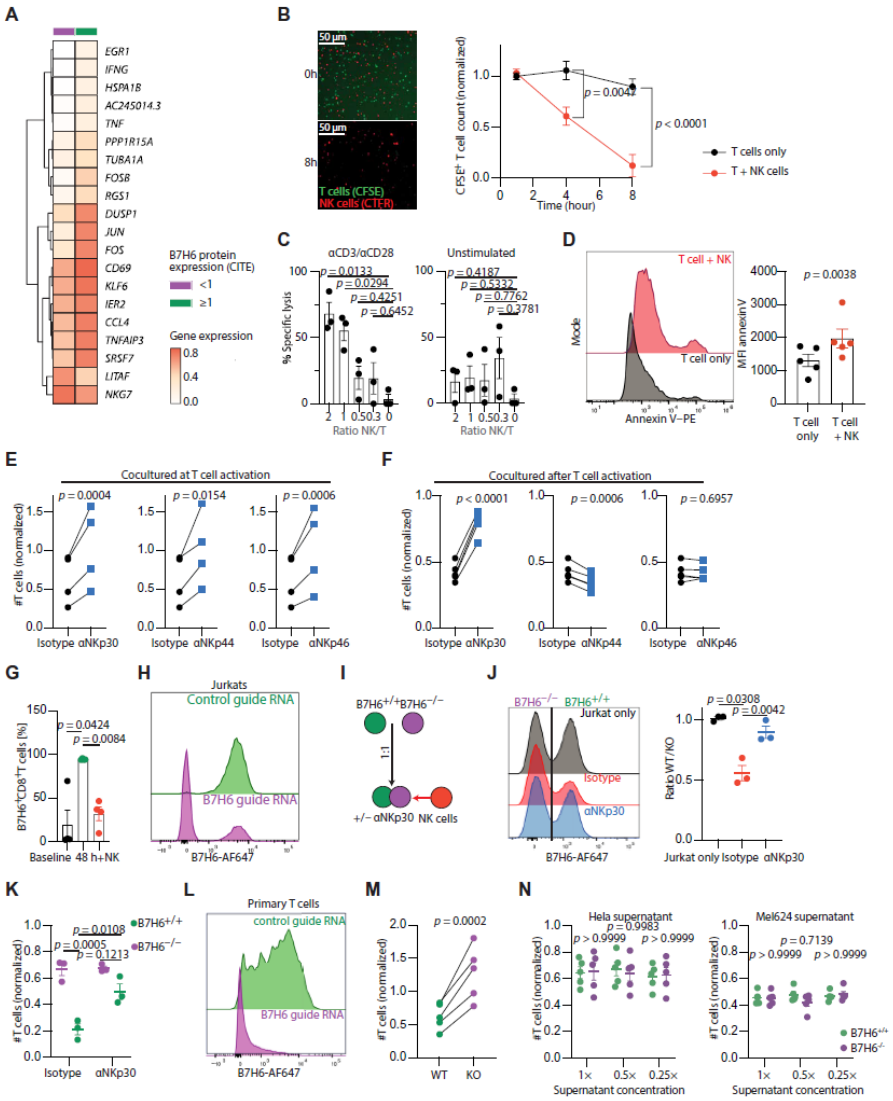
The Immunoglobulin Superfamily Ligand B7H6 Subjects T Cell Responses to NK Cell Surveillance

Kilian, M. et.al., *Science Immunology*, May 3, 2024

Natural killer (NK) cells can eliminate infected or malignant cells, but they are also believed to be capable of killing host immune cells. By screening NK cell ligands on human T cells, Kilian et al. found that the immunoglobulin superfamily ligand B7H6 promotes cytolysis of activated T cells by NK cells. In leukemia-bearing humanized mice, NK cells restricted the antitumor activity of chimeric antigen receptor (CAR) T cells in a B7H6-dependent manner. A higher ratio of intratumoral NK to T cells was associated with poor response to immune checkpoint inhibition in a cohort of patients with esophageal cancer. These findings demonstrate that B7H6 recognition by NK cells can restrict human antitumor T cell responses.

Source: https://www.science.org/doi/10.1126/sciimmunol.adj7970

Fig. 3. Activated T cells are eliminated by NK cells via NKp30-B7H6 recognition.

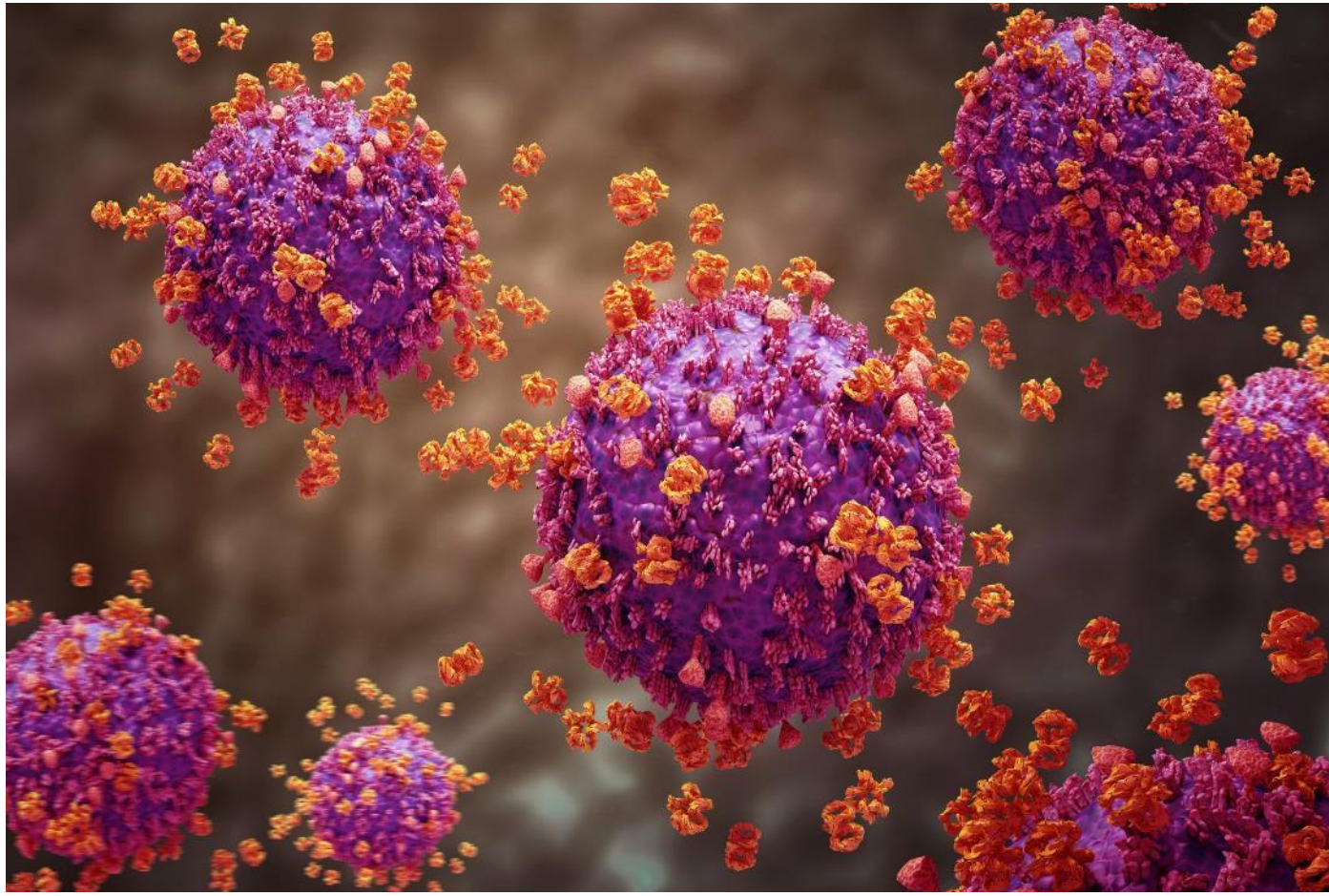


(A) Heatmap showing top 20 differentially expressed genes between B7H6hi B7H6 CITE-seq expression ≥ 1 versus B7H6low (B7H6 CITE-seq expression < 1) T cells from GBM patient samples (n = 4). Significant fold changes after multiple hypothesis correction. (B) Live cell imaging of human anti-CD3/CD28–stimulated CFSE labeled T cells (green) and CellTrace far red (CT FR) labeled autologous NK cells (red) over a time span of 8 hours. Left: Representative image after 0 and 8 hours of coculture. Right: Quantification, n = 3 healthy donors. T cell count normalized T = 0. (C) 51Cr-release assay with human peripheral T cells stimulated with anti-CD3/C28 beads or unstimulated cocultured with autologous NK cells measured after 8 hours. n =3 healthy donors. (D) Left: AnnexinV staining of activated primary T cells cocultured with autologous NK cells. T cells were gated for single, live, CD3+ cells. Right: Quantification, n = 5 healthy donors. (E and F) Coculture of activated T cells with autologous NK cells with NKp-blocking antibodies, analyzed using flow cytometry after 72 hours. T cells were activated with anti-CD3/CD28 beads at the time (E) or 3 days before (F) of coculture. Normalized to T cells only. (G) B7H6 expression on CD8+ T cells at baseline, 48 hours after activation and 24 hours after coculture with autologous NK cells. n = 4 healthy donors.

Progress on Universal Flu Vaccine

Z Luo, et.al., "Vaccination with antigenically complex hemagglutinin mixtures confers broad protection from influenza disease," *Science Translational Medicine,* May 1, 2024

Current seasonal influenza virus vaccines induce responses primarily against immunodominant but highly plastic epitopes in the globular head of the hemagglutinin (HA) glycoprotein. Because of viral antigenic drift at these sites, vaccines need to be updated and readministered annually. To increase the breadth of influenza vaccine–mediated protection, we developed an antigenically complex mixture of recombinant HAs designed to redirect immune responses to more conserved domains of the protein. Vaccine-induced antibodies were disproportionally redistributed to the more conserved stalk of the HA without hindering, and in some cases improving, antibody responses against the head domain. These improved responses led to increased protection against homologous and heterologous viral challenges in both mice and ferrets compared with conventional vaccine approaches. Thus, antigenically complex protein mixtures can at least partially overcome HA head domain antigenic immunodominance and may represent a step toward a more universal influenza vaccine.



Source: https://www.science.org/doi/10.1126/scitranslmed.adj4685

Potential Concern with CDK4/6 Inhibitors

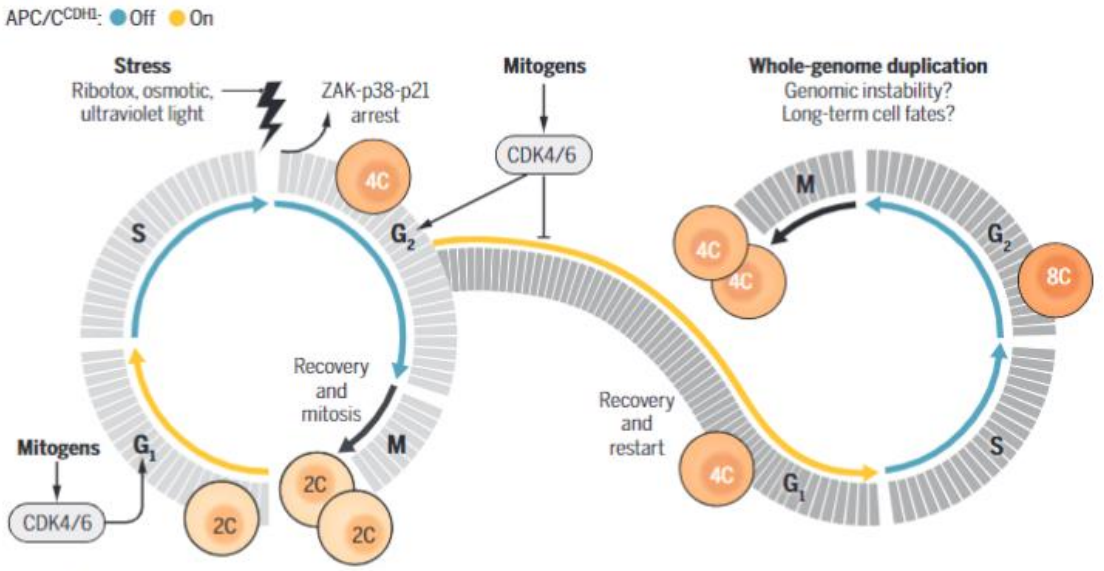
Bart Westendorp, "A Reverse Brake for the Cell Cycle," *Science*, May 3 (excerpt)

The work by McKenney et al. complements a recent study showing that in the absence of mitogenic signaling and CDK4/6, a 2-hour delay in progression toward mitosis can cause premature reactivation of APC/CCDH1 during G2 phase. In addition, inhibition of CDK2 was shown to be rapidly compensated by CDK4/6 to sustain S-phase progression. Together with these studies, the work by McKenney et al. demonstrates that CDK4/6 activity during S phase and G2 phase can compensate for loss of other CDKs to sustain cell cycle progression and prevent slipping back toward a second S phase.

Whole-genome doubling is a hallmark event in the development of cancer, which can lead to chromosomal instability and worsen prognosis across cancer types. p53 is a crucial gatekeeper of genomic stability that blocks proliferation after whole-genome doubling. Finding that SAPK signaling and CDK4/6 inhibition can prime cells to undergo whole-genome doubling im-plies a risk of clonal outgrowth of tetraploid and genomically unstable cells, especially in p53-mutant cancer. Given that CDK4/6 inhibition is now standard-of-care therapy for estrogen receptor–positive breast cancer, it is important to study whether these inhibitors may promote unwanted whole-genome doubling events and genomic instability in patients. To answer such questions, innovative approaches will be needed for *in vivo* tracking of the long-term fates and clonal outgrowth of tetraploid cells arising from the G2 phases in which CDK4/6 activity is disrupted.

A reverse brake to prevent whole-genome doubling

Mitogenic signaling is crucial to sustain a delayed G_2 phase. Various types of transient stress can cause such delay. If CDK4/6 are inactivated during G_2, such delay results in a restart of the cell cycle and whole-genome duplication. Chromosome content: 2C, a normal diploid cell; 4C, a tetraploid cell; 8C, an octoploid cell.



APC/C^CDH1, anaphase-promoting complex or cyclosome-CDH1; CDK, cyclin-dependent kinase; ZAK, leucine-zipper and sterile-alpha motif kinase.

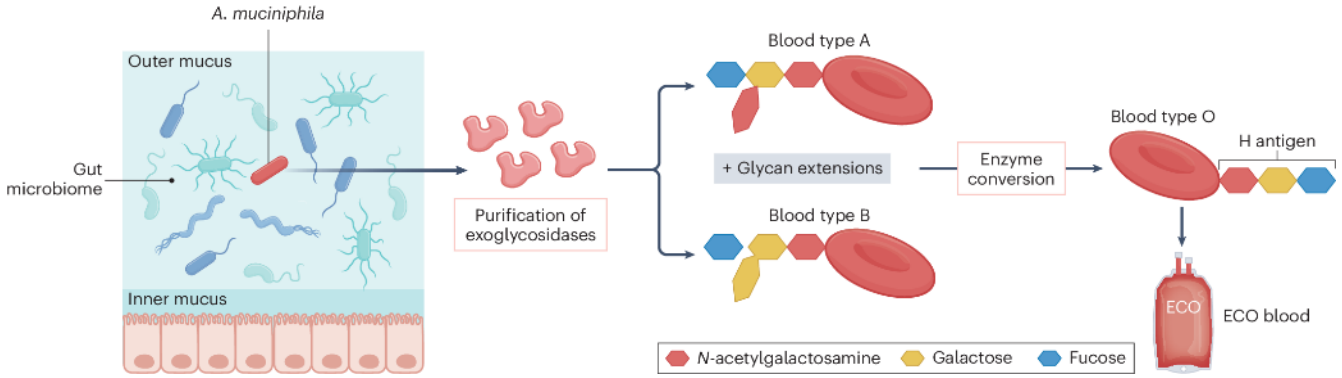
512 3 MAY 2024 • VOL 384 ISSUE 6695

Source: https://www.science.org/doi/epdf/10.1126/science.adp1866

Akkermansia Muciniphila Exoglycosidases Target Extended Blood Group Antigens to Generate ABO-Universal Blood

Jensen, M., Stenfelt, L., Ricci Hagman, J. et al. Akkermansia muciniphila exoglycosidases target extended blood group antigens to generate ABO-universal blood. *Nat Microbiol* (2024).

"Matching donor and recipient blood groups based on red blood cell (RBC) surface ABO glycans and antibodies in plasma is crucial to avoid potentially fatal reactions during transfusions. Enzymatic conversion of RBC glycans to the universal group O is an attractive solution to simplify blood logistics and prevent ABO-mismatched transfusions. The gut symbiont *Akkermansia muciniphila* can degrade mucin O-glycans including ABO epitopes. Here we biochemically evaluated 23 Akkermansia glycosyl hydrolases and identified exoglycosidase combinations which efficiently transformed both A and B antigens and four of their carbohydrate extensions. Enzymatic removal of canonical and extended ABO antigens on RBCs significantly improved compatibility with group O plasmas, compared to conversion of A or B antigens alone. Finally, structural analyses of two B-converting enzymes identified a previously unknown putative carbohydrate-binding module. This study demonstrates the potential utility of mucin-degrading gut bacteria as valuable sources of enzymes for production of universal blood for transfusions."



These exoglycosidases remove specific sugars from blood group A and B antigens, converting them to H antigen on RBCs to produce a more universal RBC phenotype known as enzymatically converted group O or ECO-RBCs.

Source: https://www.nature.com/articles/s41564-024-01682-1/

Disclosure

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