Biopharmaceutical Sector

Weekly Update – April 29, 2024

STIFEL | Healthcare

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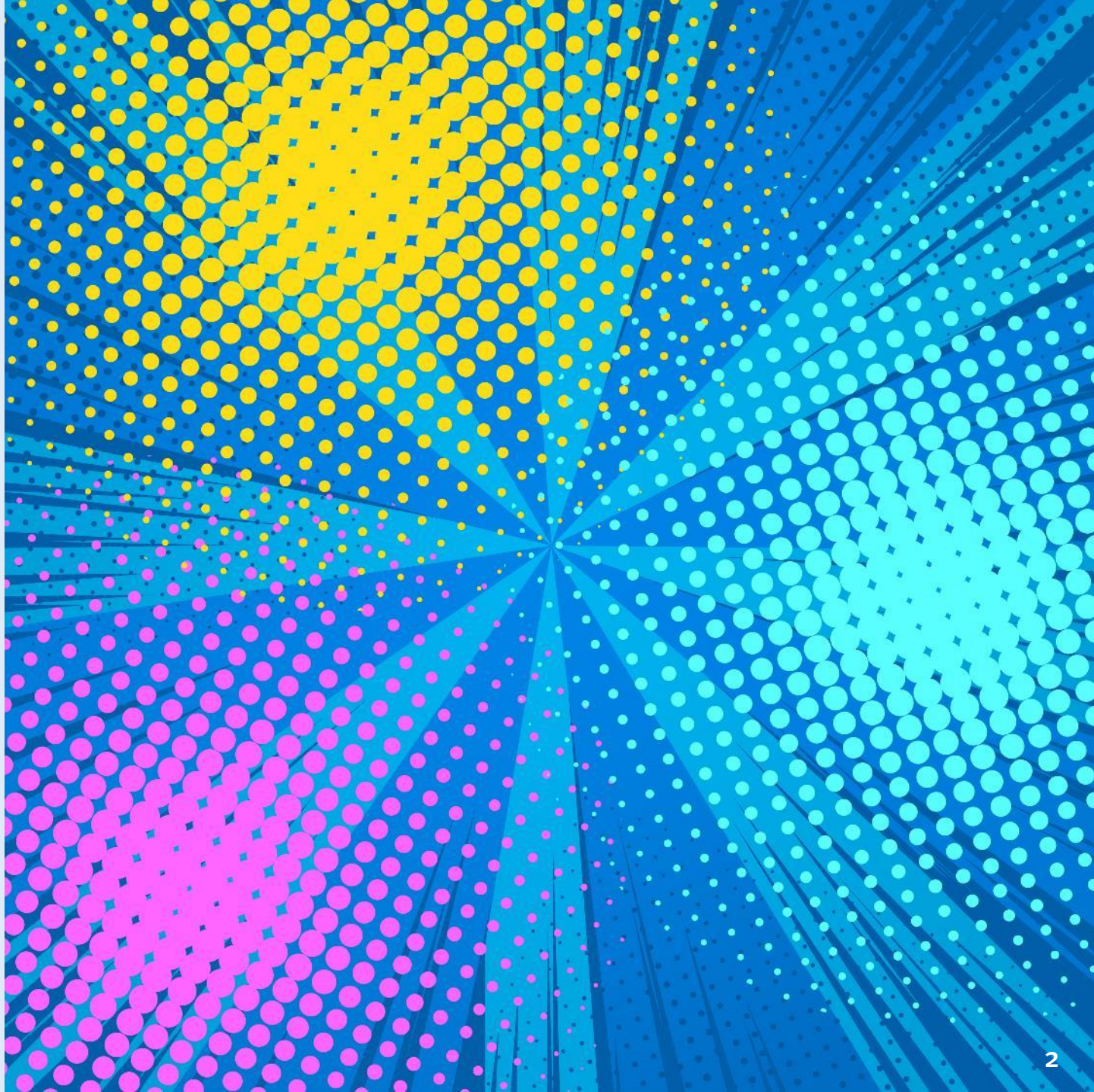

Accessing Past Issues

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

April 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)
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March 11, 2024 (IRA, Immunology)
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Feb 26, 2024 (Biotech Strategy)
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October 23, 2023 (ESMO Review)
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June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

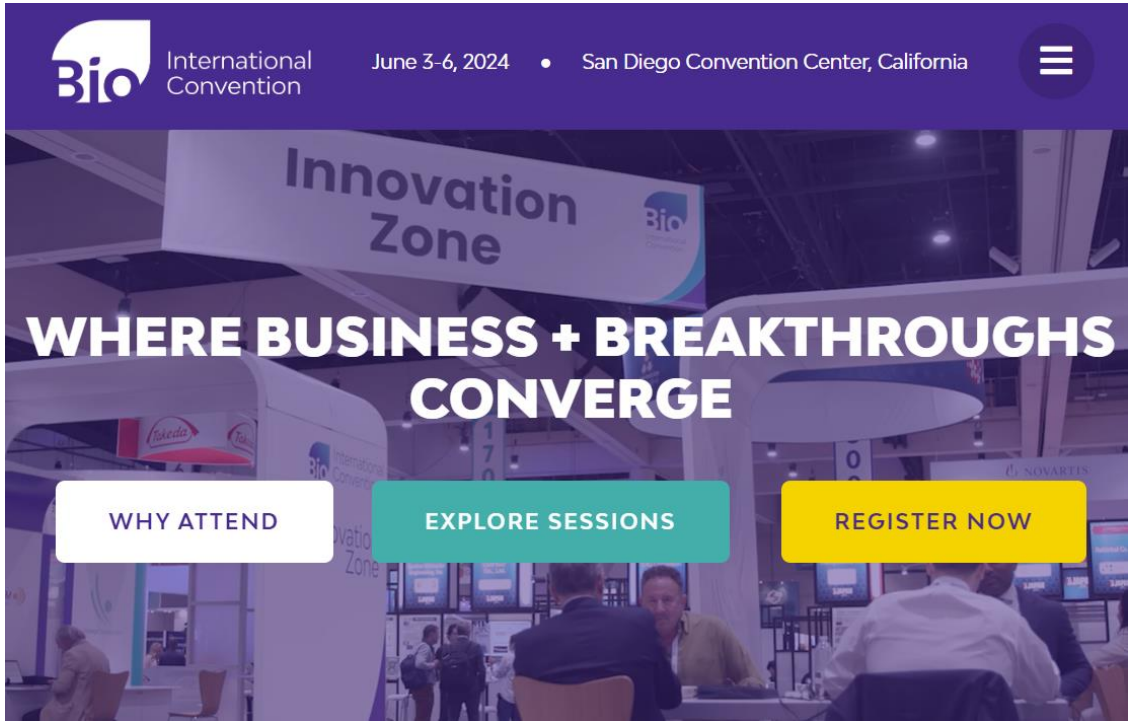
Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on April 26, 2024.

The next event will be on May 3, 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

PCE Inflation Was 0.3% in March (3.6% Annualized)

This was the expected PCE inflation rate forecast by economists.

Jeffry Bartash, *Marketwatch*, April 26, 2024 (excerpt)

Prices in the U.S. jumped again in March based on the Federal Reserve's preferred PCE index, signaling that progress on reducing inflation has stalled.

The PCE index rose 0.3% last month, the government said Friday. Economists polled by The Wall Street Journal had forecast a 0.3% gain.

The more closely followed core rate that strips out food and energy also increased 0.3%. The core index is viewed as a better predictor of future inflation.

The inflation readings in February and January, meanwhile, were revised to show slightly bigger increases than previously reported. But the changes were small enough that the prior estimates for headline and core PCE were basically unchanged due to rounding.

The yearly rate of inflation, meanwhile, climbed to 2.7% from 2.5%.

The rate of core inflation in the 12 months ended in March was unchanged at 2.8%.

The latest reading on inflation has sown further doubts about the Fed cutting U.S. interest rates anytime soon.

Source: https://www.marketwatch.com/livecoverage/march-pce-report-hot-inflation-reading-forecasted-after-gdp-data/card/prices-rises-sharply-again-pce-shows-and-signals-progress-on-slowing-inflation-stalls-ybnTskvnrmraHcqNYnbW

The Dream of Fed Rate Cuts Is Slipping Away

Nick Timiraos, *Wall Street Journal*, April 25, 2024 (excerpt)

Thursday's report on economic activity delivered the latest in a series of rude awakenings to investors and Federal Reserve policymakers who have held their breath in anticipation that lower inflation would allow interest-rate cuts to begin in earnest this summer.

Instead, Commerce Department data showed that, for the third straight month, inflation was proving stickier than expected after an immaculate cooling in the second half of last year.

Individual readings on growth and prices so far this year haven't been enough on their own to dramatically change the outlook for the Fed. But the cumulative effect of those serial disappointments has been notable.

In particular, inflation data has consistently been firmer than expected, with recent months getting revised somewhat higher in subsequent reports. This trend has led investors and Fed officials to rethink whether rate cuts will be appropriate this year.

"I always say, one month is no months, but three months—that's at least one real month," said Chicago Fed President Austan Goolsbee in an interview last week. "Now that we're seeing—after six, seven months of very strong improvement and close-to-2% inflation—something that's well above that, we have to recalibrate, and we have to wait and see."

The Fed targets 2% inflation over time. Officials have signaled since late last year they could begin lowering interest rates on the assumption that price growth would slow to around 2.5% later this year and reach 2% after that. The core PCE index rose at a 2% annualized rate in both the third and fourth quarters of last year, buoying optimism that the Fed might have finished its inflation battle without the hand-to-hand combat for which senior officials had braced themselves.

The Fed has been especially focused on monthly inflation readings in part because central bank economists and the economics profession more broadly have struggled to forecast inflation since the pandemic. Many failed to anticipate just how much it would rise in 2021 and 2022, and then they likewise were surprised by how quickly it appeared to fall last year despite solid hiring and spending.

Source: https://www.wsj.com/economy/central-banking/the-dream-of-fed-rate-cuts-is-slipping-away-55903ca5

Fed Rate-Cut Debate Shifts From When Toward If on Inflation Data

Steve Matthews, *Bloomberg*, April 28, 2024 (excerpt)

The debate for the Federal Reserve is beginning to shift from how many times to cut interest rates this year to whether to cut them at all in 2024.

Policymakers are widely expected to hold rates steady at a more than two-decade high at the conclusion of their meeting Wednesday, so much of the focus will be on any pivot in the tone of the post-meeting statement and Chair Jerome Powell's press conference.

Officials are also expected to announce a near-term slowing in the reduction of the Fed's $7.4 trillion balance sheet — a move that's independent from any decision on interest-rate timing. Policymakers have voiced the need for a cautious approach to further runoff, hoping to avoid market turmoil.

While Fed leadership has suggested a delay for rate reductions, it's starting to look like a real possibility policymakers may not cut at all this year.

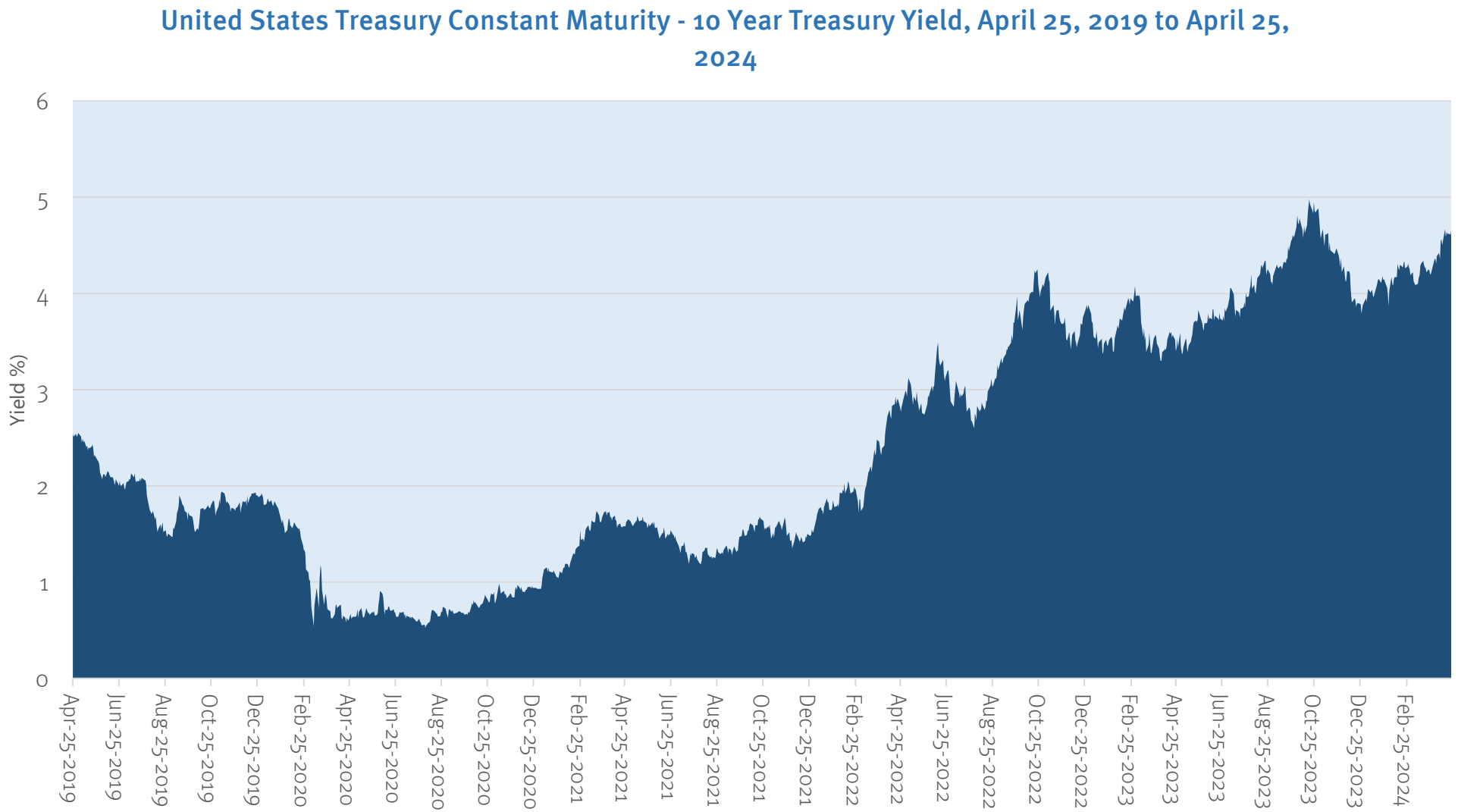
"If the inflation numbers just don't improve enough, then they'll stay on hold indefinitely," said Dean Maki, chief economist at Point72 and a former Fed economist. "We have had a setback in the first quarter, but I don't think the center of the committee thinks of it as a permanent setback. They think it's a bumpy road still."

Powell's colleagues on the Federal Open Market Committee see no urgency to lower rates.

Governor Michelle Bowman said she sees "upside risks" to inflation, and Minneapolis Fed President Neel Kashkari floated the possibility of having no rate cuts this year. The Atlanta Fed's Raphael Bostic, meanwhile, said he could favor hiking them if inflation gets worse.

Source: https://www.bloomberg.com/news/articles/2024-04-28/fed-rate-cut-debate-shifts-from-when-toward-if-on-inflation-data

U.S. Treasury Yield Rising This Year



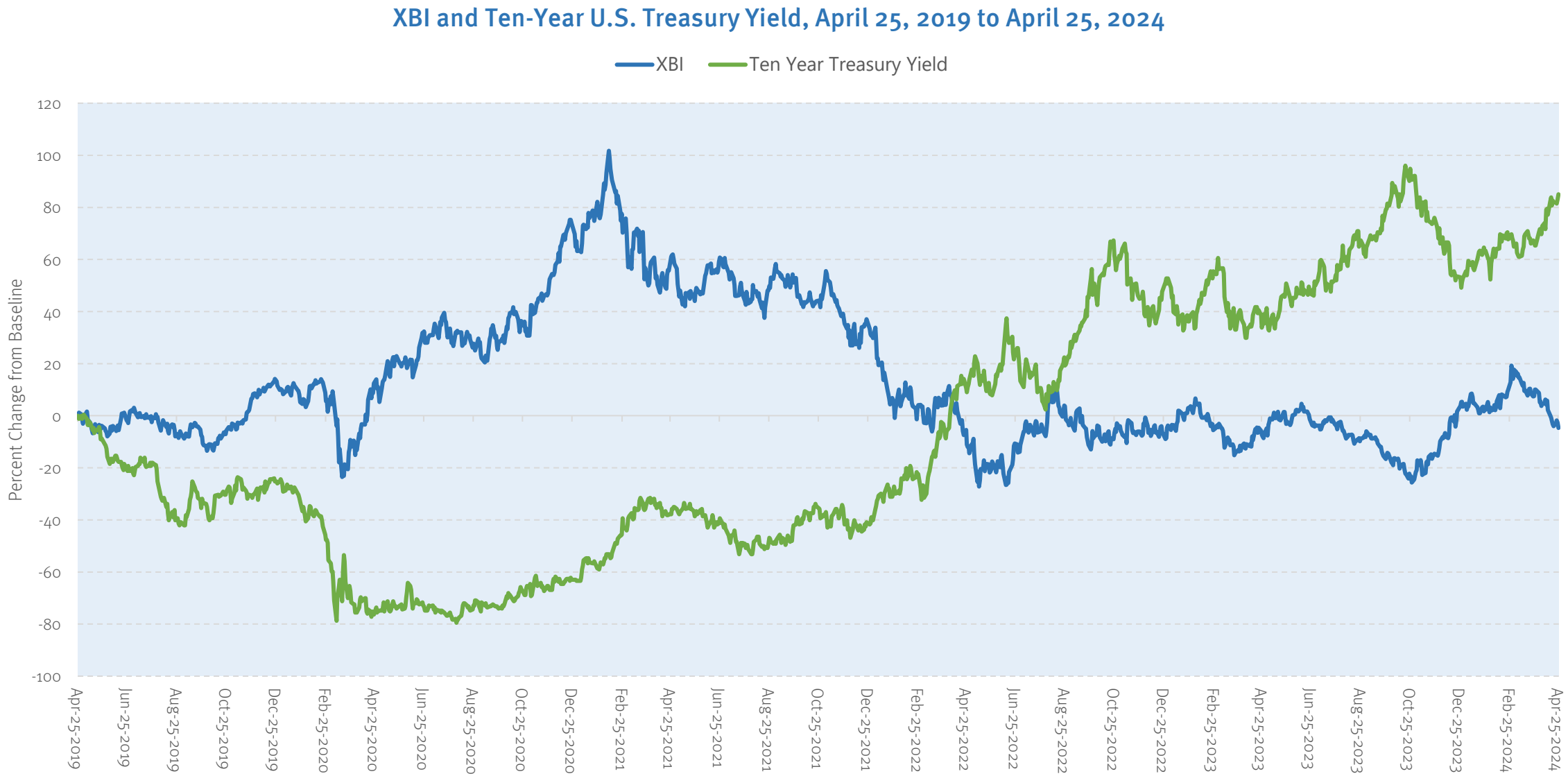
The 10-year Treasury bond started the year with a 3.88% yield, and it is now around 4.66%.

That's a huge rise and it's not been good for the biotech market at all.

This trend continued last week.

Source: S&P CapitalIQ

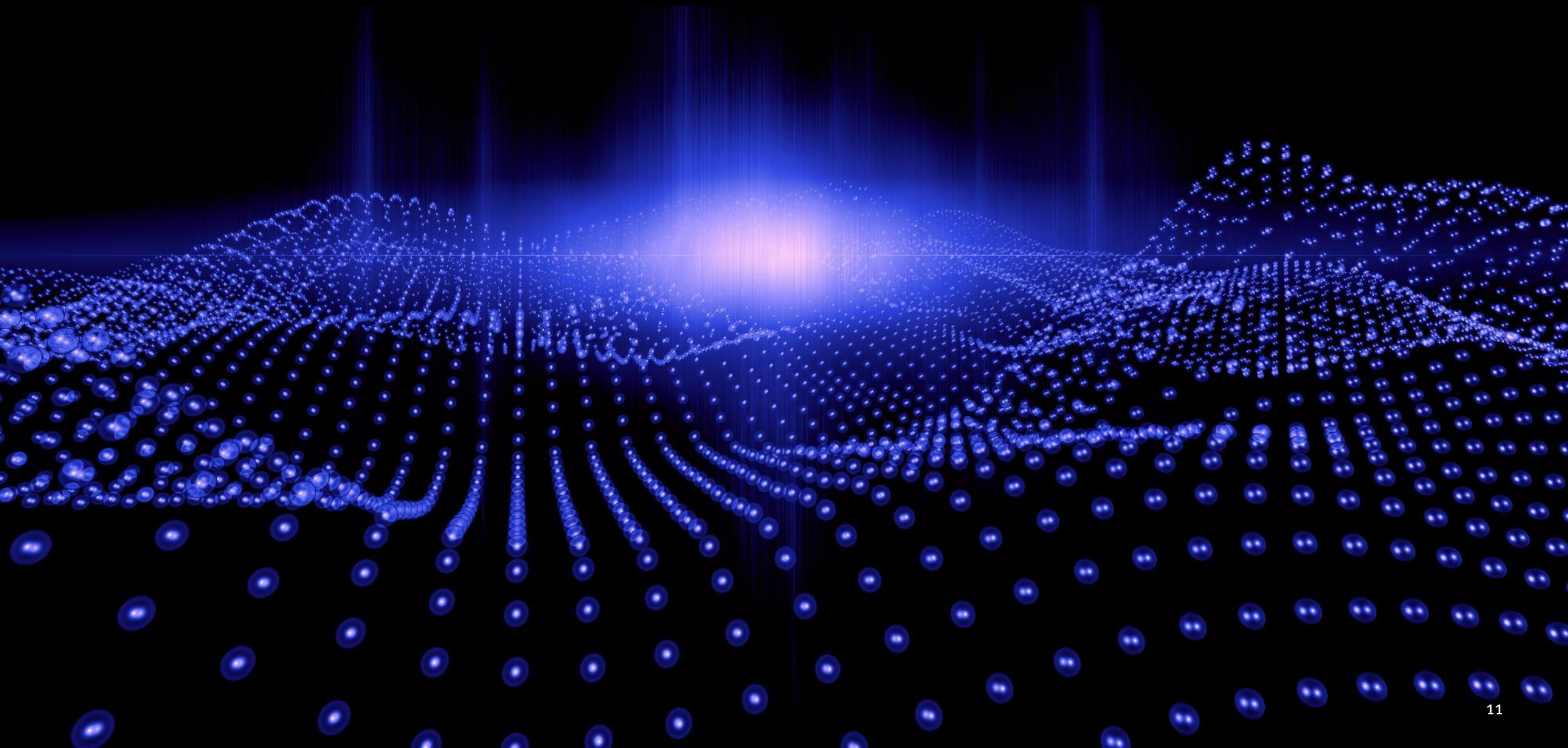
As Treasury Yields Rise, the Biotech Market Has Fallen



Source: S&P CapitalIQ

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

Biopharma Market Update



The XBI Closed at 83.49 Last Friday (April 26), Up 0.7% for the week

The XBI is down 5% since the year began. Last week saw Treasury yields continue to rise but a bit of market relief after the Friday's PCE inflation number wasn't as bad as feared. The S&P 500 did well last week – also in relief to a better than feared inflation number.

Biotech Stocks Up Slightly Last Week

Return: April 20 to Apr 26, 2024

Nasdaq Biotech Index: +1.7%
Arca XBI ETF: +0.8%
Stifel Global Biotech EV (adjusted): +3.2%*
S&P 500: +2.7%

Return: Dec 29, 2023 to Apr 19, 2024 (YTD)

Nasdaq Biotech Index: -5.4%
Arca XBI ETF: -6.5%
Stifel Global Biotech EV (adjusted): +14.7%*
S&P 500: +6.9%

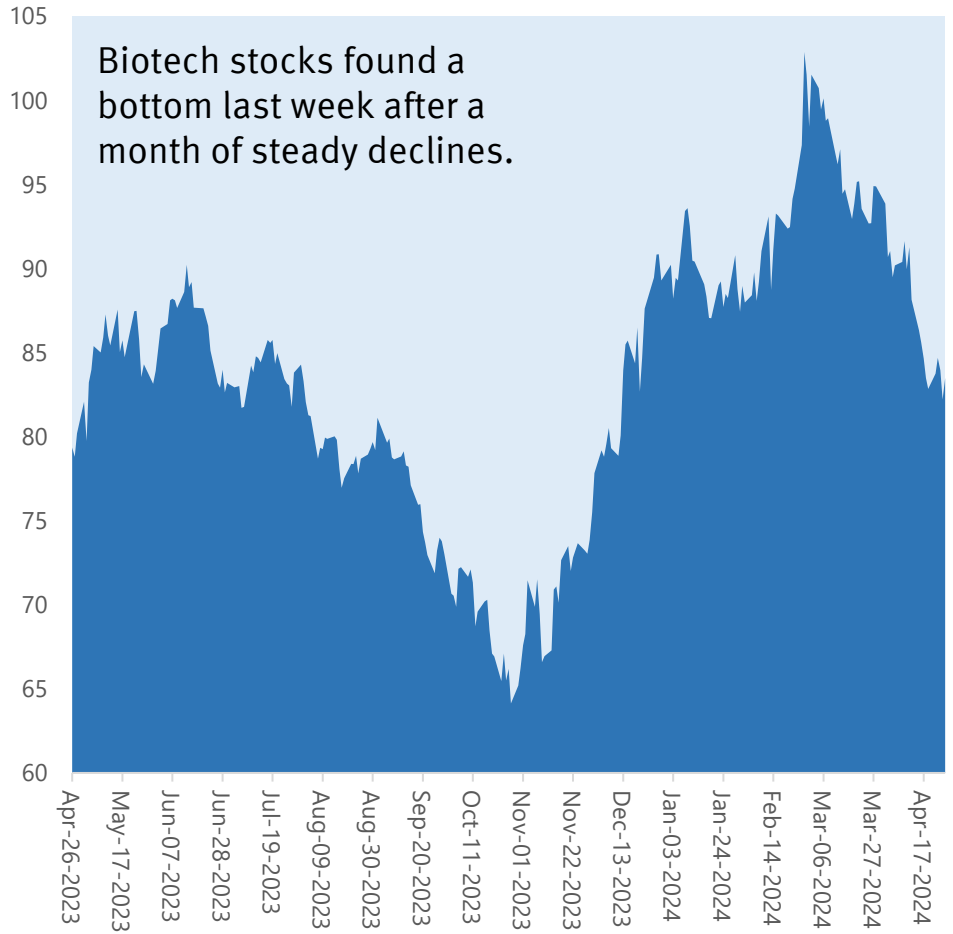
VIX Down Big

Jan 20, 2023: 19.9%
July 21, 2023: 13.6%
Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Feb 23, 2024: 13.5%
Mar 29, 2024: 13.0%
Apr 5, 2024: 18.7%
Apr 26, 2024: 15.0%

10-Year Treasury Yield Up

Jan 20, 2023: 3.48%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Feb 23, 2024: 4.26%
Mar 29, 2024: 4.20%
Apr 5, 2024: 4.39%
Apr 26, 2024: 4.66%

XBI, April 26, 2023 to Apr 26, 2024



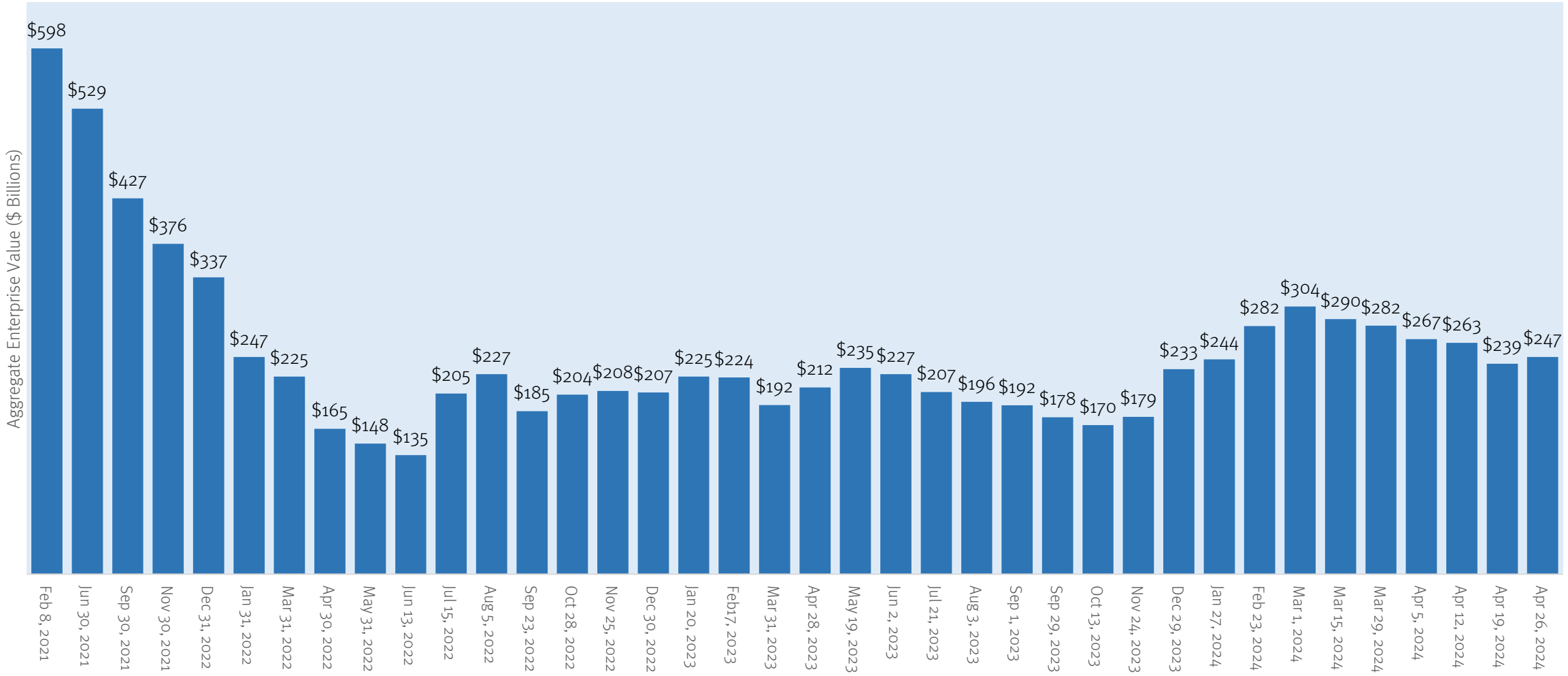
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Up 3.2% Last Week

Biotech stocks bounced back last week after seven straight weeks of declines. Biotech stocks are up 14.7% for the year on an exit adjusted basis.

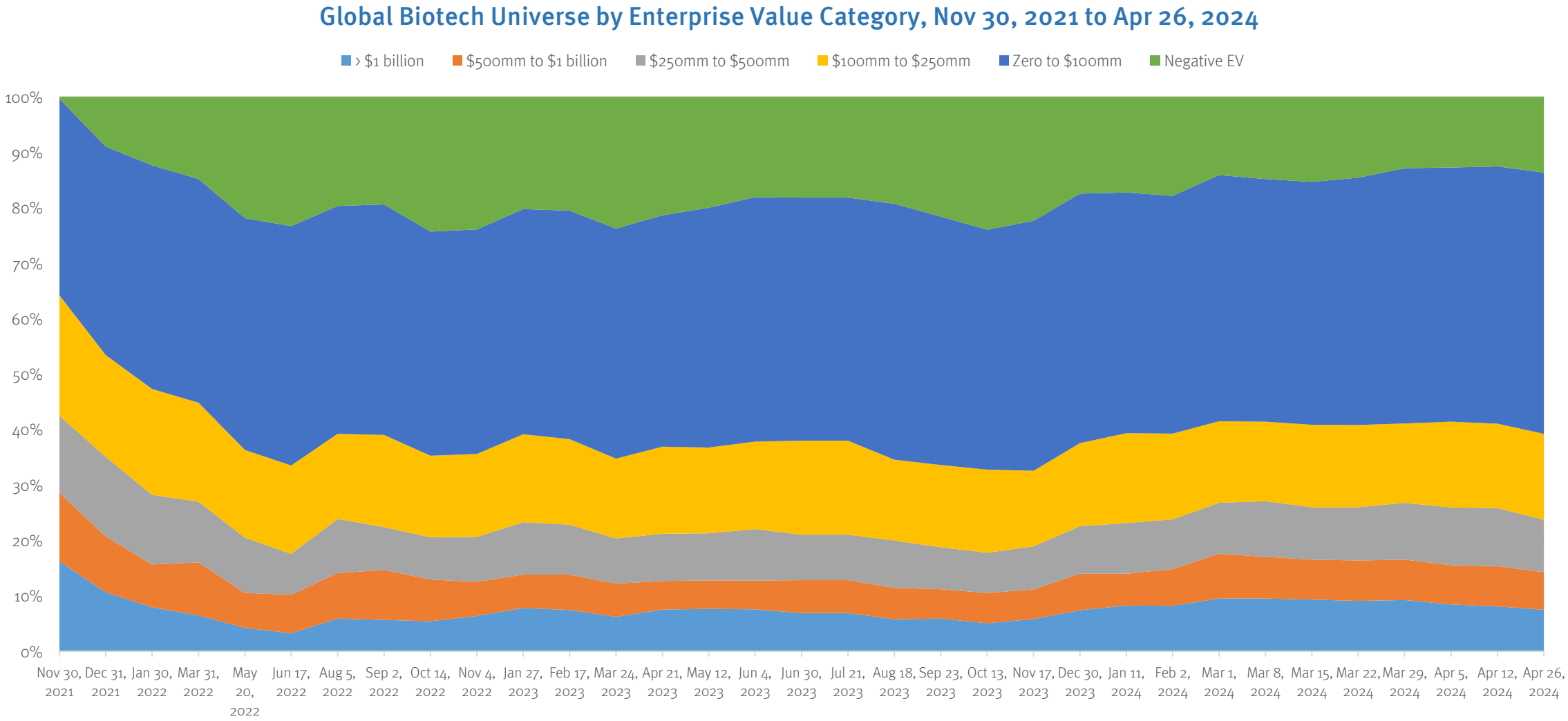
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Apr 26, 2024 ($ Billions)



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 zero to $250mm enterprise value has grown substantially in the last two weeks.



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

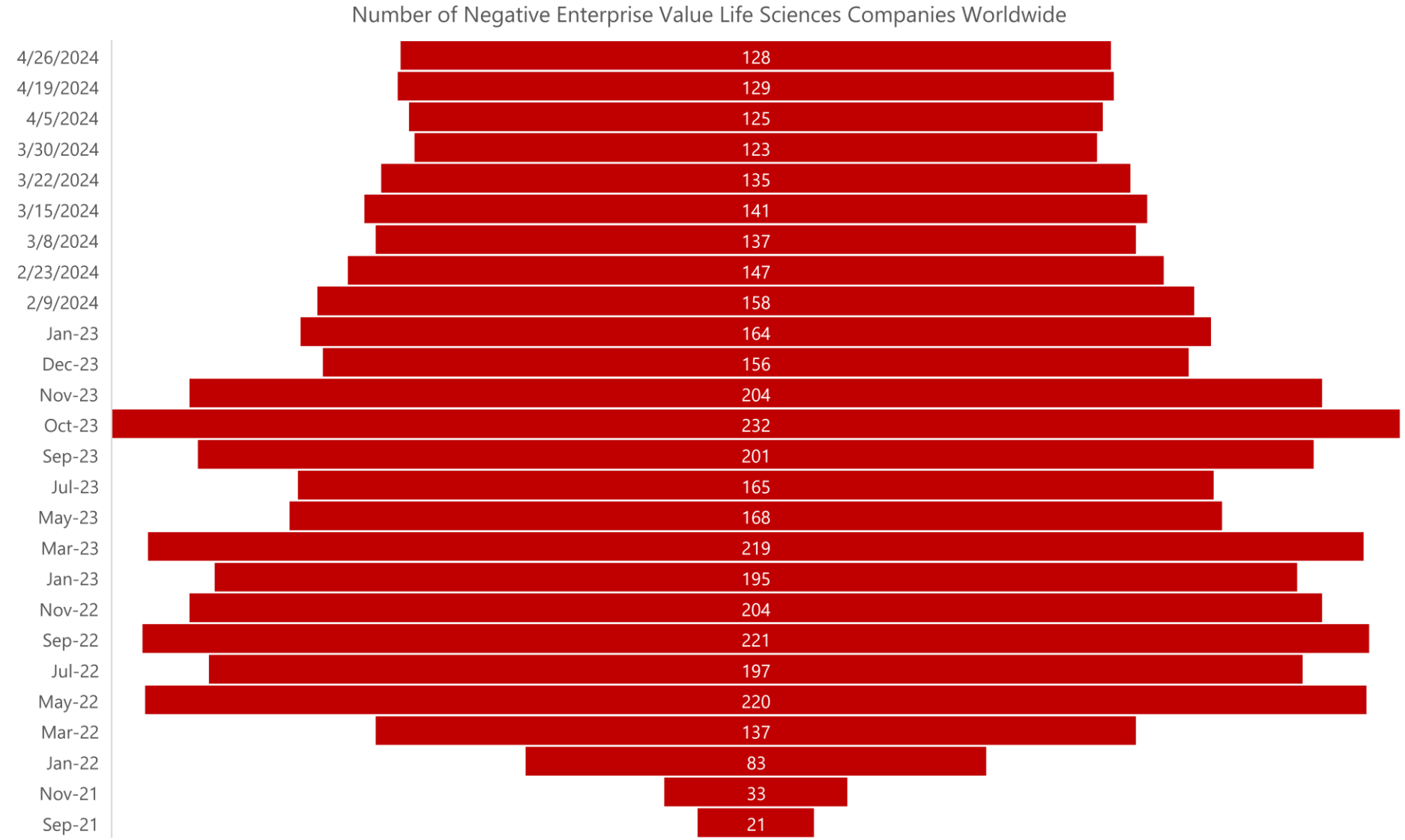
Life Sciences Sector Total Value Up 2.2% Last Week

All subsectors of the life sciences were up last week with best relative performance from API, HCIT and life science tools.

Sector	Firm Count	Enterprise Value (Apr 25, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$81,046	5.2%	4.1%	1.4%
Biotech	795	$237,345	3.2%	-12.1%	-5.1%
CDMO	39	$144,070	2.2%	-6.0%	-20.0%
Diagnostics	81	$260,302	2.3%	-6.7%	-4.9%
OTC	30	$26,870	1.7%	-4.8%	-9.0%
Pharma	716	$6,065,755	2.0%	-3.5%	4.4%
Services	38	$186,218	1.7%	-5.9%	-3.4%
Tools	51	$691,069	3.8%	-4.8%	-2.4%
Devices	181	$1,655,230	2.2%	-4.4%	-3.2%
HCIT	10	$17,565	3.3%	-10.9%	-33.8%
Total	**2022**	**$9,366,470**	**2.2%**	**-4.1%**	**2.0%**

Source: CapitalIQ

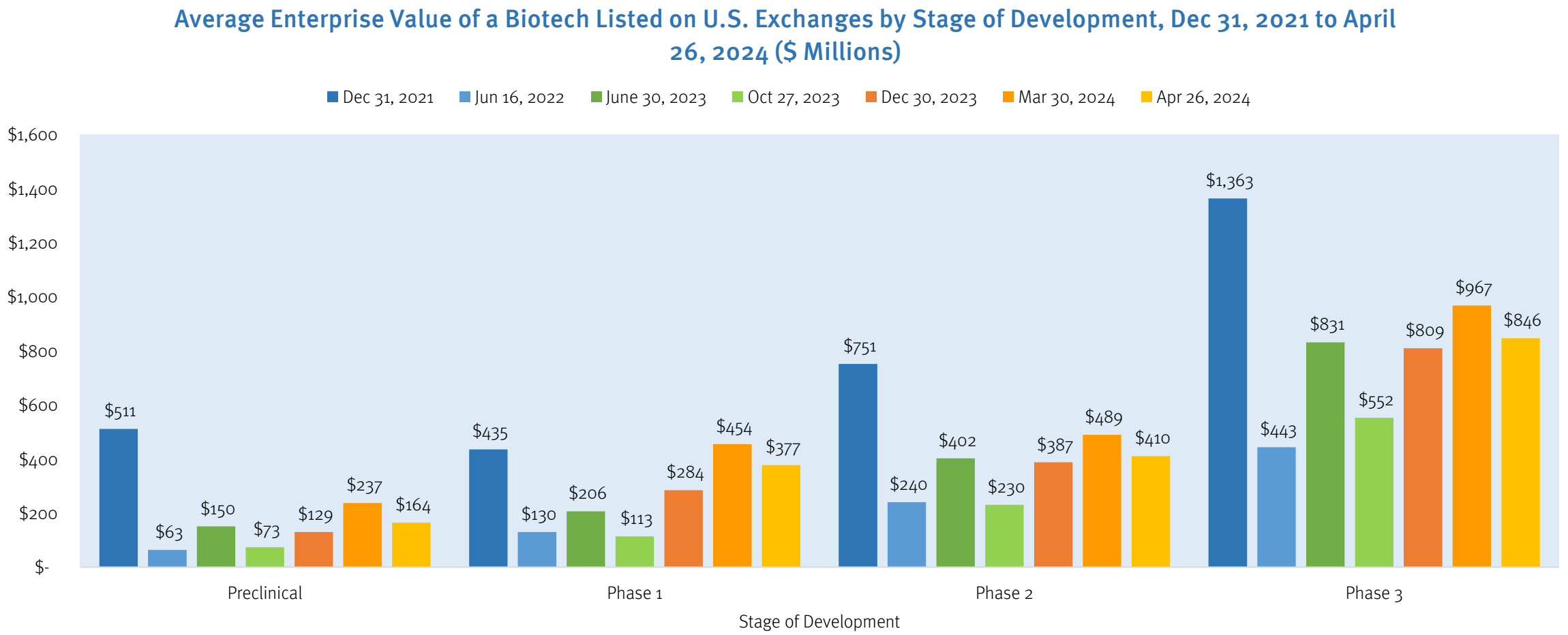
Number of Negative Enterprise Value Life Sciences Companies Was Flat Last Week



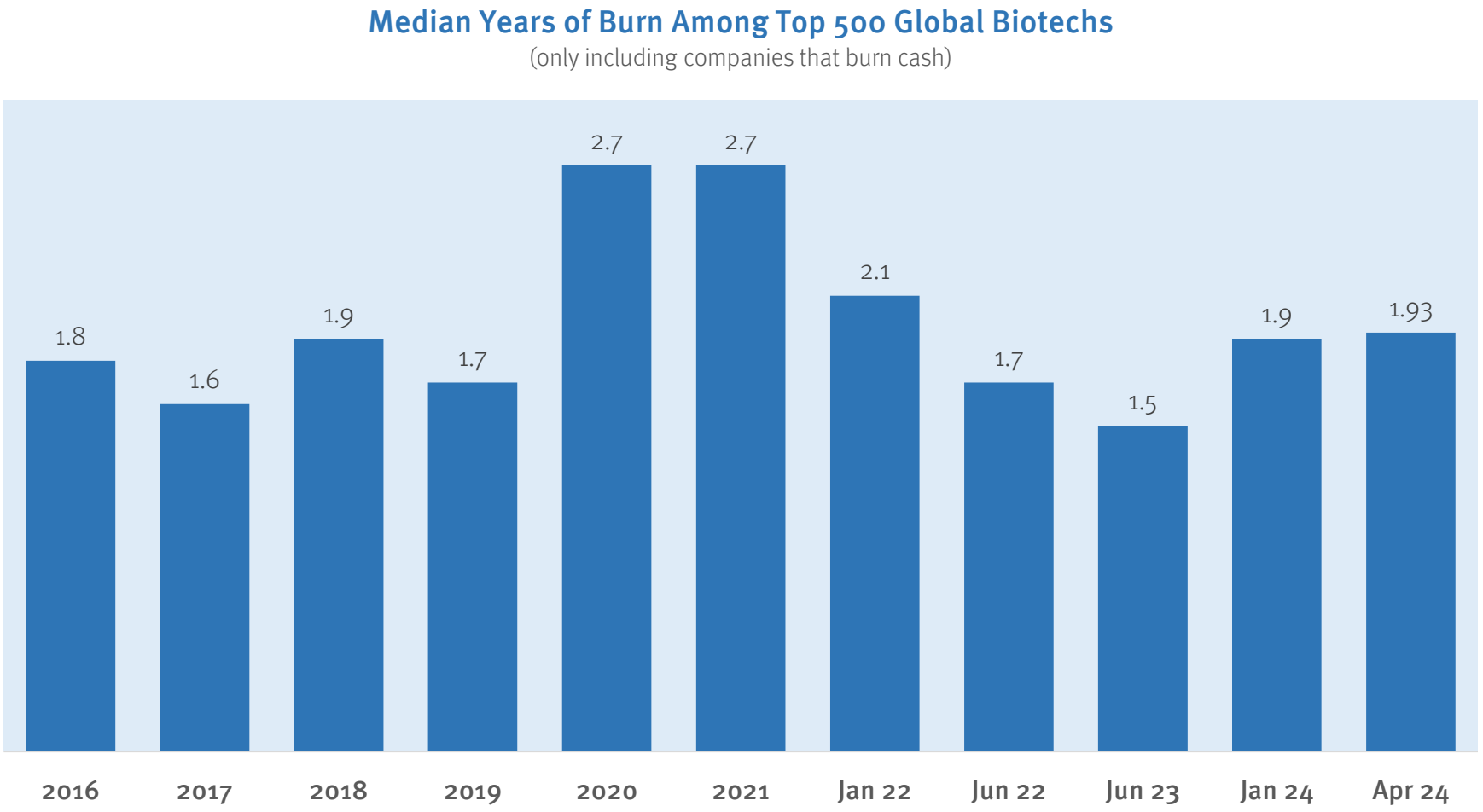
Source: CapitalIQ

Biotech Valuations Down in the Most in Last Month for Early-Stage Biotech.

The average preclinical biotech gave up 31% of its value in the last month. In contrast, the average Phase 3 biotech only lost 15% of its value.



Median Years of Burn of Top 500 Public Biotechs Flat Through Q1 2024



This page looks at the top 500 biotechs by market cap.*

Cash positions for quarter ended Dec 30, 2023 have now been fully reported and some cash positions for Q1 are in.

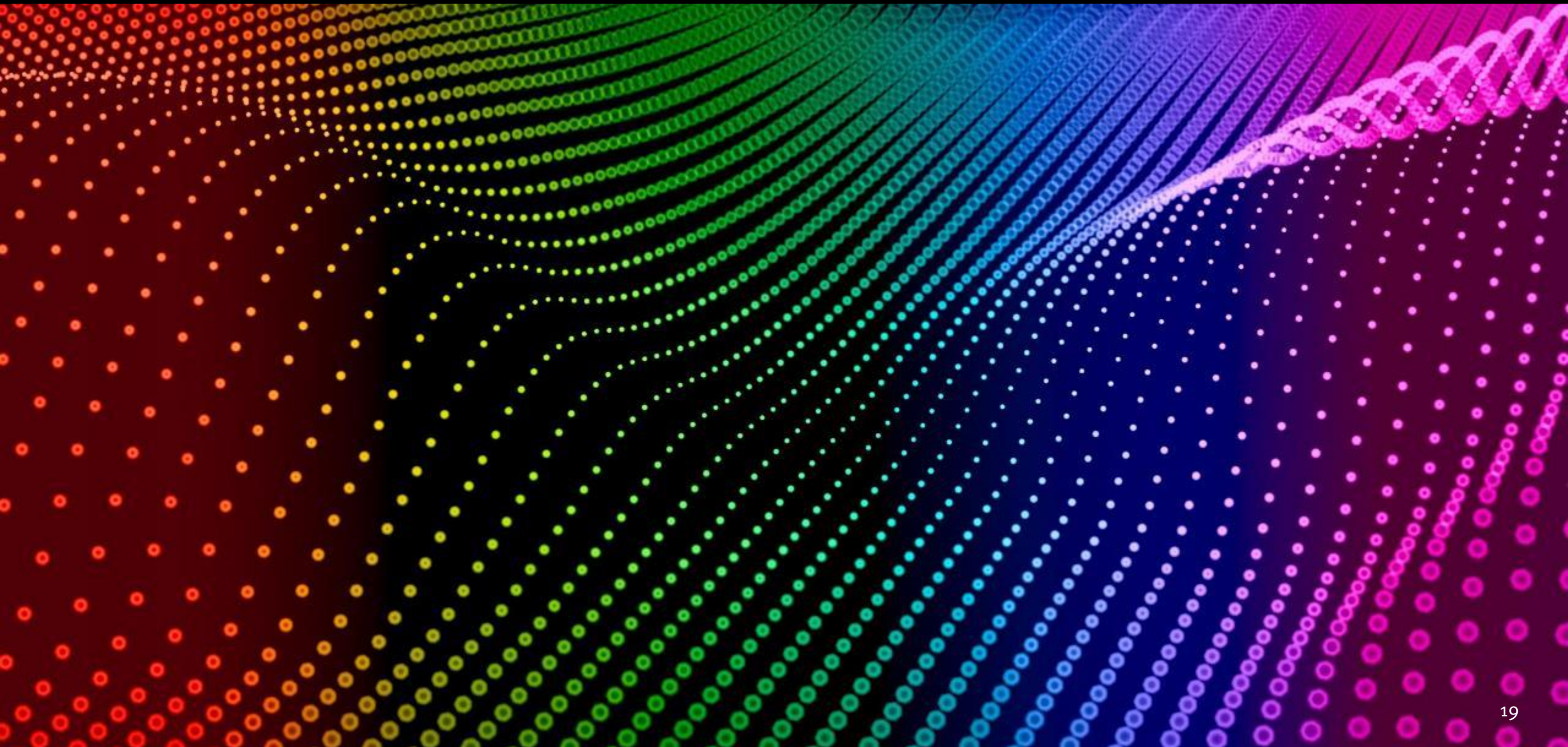
The median Top 500 biotech company at 2023 year-end had 1.9 years of burn on its balance sheet.

By the end of the first quarter of 2024 the median years of burn at risen to 1.93 years.

Basically unchanged. We'll update this again when all the quarterly data are in.

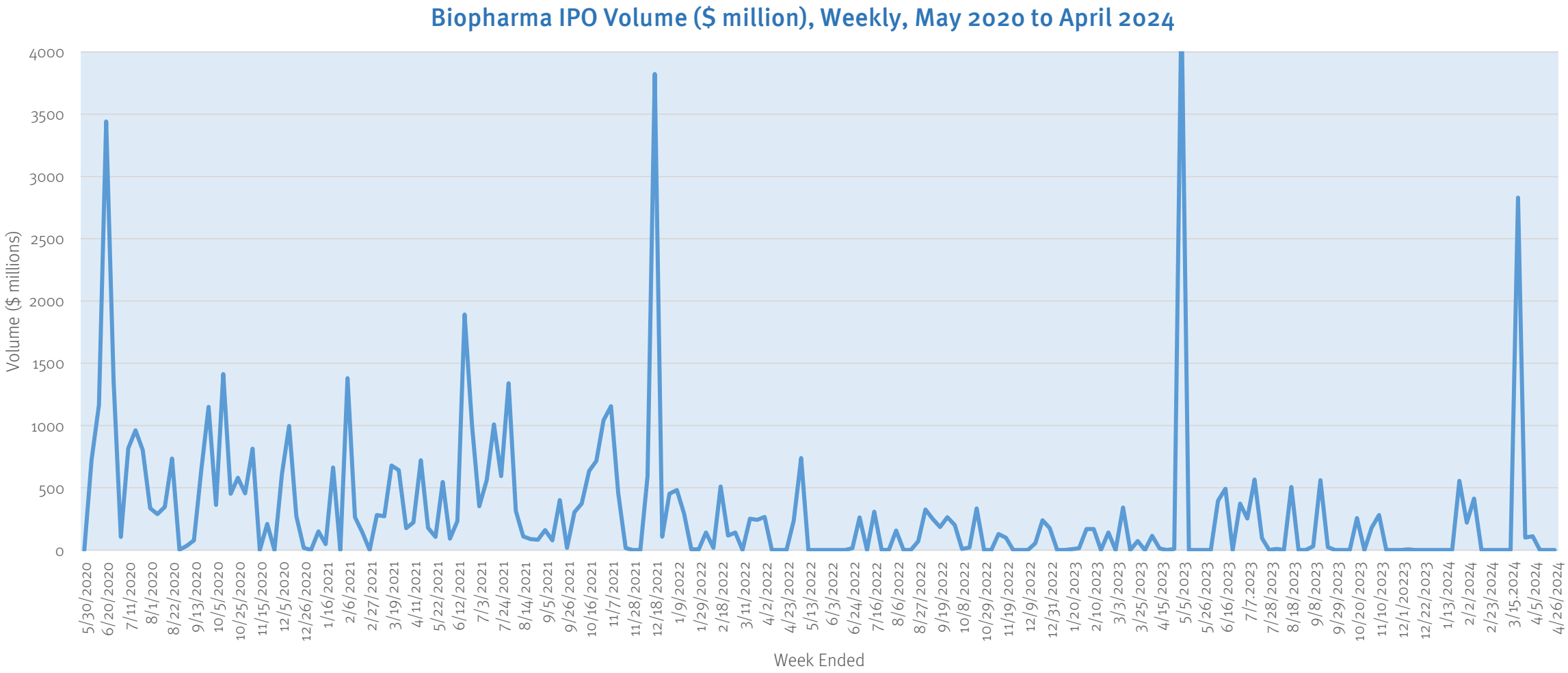
* Data from CapitalIQ. We took all public biotech companies in Sep 2021 and chose the largest 500 by enterprise value at the time for this analysis. This chart tracks the balance sheets of this cohort to June 2023 (and back to 2016 for historic reference). Years of burn is defined as net cash at last quarter end dividend by trailing 12-month EBITDA. After that we looked at the top 500 companies by market cap at quarter end 2024. For April 2024 estimated burn we added funds raised via disclosed ATM use, follow-ons, royalty deals and debt deals. We then deducted 25% of trailing annual EBITDA.

Capital Markets Update



No IPO Activity Last Week

The IPO market was quiet last week.



Source: Data from CapitalIQ and Stifel research.

IPO Outlook for Rest of 2024 Dependent on Macro Picture

Annika Kim Constantino and Ashley Capoot, *CNBC*, April 23, 2024 (excerpt)

After a two-year dry spell, initial public offerings by biotech companies showed signs of life during the first three months of 2024.

But it's too early to say that the biotech IPO market has fully recovered.

Biotech IPOs appeared to reach pre-pandemic levels during the first quarter, with nine companies collectively raising more than $1.3 billion, according to a database from BioPharma Dive. That is more than three times the roughly $375 million raised from biotech IPOs in the first quarter of 2023.

So, what will biotech IPO activity look like for the rest of the year?

A typical "strong year" looks like about 50 IPOs based on the last 10 years, according to Arda Ural, EY's Americas industry markets leader in health sciences and wellness. The biotech sector isn't on pace to meet that number, with only 10 IPOs well into 2024.

"Things will probably stay below the normal year," Ural said. But that may change, he noted.

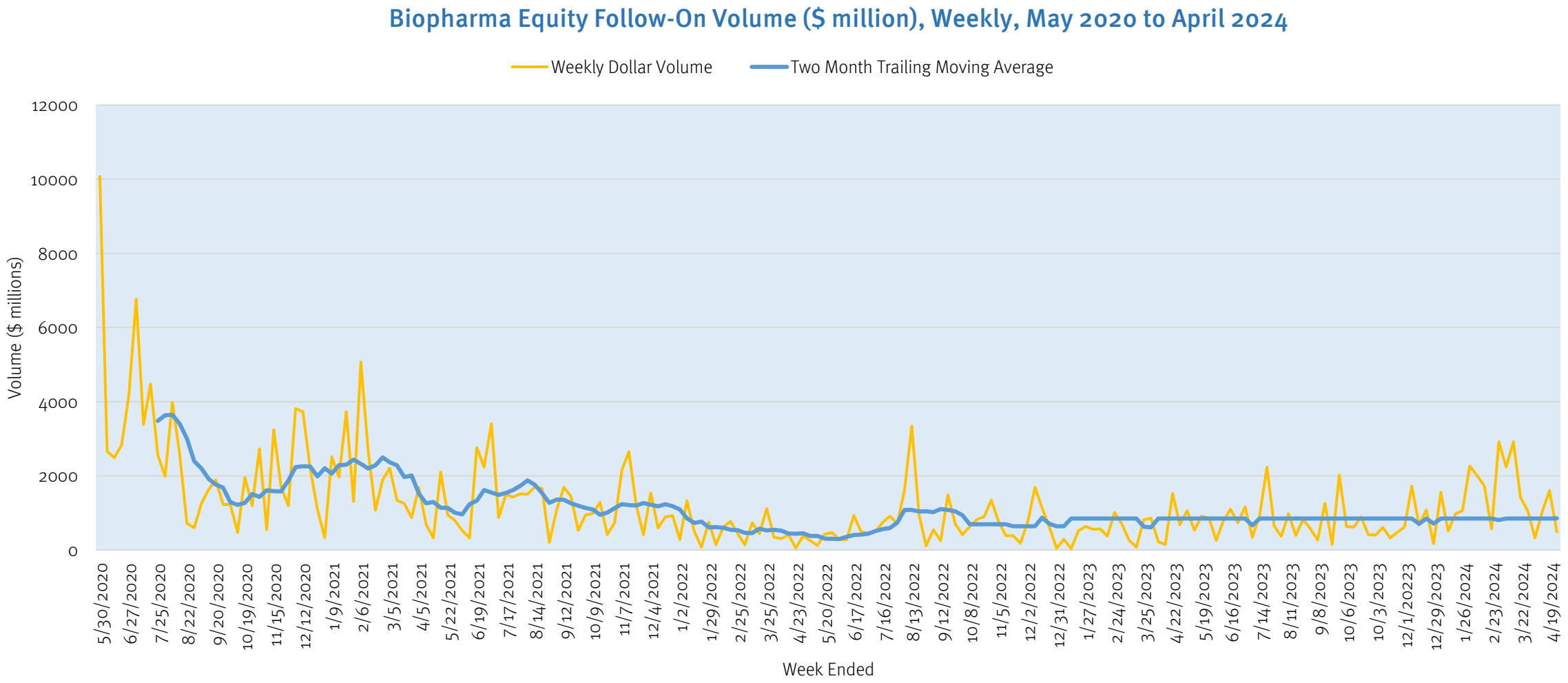
If the Federal Reserve starts interest-rate cuts as early as its late-July meeting, "you're looking at a different second half of the year for IPOs … it will certainly send us in a very positive direction," Ural said.

He called it "delayed cautious optimism."

Source: https://www.cnbc.com/2024/04/23/healthy-returns-biotech-ipos-heated-up-but-havent-fully-recovered.html

Follow-On Market Quiet Last Week

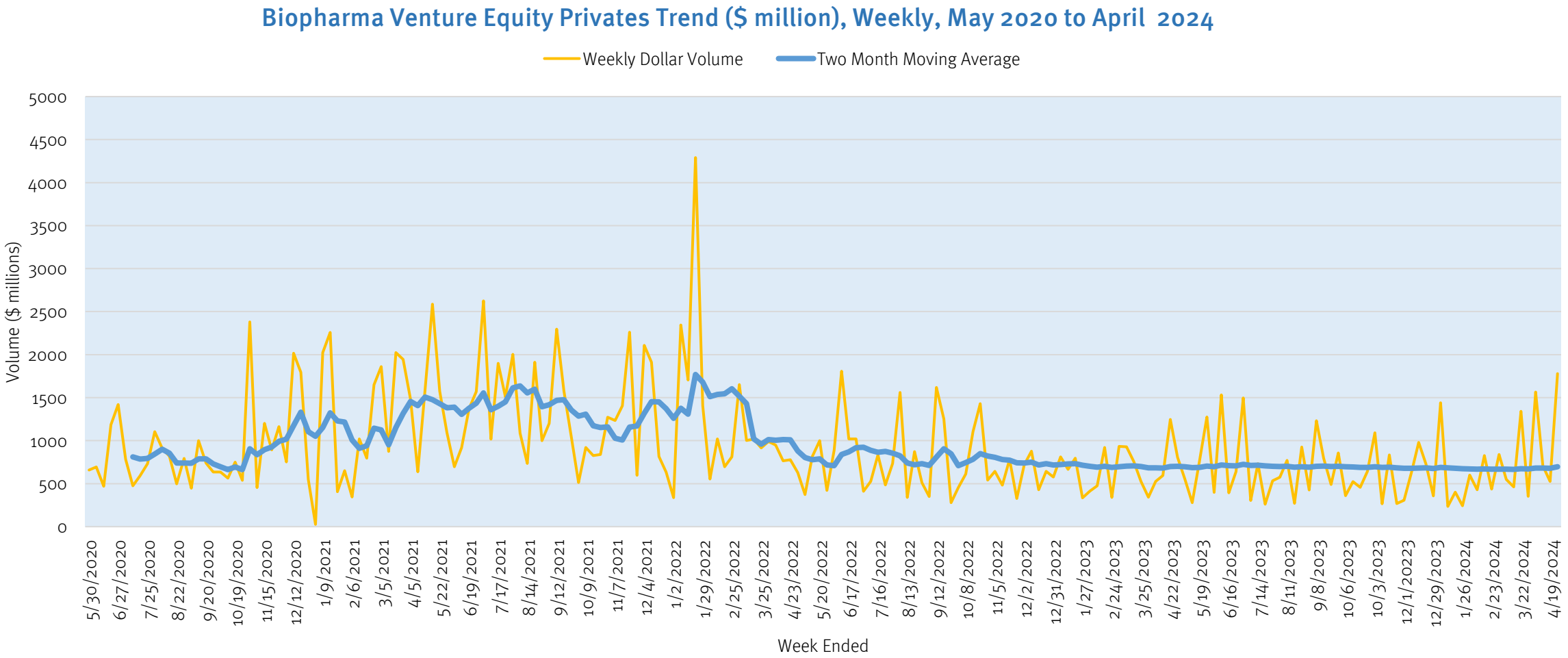
The follow-on market was slow last week. The largest deals was a $240mm PIPE by Cidara and a $100mm registered offering from Centessa.



Source: Data from CapitalIQ.

Private Venture Equity Investment Activity Brisk Last Week

The venture private market was brisk last week with $1.7 billion raised by issuers across the globe in this market. The largest offering was a $1bn raise by Xaira. This was the busiest week since June of 2022.



Source: Data from CapitalIQ, Crunchbase.

Xaira Therapeutics Raises $1 Billion for AI StartUp

Andrew Dunn and Ryan Cross, *Endpoints News*, April 23, 2024 (excerpt)

A star-studded mix of venture capitalists and scientists, backed by more than a billion dollars, is launching an ambitious biotech that aims to reinvent drug R&D using artificial intelligence, the group exclusively told Endpoints News.

The company, Xaira Therapeutics, is one of this year's most richly funded new companies, not only in biotech but across the startup world, reflecting the enthusiasm and technological progress in using AI to unlock the mysteries of biology. The group has tapped Marc Tessier-Lavigne, formerly the president of Stanford University and chief scientific officer of Genentech, as CEO to turn a "cash-flush vision into reality."

"AI is going to transform every step of the drug discovery process," Tessier-Lavigne said in an interview with Endpoints. "At the very least, everybody would agree it's going to improve things incrementally: 10% here, 20% there, 30%. You multiply all of that out and you could get two-, three-fold improvements in speed and success rates."

Much of the new startup's technology comes from the University of Washington's Institute for Protein Design, the legendary protein science lab run by Xaira co-founder David Baker. Several scientists from Baker's lab who helped develop models to design antibodies and other protein-based drugs have joined Xaira full-time.The company, which has about 50 employees today at sites in Seattle and California, was co-founded by two of biotech's biggest venture capitalists, Bob Nelsen of ARCH Venture Partners and Vik Bajaj at Foresite Labs, an incubator affiliated with Foresite Capital. Other investors include F-Prime Capital, NEA, Sequoia Capital, Lux Capital, Lightspeed Venture Partners, Menlo Ventures, Two Sigma Ventures, and SV Angel.

Largest VC-backed biopharma raises since 2010

With over $1 billion in committed capital, Xaira ranks among the largest rounds in biotech history

Company	Size (M)	Date
Altos Labs	$3,000	2022
Roivant Sciences	$1,100	2017
Xaira Therapeutics	**$1,000**	**2024**
Suzhou Abogen Biosciences	$720	2021
Sana Biotechnology	$700	2019
Boston Pharmaceuticals	$600	2015
FerGene	$570	2019
ElevateBio	$525	2021
Eikon Therapeutics	$518	2022
EQRx	$500	2021
Moderna	$500	2018

Source: DealForma • Get the data • Created with Datawrapper

Source: https://endpts.com/in-biggest-ever-bet-on-using-ai-to-design-drugs-biotech-heavyweights-launch-xaira-with-1b-in-backing/

Endeavor BioMedicines Raises $132.5 Million Series C for Fibrosis Drug

SAN DIEGO--(BUSINESS WIRE) – April 24, 2024: Endeavor BioMedicines, a clinical-stage biotechnology company developing medicines with the potential to deliver transformational clinical benefits to patients with life-threatening diseases, today announced the closing of a $132.5 million Series C financing, including the conversion of a $5 million convertible instrument. The oversubscribed round was led by AyurMaya, an affiliate of Matrix Capital Management, with participation from new investors including Fidelity Management & Research Company, Invus, SymBiosis, Velosity Capital, and Woodline Partners; and strong support from existing investors including funds managed by abrdn Inc. (formerly Tekla Capital Management LLC), Ally Bridge Group, Avidity Partners, Eckuity Capital, Longitude Capital, Omega Funds, Perceptive Advisors, Piper Heartland Healthcare Capital, Silver Arch Bio, and T. Rowe Price Associates.

Endeavor will use the financing proceeds to advance the clinical development of ENV-101, its lead candidate for the treatment of idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF); and to advance ENV-501, a human epidermal growth factor 3 (HER3) antibody-drug conjugate (ADC) for the treatment of HER3-positive solid tumors through clinical proof-of-concept studies.

Endeavor's lead investigational candidate, ENV-101, has the potential to improve lung function and reverse the fibrotic process in the lungs of individuals with IPF and PPF. ENV-101 blocks a cellular wound-healing pathway known as Hedgehog (Hh) that is abnormally activated in IPF and PPF and causes the buildup of scar tissue in the lungs. Preliminary results from the recently completed randomized, double-blind, placebo-controlled Phase 2a clinical trial of ENV-101 (NCT04968574) underscore its potential to modify disease and offer treatment outcomes that go beyond slowing disease progression for patients with IPF.

ENDEAVOR BioMedicines

"We appreciate the support from this group of leading life sciences investors, who recognize the tremendous progress we've made since our initial funding rounds as well as the life-changing potential of our therapeutic candidates to reverse the trajectory of relentless diseases."

John Hood
Chief Executive Officer
Endeavor Biomedicines

Source: https://www.businesswire.com/news/home/20240424918145/en/Endeavor-BioMedicines-Raises-132.5-Million-Oversubscribed-Series-C-Financing-to-Advance-Pipeline-of-Transformational-Medicines

RA Capital's Buying Spree

RACAPITAL

Stephen Taub, *Institutional Investor*, April 23, 2024 (excerpt)

Biopharma hedge funds have been on a buying spree the past several weeks. Many of them reported in regulatory filings that they have initiated positions of at least 5 percent in individual stocks or boosted positions to well in excess of 5 percent of outstanding shares.

No firm, however, has been nearly as aggressive as RA Capital Management. In just the past four weeks, it has filed seven initial 13G or 13D documents indicating new investments of 5 percent or more. It also filed amended documents saying it has added to positions in at least four companies that are now holdings of 5 percent or more. Two of the new positions currently rank among the firm's top-18 holdings, and three stocks in which RA Capital increased existing stakes were catapulted into the firm's top eight.

This flurry of activity is unusual among life sciences and biopharma hedge funds, which rarely shuffle their portfolio's largest positions from quarter to quarter. They are generally more of a buy-and-hold crowd, betting on firms they believe have the next drugs with the potential to receive FDA approval. Of course, given these fledgling companies' small market caps, it does not take much capital to reach the 5 percent that triggers a 13D or 13G filing.

RA Capital is headed by founder Peter Kolchinsky and managing partner Rajeev Shah. As Institutional Investor previously reported, its hedge fund is up 14 percent for the year through March.

Janux Therapeutics is the firm's fourth-largest long, representing 5.72 percent of RA Capital's U.S. common stock assets after the stake was boosted by more than 15 percent. The hedge fund firm now owns about 20 percent of the total shares outstanding. It is no stranger to Janux, as it was a major venture capital shareholder before the company went public in 2021. Janux is designing T cell immunotherapies that will kill tumors without impacting healthy tissue.

89bio is the seventh-largest long since RA Capital expanded its stake by nearly 25 percent. The hedge fund now has more than 15 percent of the clinical-stage biopharmaceuticals company, which develops therapies for liver and cardiometabolic diseases.

And Tyra Biosciences is the eighth-largest long after the firm recently lifted its stake by about 45 percent. RA Capital now owns more than 25 percent of the total shares. Tyra describes itself as a clinical-stage biotechnology company focused on developing next-generation precision medicines that target large opportunities in fibroblast growth factor receptor biology.

Source: https://www.institutionalinvestor.com/article/2d56mnzhscgu5psmdqb5s/hedge-funds/ra-capitals-buying-spree

General Catalyst Close to Raising $6 Billion Venture Fund

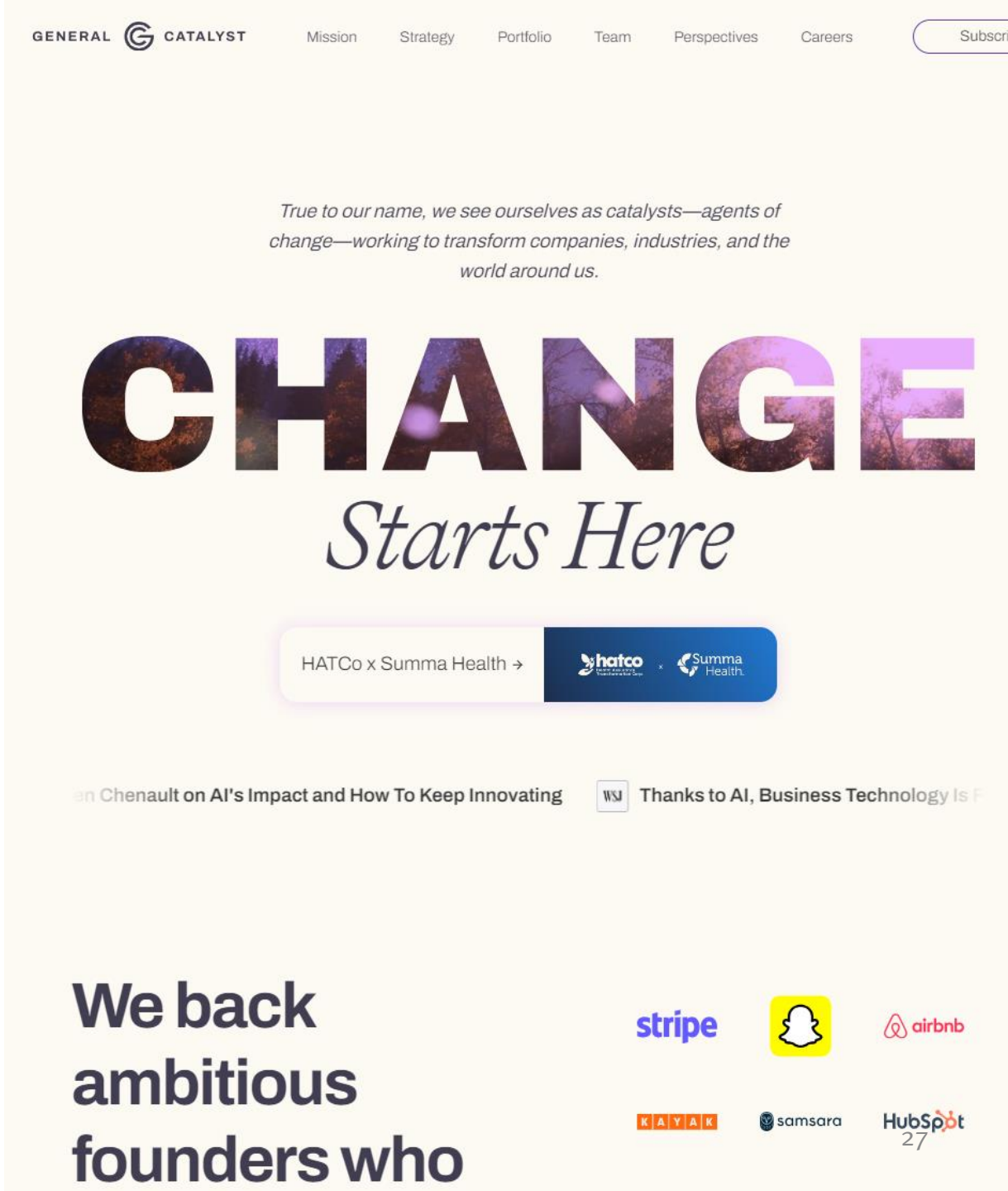
George Hammond, *Financial Times*, April 28, 2024 (excerpt)

General Catalyst is on the verge of raising almost $6bn to invest in technology start-ups, a signal that Silicon Valley's biggest venture capital firms can still attract investment even as the sector contends with a fundraising drought. The 24-year old firm — an early investor in payments company Stripe, social media company Snap and French artificial intelligence start-up Mistral — could close its latest fund as soon as next month, according to multiple people with knowledge of the matter.

General Catalyst will use the new money to invest across various sectors including defence, space, climate, fintech and healthcare in the US, Europe and India, they added. The new investment is a sign that institutional investors, endowments and foundations, known as limited partners, are willing to back the best-known firms even amid a broader fundraising crunch. General Catalyst is close to sealing its new fund just weeks after Andreessen Horowitz raised $7.2bn for a series of vehicles targeting artificial intelligence, infrastructure and defence. The two funds will be the largest raised since the end of 2022, according to private markets data company PitchBook.

Overall, fundraising for US VCs has tanked: the total raised last year was $81bn, less than half the haul in 2022, and this year is on course to be the weakest for fundraising since 2015, according to PitchBook.

Source: https://www.ft.com/content/17c03819-4566-4fd2-b0b4-45f5677d8749



The Biotech Startup Contraction Continues… And That's A Good Thing

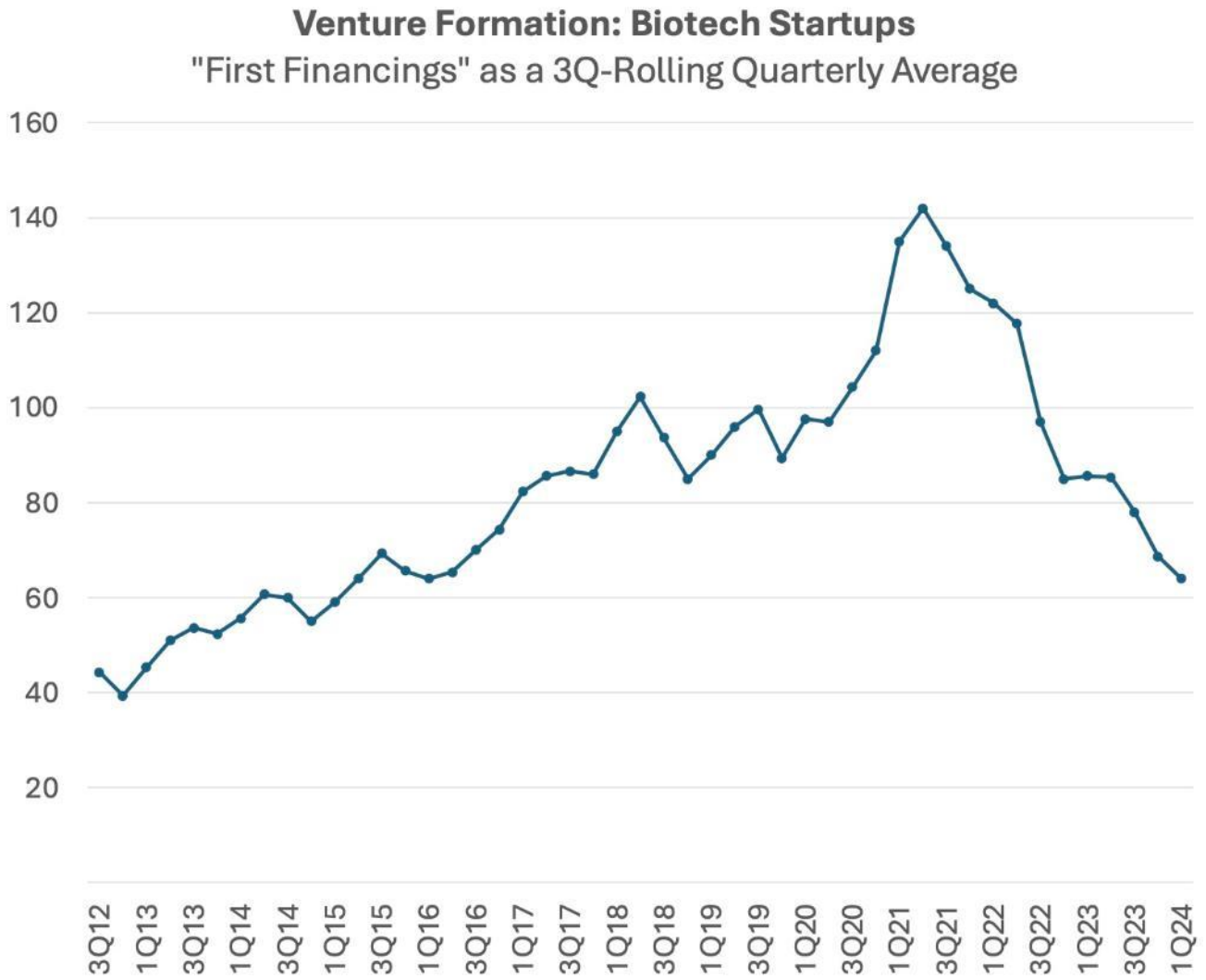
Bruce Booth, LifeSciVC, April 26, 2024 (excerpt)

Venture creation in biotech is witnessing a sustained contraction. After the pandemic bubble's over-indulgence, the venture ecosystem appears to have reset its pace of launching new startups.

According to the latest Pitchbook data, venture creation in biotech hit its slowest quarterly pace in eight years during 1Q 2024. With just over 60 new biotechs raising their first round of financing, the sector's company formation activity has slowed 50-60% from its historic peak in 2021.

Overall, this contraction is a strong positive sign of healthy discipline, and should be good for the sector's mid- and long-term prospects. Back in April 2023, in the midst of the second year of the market pullback, I shared some reflections on why it was likely to be "for the better."

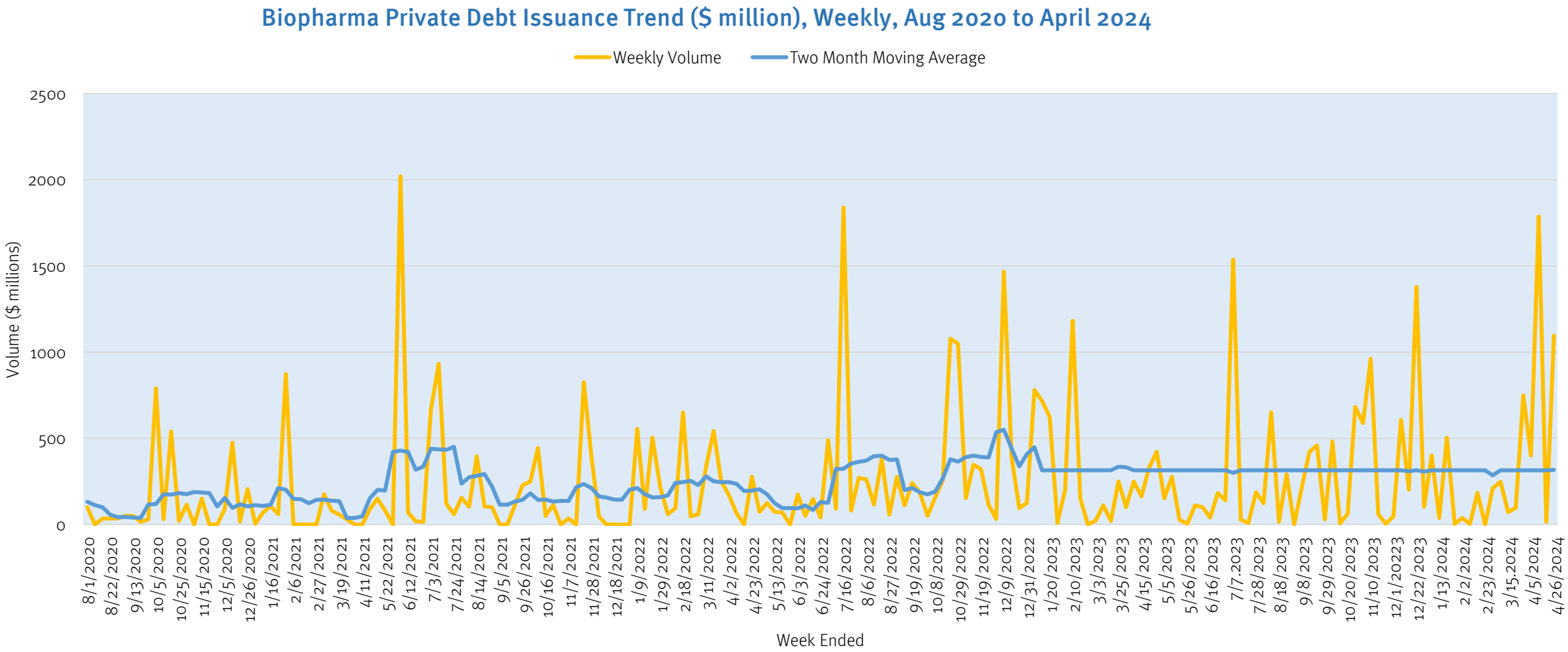
Source: https://lifescivc.com/2024/04/the-biotech-startup-contraction-continues-thats-a-good-thing/



Source: Pitchbook; LifeSciVC analysis
Data includes US-based biopharma startups with their First Financing

Biopharma Private Debt Market Active Last Week

Last week saw Grifols borrow €1bn privately and Tarsus take down $75mm in debt from Pharmakon with the ability to ultimately expand the amount to $200mm.



Source: Data from CapitalIQ, Crunchbase, Stifel research.

Grifols Announces Private Offering of EUR 1 Billion Senior Secured Notes due 2030

Barcelona, Spain, April 23, 2024. Grifols, a global healthcare company and leading manufacturer of plasma-derived medicines, announced today the successful signing subject to customary closing conditions of the private offering of EUR 1 billion of 7.5% senior secured notes due April 2030 (“the Notes”).

The full proceeds from this transaction will be used to redeem Grifols' Senior Unsecured Notes due in 2025. The features and terms of these Notes are significantly consistent with the Company’s existing senior secured documentation including with respect to collateral and guarantors.

This transaction marks a significant financial milestone, underscoring the financial markets' confidence in Grifols' solid business and operational resilience. This proactive financial strategy not only represents a significant step towards addressing the Company’s 2025 maturities but also fortifies the Company’s long-term financial framework.

“We are extremely pleased with the seamless signing of this transaction, which reflects the strength of our business and the confidence the debt market has in our financial health. This placement not only enhances our capital structure but also reinforces our ongoing commitment to innovation and leadership in the healthcare industry.” said Thomas Glanzmann, Executive Chairman of Grifols.

At the same time, Grifols is progressing towards the finalization of divesting a 20% stake in Shanghai RAAS to the Haier Group for USD 1.8 billion. This strategic partnership is on track for completion in the first half of 2024. The proceeds from this divestiture will be applied towards reducing Grifols' secured debt obligations due in 2025, further enhancing its financial stability.

Grifols announces signing of private offering of EUR 1 billion senior secured notes due 2030

April 23, 2024

Source: https://www.grifols.com/en/view-news/-/news/grifols-announces-signing-of-private-offering-of-eur-1-billion-senior-secured-notes-due-2030

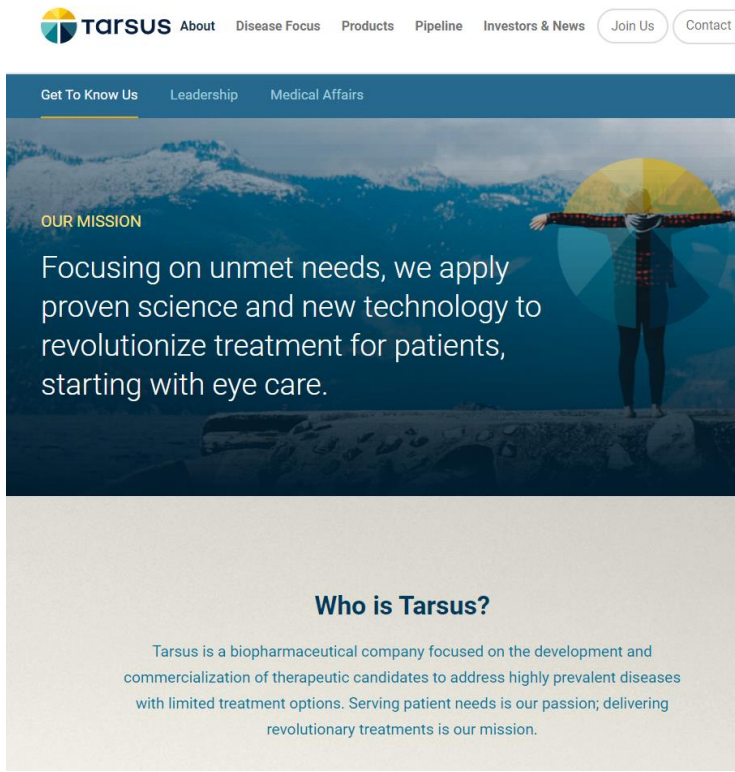
Tarsus Refinances Existing Debt with up to $200 Million Non-Dilutive Financing Commitment from Pharmakon

IRVINE, Calif., April 23, 2024 (GLOBE NEWSWIRE): Tarsus Pharmaceuticals, Inc. (NASDAQ: TARS), whose mission is to focus on unmet needs and apply proven science and new technology to revolutionize treatment for patients, starting with eye care, today announced that it has secured $200 million in committed capital from funds associated with Pharmakon Advisors, LP. Tarsus has elected to draw $75 million on the closing date, April 19, 2024, with the remaining $125 million of committed capital available at the company's option in three tranches through specified time windows, the last ending in December 2025.

Net proceeds to the Company at closing will be approximately $40 million following the repayment of the existing credit facility, as well as fees and expenses associated with the transaction.

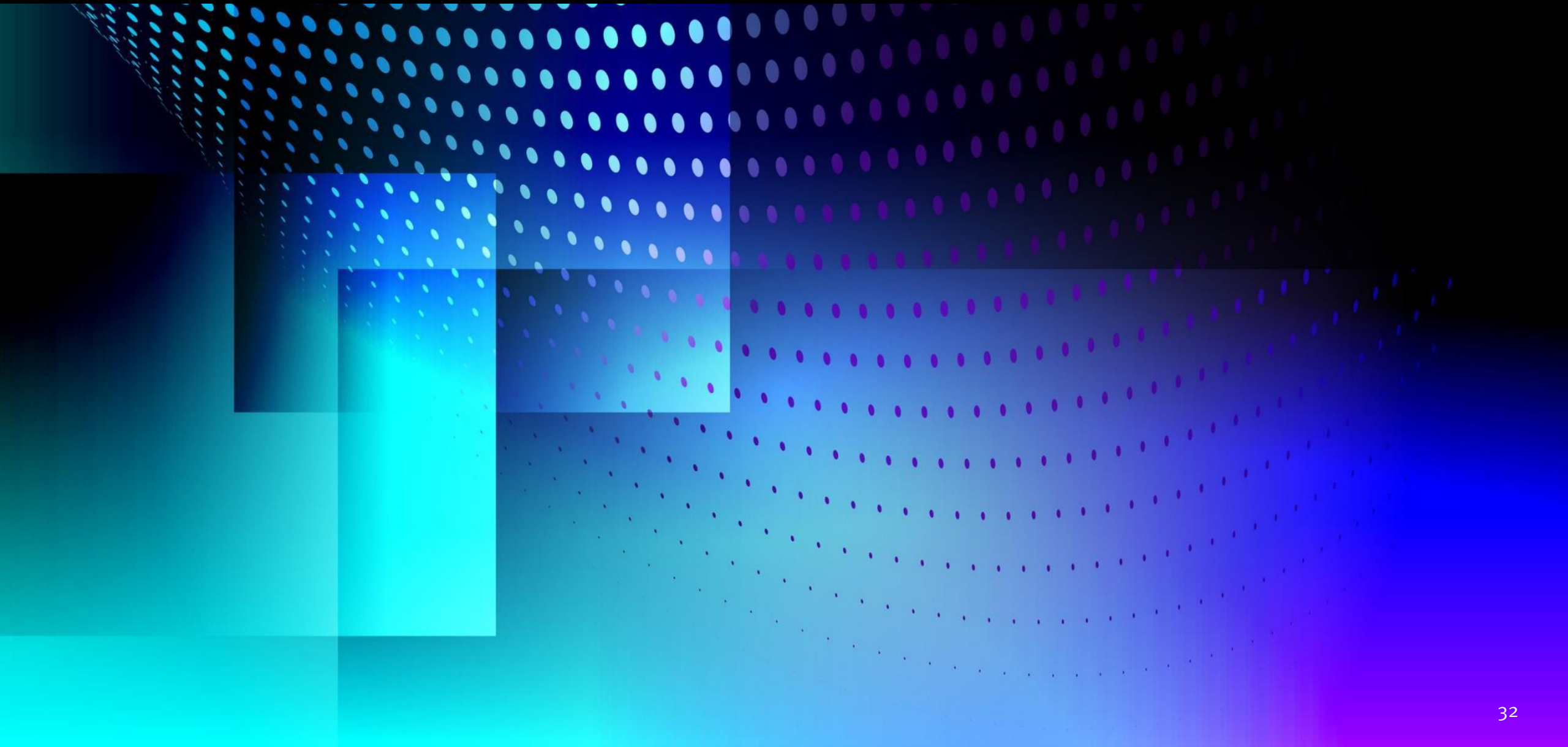
The new five-year interest-only credit facility with Pharmakon provides for three potential additional loan tranches, to be drawn at the Company's option, in principal amounts up to $25 million, $50 million and $50 million, respectively, the latter two tranches available upon achievement of certain revenue thresholds. The credit facility bears interest at a floating rate based upon the secured overnight financing rate (SOFR), plus a margin of 6.75% per annum. SOFR is subject to a 3.75% floor. Interest on the funded loan is paid quarterly in arrears until April 19, 2029, the Maturity Date, with the unpaid principal amount of the outstanding loan due and payable on the Maturity Date. There is no warrant coverage to the lenders and no financial covenants associated with the financing.

Pharmakon Advisors, LP is a leading investor in non-dilutive debt for the life sciences industry and is the investment manager of the BioPharma Credit funds. Established in 2009, funds managed by Pharmakon Advisors, LP have committed $7.8 billion across 51 investments.



Source: https://ir.tarsusrx.com/news-releases/news-release-details/tarsus-strengthens-financial-position-and-refinances-existing

M&A News and Trends



Incyte Acquiring Escient Pharma for $750 Million

WILMINGTON, Del. and SAN DIEGO, Calif. – April 23, 2024 – Incyte (Nasdaq:INCY) and Escient Pharmaceuticals, a clinical-stage drug discovery and development company advancing novel small molecule therapeutics for systemic immune and neuro-immune disorders, have entered into a definitive agreement under which Incyte has agreed to acquire Escient, including EP262, a first-in-class, potent, highly selective, once-daily small molecule antagonist of Mas-related G protein-coupled receptor X2 (MRGPRX2) and EP547, a first-in-class oral MRGPRX4 antagonist.

"As a company dedicated to innovation and the discovery of transformative medicines, we are excited to add EP262 and EP547 to our portfolio. This acquisition builds on our strategy to develop differentiated and first-in-class medicines with high potential," said Hervé Hoppenot, Chief Executive Officer, Incyte. "EP262 and EP547 are complementary additions to our portfolio, providing an opportunity to leverage our expertise, address the needs of patients with inflammatory diseases and additional potential launch opportunities starting in 2029."

By blocking MRGPRX2 and degranulation of mast cells, EP262 has the potential to effectively treat multiple mast cell-mediated diseases including atopic dermatitis (AD), chronic inducible urticaria (CIndU) and chronic spontaneous urticaria (CSU). Preclinical studies presented at the American Academy of Dermatology annual meeting in March 2023 showed that EP262 improved AD-like skin lesions and markers of type 2 inflammation. Additionally, in a Phase 1 study of 64 healthy volunteers, EP262 was safe and well tolerated at all doses tested, with no serious or severe adverse events, no adverse events leading to discontinuation and no clinically meaningful adverse changes in safety laboratory parameters, vital signs or ECG parameters. Treatment-emergent adverse events for EP262 were mild, with an incidence that was lower than placebo (33.3% vs. 62.5%) and did not increase with dose.

"These drug candidates are the result of the highly innovative research performed by Escient's employees and scientific collaborators," said Joshua A. Grass, President and Chief Executive Officer, Escient. "With its experienced development and commercial teams in Inflammation and Autoimmunity and portfolio of commercial and development stage products, Incyte is well positioned to translate this new science into valuable medicines for patients."

Under the terms of the agreement, Incyte will acquire Escient and its assets for $750 million plus Escient's net cash remaining at the close of the transaction, subject to customary adjustments. The acquisition is subject to clearance under the Hart-Scott-Rodino Act, among other customary conditions, and will become effective promptly following the satisfaction or waiver of these conditions which is currently anticipated to be by the third quarter of 2024.

Source: https://www.escientpharma.com/incyte-announces-acquisition-of-escient-pharmaceuticals-and-its-pipeline-of-first-in-class-oral-mrgpr-antagonists/

Perrigo to Divest HRA Rare Disease Business to Esteve for €190 Million Upfront

DUBLIN, IRELAND – April 25, 2024 – Perrigo Company plc (NYSE PRGO) ("Perrigo" or the "Company"), a leading provider of Consumer Self-Care Products, today announced that pharmaceutical company Esteve Healthcare, S.L. ("ESTEVE") has signed a binding offer to acquire Perrigo's HRA Pharma Rare Diseases business for a total consideration of up to €275 million, consisting of an upfront cash payment of €190 million and up to €85 million in potential earnout payments based on the Rare Diseases business achieving certain sales milestones. Following the information and consultation process with HRA Pharma Works Council in France, Perrigo would be able to exercise the put option granted by ESTEVE and enter into a definitive agreement with ESTEVE for the sale of the Rare Diseases business. The proposed final transaction is expected to close during the third quarter of 2024, subject to the satisfaction of the HRA Works Council consultation and customary closing conditions, including receipt of regulatory approvals.

"Divesting the HRA Pharma Rare Diseases business further supports our position as a leading fast-moving consumer goods company," said Patrick Lockwood-Taylor, Perrigo President and Chief Executive Officer. "The cash upfront proceeds from this proposed transaction would enable us to reduce net leverage to below 4.0x by the end of 2024."

Lockwood-Taylor continued, "We are pleased that ESTEVE, with their successful track record, will benefit from this great business and team. We thank all HRA Rare Diseases colleagues for their dedication and wish them all the best on continuing to improve the lives of patients with rare diseases."

"This transaction aims to advance on the path of covering the unmet patients' needs, in line with ESTEVE's purpose of improving people's lives, and is another step towards the company's vision of being an international and specialist pharma company," said Staffan Schüberg, Chief Executive Officer of ESTEVE.

Source: https://www.prnewswire.com/news-releases/perrigo-receives-binding-offer-to-divest-its-hra-pharma-rare-diseases-business-for-up-to-275-million-302127347.html

Lilly Acquires Injectable Medicine Manufacturing Facility from Nexus

INDIANAPOLIS and LINCOLNSHIRE, Ill., April 22, 2024– Eli Lilly and Company and Nexus Pharmaceuticals, LLC today announced a definitive agreement for Lilly to acquire an 84,000 square foot manufacturing facility from Nexus, a leading sterile manufacturer in the pharmaceutical industry.

The acquisition of this FDA-approved facility in Pleasant Prairie, Wisconsin will further expand Lilly's global parenteral (injectable) product manufacturing network and support increased demand for the company's medicines. Lilly estimates that production at this facility could begin at the end of 2025.

“The acquisition of this state-of-the-art facility underscores our unwavering commitment to growth and innovation, and we look forward to welcoming talented new Nexus colleagues to Lilly from the Pleasant Prairie facility,” said Edgardo Hernandez, executive vice president and president, Lilly manufacturing. “We are investing boldly to serve our patients, to meet product demand and to build capabilities for our robust pipeline of the future.”

The Pleasant Prairie facility does not provide contract manufacturing services, allowing the facility to be solely dedicated to Lilly’s manufacturing mission to deliver medicines to patients with safety first and quality always.

Source: https://investor.lilly.com/news-releases/news-release-details/lilly-acquires-new-injectable-medicine-manufacturing-facility

Top Ten Biopharma M&A Deals YTD in 2024

Ranked by Upfront Cash Paid ($mm) on Announced and Closed Transactions in the Pharmaceutical Sector, Jan to Apr 23, 2024

Date	Target	Buyer	Status	Product Stage	Therapeutic Area	Modality	Upfront Cash ($mm)	Contingent Payments (M)
4/10/2024	Alpine Immune Sciences	Vertex	Pending	Phase 2	Immunology	Antibody	$4,900	$0
2/12/2024	CymaBay Therapeutics	Gilead	Closed	Phase 3	Hepatology	Small Molecule	$4,300	$0
2/05/2024	MorphoSys	Novartis	Pending	Commercial	Oncology	Antibody	$2,900	$0
3/18/2024	Fusion Pharmaceuticals	AstraZeneca	Pending	Phase 2	Oncology	Radiopharma	$2,000	$400
1/08/2024	Ambrx	Johnson&Johnson	Closed	Phase 2	Oncology	ADC	$2,000	$0
4/03/2024	ProfoundBio	Genmab	Pending	Phase 2	Oncology	ADC	$1,800	$0
1/23/2024	Inhibrx	Sanofi	Pending	Phase 2	Endocrinology	Fusion Protein	$1,700	$800
1/09/2024	Aiolos Bio	GSK	Closed	Phase 2	Immunology	Antibody	$1,000	$400
3/14/2024	Amolyt Pharma	AstraZeneca	Pending	Phase 3	Endocrinology	Peptide	$800	$250
4/23/2024	Escient Pharmaceuticals	Incyte	Pending	Phase 2	Immunology	Small Molecule	$750	$0

Source: DealForma. Therapeutics only were included.

Four of the top ten M&A deals this year have been in oncology, followed by three in immunology and then three others in endocrinology and hepatology. These deals all were Phase 2 or later.

This year's M&A market is relatively "plain vanilla" with pharma scooping up attractive assets.

Notably, six of ten transactions did not have a contingent payment (a sign of agreement on price between parties).

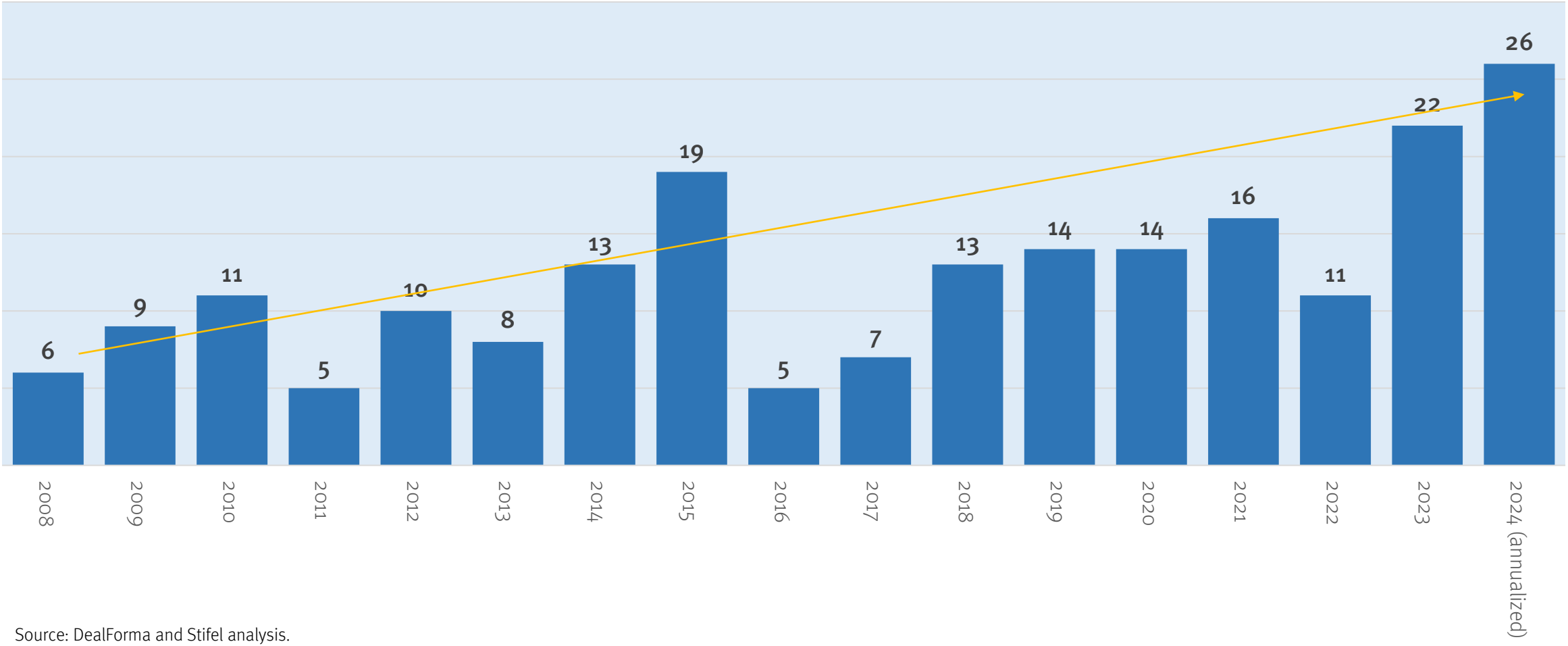
Also, it's worth noting that four targets were private.

Record Level of $1Bn+ M&A Deals in 2024…

If one annualizes the data, this year is on track to have more $1 billion and up M&A deals in our industry than in any previous year.

Number of $1 Billion Plus M&A Deals, 2008 to 2024 (annualized)

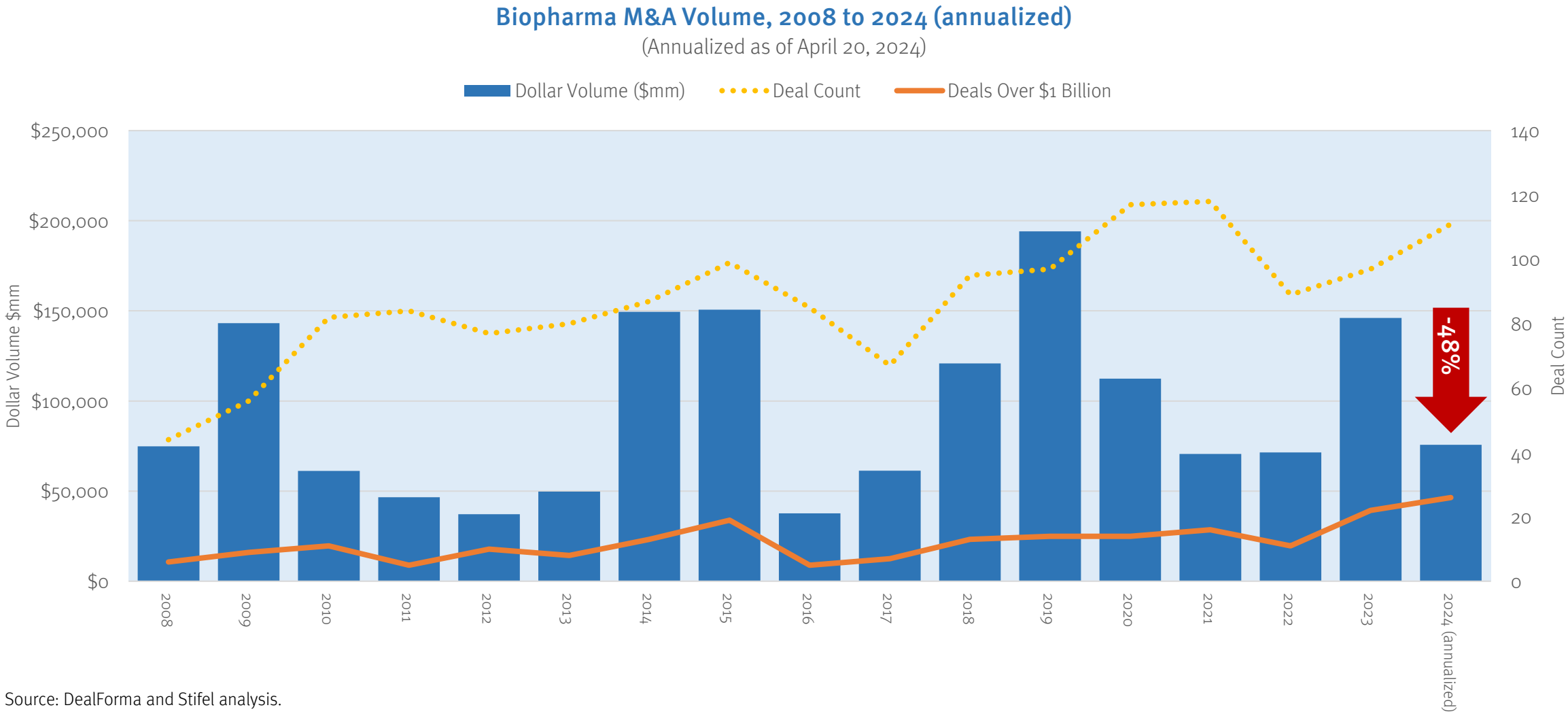
(Annualized as of April 20, 2024)



Source: DealForma and Stifel analysis.

… But Total Dollar Volume is Down

We haven't seen any M&A deals this year over $5 billion. We believe that this reflects election year politics combined with a vigilant FTC.

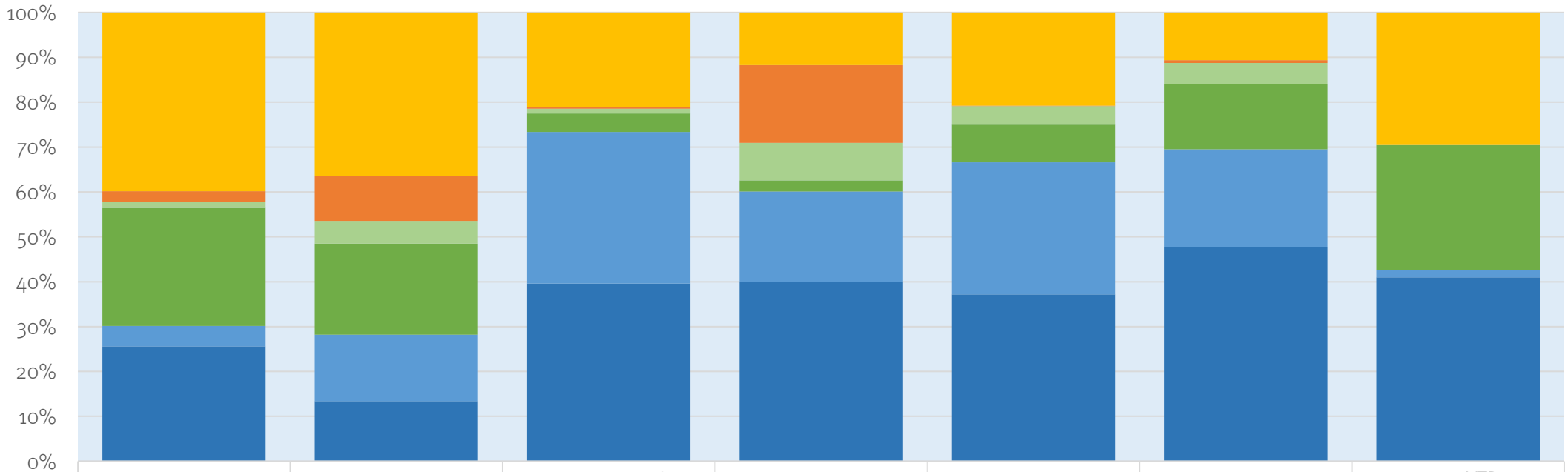


Source: DealForma and Stifel analysis.

2024 YTD is a Record Year for Immunology & Inflammation M&A Deal Share

Through the third week of April we are seeing more I&I deals than in 2023 and far fewer deals in neuro, derm and cardiometabolic.

Composition of M&A by Primary Therapeutic Area, Jan 2008 to Apr 22, 2024

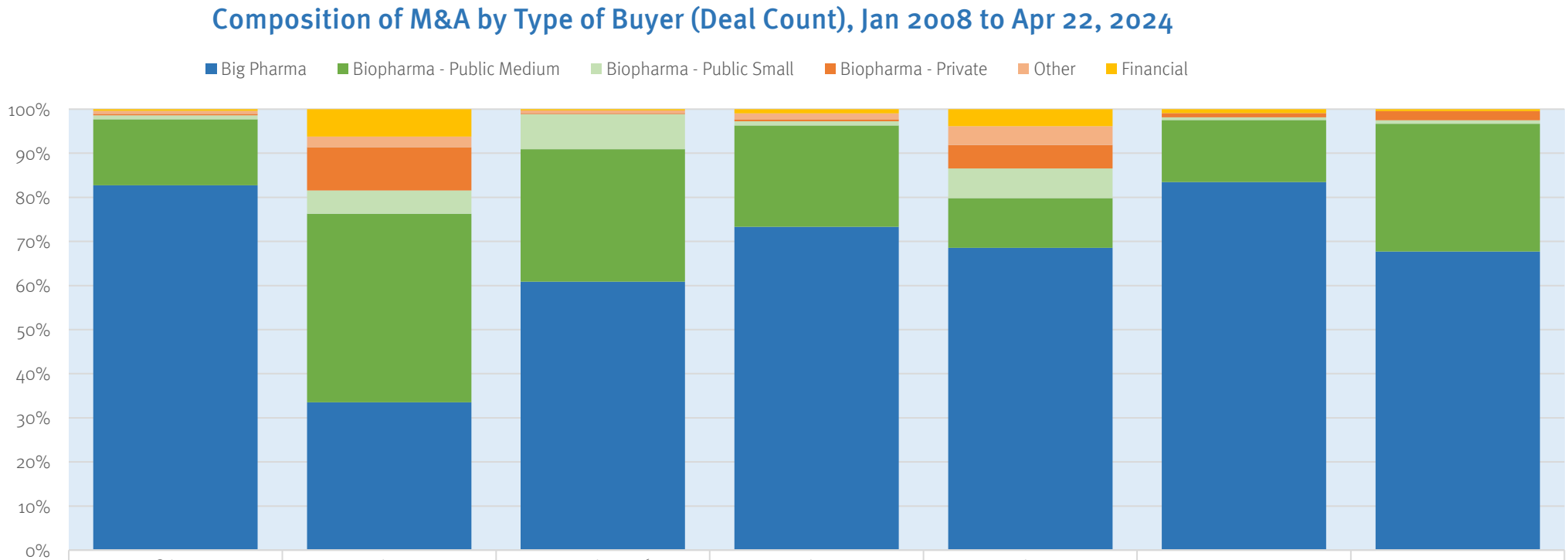


	2008 to 2010	2011 to 2013	2014 to 2016	2017 to 2019	2020 to 2022	2023	2024 YTD
Other TA's	40%	37%	21%	12%	21%	11%	30%
Dermatology	2%	10%	0%	17%	0%	1%	0%
Cardiometabolic	1%	5%	1%	8%	4%	5%	0%
I&I	26%	20%	4%	2%	8%	14%	28%
Neurology	5%	15%	34%	20%	29%	22%	2%
Oncology	26%	13%	40%	40%	37%	48%	41%

Source: DealForma and Stifel analysis.

Medium Sized Pharma is Much More Active This Year in M&A

The presence of Genmab and Vertex as M&A buyers is clearly evident in the statistics thus far.



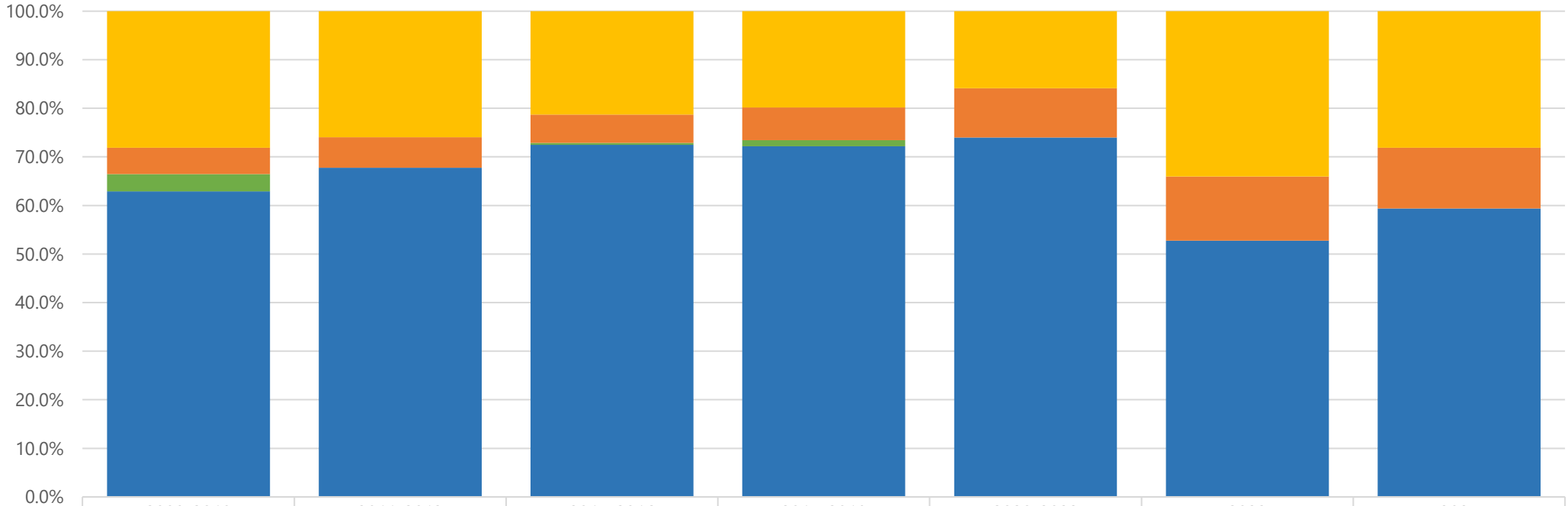
	2008 to 2010	2011 to 2013	2014 to 2016	2017 to 2019	2020 to 2022	2023	2024
Financial	0.4%	6.2%	0.3%	1.0%	3.9%	0.9%	0.5%
Other	0.7%	2.4%	0.6%	1.4%	4.3%	0.0%	0.0%
Biopharma - Private	0.3%	9.8%	0.2%	0.4%	5.3%	0.9%	2.1%
Biopharma - Public Small	0.9%	5.3%	7.9%	1.0%	6.7%	0.7%	0.8%
Biopharma - Public Medium	15%	43%	30%	23%	11%	14%	29%
Big Pharma	83%	34%	61%	73%	69%	83%	68%

Source: DealForma and Stifel analysis. Global mergers and acquisitions of all sizes of 1,366 therapeutics companies across all countries. Biopharma - Public Small is <$1 billion market cap, Public Medium is $1B to $50B, and Big pharma is $50B+ market cap.

Targets in 2023 and 2024 More Likely to be Public Than Before

Because of the downturn and its effect on valuations, M&A buyers in 2023 and 2024 have shifted their attention much more to public markets than before. Nonetheless, in all periods, over half of targets have been private. This is not surprising because the public pool of biopharmas is far smaller than the private pool of targets.

Composition of M&A by Type of Seller (Deal Count), Jan 2008 to Apr 22, 2024



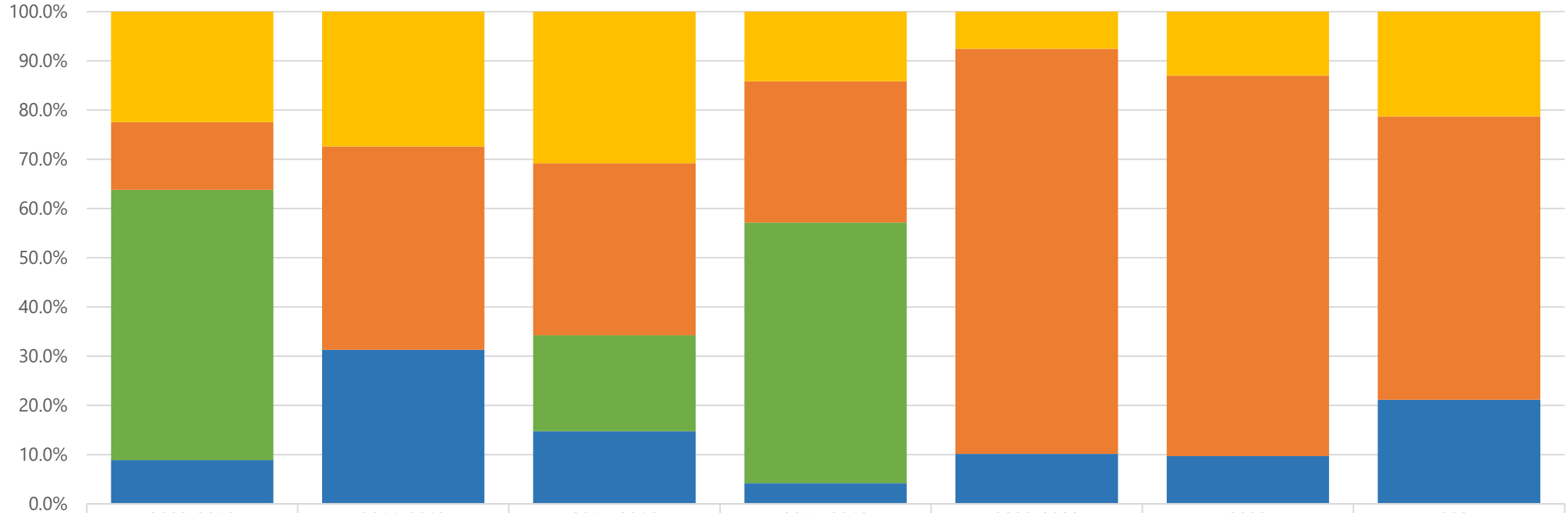
	2008-2010	2011-2013	2014-2016	2017-2019	2020-2022	2023	2024
Biopharma - Public Small	28.1%	25.9%	21.3%	19.8%	15.9%	34.1%	28.1%
Biopharma - Public Medium	5.4%	6.3%	5.8%	6.8%	10.1%	13.2%	12.5%
Biopharma - Public Large	3.6%	0.0%	0.4%	1.3%	0.0%	0.0%	0.0%
Biopharma - Private	62.9%	67.8%	72.5%	72.2%	74.0%	52.7%	59.4%

Source: DealForma and Stifel analysis. Global mergers and acquisitions of all sizes of 1,366 therapeutics companies across all countries. Biopharma - Public Small is <$1 billion market cap, Public Medium is $1B to $50B, and Public Large is $50B+ market cap.

Target Composition Over Time by Dollar Volume

The previous chart looked at the count of deals. This chart looks at total dollar volume by target type. Not surprisingly, in years, where large public takeovers are possible (2008 to 2019) we see these targets be a large part of volume. In the 2020 to 2023 period, the largest dollar volume is dedicated to medium size public companies such as Alexion, Horizon etc. In 2024 we have not seen large, or even, many medium targets get purchased. Thus, there is more volume taking place among private and smaller public companies.

Composition of M&A by Type of Seller (Dollar Volume), Jan 2008 to Apr 22, 2024



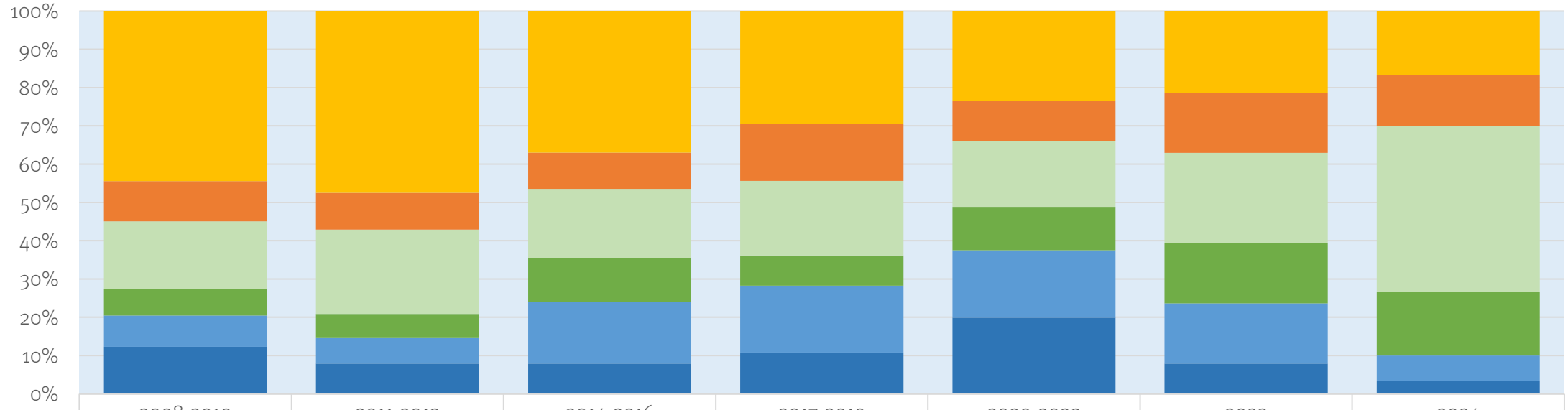
	2008-2010	2011-2013	2014-2016	2017-2019	2020-2022	2023	2024
Biopharma - Public Small	22.5%	27.4%	30.8%	14.1%	7.6%	13.0%	21.3%
Biopharma - Public Medium	13.8%	41.3%	34.9%	28.7%	82.3%	77.3%	57.5%
Biopharma - Public Large	54.9%	0.0%	19.5%	53.0%	0.0%	0.0%	0.0%
Biopharma - Private	8.9%	31.3%	14.7%	4.2%	10.1%	9.7%	21.1%

Source: DealForma and Stifel analysis. Global mergers and acquisitions of all sizes of 1,366 therapeutics companies across all countries. Biopharma - Public Small is <$1 billion market cap, Public Medium is $1B to $50B, and Public Large is $50B+ market cap.

Far More Mid-Stage M&A This Year Than Before (Deal Count)

We are seeing much more M&A this year in Phase 1 and Phase 2 than before. There are fewer platform and Phase 3 deals happening and fewer deals happening at the approved stage.

Biopharma M&A Deal Count by Stage of Development, 2008 to Apr 22, 2024



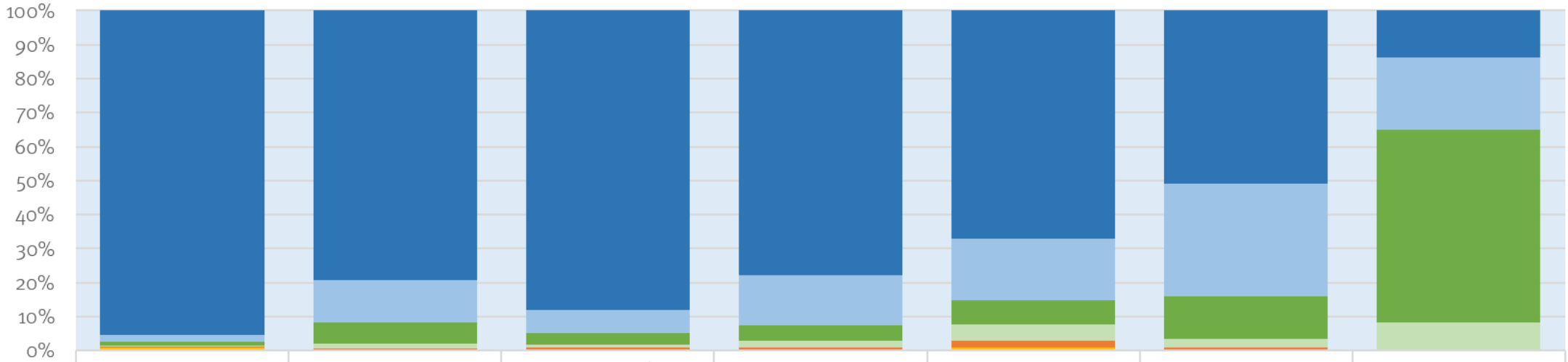
	2008-2010	2011-2013	2014-2016	2017-2019	2020-2022	2023	2024
Approved	44.4%	47.5%	37.0%	29.5%	23.4%	21.3%	16.7%
Phase 3	10.5%	9.6%	9.4%	14.9%	10.5%	15.7%	13.3%
Phase 2	17.5%	22.1%	18.1%	19.5%	17.2%	23.6%	43.3%
Phase 1	7.0%	6.3%	11.4%	7.9%	11.3%	15.7%	16.7%
Pre-Clinical	8.2%	6.7%	16.1%	17.4%	17.6%	15.7%	6.7%
Platform	12.3%	7.9%	7.9%	10.8%	19.9%	7.9%	3.3%

Source: DealForma and Stifel analysis. Global mergers and acquisitions of all sizes of 1,366 therapeutics companies across all countries. Stage of development is determined by whether a company is in that stage as opposed to having completed that stage of development with its lead molecule.

Far More Mid-Stage M&A This Year Than Before (Deal Dollars)

The previous page shows deal count. This page shows dollars spent by stage of development. There is quite an interesting trend that emerges which is a big shift in spend on mid-stage (Phase 2) and late-stage (Phase 3) biotech relative to commercial stage companies. This trend was evident in 2023 but has become much important in the first four months of 2024 where real money is being spent on mid-stage biotech. This likely reflects the antitrust environment which strongly discourages horizontal mergers at present.

Biopharma M&A Deal Volume (Dollars) by Stage of Development, 2008 to Apr 22, 2024



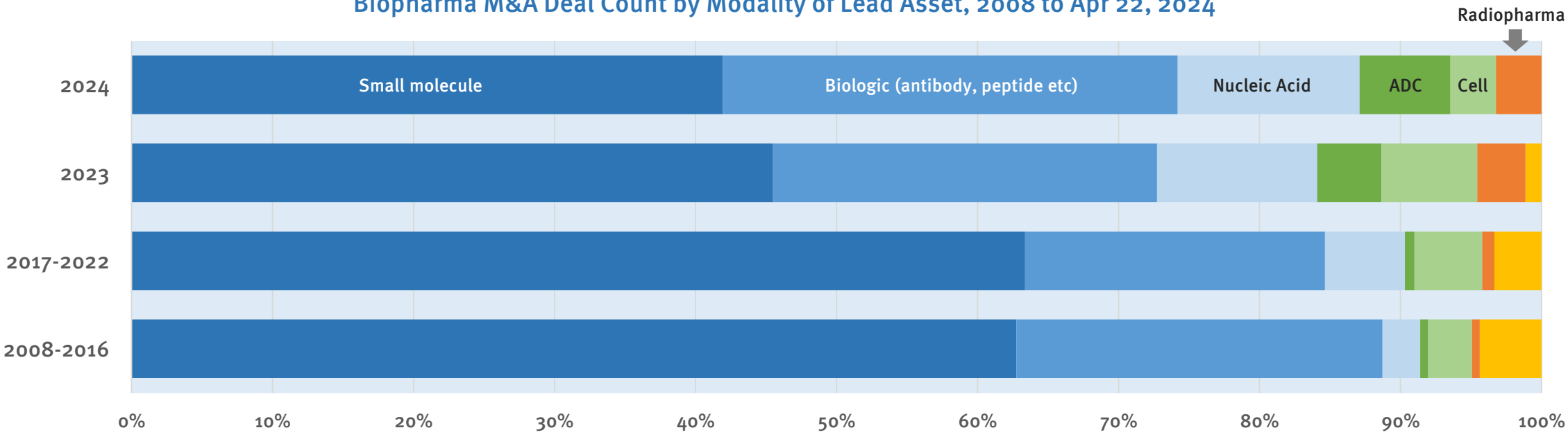
	2008-2010	2011-2013	2014-2016	2017-2019	2020-2022	2023	2024
Approved	95.5%	79.4%	88.1%	77.8%	67.1%	50.9%	13.7%
Phase 3	2.0%	12.3%	6.7%	14.8%	18.2%	33.1%	21.3%
Phase 2	1.1%	6.4%	3.5%	4.5%	7.0%	12.7%	56.6%
Phase 1	0.4%	1.5%	0.7%	2.0%	4.8%	2.5%	8.0%
Pre-Clinical	0.1%	0.1%	0.7%	0.7%	2.0%	0.4%	0.1%
Platform	1.0%	0.4%	0.3%	0.2%	0.9%	0.4%	0.3%

Source: DealForma and Stifel analysis. Global mergers and acquisitions of all sizes of 1,366 therapeutics companies across all countries. Stage of development is determined by whether a company is in that stage as opposed to having completed that stage of development with its lead molecule.

Novel Modalities Much More Important in 2024 M&A

In the 2008 to 2016 period, two-thirds of M&A involved small molecule therapies, another quarter involved biologics and just 12% involved novel modalities. By the 2024 the fraction involving novel modalities has more than doubled at the cost of small molecule therapies.

Biopharma M&A Deal Count by Modality of Lead Asset, 2008 to Apr 22, 2024



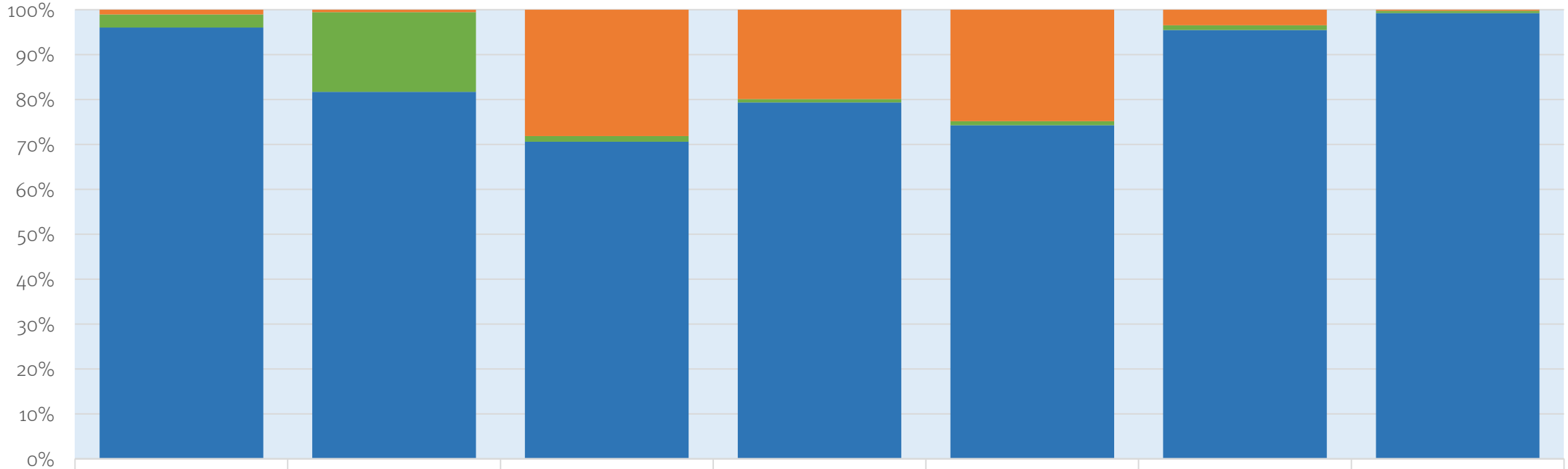
	2008-2016	2017-2022	2023	2024
Small Molecule	445	739	40	13
Biologic	184	248	24	10
Nucleic Acid	19	66	10	4
ADC	4	8	4	2
Cell Therapy	22	56	6	1
Radiopharma	4	10	3	1
Vaccine	31	39	1	0

Source: DealForma and Stifel analysis. Global mergers and acquisitions of all sizes of 1,366 therapeutics companies across all countries.

Cash is Dominant Form of Payment in 2023 and 2024

We saw much more use of equity as a form of payment in the 2011 to 2022 period than today. This likely reflects more roll-up type strategies used in that time by companies like Shire and Valeant. In addition, some large pharma deals including Celgene and Alexion had large equity portions. In the 2023 to 2024 period which has been characterized by tuck-in M&A and an absence of large stretch deals, buyers are using cash consistently.

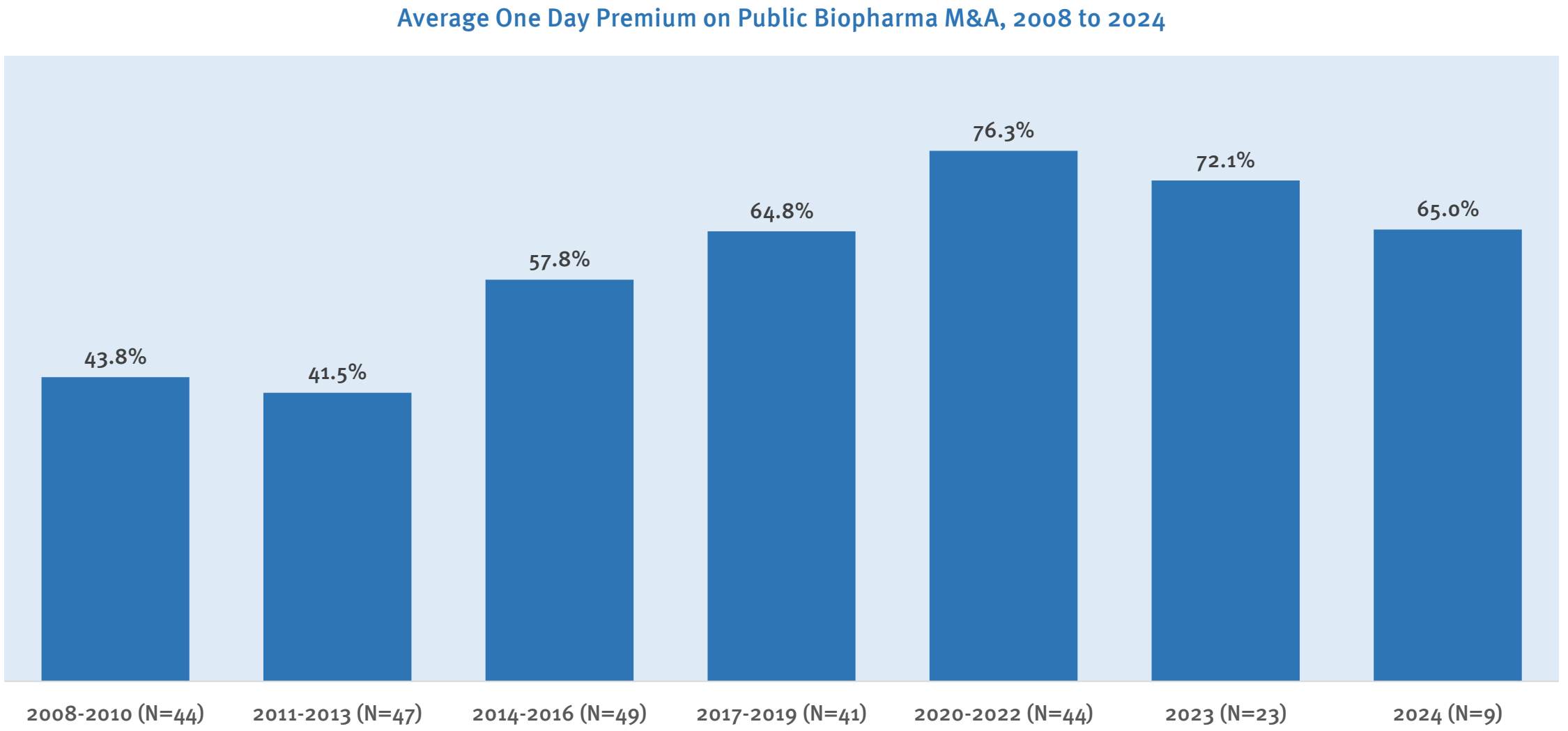
Biopharma M&A Deal Count by Form of Payment, 2008 to Apr 22, 2024



	2008-2010	2011-2013	2014-2016	2017-2019	2020-2022	2023	2024
Mix	1.1%	0.6%	28.2%	19.9%	24.8%	3.5%	0.2%
Equity	2.9%	17.7%	1.3%	0.7%	0.9%	1.0%	0.5%
Cash	96.0%	81.7%	70.6%	79.4%	74.3%	95.5%	99.3%

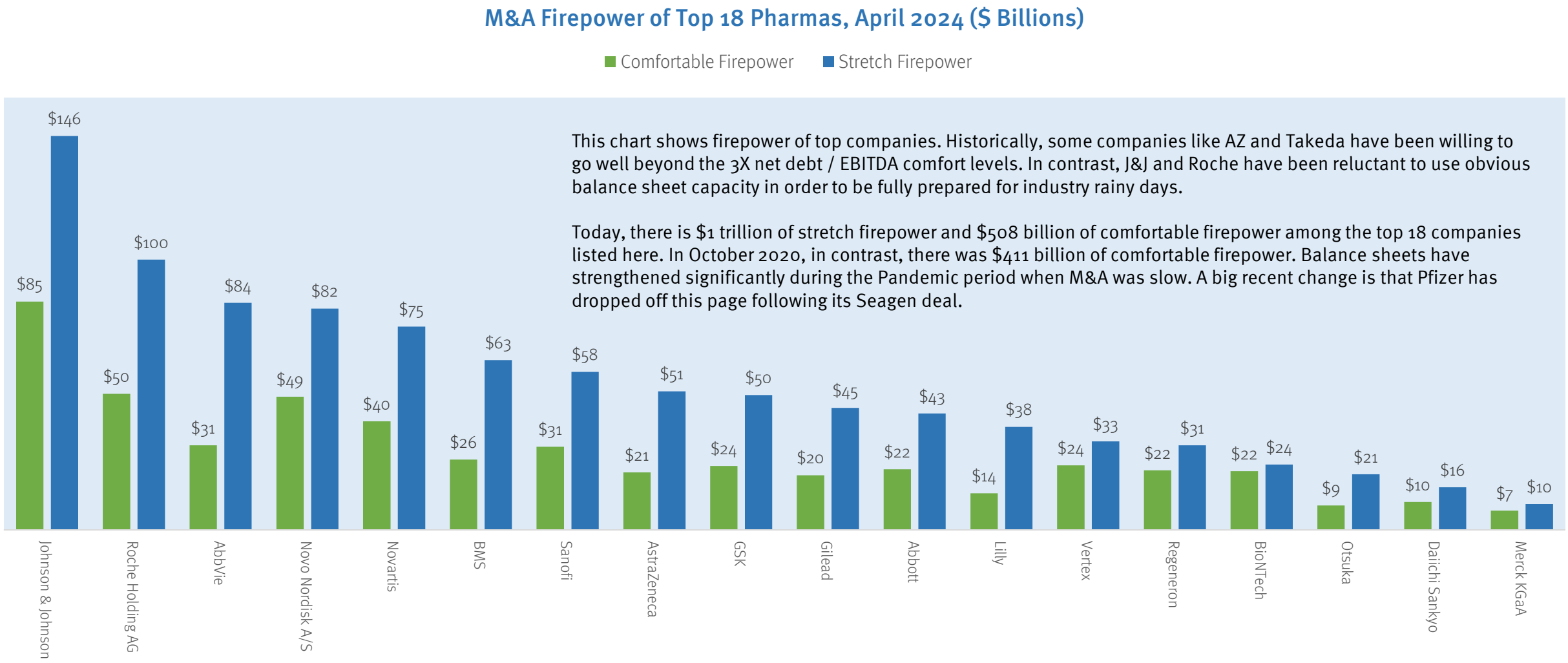
Source: DealForma and Stifel analysis. Global mergers and acquisitions of all sizes of 1,366 therapeutics companies across all countries.

M&A Premia Are Coming Down in 2024



Source: DealForma and Stifel analysis. Global mergers and acquisitions of all sizes of 1,366 therapeutics companies across all countries.

Large Pharma Has $1 Trillion of M&A Firepower Based on Latest Financials

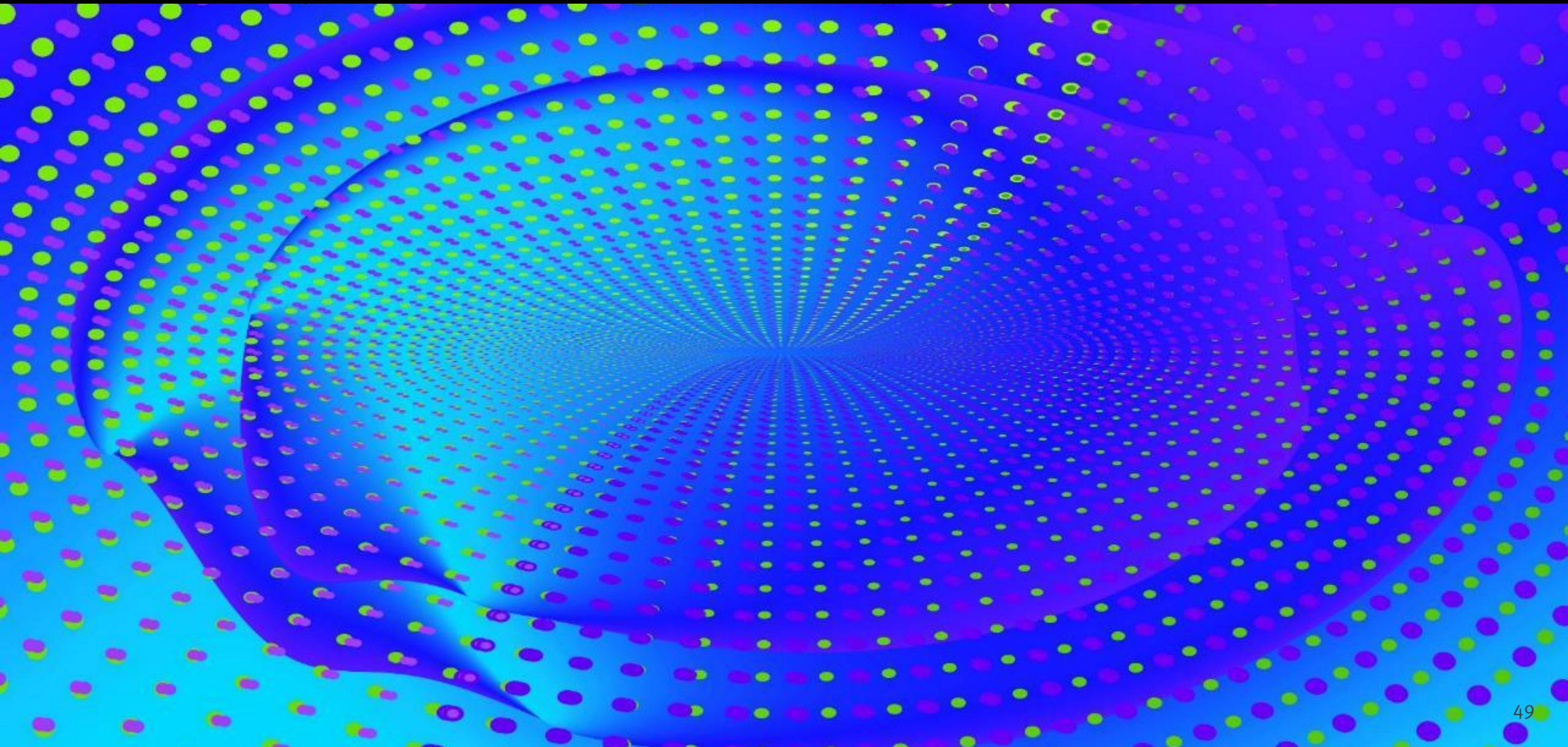


This chart shows firepower of top companies. Historically, some companies like AZ and Takeda have been willing to go well beyond the 3X net debt / EBITDA comfort levels. In contrast, J&J and Roche have been reluctant to use obvious balance sheet capacity in order to be fully prepared for industry rainy days.

Today, there is $1 trillion of stretch firepower and $508 billion of comfortable firepower among the top 18 companies listed here. In October 2020, in contrast, there was $411 billion of comfortable firepower. Balance sheets have strengthened significantly during the Pandemic period when M&A was slow. A big recent change is that Pfizer has dropped off this page following its Seagen deal.

Source: CapitalIQ and Stifel Analysis

Pharma Earnings Update



Last Week Was Big Pharma Earnings Week

Last week was the biggest week for pharma earnings of the quarter. We saw Q1 earnings released by Novartis, Roche, Biogen, AZ, BMS, Gilead, Merck, Sanofi and AbbVie.

The most important factor we were paying attention to was long-term topline growth. We were looking for evidence of improving growth and hope not to see repeats of downward growth guidance as happened last quarter with BMS, Sanofi and Takeda

AstraZeneca, Biogen, Sanofi and Merck were the stars of the week, all delivering better than expected topline growth pictures.

Biogen showed slow uptake with Leqembi® but Skyclarys for Friedrich's Ataxia did quite well.

Roche continued to be hit by biosimilars but delivered spectacular Vabysmo® growth.

Both BMS and Gilead struggled with cell therapy for oncology, showing flat sales overall in what should be a growth category. Sotyktu sales growth was surprisingly tepid at BMS.

BMS announced plans to cut costs by $1.5 billion by the end of 2025. This restructuring includes laying off more than 2,000 employees. The company aims to be more "agile" by implementing changes such as site closures, pipeline rationalization, and a reduction of management layers. Other major players like Sanofi, Pfizer, and Biogen have also implemented cost-saving measures.

It's hard to identify a single narrative thread for what's going on in pharma but if we had to pick one it would be market crowding and infrastructure. The struggles with Sotyktu and Abecma at BMS highlight the challenges of a crowded psoriasis market and lack of cell therapy infrastructure. On the other hand, Roche is doing very well with Vabysmo® in a crowded back of the eye market.

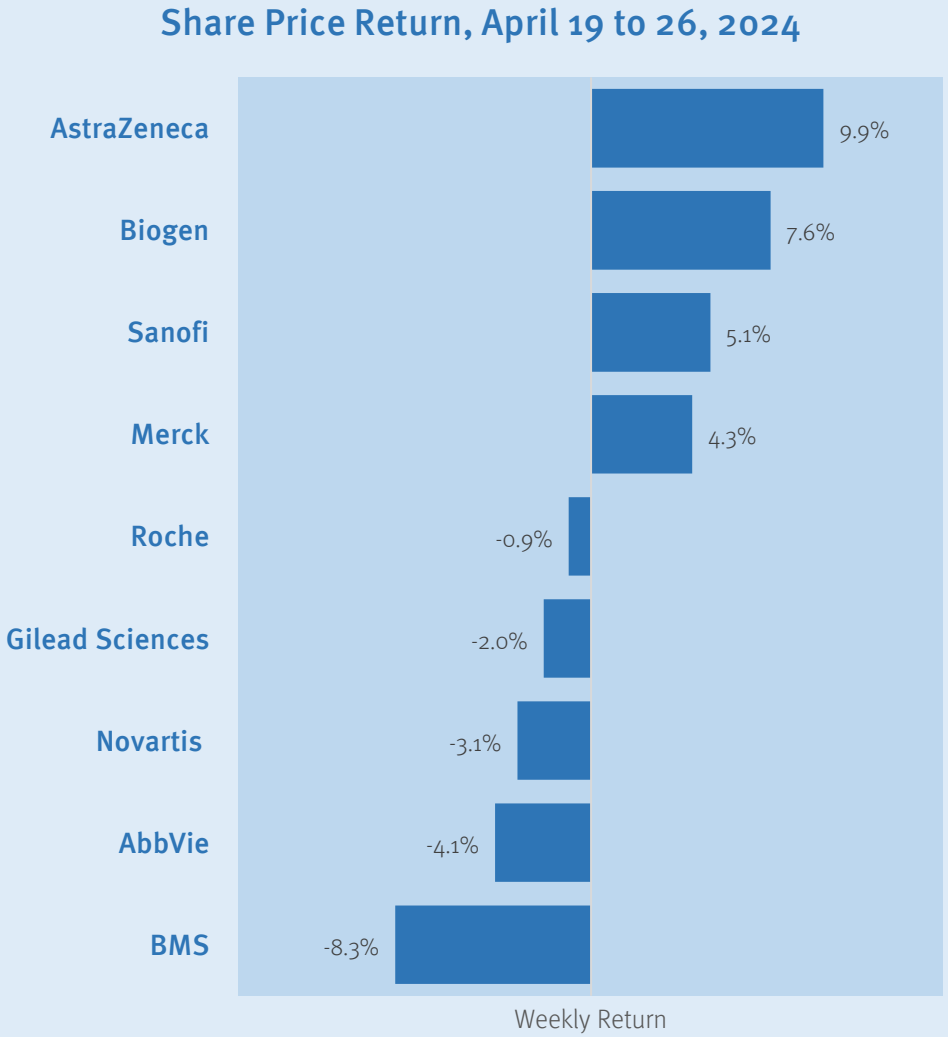
In this case, buy-and-bill physician incentives (see two page hence), pricing strategy and a very good product must be given credit. The same credit has to be given to Sanofi and Merck which continue to execute brilliantly with Dupixent® and Keytruda®.

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
Novo Nordisk	5/2/2024
Vertex	5/6/2024

Big Pharma "Earnings Week"

Deconvoluting Earnings Week – Share Price Evolution



AZ got the biggest share price bump up for earnings week after reporting 19% topline YoY growth and strong pipeline progress. AZ total revenue in the first quarter reached $10.2 billion, almost $700 million over Wall Street estimates of $9.5 billion.* Biogen had better than expected traction with Skyclarys and zuranalone launches. Sanofi's progress with Dupixent and its immunology pipeline was impressive and there was no more negative news (Sanofi top line for the quarter was 2% over consensus). Merck had impressive topline growth and passed J&J to take the #3 spot for top pharma EV in the world last week. BMS lack of traction with Sotyktu and Abecma may have explained their 8% share price decline last week. Further, AbbVie's clearly visible Humira erosion was not a positive.

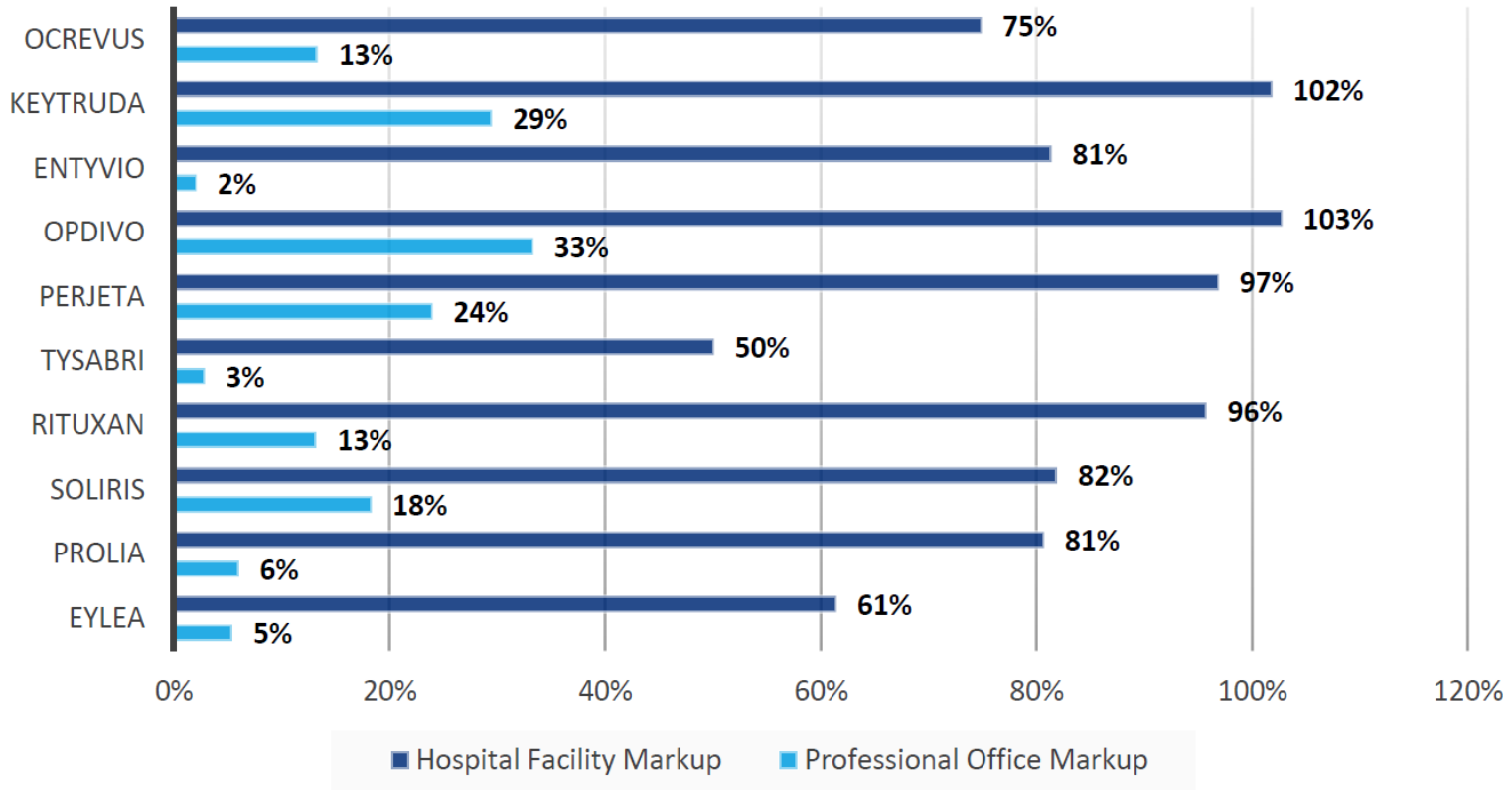
Company	Change in Market Cap for the Week	Stock Return for the Week	Market Cap (4/26/24, $mm)	Enterprise Value (4/26/24, $mm)
BMS	-$8,254	-8.3%	$90,915	$138,393
AbbVie	-$12,023	-4.1%	$282,631	$330,431
Novartis	-$6,446	-3.1%	$199,642	$217,059
Gilead Sciences	-$1,671	-2.0%	$81,577	$102,681
Roche	-$1,857	-0.9%	$194,833	$221,384
Merck	$13,729	4.3%	$332,333	$361,562
Sanofi	$5,884	5.1%	$121,612	$132,316
Biogen	$2,160	7.6%	$30,370	$36,287
AstraZeneca	$20,837	9.9%	$231,480	$257,841

Source: CapitalIQ

* AstraZeneca has further announced that it will hold an Investor Day that will take place on 21 May in Cambridge which is intented to explain how AZ is looking at "today, tomorrow and the day after". This will involve a focus on growth drivers to 2030 and beyond.

Significant Incentives for Physicians / Hospitals to Use Buy and Bill Drugs

Oliver Wyman, "The Pricing of Specialty Drugs," April 2024



Source: https://www.ahip.org/resources/pricing-of-specialty-drugs

The ability of physicians to mark up Medicare Part B drugs using "buy and bill" economics is a well understood and quite an important incentive.

This quarter's pharma results feature a number of interesting surprises. On the negative side:

1. Sotyktu
2. CAR-T drugs

On the positive side:

1. ENHERTU
2. Keytruda
3. Skyclarys
4. Zurzuvae
5. Pluvicto
6. Vabysmo

It would be a vast oversimplification to attribute these successes and failures to just "buy and bill" incentives but we think there is an argument that these incentives are the most important factor. Of the six "upside" drugs four are buy and bill. On the negative side, Sotyktu is not and CAR-T's have a reduced markup provision in Medicare Part B. Sotyktu is going up a formidable competitor in Amgen as well.

The good results last quarter for Zurzurvae and Skyclarys (both Biogen drugs) reflects the availability of new drugs for heretofore unmet medical needs. Patients were waiting and, finally, got the drugs they needed.

Flat CAR-T Cell Therapy Growth Linked to Infrastructure Bottleneck

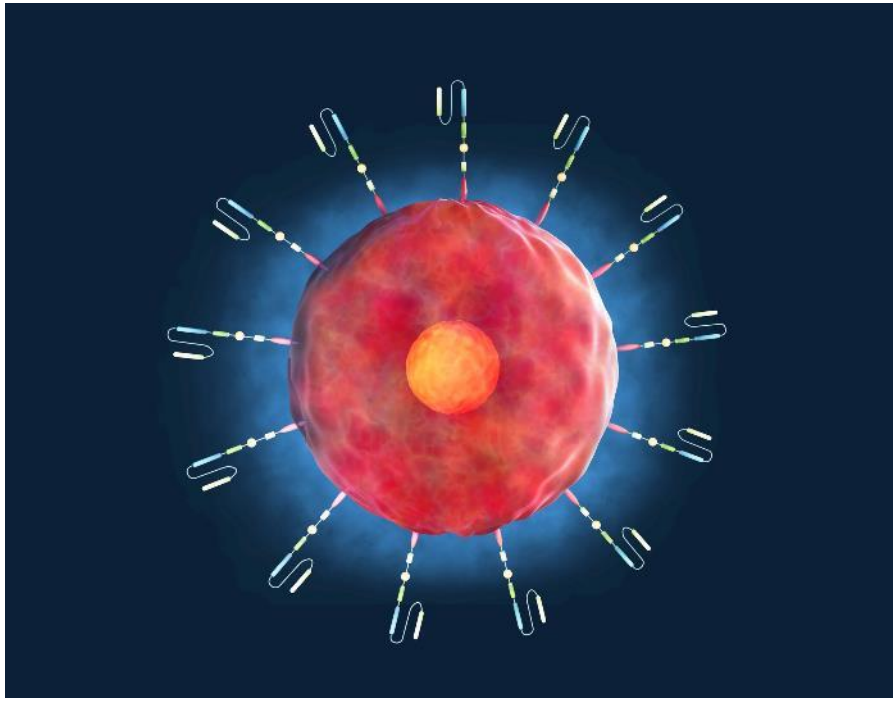
Angus Liu, *FiercePharma*, April 26, 2024 (excerpt)

Cell therapies, the other pillar of Gilead's growing oncology portfolio, have recently reached a bottleneck. Sales from the CD19 CAR-Ts, Yescarta and Tecartus, have been relatively flat sequentially for the last three quarters. The two therapies together brought in $480 million in sales in the first quarter, versus $486 million in the third quarter of 2023 and $466 million in the last three months of the year. The FDA has installed new boxed warnings on the two CAR-T therapies' labels reflecting a class-wide concern of secondary T-cell malignancies following the treatment of existing CAR-Ts.

The lack of growth momentum was the result of an infrastructure bottleneck at designated treatment centers. To solve the problem, Gilead is working to expand the number of authorized centers and affiliated satellites, while also driving increased referrals from community doctors, chief commercial officer, Johanna Mercier, said on the call. The company earlier this year established a flagship community collaboration with Tennessee Oncology, she said.

"We've identified many critical learnings on how we can partner effectively with community oncology practices for cell therapy, and we will continue to refine this blueprint so that we become more efficient at onboarding new centers over time," Mercier said.

Gilead expects to see the fruits of the expansion toward the end of 2024, she added.



CAR-T Cell

Source: https://www.fiercepharma.com/pharma/gilead-writes-24b-trodelvy-ceo-underscores-time-focused-execution


Bristol Myers
Squibb™

Q1 2024 overview

Solid Commercial Performance	Topline growth: +5% or +6% Ex-FX*
Advanced our Pipeline	Multiple regulatory approvals & clinical development milestones
Closed Four Significant Deals	Strengthened long-term growth profile by diversifying in Oncology & expanding in Neuroscience
Executing productivity initiative	Actions underway to increase productivity & efficiency across the organization

No change to the underlying business outlook from February 2024

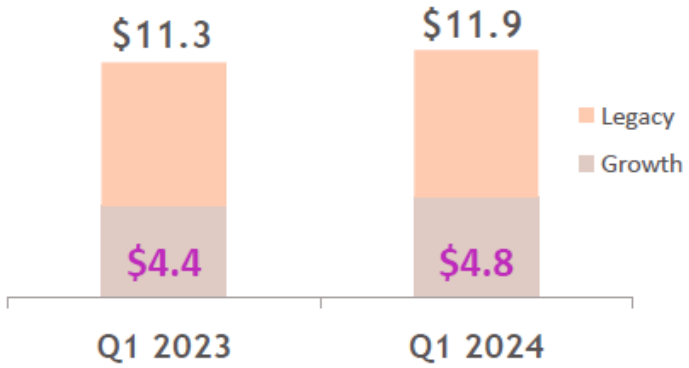
*See "Forward-Looking Statements and Non-GAAP Financial Information"

Q1 2024 Performance

Commercial

Growth Portfolio Revenues: +8% or +11% Ex-FX* YoY

$ in billions



+51% Breyanzi (lisocabtagene maraleucel)

+72% Reblozyl (luspatercept-aamt) for injection 25mg - 75mg

+76% Opdualag (nivolumab and relatlimab-rmbw) Injection for intravenous use | 480 mg/160 mg

>100% CAMZYOS (mavacamten) capsules

>100% SOTYKTU (deucravacitinib) 6 mg tablets

Research & Development[1]

Regulatory approvals:

- Breyanzi in 3L+ CLL/SLL in U.S.
- Abecma in 3L+ MM in U.S. & EU
- Reblozyl 1L MDS in EU & Japan

Achieved multiple clinical development milestones:

- Opdualag PoC in NSCLC established[2]
- Krazati 2L+ NSCLC (confirmatory trial)
- KarXT long-term efficacy & safety data
- GPRC5D CAR T in RRMM & golcadomide in NHL in registrational trials

Business Development

Closed key acquisitions & global licensing deal

MIRATI THERAPEUTICS®

SYSTIMMUNE

RαyzeBio

KARUNA THERAPEUTICS

*See "Forward-Looking Statements and Non-GAAP Financial Information" 1. Not an exhaustive list of assets, programs, or indications; 2. Moving to registrational trial in a segment of NSCLC based on pre-specified analysis

Strengthening the Company for the Transition Period & long-term growth

Realizing internal cost savings of ~$1.5B by the end of 2025*

- Identifying key assets and programs with highest potential
- Streamlining decision-making & reducing management layers
- Focusing R&D on higher ROI programs
- Investing in highest-priority growth brands

Cost savings to be reinvested in the highest potential opportunities

*The Company does not reconcile forward-looking non-GAAP measures. See "Forward-Looking Statements and Non-GAAP Financial Information"

Bristol Myers Squibb

"Then starting around 2026, our exposure is most acute and our focus will be on shortening the transition period as much as possible by accelerating our R&D programs, executing on product approvals and launches while maintaining P&L discipline. Finally, in the latter part of the decade, around 2028 and beyond, we plan to deliver sustainable top-tier growth, and we have the portfolio, pipeline and financial flexibility to support this opportunity.

Many of you recognize the first two periods. However, the late-decade return-to-growth phase is less appreciated externally, including a number of important products that are not fully appreciated in consensus models today."

Chris Boerner
Chief Executive Officer
Bristol-Myers Squibb

Source: earnings call transcript, 4/25/2024

Slow Uptake of Sotyktu®

Sotyktu: First-in-class TYK2 inhibitor

- Achieved goal of ~10K commercial scripts in Q1
- Additional momentum driven by continued volume growth and access improvement
- Continued focus on demand growth and access improvements

Sotyktu Commercially Paid Scripts[1]

Q2'23	Q3'23	Q4'23	Q1'24
~4,400	~6,500	~8,700	~9,800

Source: https://www.bms.com/assets/bms/us/en-us/pdf/investor-info/doc_presentations/2024/BMY-2024-Q1-Results-Investor-Presentation-with-Appendix.pdf

These results show the challenge of launching products in immunology in competitive categories.

Otezla looks to be significant challenger.

Amgen has obviously had plenty of time to use contracting tools to prepare for the Sotyktu® launch.


NOVARTIS

Strong Earnings at Novartis in Q1

NOVARTIS | Reimagining Medicine

Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

https://www.novartis.com
https://twitter.com/novartisnews

Ad hoc announcement pursuant to Art. 53 LR

FINANCIAL RESULTS | RÉSULTATS FINANCIERS | FINANZERGEBNISSE

Novartis delivers double-digit sales growth and core margin expansion in Q1; FY 2024 guidance raised

- **Q1 net sales grew +11% (cc[1], +10% USD) with core operating income up +22% (cc, +16% USD)**
  - Key growth drivers continued strong sales momentum including *Entresto* (+36% cc), *Cosentyx* (+25% cc), *Kesimpta* (+66% cc), *Kisqali* (+54% cc), *Pluvicto* (+47% cc) and *Leqvio* (+139% cc)
  - Core operating income margin 38.4%, +340 basis points (cc), mainly driven by higher net sales
- **Operating income grew +39% (cc, +29% USD) and net income grew +37% (cc, +25% USD)**, mainly driven by higher net sales
- **Core EPS grew +23% (cc, +17% USD) to USD 1.80**
- **Full-year 2024 guidance raised[2]** – net sales expected to grow high-single to low double-digit; core operating income expected to grow low double-digit to mid-teens
- **Novartis proposes Dr. Giovanni Caforio** as Chair of the Board of Directors at AGM 2025

Source: https://www.novartis.com/investors/financial-data/quarterly-results

The news that Giovanni Caforio would become Chair of the Board is important.

Retiring Chair of the Board, Dr. Joerg Reinhardt, played an important role in Novartis and was far from silent in guiding the company away from a conglomerate business model towards one focused on innovative drugs.

Q1 growth was broad-based, with strong contributions from Entresto®, Kesimpta®, Cosentyx® and Kisqali®

Q1 sales

	Sales USD million	Growth vs. PY USD million	Growth vs. PY cc
Entresto	1,879	480	36%
Kesimpta	637	253	66%
Cosentyx	1,326	250	25%
KISQALI ribociclib	627	212	54%
PLUVICTO®	310	99	47%
LEQVIO	151	87	139%
SCEMBLIX	136	60	83%
JAKAVI ruxolitinib	478	64	18%
Xolair Omalizumab	399	45	15%
ILARIS canakinumab	356	28	14%
LUTATHERA	169	20	14%

Strong growth (+41% cc); expected to continue

Constant currencies (cc) is a non-IFRS measure. An explanation of non-IFRS measures can be found on page 34 of the Interim Financial Report. Unless otherwise noted, all growth rates refer to same period in PY.

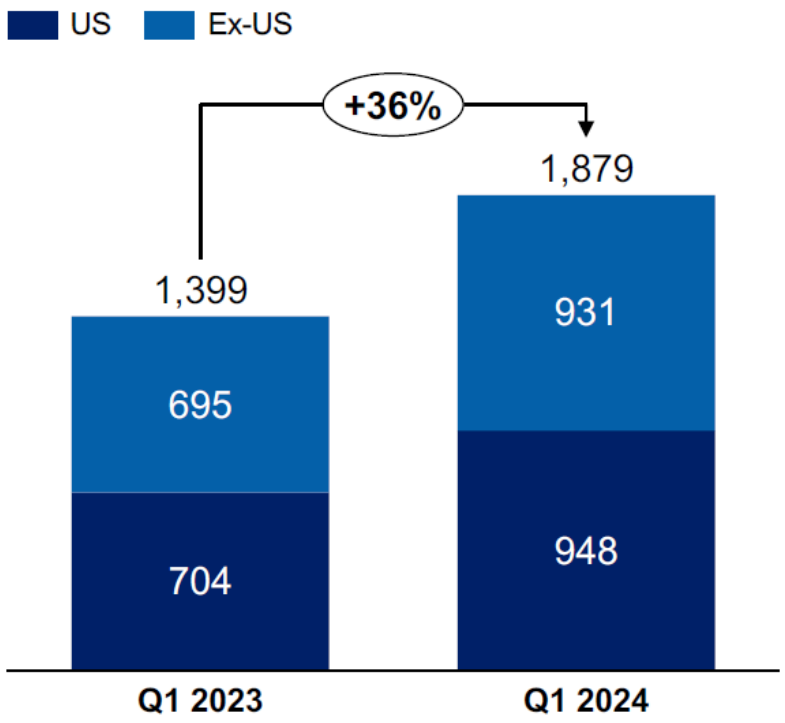
Source: https://www.novartis.com/investors/financial-data/quarterly-results

Entresto® continued strong double-digit growth, +36% in Q1

Entresto

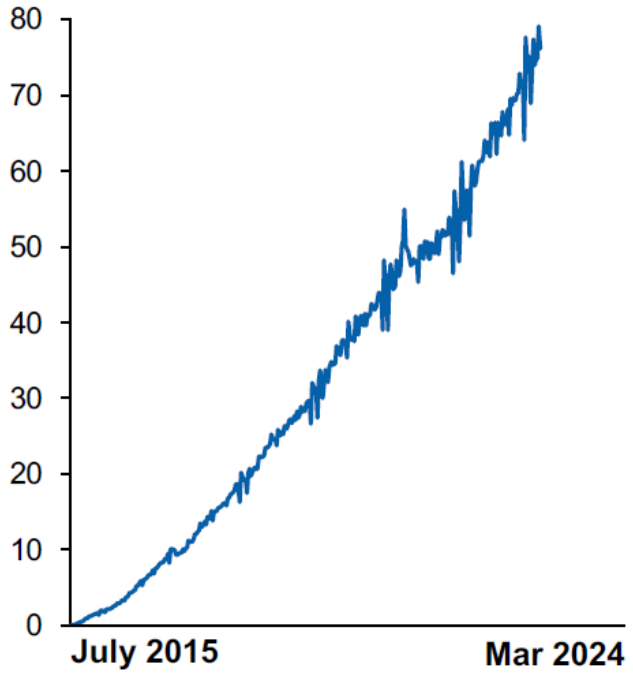
Sales evolution

USD m, % cc



US weekly TRx[1]

Total prescriptions (000)



Maintains strong momentum

- US: +35% cc
- Ex-US: +38% cc

Confidence in future growth

- Strong guideline position[2] (US/EU); 2024 ACC ECDP update strengthens ARNI position as 1L RASi for HFrEF
- Further penetration in HF globally and HTN in China/Japan[3]
- US: For forecasting purposes, we assume Entresto® LoE in mid-2025
- EU: RDP to Nov 2026[4]

See last page for references (footnotes 1-4). ACC ECDP – American College of Cardiology Expert Consensus Decision Pathway. ARNI – angiotensin receptor neprilysin inhibitor. HFrEF – heart failure ejection fraction. TRx – total prescriptions. HTN – hypertension. LoE – loss of exclusivity. RDP – Regulatory data protection. Constant currencies (cc) is a non-IFRS measure. Explanation of non-IFRS measures can be found on page 34 of Interim Financial Report.

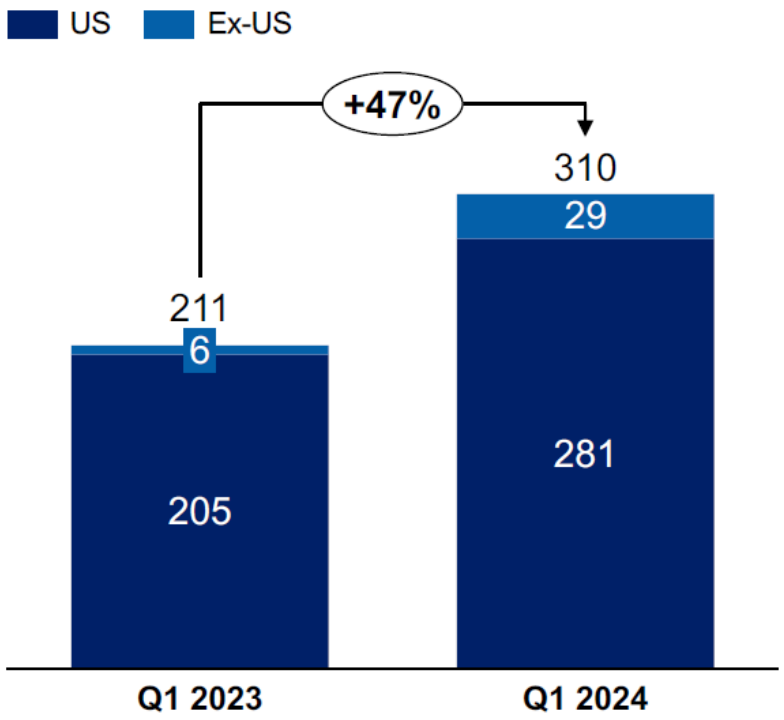
Source: https://www.novartis.com/investors/financial-data/quarterly-results

Pluvicto® demonstrated strong growth of +47% in Q1, driven by new patient starts in the US

PLUVICTO®

Sales evolution

USD m, % cc



Q1 performance

- Q1 sales grew +47% cc vs. PY, driven by demand
- 400+ treatment sites in the US
- Robust supply with >99.5% of injections administered on planned day[1]

Building momentum through 2024

- Continued focus on share expansion within established sites and expanding referral network
- Increasing contribution from ex-US

Additional indications

- PSMAfore (pre-taxane) submission-enabling OS readout achieved
- PSMAddition in mHSPC ongoing and PSMA-DC in localized oligometastatic disease started in Q1

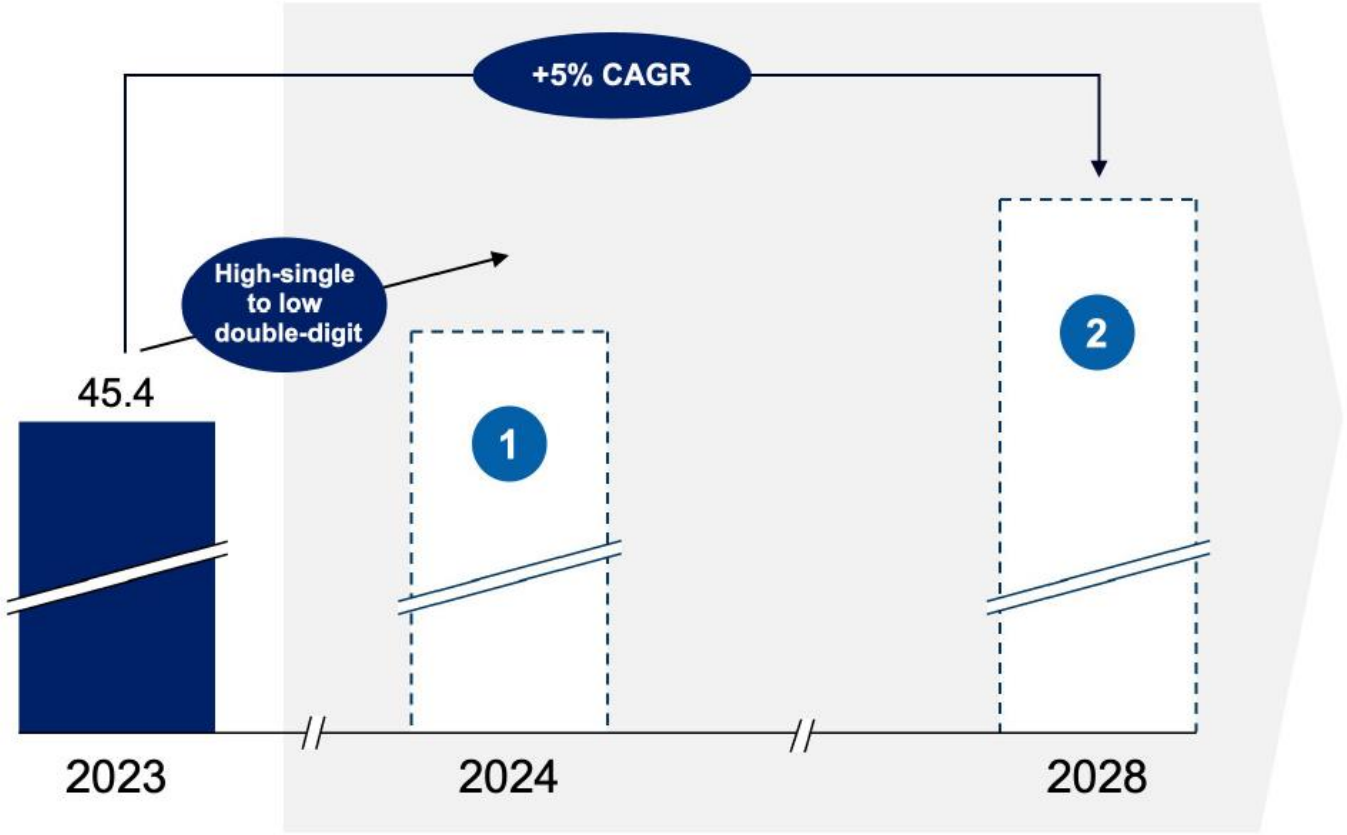
mHSPC – metastatic hormone-sensitive prostate cancer. OS – overall survival. Constant currencies (cc) is a non-IFRS measure. An explanation of non-IFRS measures can be found on page 34 of Interim Financial Report. 1. Apr 2024 YTD.

Source: https://www.novartis.com/investors/financial-data/quarterly-results

Momentum in our key growth drivers strongly supports our mid-term outlook of +5% sales CAGR 2023-2028

Net sales

Illustrative, USD billion, % CAGR cc



1 2024
High-single to low double-digit

2 2023-2028
+5% CAGR

In-market growth brands grew 41% in Q1

KISQALI
Kesimpta
Cosentyx
SCEMBLIX
PLUVICTO
LEQVIO
Entresto
zolgensma

Pipeline assets

FABHALTA (iptacopan)
remibrutinib
atrasentan
pelacarsen
ianalumab

NOVARTIS | Reimagining Medicine

Source: https://www.novartis.com/investors/financial-data/quarterly-results

Novartis is Going All In On the Chinook BAFF-R Inhibitor

Novartis is running ten Phase 2 and Phase 3 studies with its BAFF inhibitor including autoimmune hepatitis, lupus nephritis, Sjogren's, HS, lupus, ITP and WAIHA.

ianalumab - BAFF-R inhibitor

NCT03217422 AMBER (CVAY736B2201)	
Indication	Autoimmune hepatitis
Phase	Phase 2
Patients	68
Primary Outcome Measures	Alanine aminotransferase (ALT) normalization
Arms Intervention	VAY736 Placebo control with conversion to active VAY736
Target Patients	Autoimmune hepatitis patients with incomplete response or intolerant to standard treatment of care
Readout Milestone(s)	2024
Publication	TBD

ianalumab - BAFF-R inhibitor

NCT05126277 SIRIUS-LN (CVAY736K12301)	
Indication	Lupus Nephritis
Phase	Phase 3
Patients	420
Primary Outcome Measures	Frequency and percentage of participants achieving complete renal response (CRR) [Time Frame: week 72]
Arms Intervention	Arm 1: Experimental - ianalumab s.c. q4w in addition to standard of care (SoC) Arm 2: Experiemental - ianalumab s.c. q12w in addition to SoC Arm 3: Placebo comparator - Placebo s.c. q4w in addition to SoC
Target Patients	Patients with active Lupus Nephritis
Readout Milestone(s)	Primary 2027
Publication	TBD

NCT05653349 VAYHIT1 (CVAY736I12301)	
Indication	1L Immune Thrombocytopenia
Phase	Phase 3
Patients	225
Primary Outcome Measures	Time from randomization to treatment failure (TTF)
Arms Intervention	Arm 1: Experimental: lanalumab Lower dose administered intravenously with corticosteroids oral or parentally (if clinically justified) Arm 2: lanalumab Higher dose administered intravenously with corticosteroids oral or parentally (if clinically justified) Arm 3: Placebo Comparator administered intravenously with corticosteroids oral or parentally (if clinically justified)
Target Patients	Adult patients with primary ITP
Readout Milestone(s)	2025
Publication	TBD

NCT05653219 VAYHIT2 (CVAY736Q12301)	
Indication	2L Immune Thrombocytopenia
Phase	Phase 3
Patients	150
Primary Outcome Measures	Time from randomization to treatment failure (TTF)
Arms Intervention	Arm 1: Experimental: eltrombopag and ianalumab lower dose Arm 2: Experimental: eltrombopag and ianalumab higher dose Arm 3: eltrombopag and placebo
Target Patients	Primary ITP patients who failed steroids
Readout Milestone(s)	2025
Publication	TBD

NCT05349214 NEPTUNUS-2 (CVAY736A2302)	
Indication	Sjögren's syndrome
Phase	Phase 3
Patients	489
Primary Outcome Measures	Change from baseline in EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) score at Week 48 as compared to placebo
Arms Intervention	Arm 1: Experimental - ianalumab exposure level 1 Arm 2: Experimental - ianalumab exposure level 2 Arm 3: Placebo comparator
Target Patients	Patients with active Sjogren's syndrome
Readout Milestone(s)	Primary 2026
Publication	TBD

NCT05350072 NEPTUNUS-1 (CVAY736A2301)	
Indication	Sjögren's syndrome
Phase	Phase 3
Patients	268
Primary Outcome Measures	Change from baseline in EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) score at Week 48 as compared to placebo
Arms Intervention	Arm 1: Experimental - ianalumab Arm 2: Placebo comparator
Target Patients	Patients with active Sjogren's syndrome
Readout Milestone(s)	Primary 2026
Publication	TBD

NCT05639114 SIRIUS-SLE 1 (CVAY736F12301)	
Indication	Systemic lupus erythematosus
Phase	Phase 3
Patients	406
Primary Outcome Measures	Proportion of participants on monthly ianalumab achieving Systemic Lupus Erythematosus Responder Index -4 (SRI-4) [Time Frame: Week 60]
Arms Intervention	Experimental: lanalumab s.c. monthly Experimental: lanalumab s.c. quarterly Placebo Comparator: Placebo s.c. monthly
Target Patients	Patients with active systemic lupus erythematosus (SLE)
Readout Milestone(s)	2027
Publication	TBD

NCT05624749 SIRIUS-SLE 2 (CVAY736F12302)	
Indication	Systemic lupus erythematosus
Phase	Phase 3
Patients	280
Primary Outcome Measures	Proportion of participants achieving Systemic Lupus Erythematosus Responder Index -4 (SRI-4) [Time Frame: Week 60]
Arms Intervention	Experimental: ianalumab s.c. monthly Placebo Comparator: placebo s.c. monthly
Target Patients	Patients with active systemic lupus erythematosus (SLE)
Readout Milestone(s)	2027
Publication	TBD

NCT05648968 VAYHIA (CVAY736O12301)	
Indication	Warm autoimmune hemolytic anemia
Phase	Phase 3
Patients	90
Primary Outcome Measures	Binary variable indicating whether a patient achieves a durable response Durable response: hemoglobin level ≥10 g/dL and ≥2 g/dL increase from baseline, for a period of at least eight consecutive weeks between W9 and W25, in the absence of rescue medication or prohibited treatment
Arms Intervention	Arm 1: experimental lanalumab low dose (intravenously) Arm 2: experimental lanalumab high dose (intravenously) Arm 3: placebo Comparator (intravenously)
Target Patients	Previously treated patients with warm Autoimmune Hemolytic Anemia
Readout Milestone(s)	2026
Publication	TBD

Source: https://www.novartis.com/investors/financial-data/quarterly-results

Novartis Going into Cardiovascular Disease and OA with its NLRP3 Inhibitor and Sjogren's with It's TLR7/8 Antagonist

Phase 1 Studies

Oncology

Code	Name	Mechanism	Indication(s)
Solid tumors			
AAA603	^{177}Lu-NeoB	Radioligand therapy target GRPR	Multiple solid tumors
			Breast cancer
			Glioblastoma multiforme
AAA604	AAA604	Radioligand therapy target integrin alpha-v, beta-3/beta-5	Solid tumors
AAA614	AAA614	Radioligand therapy target FAP	Solid tumors
AAA802	^{225}Ac-PSMA-R2	Radioligand therapy target PSMA	Prostate cancer
AAA817	^{225}Ac-PSMA-617	Radioligand therapy target PSMA	Metastatic castration-resistant prostate cancer
HRO761	HRO761	Werner inhibitor	Solid tumors
IAG933	IAG933	-	Mesothelioma
KFA115	KFA115	Novel immunomodulatory Agent	Solid tumors
MGY825	MGY825	-	NSCLC
QEQ278	QEQ278	NKG2D/-L pathway modulator	Solid tumors
Hematology			
DFV890	DFV890	NLRP3 inhibitor	Low risk myelodysplastic syndrome
PIT565	PIT565	-	B-cell malignancies
YTB323	rapcabtagene autoleucel	CD19 CAR-T	Adult ALL

Cardiovascular, Renal and Metabolic

Code	Name	Mechanism	Indication(s)
DFV890	DFV890	NLRP3 inhibitor	Cardiovascular risk reduction

Phase 2 Studies

Immunology

Code	Name	Mechanism	Indication(s)
CFZ533	iscalimab	CD40 inhibitor	Sjögren's
DFV890	DFV890	NLRP3 inhibitor	Osteoarthritis
LNA043	LNA043	ANGPTL3 agonist	Osteoarthritis
LOU064	remibrutinib	BTK inhibitor	Food allergy
			Hidradenitis suppurativa
LRX712	LRX712	-	Osteoarthritis
MAS825	MAS825	IL1B, IL18 Inhibitor	NLRC4-GOF indications
MHV370	MHV370	TLR7, TLR8 Antagonist	Sjögren's
NGI226	NGI226	-	Tendinopathy
QUC398	QUC398	ADAMTS5 inhibitor	Osteoarthritis
RHH646	RHH646	-	Osteoarthritis
VAY736	ianalumab	BAFF-R inhibitor, ADCC-mediated B-cell depletor	Autoimmune hepatitis
			Hidradenitis suppurativa
YTB323	rapcabtagene autoleucel	CD19 CAR-T	srSLE/LN

Source: https://assets.cwp.roche.com/f/176343/x/14b2fa29c8/irp240424.pdf


Roche

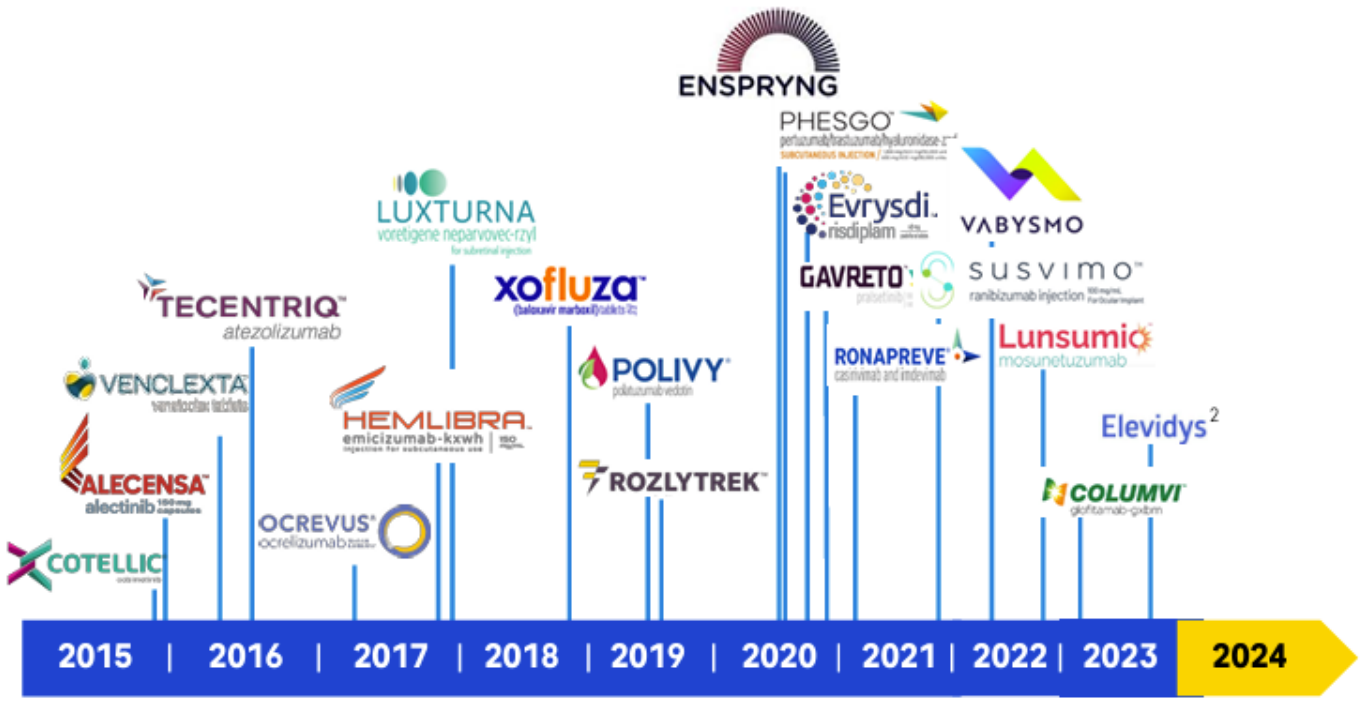
Roche Q1 Revenue Grew at 2% on a Constant Exchange Rate Basis

	2024 CHFbn	2023 CHFbn	Change in % CHF	Change in % CER	Excl. C19[1]
Pharmaceuticals Division	10.9	11.6	-6	2	7
Diagnostics Division	3.5	3.7	-6	2	8
Roche Group	14.4	15.3	-6	2	7

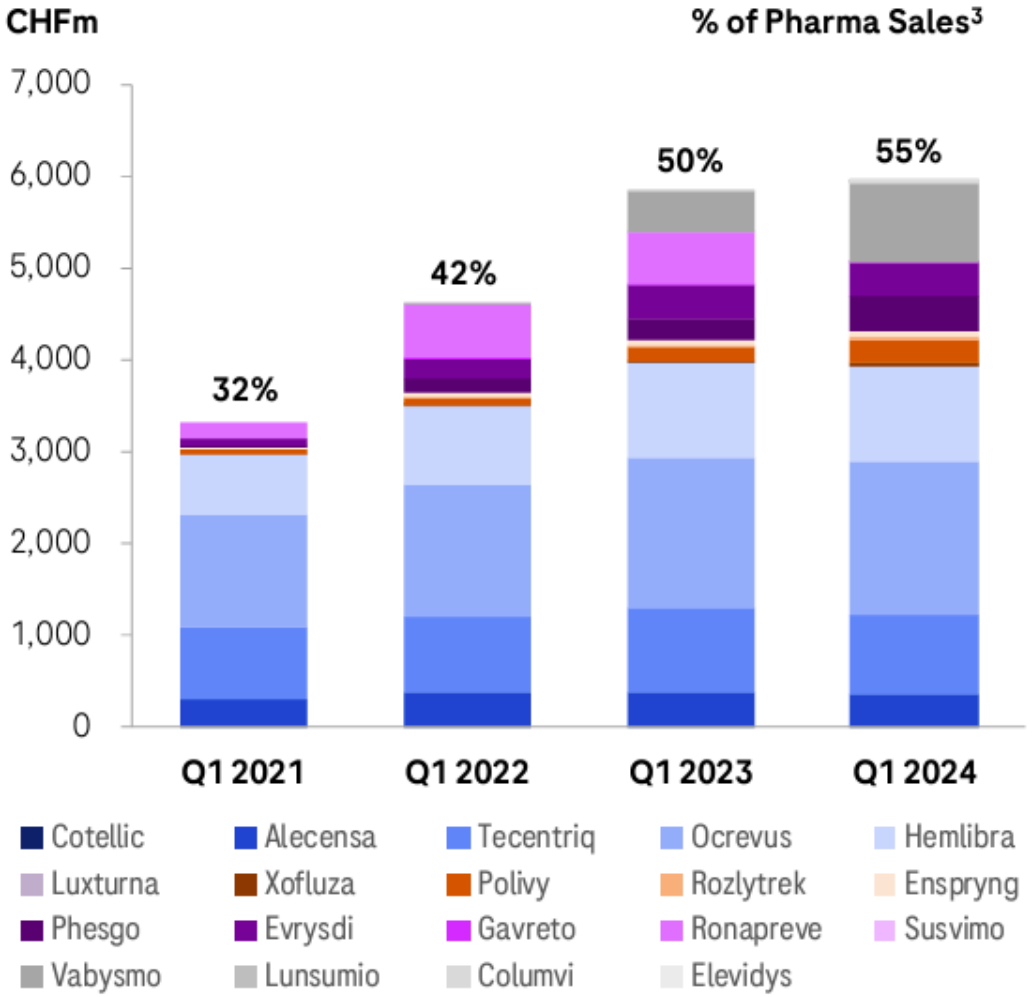
Source: https://assets.cwp.roche.com/f/176343/x/14b2fa29c8/irp240424.pdf

Young portfolio to drive growth in the near- to mid-term

Two NME approvals expected for 2024: PiaSky (crovalimab) in PNH[1] and inavolisib in HR+ breast cancer



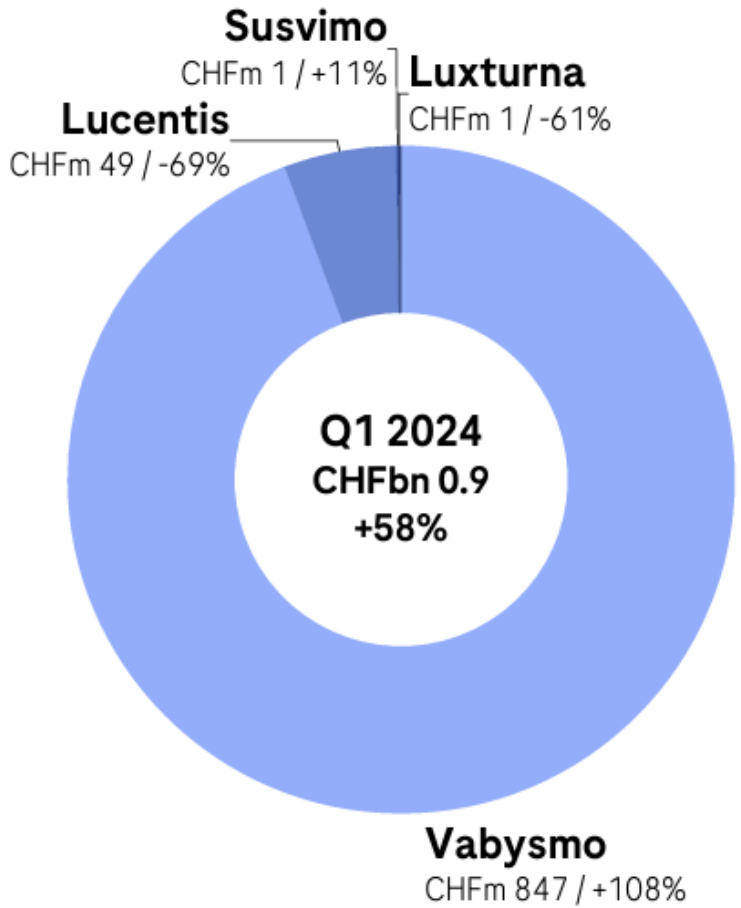
Potential NME launches:
- **crovalimab**
- **inavolisib**



Young portfolio defined as all launches since end of 2015; [1]PiaSky (crovalimab) in PNH approved in Japan and China with US/EU approvals expected in 2024; [2]Elevidys: Accelerated US approval by partner company Sarepta; [3]Venclexta sales booked by AbbVie and therefore not included; NME=new molecular entity; PNH=Paroxysmal Nocturnal Hemoglobinuria; HR=hormone receptor

Vabysmo US market share further expanding in nAMD and DME

Strong momentum for US launch of Vabysmo in RVO reaching 8% market share after only 4 months*



CHFm / YoY CER growth

IR event at ASRS on July 23rd

Q1 update

- Vabysmo: Continued market share gains across early launch countries and ongoing global expansion
  - US: Increasing penetration in naïve patients
  - Network meta-analysis shows improved anatomic outcomes at 12 weeks for Vabysmo vs. aflibercept 8mg in nAMD and DME
  - Rapidly growing body of RWD confirming drying effect and durability seen in the pivotal studies

Outlook 2024

- Vabysmo in RVO (BALATON/COMINO): EU approval
- Susvimo in nAMD (ARCHWAY): US commercial relaunch
- Susvimo in DME/DR (PAGODA/PAVILION): US filing
- Ph II (BARDENAS/ALLUVIUM) vamikibart in DME
- Ph II (GOLDEN STUDY) ASO factor B in GA

*based on February 2024 Verana patient claims data; CER=Constant Exchange Rates; nAMD=neovascular age-related macular degeneration; DME=diabetic macular edema; RVO=retinal vein occlusion; DR=diabetic retinopathy; RWD=real-world data; GA=geographic atrophy; ASO=antisense oligonucleotide; ASO factor B in collaboration with Ionis

PHARMA

Roche's juggernaut Vabysmo rout analyst consensus

In the first quarter, Roche's Vabysmo racked up sales of 847M Swiss francs, which was up 108% and demolished analysts' consensus.

Kevin Dunleavy • Apr 24, 2024 11:29am

Large Revenue Drop in Japan Due to Biosimilars / Covid19 Change

Geographical sales split by Divisions and Group*

CHFm	Q1 2023	Q1 2024	% change CER
Pharmaceuticals Division	**11,608**	**10,921**	**+2**
United States	5,763	5,692	+5
Europe	2,071	2,200	+11
Japan	1,390	649	-45
International	2,384	2,380	+12
Diagnostics Division	**3,714**	**3,478**	**+2**
United States	1,027	937	-3
Europe	995	928	-3
Japan	156	111	-15
International	1,536	1,502	+9
Group	**15,322**	**14,399**	**+2**
United States	6,790	6,629	+3
Europe	3,066	3,128	+6
Japan	1,546	760	-42
International	3,920	3,882	+11

CER=Constant Exchange Rates; *Geographical sales split shown here does not represent operational organization

Source: https://assets.cwp.roche.com/f/176343/x/14b2fa29c8/irp240424.pdf

Biogen

Advancing the global launch of SKYCLARYS

Delivering SKYCLARYS to more patients in the U.S. with over *1,100* patients now on therapy*

E.U. represents an important opportunity to unlock SKYCLARYS value and first commercial launches underway

- ***Over 300*** *patients on SKYCLARYS in the E.U.#*
- *Expect commercial launch or early access paid mechanism in* ***10-20*** *ex-U.S. markets by year-end 2024*

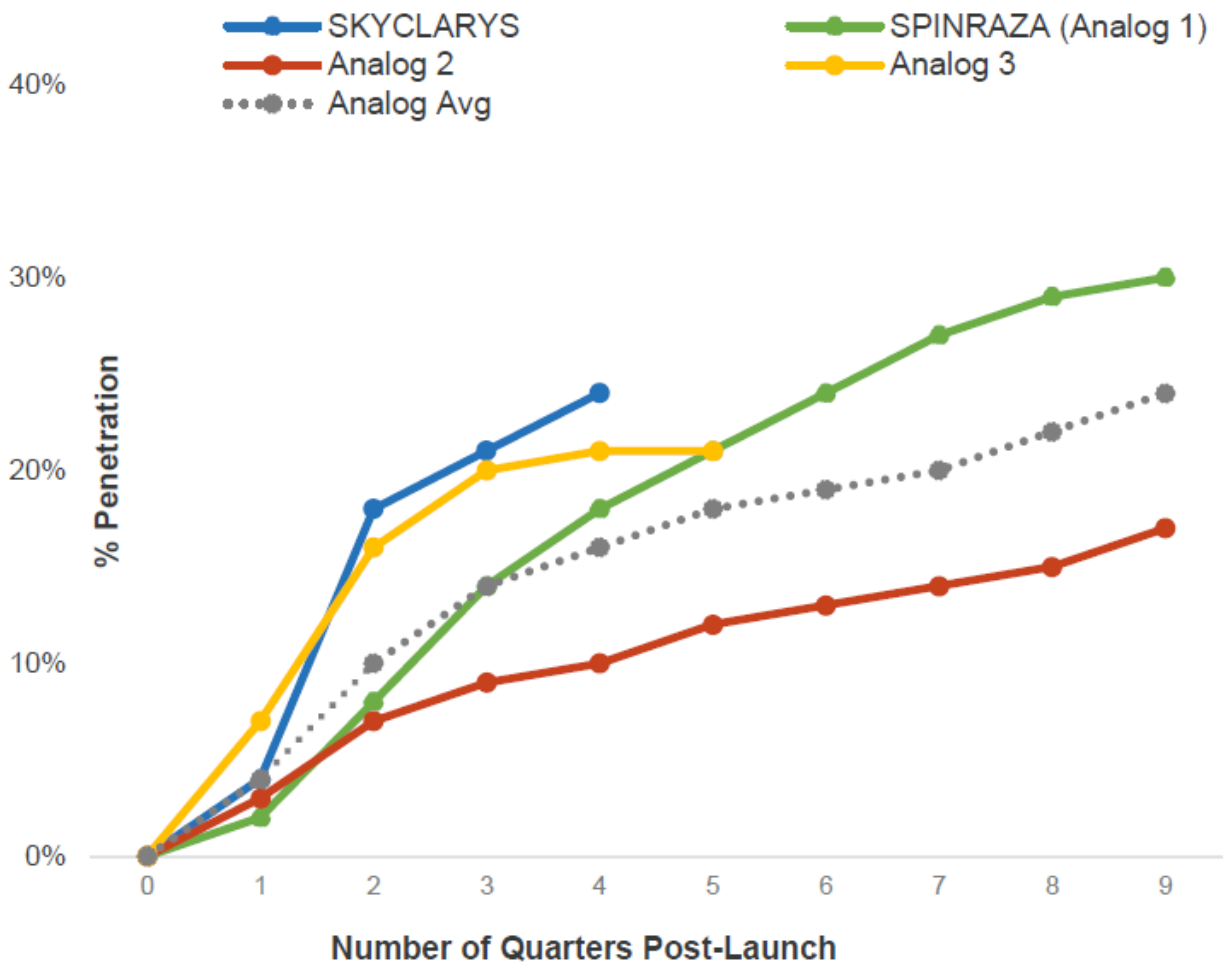
Accelerating LATAM filing strategy with regulatory filings submitted in Brazil and Argentina

Expect to initiate the Phase 1 dose finding study for pediatric FA population by summer 2024

Biogen

See SKYCLARYS USPI for full prescriber information
* Numbers as of April 19, 2024; Patients on therapy includes individuals on free drug program; # Numbers as of April 19, 2024; Includes commercial and early access mechanisms
FA = Friedreich's ataxia; LATAM = Latin American

SKYCLARYS launch continues to exceed rare disease analogs[1]



Sustained patient adoption

Over 1,100 patients now on SKYCLARYS[2] representing ~24% of estimated 4,500 addressable U.S. patient population[3]

Strong progress with payers

~80% of all U.S. pharmacy lives now have coverage for SKYCLARYS[4]

Building on strong launch foundation

Focus on two key areas: educating community neurologists and PCPs about Friedreich's ataxia, and engaging appropriate patients

See SKYCLARYS USPI for full prescribing information; 1. Analogs based on desk research of third-party source data for rare disease drugs with comparable attributes, inclusive of addressable market size, first to market status, dosing, and other characteristics. 2. Numbers as of April 19, 2024; Patients on therapy includes individuals on free drug program; 3. Estimated addressable patient population determined by using estimated prevalence in Williams CT, De Jesus O. Friedreich Ataxia. [Updated 2023 Aug 23]. https://www.ncbi.nlm.nih.gov/books/NBK563199/ after adjusting for ethnicity and supported by internal claims analyses; 4. Coverage estimated as of April 5, 2024
AI = artificial intelligence; FA = Friedreich's ataxia; HCP = health care provider; PCP = primary care physician

First quarter 2024 key financial highlights

- ✓ First quarter total revenue $2.3B; GAAP diluted EPS $2.70; Non-GAAP diluted EPS $3.67
- ✓ New launches produced revenue which more than offset the decline in the MS franchise
- ✓ U.S. SPINRAZA growth of 1% more than offset by revenue decline outside the U.S. - which was negatively impacted primarily by the timing of shipments, along with some increased competition and FX
- ✓ GAAP and Non-GAAP cost of sales as a percentage of revenue improved 3 and 5 percentage points, respectively, from revenue mix and lower idle capacity charges
- ✓ Fit for Growth program on track to achieve $1B in gross and $800M in net cost savings by the end of 2025
- ✓ GAAP and Non-GAAP core OPEX* decreased 12% and 13%, respectively; R&D prioritization, SG&A reduction included meaningful savings which were partially redeployed to support new product launches
- ✓ GAAP and Non-GAAP operating income increased 10% and 24%, respectively, with GAAP and Non-GAAP operating margins improving to 24% and 31%, respectively
- ✓ Generated $507M in free cash flow and paid down ~75% of $1B term loan since the Reata acquisition, expect to complete pay down in Q2 2024
- ✓ Ended the quarter with $1.1B in cash and modest debt; capacity for potential external business development opportunities
- ✓ Reaffirmed full year 2024 guidance – Expect full year 2024 EPS between $15 and $16

Advancing toward our goal of a new Biogen that creates enhanced value for patients and our shareholders

Biogen

Note: All comparisons are year-over-year (1Q 2024 vs 1Q 2023)
* Core OPEX = R&D expense plus SG&A expense

To be Better at Neuroscience, Biogen Will Invest Outside the Therapeutic Area

Annalee Armstrong, *FierceBiotech*, April 24, 2024 (excerpt)

To be a better neuroscience company, Biogen is going to have to diversify—outside of the therapeutic area that has in recent years defined the company.

“We always call ourselves a neuroscience company, but the reality of neuroscience is that this is a high-risk area,” CEO Chris Viehbacher said on the drug developer’s first-quarter earnings call Wednesday morning.

And so Biogen will be focused on business development outside of the neuroscience arena, which in turn, will support the expensive, lengthy trials required of the beat.

“While we remain committed to neuroscience, my personal view is that is not diversified enough for a company of our size,” the CEO said.

Chief Financial Officer Michael McDonnell said the balance sheet is “in a very good spot” in terms of net debt for the first quarter. He says there’s about $4 billion to $5 billion to play with for an acquisition target. In 2025 or beyond, that number could grow.

As for the pipeline, the executives had little to report with respect to concrete data, but Viehbacher promised more to come as three key readouts draw closer. A big one is Biogen’s anti-tau agent for Alzheimer’s disease called BIIB080, followed by phase 3 assets dapirolizumab pegol and litifilimab, both for systemic lupus erythematosus.

Source: https://www.fiercebiotech.com/biotech/be-better-neuroscience-biogen-will-invest-outside-therapeutic-area

For Beaten-Down Maker of Alzheimer's Drug, Good Enough Will Do

David Wainer, *Wall Street Journal*, April 25, 2024 (excerpt)

At first glance, Biogen didn't have a particularly exciting quarter.

Sales dropped yet again to $2.29 billion, missing Wall Street estimates. The company's multiple sclerosis franchise continued its steady erosion due to competition. And its most promising drug, a groundbreaking Alzheimer's treatment that it shares with partner Eisai, is hardly a blockbuster yet, bringing in $19 million for the quarter.

But for a company that is now in its fifth year of shrinking sales, glimmers of hope were good enough to send its stock surging Wednesday. The beaten up shares, which had lost 34% over the past 12 months through Tuesday's close, gained 4.6% even as the broader biotech sector declined.

The reason for hope is that the company seems to be at the very early stages of a turnaround. Since Chris Viehbacher was named chief executive officer in late 2022, he has pushed through steep cost cuts that have no doubt been painful for many of the company's employees. From a Wall Street perspective, though, those cuts helped deliver a beat for the quarter, with adjusted earnings per share coming at $3.67, above the $3.45 expected by analysts surveyed by FactSet.

Additionally, Viehbacher's key acquisition, the $7.3 billion purchase of Reata Pharmaceuticals, is showing promising signs. Biogen paid what was seen as a steep price last year to get its hands on Reata's drug Skyclarys, a treatment for the genetic disorder Friedreich's ataxia, a rare disease that damages the nervous system. At the time of the deal, one big risk was that the drug didn't yet have European approval.

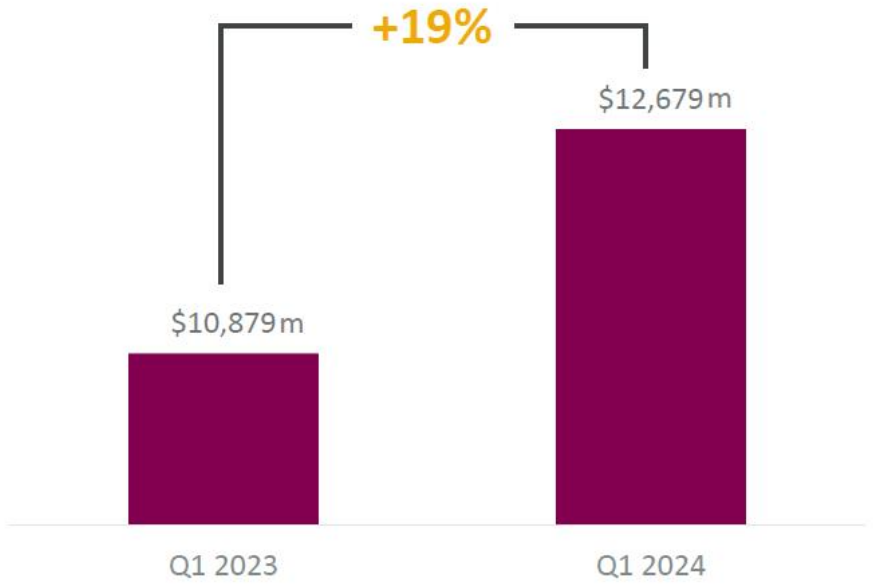
Source: https://www.wsj.com/finance/stocks/for-beaten-down-maker-of-alzheimers-drug-good-enough-will-do-a1d05a65


AstraZeneca

Strong delivery in Q1 2024

Total Revenue growth

fueled by global Product Sales



Core EPS growth

despite substantial decrease in Other Operating Income[1]

2024 dividend: 7% increase to $3.10

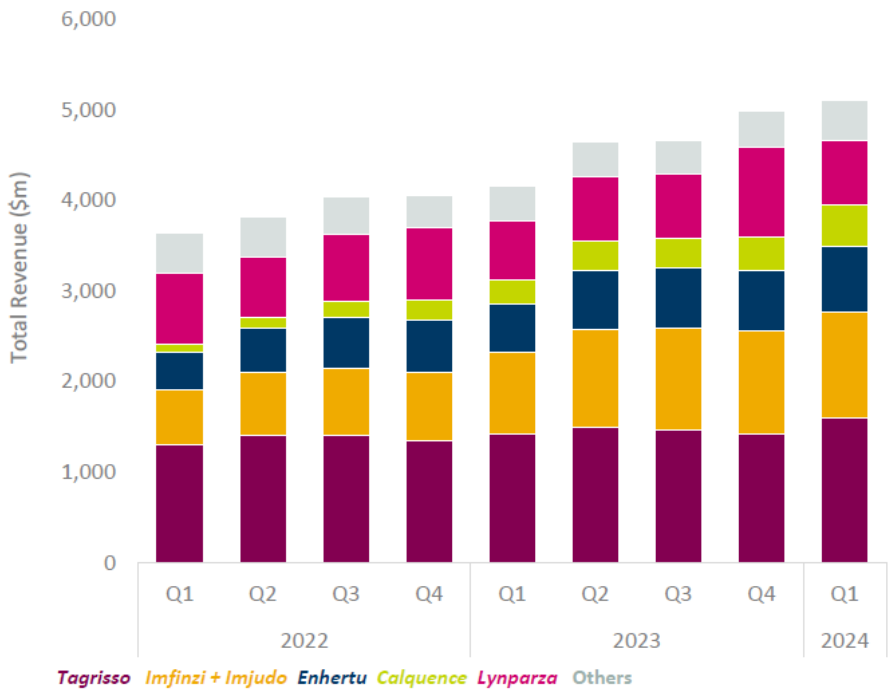
5 All growth rates at CER. Due to rounding, the sum of a number or dollar values and percentages may not agree to totals. 1. $241 million dollar gain in the first quarter of 2023 following the divestment of Pulmicort Flexhaler in the US.
Appendix: Glossary.

Oncology – Q1 2024

Total Revenue +26% with strong double-digit growth across all regions

Oncology

Q1 2024 $5.1bn, +26%



Q1 2024: key dynamics

- ***Tagrisso*** +15%, continued ADAURA and FLAURA demand, strong FLAURA2 awareness and early uptake in target patient segments
- ***Lynparza*** **PS** +11%, continued PARPi leadership
- ***Imfinzi*** +33%, achieved TOPAZ-1 (BTC) peak penetration in US, EU; JP repricing effective from February 1st
- ***Imjudo*** +70%, HIMALAYA (HCC) acceleration, durable POSEIDON (NSCLC) demand
- ***Calquence*** +35%, sustained BTKi leadership in 1L CLL
- ***Enhertu*** +79%, NPS growth in HER2+ (DB03), one-time EU pricing benefit, strong initial mBC uptake in Emerging Markets
- ***Truqap*** n/m, rapid adoption in core biomarker-altered population

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- New indications: US (*Tagrisso* FLAURA2, *Enhertu* DPT02), JP (*Truqap* CAPItello-291)
- ASCO 2024 Plenaries: *Imfinzi* ADRIATIC, *Tagrisso* LAURA

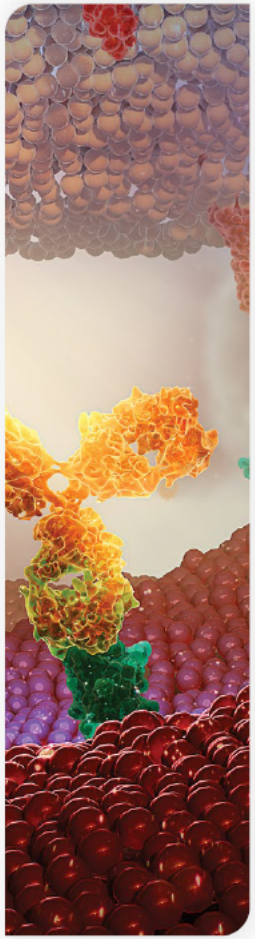
All growth rates at CER.

13 Collaboration partners: Daiichi Sankyo (*Enhertu*), Merck & Co., Inc. (*Lynparza*).

Appendix: Glossary.

Oncology – R&D highlights

Fusion Pharmaceuticals acquisition expands next-gen Radioconjugate capabilities



30-50% of patients receive conventional radiotherapy[1]

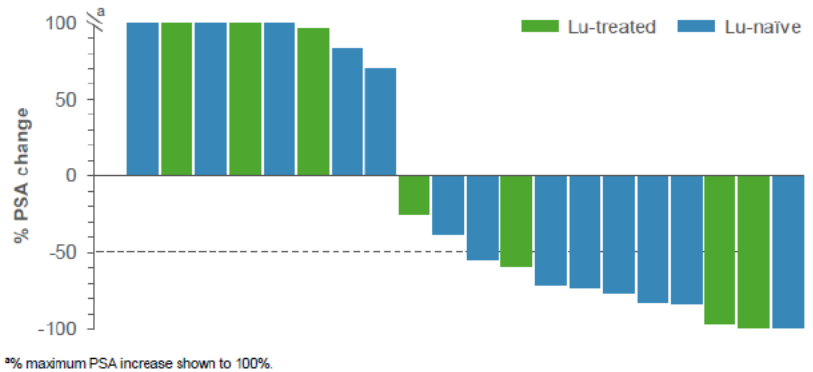
Clinical-stage portfolio, combination potential with next-gen IO and DDR

Accelerates AstraZeneca's Radioconjugate research and manufacturing to commercial build

FPI-2265 in Prostate cancer

PSMA-Actinium RC with potential post-Pluvicto and Pluvicto-naïve

Maximum percent PSA change from baseline during the treatment period (weeks 0-28) by prior Lu treatment[2]



[a]% maximum PSA increase shown to 100%.

- PSA50 achieved in 43% of Lu-treated participants
- PSA50 achieved in 54% of Lu-naïve participants
- No discontinuations from Xerostomia

Multi-blockbuster opportunity in mCRPC with FPI-2265

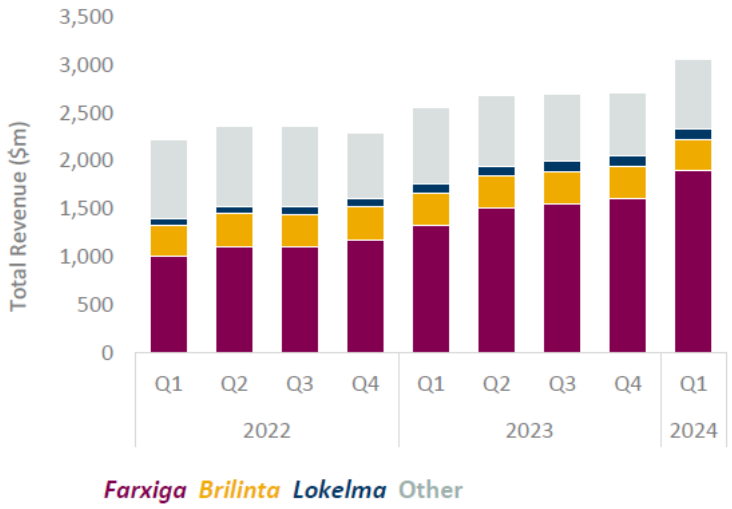
1. KANTAR data, US 2025 estimates (across lung, head and neck, prostate, bladder, endometrial, ovarian, colon, rectal and gastric cancers) 2. TATCIST data presented at AACR 2024.
Fusion Pharmaceuticals acquisition remains subject to customary closing conditions; all clinical development plans mentioned herein subject to deal closure.
Appendix: Glossary.

BioPharmaceuticals – Q1 2024

Total Revenue $5.2bn, +16% – demand growth, accelerating new launch momentum

CVRM

Q1 2024 $3.1bn, +23%

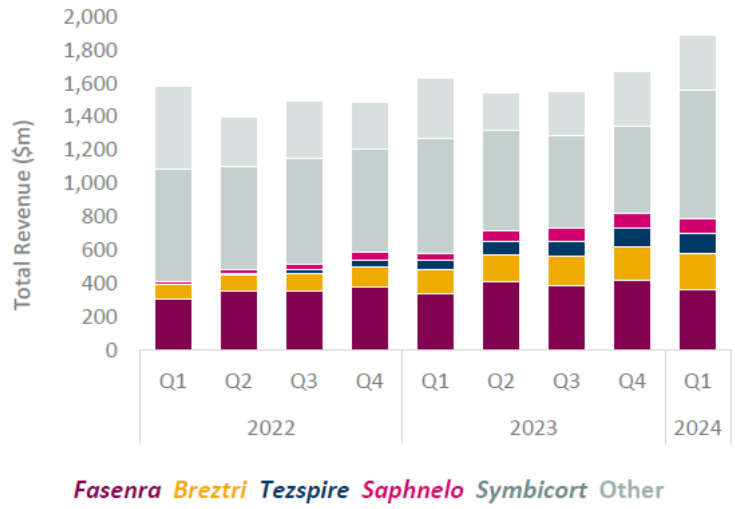


Q1 dynamics

- ***Farxiga*** +45%, demand growth outpacing SGLT2i
- ***Lokelma*** +19%, K+ Binder leadership in US
- **roxadustat** +28%, demand growth

R&I

Q1 2024 $1.9bn, +17%



Q1 dynamics

- ***Fasenra*** +6%, continued IL-5 class leadership
- ***Breztri*** +54%, global market share gains
- ***Tezspire*** >2x, strong global launch demand

AIRSUPRA™

- **>18k unique prescribers[1]**
- **65k TRx in 1Q24[2]**

WAINUA™ (eplontersen) 45 mg injection for subcutaneous use

- **Strong initial ATTRv-PN launch uptake**

Beyfortus

- **90% effective in preventing infant hospitalization[3]**

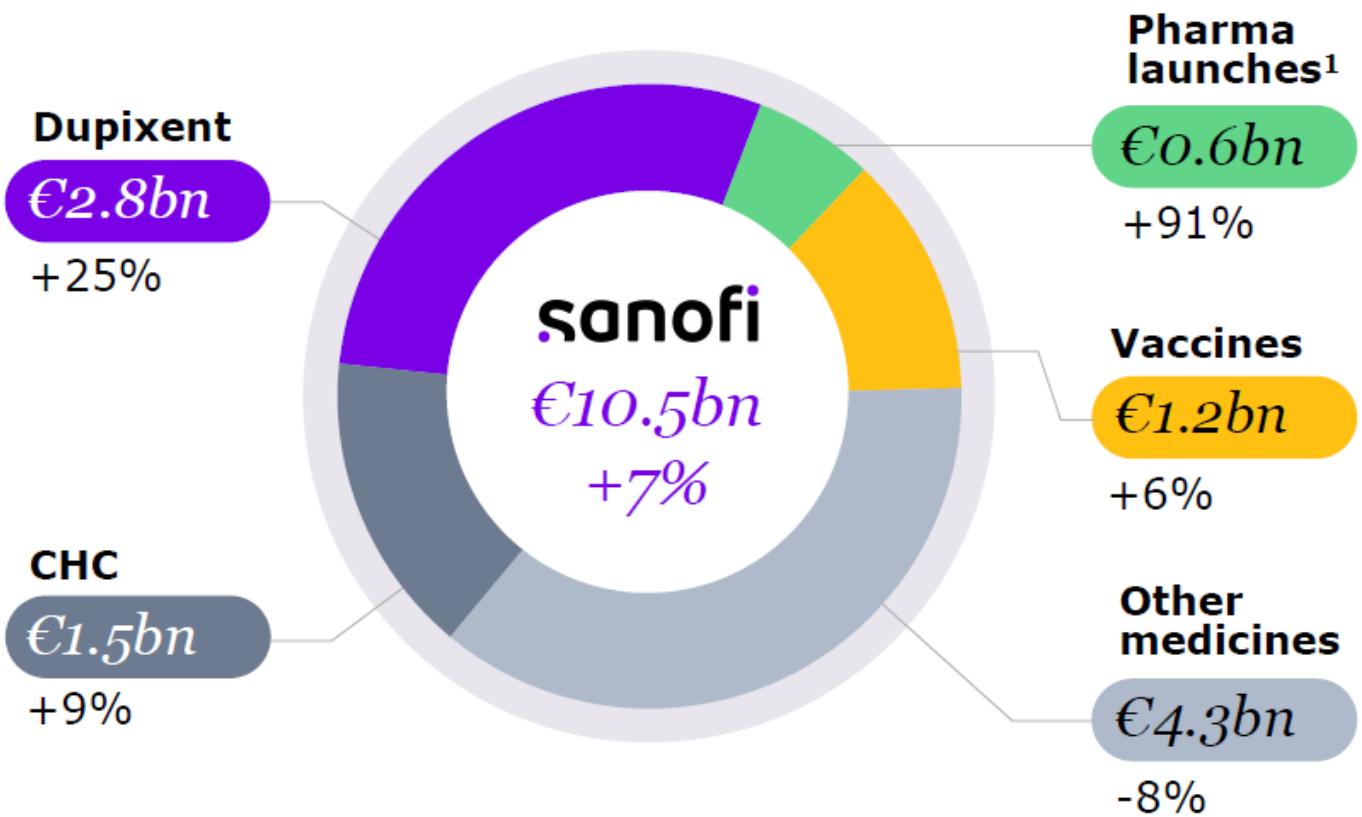
All growth rates at CER.

1. IQVIA Xponent unique prescribers data, week ending 29 March 2. IQVIA NPA Data Monthly Ending 24 March. 3. Moline, Tannis, Toepfer et. al. Centres for Disease Control and Prevention, "Early Estimate of Nirsevimab Effectiveness for Prevention of Respiratory Syncytial Virus–Associated Hospitalization Among Infants Entering Their First Respiratory Syncytial Virus Season — New Vaccine Surveillance Network, October 2023–February 2024." March 2024. Collaboration partners: Amgen (*Tezspire*); Sanofi (*Beyfortus*).

Appendix: Glossary.


sanofi

Robust growth driven by *portfolio transformation*

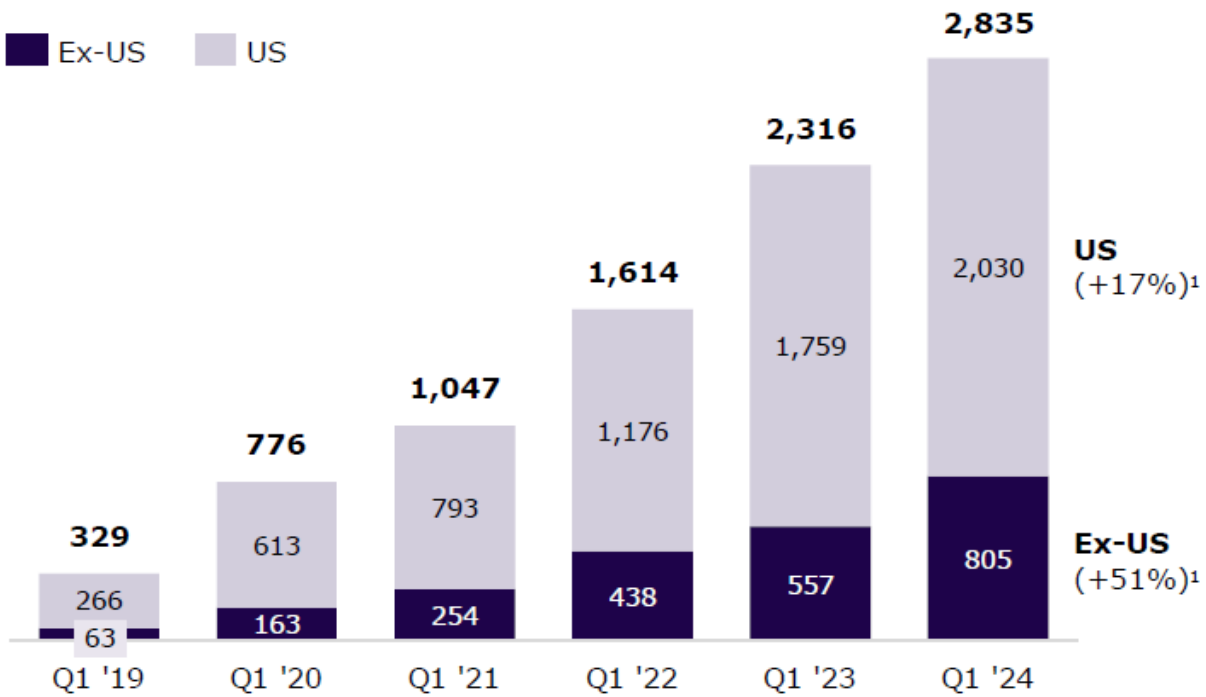


- Dupixent: continued strong growth in all indications across geographies
- Pharma launches: sustained uptake
- Vaccines: boosted by Beyfortus and flu phasing
- CHC: growth driven by focus brands and Qunol consolidation. Preparation towards separation progressing[2]

All variations at CER unless footnoted. Growth rate is vs. Q1 2023. 1. Nexviazyme, Altuviiio, Sarclisa, Rezurock, Cablivi, Xenpozyme, Enjaymo, Tzield. 2. Separation subject to markets conditions and consultations of social partners and work councils.

Dupixent: strong start and on track to deliver *~€13bn* in 2024

Global Dupixent sales (€m)



Q1 performance

- Global growth +25%
- Accelerated ex-US growth (>50%) with indication expansion
- #1 NBRx market share across ALL approved indications[2]

Expected near-term growth contributors in 2024

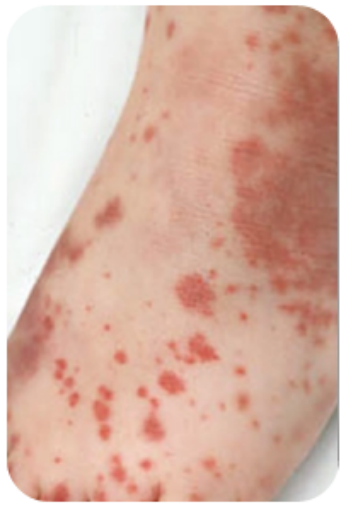
H1	*H2*
EoE US pediatric approved	**COPD** EU and CN reg. decision
CSU JP approved and reimbursed	**EoE** EU pediatric reg. decision
COPD US PDUFA June 27	

All variations at CER. 1. Represents growth Q1 2024 vs. Q1 2023. 2. IQVIA NPA Insights- weekly NBRx, data through 26/2/2024.

Rilzabrutinib: recent *positive* data support the potential as a first and best-in-class BTK inhibitor across immune diseases

Primary endpoint met in ITP phase 3 study

- Statistically significant and *clinically meaningful* durable platelet response
- Safety *consistent* with previous studies
- Confirmed previous *positive* phase 2 data
- Rare disease with high *unmet need*, **50K** chronic adult ITP patients



Regulatory submission expected in *H2 2024*

Encouraging high-dose data in asthma phase 2b study

- New high-dose data showed higher trend of relative reduction of loss of asthma control and improvement in symptoms with overall good safety confirmed
- Potential in *moderate* asthma, **1.9M+** eligible patients

Final data at *American Thoracic Society 2024*

Improved disease activity in CSU phase 2 study

- Significantly reduced weekly itch severity score (ISS7) as early as the first week of treatment
- Potential in *moderate-to-severe* CSU whose disease is inadequately controlled with H1-AH, **0.7M** eligible patients

Phase 3 start expected in *H2 2024*

€2-5bn peak sales potential across all indications | More than 2.8M eligible patients, with potential additional indications under development: wAIHA, PN, IgG4-related diseases

Rilzabrutinib LUNA 3 phase 3 study in ITP (NCT04562766). Rilzabrutinib high-dose phase 2b study in asthma (NCT05104892). Rilzabrutinib RILECSU phase 2 study in CSU (NCT05107115).
NEJM publication https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110297. All epidemiology data include UE+EU5+JP. Rilzabrutinib is currently under clinical investigation, and its safety and efficacy have not been evaluated by any regulatory authority.


MERCK

Strong Q1 sales[1] and earnings growth

Q1 Worldwide Sales

$15.8B

+9%

+12% ex-Exchange

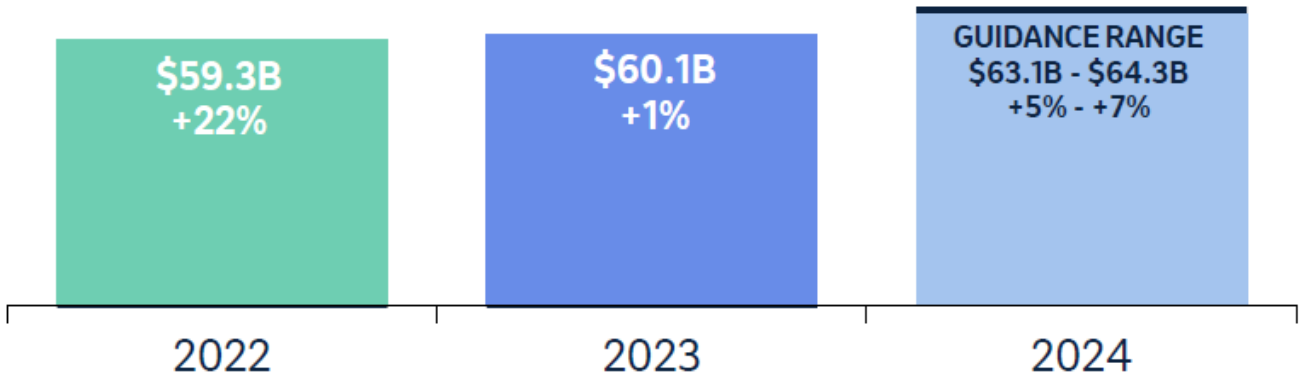
Q1 Non-GAAP EPS[3]

$2.07

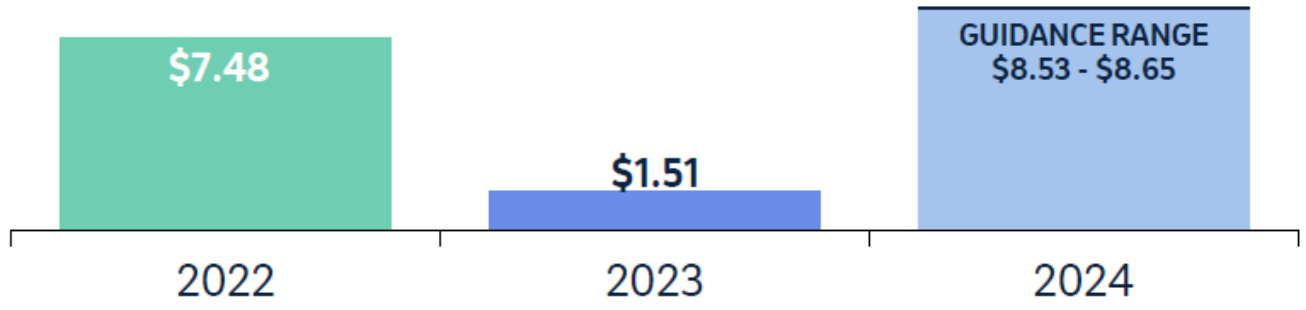
+48%

Includes one-time charge of $0.26 related to the Harpoon acquisition

Full Year Sales



Full Year Non-GAAP EPS[2]

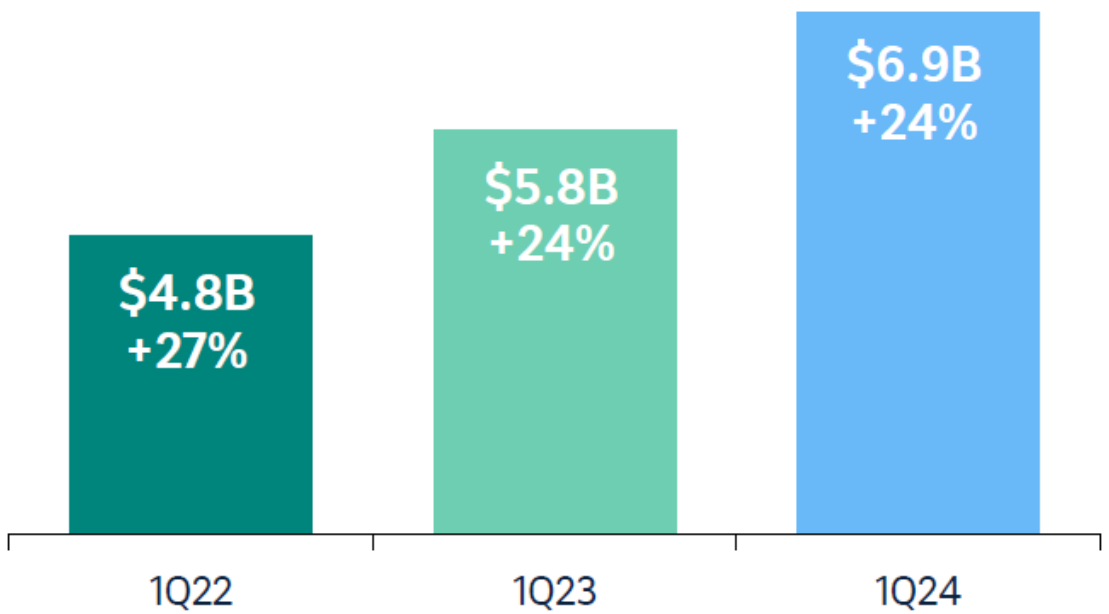


1. Results from continuing operations attributable to Merck & Co., Inc. 2. Merck does not exclude expenses for upfront and milestone payments related to certain collaborations and licensing agreements, or charges related to pre-approval assets obtained in transactions accounted for as asset acquisitions from its non-GAAP results. First quarter of 2024 and 2023 include $0.26 and $0.52 per share of such charges, respectively. Full year non-GAAP outlook for 2024 and full year reported results for 2023 and 2022 include $0.26, $6.21 and $0.22 per share of such charges, respectively. 3. GAAP EPS $1.87.

Oncology: KEYTRUDA continues to drive excellent growth

- KEYTRUDA sales of $6.9B increased 24%[1] year-over-year, driven by uptake in earlier stage cancers and continued strong demand from metastatic indications
  - In the U.S., increase largely attributable to indications in earlier stage NSCLC following launches of KN-671 and KN-091, as well as strong uptake following launch of KN-A39 in advanced urothelial cancer
  - Ex-U.S. growth reflects continued uptake in earlier stage cancers, including high-risk early-stage TNBC and adjuvant RCC, as well as demand from metastatic indications

KEYTRUDA® (pembrolizumab) Injection 100 mg



Growth rates exclude the impact of foreign exchange.
1. ~4% of the negative impact of foreign exchange was due to devaluation of Argentine peso, which was largely offset by inflation-related price increases, consistent with practice in that market.

WINREVAIR: Excited to bring a novel treatment option to adult patients with PAH

- Confident in successful launch of WINREVAIR, consistent with prior expectations
- Encouraged by high interest from patient groups and a range of relevant prescribers
- Several payers have already established coverage policies, while others are in the process of developing their policies
- Intend to provide appropriate insights to track progress, including prescription data and revenue

Broad and innovative pipeline to address significant unmet medical needs

Phase 2

Oncology

MK-1022 (patritumab deruxtecan)[6]
Gastric
Melanoma

MK-1308 (quavonlimab)
NSCLC

MK-1308A (quavonlimab +pembrolizumab)
CRC

MK-2140 (zilovertamab vedotin)
Hematological Malignancies

MK-2400 (ifinatamab deruxtecan)[6]
CRC
SCLC

MK-2870 (sacituzumab tirumotecan)[7]
Neoplasm Malignant

KEYTRUDA (MK-3475)
Advanced Solid Tumors
Prostate

KEYTRUDA (MK-3475A)
cSCC

MK-4280 (favezelimab)
NSCLC

MK-4280A (favezelimab+pembrolizumab)
Bladder
cSCC
Endometrial
Esophageal
Melanoma
RCC

MK-5890 (boserolimab)
Neoplasm Malignant

MK-5909 (raludotatug deruxtecan)[6]
Ovarian

LYNPARZA (MK-7339)[8]
Advanced Solid Tumors

LENVIMA (MK-7902)[9]
HNSCC

WELIREG (MK-6482)
Endometrial
Esophageal
HCC
Prostate
Rare Cancers

MK-7684A (vibostolimab +pembrolizumab)
Biliary
Bladder
Breast
Cervical
CRC
Endometrial
Esophageal
Gastric
HCC
HNSCC
Ovarian
Prostate
RCC

V940[10]
Bladder
RCC

Vaccines

V181
Dengue Virus

Infectious disease

MK-8527
HIV-1 prevention

MK-8591B (islatravir+MK-8507)[1]
HIV-1 infection

MK-8591D (islatravir+lenacapavir)[2,11]
HIV-1 infection

Cardiometabolic

MK-2060
Thrombosis

MK-5475
PH-COPD

MK-6024 (efinopegdutide)
NASH

WINREVAIR (MK-7962)
Pulmonary Hypertension due to Left Heart Disease

Neuroscience

MK-8189[4]
Schizophrenia

Immunology

MK-6194
Vitiligo

[1]On FDA clinical hold [2]On FDA partial clinical hold for higher doses than those used in current clinical trials
[3]Available in the US under EUA [4]Development is co-funded by Royalty Pharma [5]FDA issued CRL in December 2023
[6]In collaboration with Daiichi Sankyo [7]In collaboration with Kelun-Biotech [8]In collaboration with AstraZeneca [9]In collaboration with Eisai
[10]In collaboration with Moderna [11]In collaboration with Gilead [12]Developed under an agreement with Ridgeback Bio [13]In collaboration with Orion

Phase 3

Oncology

MK-1022 (patritumab deruxtecan)[6]
NSCLC (EU)

MK-1026 (nemtabrutinib)
Hematological Malignancies

MK-1308A (quavonlimab +pembrolizumab)
RCC

MK-2870 (sacituzumab tirumotecan)[7]
Breast
Endometrial
NSCLC

MK-3543 (bomedemstat)
Myeloproliferative Disorders

KEYTRUDA (MK-3475)
CSCC (EU)
Hepatocellular (EU)
Mesothelioma
Ovarian
SCLC

MK-3475A (pembrolizumab +hyaluronidase)
NSCLC

MK-4280A (favezelimab +pembrolizumab)
CRC
Hematological Malignancies

MK-5684 (opevesostat)[13]
Prostate

WELIREG (MK-6482)
RCC (EU)

LYNPARZA (MK-7339)[8]
NSCLC
SCLC

LENVIMA (MK-7902)[9]
Esophageal
Gastric

MK-7684A (vibostolimab +pembrolizumab)
Melanoma
NSCLC
SCLC

V940[10]
Melanoma
NSCLC

Vaccines

MK-1654 (clesrovimab)
Respiratory Syncytial Virus (RSV)

Infectious disease

MK-8591A (doravirine+islatravir)[2]
HIV-1 Infection

LAGEVRIO (MK-4482)[3,12]
COVID-19 antiviral

Immunology

MK-7240 (tulisokibart)
Ulcerative Colitis

Cardiometabolic

MK-0616
Hypercholesterolemia

Under regulatory review

Oncology

KEYTRUDA (MK-3475)
Resectable NSCLC (JPN)
1L Urothelial (EU, JPN)
1L HER2- Gastric (JPN)
1L Biliary (JPN)
Endometrial Carcinoma (US, EU, JPN)
Cervical (EU, JPN)

MK-1022 (patritumab deruxtecan)[6]
NSCLC (US)

WELIREG (MK-6482)
Certain VHL tumors (EU)
Advanced RCC (EU)

General medicine

Gefapixant (MK-7264)[5]
Cough (US)

Cardiometabolic

WINREVAIR (MK-7962)
Pulmonary Arterial Hypertension (EU)

Vaccines

V116
Pneumococcal conjugate vaccine, adult (US, EU)

As of April 25, 2024

GILEAD

Gilead Q124 Key Takeaways

Financial Results

- Total Product Sales excl. Veklury +6% YoY to $6.1B, driven by HIV, Oncology and Liver Disease
- HIV +4% YoY driven by demand, QoQ decline reflects seasonality; Oncology +18% YoY driven by demand
- CymaBay acquired IPR&D of $3.9B lowers diluted EPS by $3.14
- Non-GAAP diluted EPS $(1.32), or $1.82 excluding CymaBay impact

Virology and Inflammation

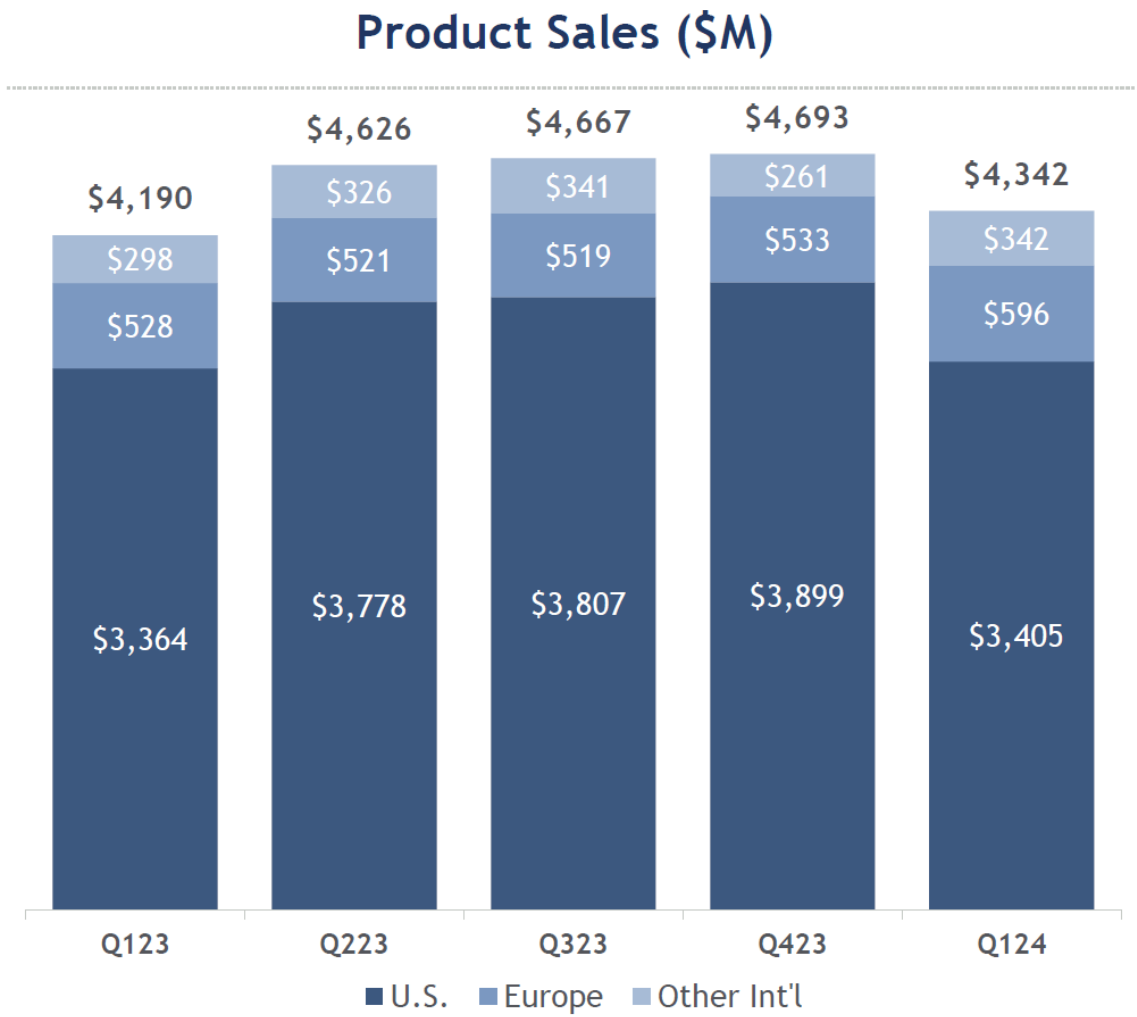
- FDA[1] and EMA[2] accepted filing for seladelpar in PBC; U.S. regulatory decision expected August 2024
- Presented ~80 abstracts at CROI, including Ph2 ARTISTRY-1, Ph2 LEN/ISL and Ph1 GS-1720 data
- Initiated Ph3 ARTISTRY trials for BIC/LEN and advancing LEN/ISL to Ph3 trials in 2024
- Expect Ph3 PURPOSE-1 update for lenacapavir for PrEP in 2H24

Oncology and Cell Therapy

- Cell Therapy event showcased Kite's global leadership across manufacturing, commercial and R&D
- Expect Ph3 FPI for earlier-line R/R MM and Ph2 iMMagine-1 update in 2H 2024
- 3 oral presentations at ASCO 2024, including Ph3 EVOKE-01, Ph2 EDGE-Gastric and Ph2 ARC-9 data
- Expect Trodelvy updates for Ph3 TROPiCS-04 in mUC in 1H24 and ASCENT-03 in mTNBC in 2H24

1. Granted breakthrough therapy designation and orphan drug status. 2. Granted priority medicines status and orphan drug designation. Note: YoY reflects Q124 vs. Q123. BIC - bictegravir, CROI - Conference on Retroviruses and Opportunistic Infections, ISL - islatravir, LEN - lenacapavir, mNSCLC - metastatic non-small cell lung cancer, mTNBC - metastatic triple-negative breast cancer mUC - metastatic urothelial cancer, OS - overall survival, PBC - primary biliary cholangitis, R/R MM - relapsed or refractory multiple myeloma.

HIV: Robust Underlying Demand



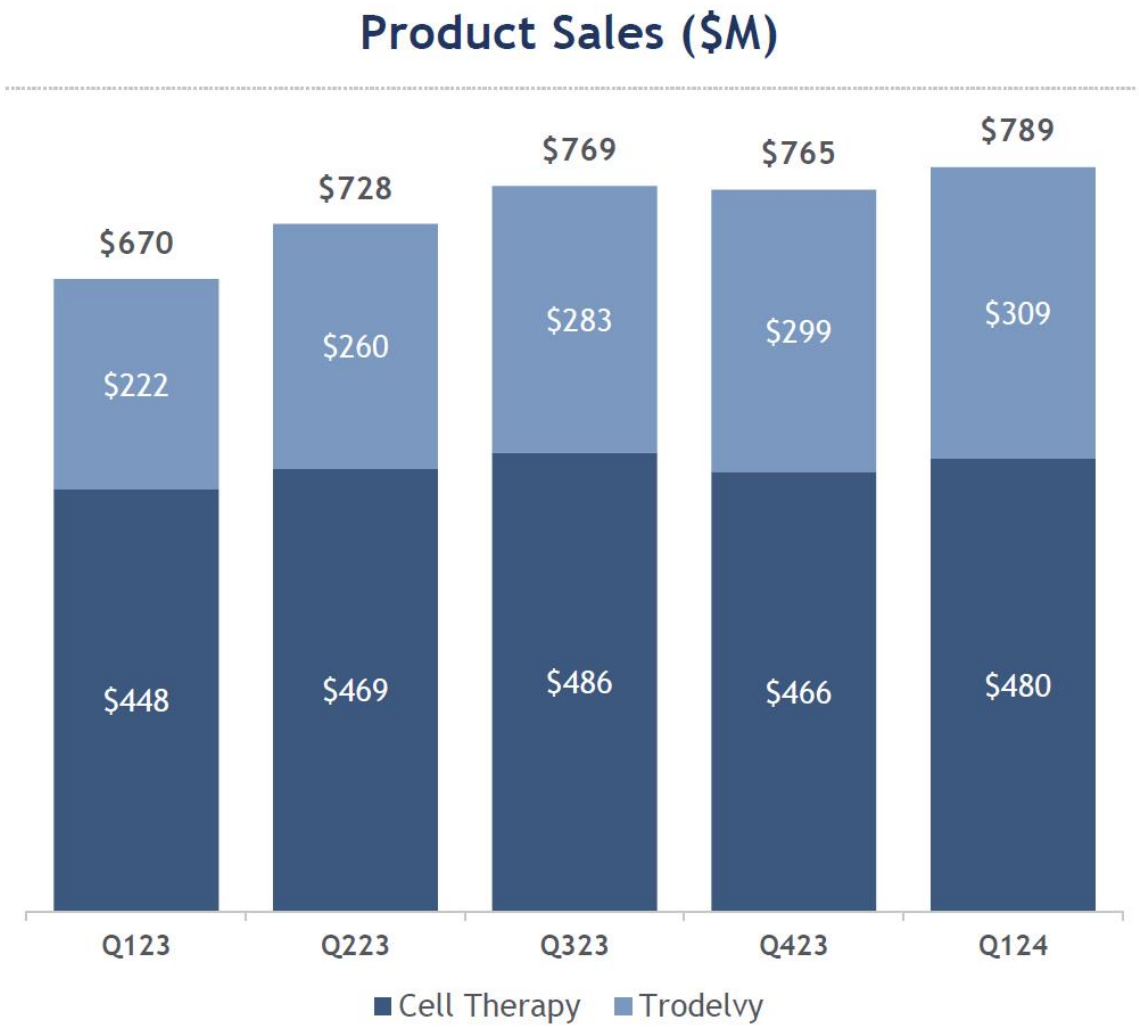
+4%
Sales growth YoY

-7%
Sales growth QoQ

- **YoY growth** primarily driven by higher demand, as well as favorable pricing dynamics in Europe that are not expected to repeat
- **QoQ decline** primarily driven by seasonal inventory and pricing dynamics, partially offset by higher demand

Note: YoY reflects Q124 vs Q123 and QoQ reflects Q124 vs Q423.

Oncology Sales: Extending Reach to New Patients



+18%
Sales growth YoY

+3%
Sales growth QoQ

>50K
Patients treated

~50
Countries approved

TRODELVY® sacituzumab govitecan

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

Note: YoY reflects Q124 vs Q123 and QoQ reflects Q124 vs Q423.

2024 Guidance

	February 6, 2024	April 25, 2024
Total Product Sales	$27.1B - $27.5B	No Change
Product Sales ex-Veklury	$25.8B - $26.2B	No Change
Veklury Sales	~$1.3B	No Change
Non-GAAP		
Product Gross Margin	85% - 86%	No Change
R&D Expense	Low to mid-single digit % growth	Mid-single digit % growth
Acquired IPR&D	$0.35B	$4.4B
SG&A Expense	Mid-single digit % decline	No Change
Operating Income	$11.2B - $11.7B	$7.0B - $7.5B
Effective Tax Rate	~19%	~30%
Diluted EPS	$6.85 - $7.25	$3.45 - $3.85
GAAP Diluted EPS	$5.15 - $5.55	$0.10 - $0.50

No Change to FY24 Revenue Guidance

- Continue to expect FY24 Total Product Sales, excl. Veklury, to grow in 4-6% range vs FY23
- Continue to expect FY24 HIV sales to grow ~4% YoY

Non-GAAP Operating Expenses

- R&D and SG&A modestly higher on a dollar basis reflecting CymaBay-related operating expenses, but within prior descriptive ranges
- Acquired IPR&D is now expected to be $4.4B driven by CymaBay acquisition and other collaboration payments

Effective Tax Rate Updated to Reflect CymaBay

- Full year tax rate reflects the negative impact of ~11% from the charge for CymaBay

This financial guidance excludes the impact of any expenses related to potential acquisitions or business development transactions that have not been executed, fair value adjustments of equity securities and discrete tax charges or benefits associated with changes in tax related laws and guidelines as Gilead is unable to project such amounts. This guidance is subject to a number of risks and uncertainties. See Forward-Looking Statements on page 2. Please refer to the accompanying press release for GAAP to non-GAAP reconciliations.


abbvie

AbbVie Topline Up Despite Humira Erosion

AbbVie Earnings Release, April 26, 2024

Worldwide net revenues were $12.310 billion, an increase of 0.7 percent on a reported basis, or 1.6 percent on an operational basis.

Global net revenues from the immunology portfolio were $5.371 billion, a decrease of 3.9 percent on a reported basis, or 3.1 percent on an operational basis, due to Humira biosimilar competition.

- Global Humira net revenues of $2.270 billion decreased 35.9 percent on a reported basis, or 35.2 percent on an operational basis. U.S. Humira net revenues were $1.771 billion, a decrease of 39.9 percent. Internationally, Humira net revenues were $499 million, a decrease of 15.8 percent on a reported basis, or 11.6 percent on an operational basis.
- Global Skyrizi net revenues were $2.008 billion, an increase of 47.6 percent on a reported basis, or 48.0 percent on an operational basis.
- Global Rinvoq net revenues were $1.093 billion, an increase of 59.3 percent on a reported basis, or 61.9 percent on an operational basis.

Global net revenues from the oncology portfolio were $1.543 billion, an increase of 9.0 percent on a reported basis, or 9.8 percent on an operational basis.

- Global Imbruvica net revenues were $838 million, a decrease of 4.5 percent, with U.S. net revenues of $610 million and international profit sharing of $228 million.
- Global Venclexta net revenues were $614 million, an increase of 14.2 percent on a reported basis, or 16.3 percent on an operational basis.
- Global Elahere net revenues were $64 million, reflecting a partial quarter of sales based on the February 12, 2024 close date of the ImmunoGen acquisition.

Source: https://investors.abbvie.com/events-and-presentations/upcoming-events

AbbVie Beats First-Quarter Expectations, but Humira Guidance Leaves Analysts Confused

Max Gelman, *Endpoints News*, April 26, 2024 (excerpt)

AbbVie's effort to protect Humira's market share is getting expensive.

On Friday, the company announced a 40% decline in the megablockbuster drug's US sales for the first quarter. While it managed to hang onto the vast majority of market share, AbbVie did so by offering substantial discounts to compete with the biosimilars that have flooded the market.

While the drop in Humira sales — which made up 18.4% of AbbVie's worldwide revenue in the first quarter — was better than Wall Street analysts had projected, the company will face far stiffer competition this quarter.

Analysts on Friday's earnings call pointed to the CVS move and asked AbbVie to clarify its expectations on Humira erosion for the rest of the year, noting execs said that it both "exceeded" and was "in line" with previous guidance. Questions also centered around whether the sales declines would continue to come from the reductions in price, or if it would stem from more physicians prescribing biosimilars, which AbbVie execs call the "price versus volume" dynamic.

Chief commercial officer Jeff Stewart said the CVS removal was anticipated, which is what fell in line with expectations that sales would continue to face pressure through 2024. Humira's first-quarter sales, meanwhile, came in higher than expected.

Source: https://endpts.com/abbvie-beats-first-quarter-expectations-but-humira-guidance-leaves-analysts-confused/

Drugmaker AbbVie expects Humira Volume Erosion to Worsen

By Leroy Leo and Christy Santhosh, *Reuters*, April 26, 2024 (excerpt)

April 26 (Reuters) – Abbvie expects a drop in sales volumes of its blockbuster arthritis drug Humira to deepen after recent changes by U.S. pharmacy benefit managers and as patients shift to other drugs.

Its shares were down nearly 5% in afternoon trade on Friday, after the company forecast U.S. Humira sales would fall 32% in the second quarter.

AbbVie's investors have been closely watching the sales trajectory of Humira - the world's top-selling drug till it lost exclusivity last year and saw the launch of nine close copies, or biosimilars, in the United States.

The company in February said it expects 36% U.S. sales erosion this year.
"What we see is that not all of the Humira prescriptions are moving to a biosimilar," Chief Commercial Officer Jeffrey Stewart said during an investor conference call.

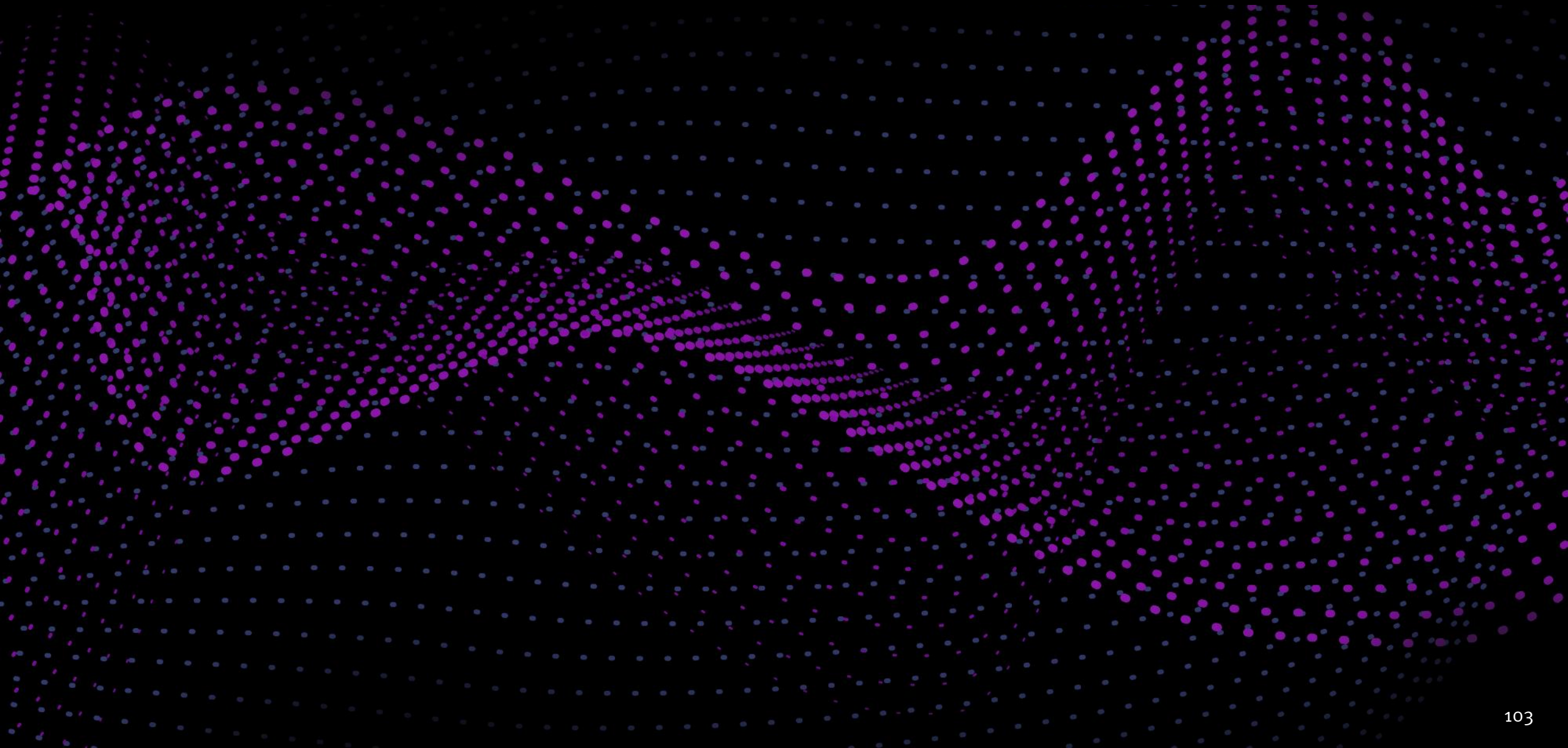
He said data showed patients were also moving to other drugs such as AbbVie's newer immunology treatments Skyrizi and Rinvoq.

The company had so far managed to retain the majority of the Humira market, with a nearly 36% fall in the sales of the drug during the quarter largely driven by price competition in the United States.

The company earlier on Friday raised its annual adjusted profit forecast to between $11.13 and $11.33 per share, compared with $10.97 to $11.17 estimated earlier. It also beat first-quarter profit estimates on strong sales of Skyrizi and cancer drug Imbruvica. Skyrizi sales of $2.01 billion beat estimates of $1.94 billion, while Rinvoq's $1.09 billion came in slightly higher than expectations of $1.06 billion.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/abbvie-raises-annual-profit-forecast-strong-skyrizi-sales-2024-04-26/

Industry News



FTC Bans Most Non-Compete Agreements

Dave Michaels and Lindsay Ellis, *Wall Street Journal*, April 23, 2024

WASHINGTON—The Federal Trade Commission on Tuesday banned employers from using noncompete contracts to prevent most workers from joining rival firms, achieving a policy goal that is popular with labor but faces an imminent court challenge from business groups.

The measure, approved by the agency's Democratic majority on a 3-to-2 vote, marks the first time in more than 50 years that FTC officials have issued a regulation to mandate an economywide change in how companies compete. The commission has historically operated like a law enforcement agency, investigating and suing individual companies over practices or deals deemed to violate the law.

The rule prohibits companies from enforcing existing noncompete agreements on anyone other than senior executives. It also bans employers from imposing new noncompete contracts on senior executives in the future.

FTC Chair Lina Khan said the rule restores rights to Americans that corporations have taken by imposing noncompete clauses in the workplace. "Robbing people of their economic liberty also robs them of all sorts of other freedoms," she said.

Source: https://www.wsj.com/politics/policy/ftc-bans-noncompete-clauses-that-restrict-job-switching-984d2187

Non-compete agreements are commonplace in the biopharma industry and can help employers to protect intellectual property.

Most biotech employees sign non-compete agreements.

This FTC order will have major effects on the biopharma sector insofar as employers will need to undertake other ways of protecting intellectual property including secrecy agreements.

Jeremy Levin: It's Moonshot Time in Neuroscience

Meagan Parrish, *Pharmavoice*, April 26, 2024 (excerpt)

PHARMAVOICE: You said in a previous interview that the industry has the potential to realize a "CNS moonshot." What kind of moonshot did you have in mind?

DR. JEREMY LEVIN: The moonshot is a fundamental array of new therapeutics. It's a change in the paradigm of thinking about how you can deal with disorders of the brain. In epilepsy, it's not just suppressing the disorder and the symptoms, but curing it at the same time. In the case of neurodegeneration, it's not just dealing with symptomatology but addressing the fundamental underlying mechanisms of the disorder. So we're entering into a phase where both of those concepts, which were never part of the daily conversation before, are now more possible.

What kinds of changes in the industry led to this moment?

In the case of CNS, there are new concepts about how small molecules can target diseases. AI … has also revolutionized how you can get a compound to target multiple targets.

And with high-resolution MRI you can look at the actual anatomy of the brain … so you can see target engagements, and then you can link that to a functional EEG test so you can build a picture of how the brain is [responding]. And then you can look at the energetics of glial cells, which really are the infrastructure of the brain. These are all things you couldn't do before. Underlying that concept is a shift in science away from the one broad-acting drug to specific treatments and cures. There are also more resources. The FDA has turned on the spigot for these drugs. Neuroscience was one of the top three FDA approval areas in the last eight years and was many of the 2023 approvals. Within that change you are also seeing … a much clearer idea of how to stratify and optimize trials.

We've got lots of reasons to dream … and there are a lot of areas that should intrigue all of us. In psychiatry you've got a whole slew of new modalities being brought into play [like] psychedelics. Then there's the idea of regenerative treatments using cell modalities … like what a company called Neurona Therapeutics [is doing]. And we are finally seeing implantable devices … that can merge mind and machine [and] help a paralyzed patient move. I've never seen a more exciting milieu of drug development. This has developed in the last 10 years and gives rise to a lot of optimism.

Jeremy Levin
Chief Executive Officer
Ovid Therapeutics

Source: https://www.pharmavoice.com/news/neuroscience-era-ovid-takeda-jeremy-levin/714381/

“My prediction stands: the bioeconomy will surpass the tech economy in impact and scale.”

Eric Schmidt
Former CEO
Google
April 25, 2024

Source: https://twitter.com/ericschmidt

Evaluate Pharma Orphan Drug Report: J&J and Roche Lead in Orphan Drug Sales

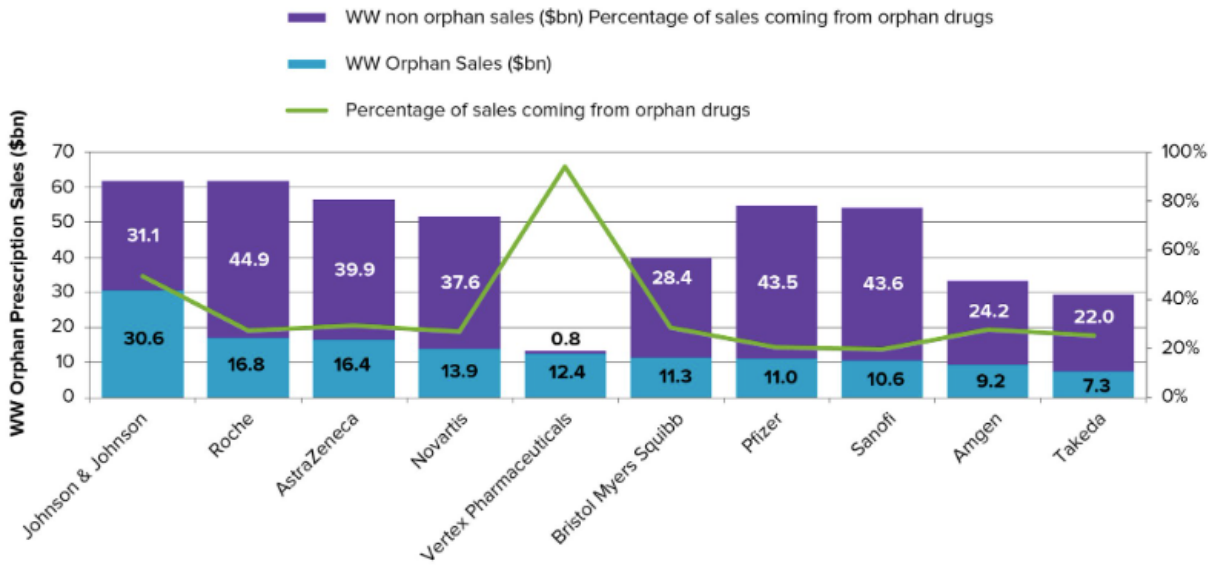
Melanie Senior, Evaluate Pharma Report, April 23, 2024

Company Rankings – Amgen Replaces AbbVie in Top Ten Company Ranking

AMGEN REPLACES ABBVIE IN TOP TEN COMPANY RANKING

AbbVie has lost its top ten spot in 2028's ranking of the largest companies by orphan drug sales. It is replaced by Amgen, whose rare diseases franchise – and ambition – was boosted thanks to the 2022 Horizon Therapeutics acquisition. That deal – bringing Tepezza for thyroid eye disease, Krystexxa for gout and Uplinza for neuromyelitis optica spectrum disorder, plus a pipeline – pushes the Big Biotech into ninth place by forecast 2028 orphan drug sales.

WW Orphan Prescription Drug Sales in 2028: Top 10 Companies



Amgen joins the top ten companies by 2028 orphan sales thanks to its Horizon acquisition

Source: https://www.evaluate.com/thought-leadership/orphan-drug-report-2024/

Evaluate Pharma Orphan Drug Report: Vertex to Have Lead Drug in 2028

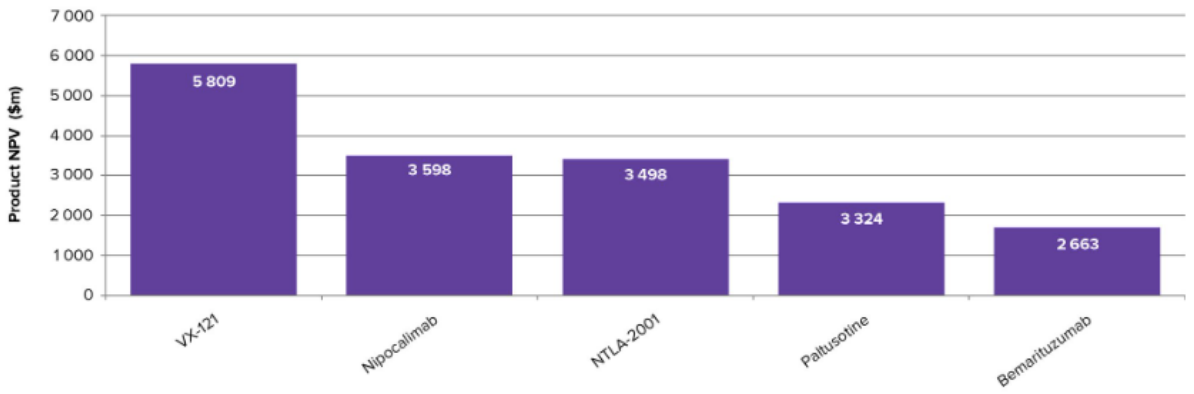
Melanie Senior, Evaluate Pharma Report, April 23, 2024

The Orphan Pipeline – The 'Vanza Triple' Dominates

VERTEX'S 'VANZA TRIPLE' DOMINATES ORPHAN PIPELINE, AFTER SOTATERCEPT APPROVAL

Vertex's Phase 3 VX-121 or "vanza triple" for cystic fibrosis – a once daily treatment that combines new molecule vanzacaftor with tezacaftor and deutivacaftor – tops the pipeline in net present value (NPV) terms. But it has done so only since March 26, 2024, when Merck's pulmonary arterial hypertension (PAH) drug sotatercept, with an NPV of close to $9 billion, was approved by FDA at Winrevair, removing it from the pipeline rankings.

Top 5 Orphan Drugs in 2028 (Phase III/ Filed) by NPV



Vertex's 'vanza triple' dominates the orphan pipeline thanks in part to its high approval likelihood

Source: https://www.evaluate.com/thought-leadership/orphan-drug-report-2024/

'Perfect Storm': Early 2024 Biotech Bounce Isn't Helping Deflated Life Sciences Real Estate Market

Patrick Sisson, *Bisnow*, April 22, 2024 (excerpt)

The stubborn mismatch of life sciences lab space — a growing glut of supply and moderation of demand — hasn't shown signs of any correction thus far in 2024.

Early analysis and data suggest that despite positive market signs and financial activity, including increased Big Pharma merger activity, the runaway success of anti-obesity drugs and a thawing of the initial public offerings market, the biotech real estate slump isn't ending soon.

"In the major life science markets, like San Diego, Boston and the Bay Area, it's still the perfect storm when it comes to the real estate side," said Savills Vice Chairman Shane Poppen, market leader for the firm's San Diego life sciences practice. "Companies just aren't taking down space at the same clip they used to. And there's no scarcity of supply anymore. In fact, it's mind-numbing how much space there is."

Preliminary data and anecdotal observations before first-quarter data is officially released show a slight uptick in absorption, as well as significant increases in vacancy and sublease space. In San Diego, early Q1 data from Savills shows the vacancy rate stubbornly high at 11.6%, reaching 15.4% if you include sublease space. Asking rents hit $78 per SF, down from $82 per SF the same quarter last year.

There has been leasing activity for lab space, as well as some significant fundraising. Matt Gardner, leader of CBRE's advisory life sciences practice, estimated $15B in Q1 alone. But the leases are typically smaller and representative of more conservative deal-making, according to Gardner. There's still a significant lag between landing funding and expanding square footage, and the likely delay of an interest rate cut from the Federal Reserve isn't accelerating a return to the energy of 2020 and 2021.

The space needs of big firms can fluctuate. In San Diego, Pfizer just signed a new 250K SF lease, but it also vacated 600K SF, creating a net loss for the market.

Leasing rates look exceptionally bad compared to 2021 because of artificial demand during the peak. Firms took extra space whenever it was available, fearing they would lose out in a low-vacancy-rate era. That means more conservative startups, battling for less VC funding and more concerned about their runway, are taking significantly less space today. Poppen said he is starting to see the first trickles of defaults, like the recent bankruptcy filing from Sorrento Therapeutics, that could become a wave.

Source: https://www.bisnow.com/national/news/life-sciences/perfect-storm-early-24-biotech-bounce-isnt-helping-deflated-life-science-real-estate-market-123913

Post-Pandemic Hangover in Bay Area Biotech Real Estate Market

Ron Leuty, *San Francisco Business Times*, April 19, 2024 (excerpt)

Crossover developers that jumped into the booming biotech space a couple years ago are seeing their buildings come online during a space glut now, driving Bay Area biotech real estate vacancy to more than 20% and setting up subleases at 30% to 40% discounts.

The good news, according to a report from real estate brokerage CBRE, Tenant demand of 2.3 million square feet in the first quarter outpaced the fourth-quarter figure by 500,000 square feet.

The problem is the demand can't match the flow of new projects hitting the market. Nine projects — new projects and conversions — were delivered from January to March, adding nearly 1 million square feet, and 7.3 million square feet of projects remain under construction. At the same time, biotech companies pressed by a nearly three-year pullback from the sector by investors have responded by cutting jobs, shelving programs and subleasing space, adding to the glut of labs and offices. **Vacancy rates that only a few years ago were 5% — or nonexistent in some submarkets, like San Francisco's Mission Bay — have skyrocketed.** The Peninsula, which accounts for nearly half of the Bay Area's net rentable biotech space, hit a first-quarter vacancy rate of 22.2%. More than half of the 1.4 million square feet of net rentable space in San Francisco was empty in the January-March period.

"What we're dealing with is a postpandemic hangover," said James Bennett, vice president of the life science practice at CBRE. "It's a convergence of that sublease space with new deliveries over the past 18 to 24 months. That will continue into the rest of 2024 and 2025 with an unprecedented wave of development."

Some 33 projects still are in development — ground-up construction as well as building conversions — totaling 7.4 million square feet, according to the CBRE report. Five projects totaling nearly 2.9 million square feet that will be delivered over the next 12 months, including the 900,000-square-foot second phase of Kilroy Realty Corp.'s (NYSE: KRC) Kilroy Oyster Point in South San Francisco and IQHQ's 592,000-square-foot Elco Yards lab-office-retail project in Redwood City, were 0% preleased as of the end of March.

Source: https://www.bizjournals.com/sanfrancisco/news/2024/04/19/vacancy-rate-bay-area-biotech-cbre.html

Biosimilar Sales Up as Insurers Begin Dropping Humira Coverage

Mollie Barnes, *Biospace*, Apr 24, 2024 (excerpt)

AbbVie has so far defended its majority market share among biologics for rheumatoid arthritis despite the loss of exclusivity for its flagship drug Humira (adalimumab). But for the first time since Humira biosimilars appeared last summer, the company's dominance might be slipping as insurers change coverage policies.

This month, **new prescriptions for Humira biosimilars surged 36%** after pharmacy benefit manager CVS Caremark removed the AbbVie product from its major formularies in favor of biosimilars for reimbursement. Sandoz's Hyrimoz accounted for 93% of that growth.

"We attribute much of the success Hyrimoz has had in the last few weeks to the formulary change, and we are building on this," a Sandoz spokesperson told BioSpace. The spokesperson said the company is negotiating with other health insurers as well. "We are hopeful that the market will further open up in 2025, and we will see [other biosimilars] displace Humira."

'Center of the Storm'

Hyrimoz is seen as one of three main competitors to Humira. The drug is currently co-preferred with Humira on both Optum and Express Scripts national formularies and has a list price more than 80% below Humira's. But despite the surge in Hyrimoz prescriptions over the past few weeks, Mizuho analyst Jared Holz said there haven't been many changes to previous estimates of a 30%–50% loss of market share for AbbVie over five years after Humira's loss of exclusivity.

So far, though, AbbVie has only lost 4% of the market to biosimilars, according to a February Samsung Bioepis report. The Big Pharma company has also made some strategic acquisitions to help offset the impact of Humira's loss of exclusivity, Holz said.

Source: https://www.biospace.com/article/biosimilar-sales-up-as-insurers-begin-dropping-humira-coverage/

ImmunityBio Announces FDA Approval of ANKTIVA®, First-in-Class IL-15 Receptor Agonist for BCG-Unresponsive Non-Muscle Invasive Bladder Cancer

CULVER CITY, Calif., April 22, 2024 — ImmunityBio, Inc. (NASDAQ: IBRX), an immunotherapy company, today announced that the U.S. Food and Drug Administration (FDA) has approved ANKTIVA (N-803, or nogapendekin alfa inbakicept-pmln) plus Bacillus Calmette-Guérin (BCG) for the treatment of patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS), with or without papillary tumors. "The FDA's approval of ANKTIVA marks our launch of a next-generation immunotherapy beyond checkpoint inhibitors," said Patrick Soon-Shiong, M.D., Executive Chairman and Global Chief Scientific and Medical Officer at ImmunityBio. "ANKTIVA not only proliferates and activates the patient's own NK cells and CD8+ killer T cells, but also activates CD4+ T helper cells, thus enhancing the proliferation of memory killer T cells. This novel mechanism of action, which mimics the biology of the dendtritic cell, begins the evolution of immunotherapy beyond T cells alone. The combination of the proliferation of key cancer-killing immune cells, together with the activation of T cells with memory, results in durable complete responses. The 'triangle offense' of tumor cell killing by the body's immune system with long-term memory is the foundation of our efforts to develop a therapeutic cancer vaccine across multiple tumor types, regardless of the site of origin."

ANKTIVA, a first-in-class IL-15 agonist immunotherapy for NMIBC, received Breakthrough Therapy Designation and approval from the FDA based on the safety and efficacy outcome of complete responses (CR) and duration of complete response (DOR). The 77 evaluable patients in this single-arm, multicenter trial received ANKTIVA with BCG maintenance therapy for up to 37 months. The tumor status was assessed with cystoscopy and urine cytology and will continue for up to five years after each patient began their participation in the trial.

The CR rate for the 77 evaluable patients was 62% with the upper end of the confidence interval being 73%. The duration of complete response as of the November 2023 cut-off was more than 47 months and is ongoing to date. These prolonged duration of complete response results beyond 24 months with ANKTIVA and BCG exceed the benchmark for the magnitude of meaningful clinical results suggested by a panel of experts at the IBCG.

Source: https://immunitybio.com/immunitybio-announces-fda-approval-of-anktiva-first-in-class-il-15-receptor-agonist-for-bcg-unresponsive-non-muscle-invasive-bladder-cancer/

U.S. FDA Approves Pfizer's BEQVEZ™ (fidanacogene elaparvovec-dzkt), Gene Therapy for Adults with Hemophilia B

April 26, 2024 — NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) announced today that the U.S. Food and Drug Administration (FDA) has approved BEQVEZ™ (fidanacogene elaparvovec-dzkt) for the treatment of adults with moderate to severe hemophilia B who currently use factor IX (FIX) prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes, and do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test. BEQVEZ is a one-time treatment that is designed to enable people living with hemophilia B to produce FIX themselves rather than the current standard of care, which requires regular intravenous infusions of FIX that are often administered multiple times a week or multiple times a month.1,2

"Many people with hemophilia B struggle with the commitment and lifestyle disruption of regular FIX infusions, as well as spontaneous bleeding episodes, which can lead to painful joint damage and mobility issues," said Adam Cuker, M.D., M.S., Director, Penn Comprehensive and Hemophilia Thrombosis Program. "A one-time treatment with BEQVEZ has the potential to be transformative for appropriate patients by reducing both the medical and treatment burden over the long term."

Hemophilia B is a rare genetic bleeding disorder that prevents normal blood clotting because of a deficiency in FIX that causes those with the disease to bleed more frequently and longer than others.3,4 The standard of care for hemophilia B treatment is prophylactic infusions of FIX replacement therapy that temporarily replace or supplement low levels of blood-clotting factor.2,4 Despite prophylaxis and regular intravenous infusions, many people living with moderate to severe hemophilia B are at risk of spontaneous bleeding episodes.5,6,7 The current standard of care also places strain on healthcare systems' budgets and resource utilization.6,8,9,10 According to the World Federation of Hemophilia, more than 38,000 people worldwide are living with hemophilia B.11

"This milestone is a testament to Pfizer's continued effort to advance the standard of care for people living with hemophilia, with the delivery of a medicine that has the potential to offer both long-term bleed protection and value to the healthcare system because of its one-time administration," said Aamir Malik, Chief U.S. Commercial Officer and Executive Vice President, Pfizer. "We are leveraging our expertise that comes with more than 40 years of experience in the hemophilia space, and are proactively working with treatment centers, payers, and the hemophilia community to appropriately help ensure the healthcare system is prepared to readily deliver BEQVEZ to the patients who can benefit from it."

With BEQVEZ now approved for use, Pfizer is launching an innovative warranty program based on durability of patient response to treatment. The goal of the warranty is to provide greater certainty to payers, maximize access for eligible patients who receive BEQVEZ, and offer financial protection by insuring against the risk of efficacy failure.

Source: https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-pfizers-beqveztm-fidanacogene-elaparvovec

Day One's Tovorafenib Receives FDA Approval for R/R BRAF-altered Pediatric Low-Grade Glioma

BRISBANE, Calif., April 23, 2024 (GLOBE NEWSWIRE)— Day One Biopharmaceuticals, Inc. (Nasdaq: DAWN) ("Day One" or the "Company"), a commercial-stage biopharmaceutical company dedicated to developing and commercializing targeted therapies for people of all ages with life-threatening diseases, today announced that the U.S. Food and Drug Administration (FDA) has approved OJEMDA (tovorafenib), a type II RAF inhibitor, for the treatment of patients 6 months of age and older with relapsed or refractory pLGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. This indication is approved under accelerated approval based on response rate and duration of response. With the approval, Day One received a rare pediatric disease priority review voucher from the FDA.

"OJEMDA ushers in a new day for children living with relapsed or refractory pLGG, and we are pleased that we can deliver a new medicine for these patients in desperate need of new treatment options. Moreover, OJEMDA is the first and only FDA-approved medicine for children with BRAF fusions or rearrangements, which are the most common molecular alteration in pLGG," said Jeremy Bender, Ph.D., chief executive officer of Day One. "We are very proud that our first approved medicine addresses this serious and life-threatening disease of childhood and adolescence. We are grateful to the pLGG community, including patients and their families, study investigators, non-profit organizations, and advocacy groups, for their collaboration and support as we strive to close the innovation gap for children with cancer awaiting new treatments."

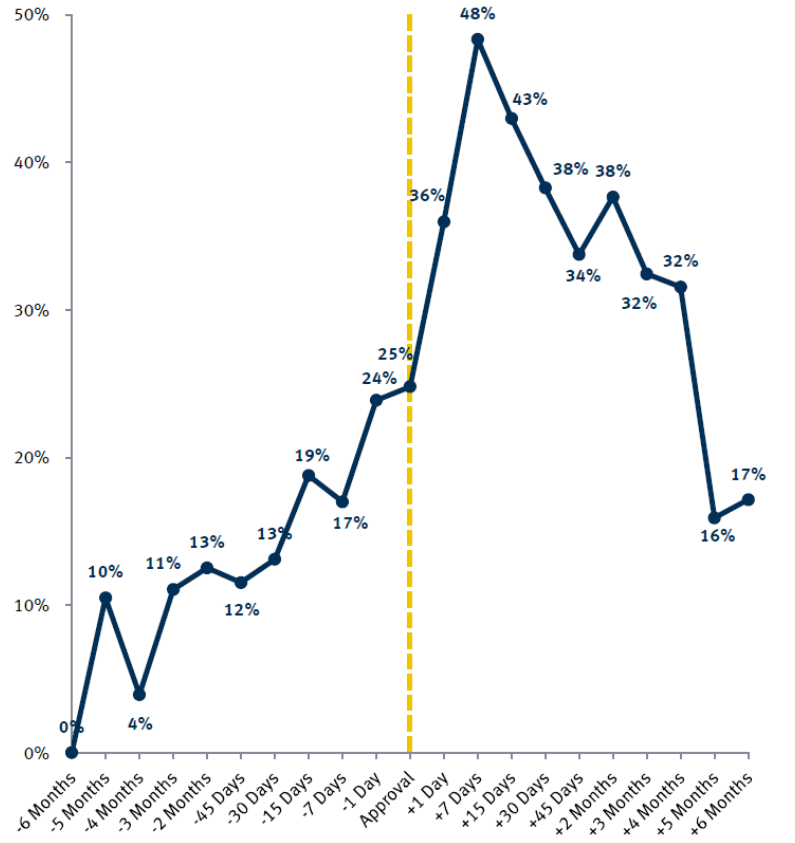
pLGG is the most common brain tumor diagnosed in children, with patients suffering profound tumor- and treatment-associated morbidities that can impact their life trajectory. BRAF is the most commonly altered gene in pLGG, with up to 75 percent of children having a BRAF alteration. Until now, there had been no medicines approved for patients with pLGG driven by BRAF fusions.

"pLGG is a chronic and relentless cancer that can devastate children and their families, often stealing their vision, balance and speech," said Dr. Sabine Mueller, pediatric neuro-oncologist, University of California San Francisco Benioff Children's Hospitals. "The goal of pLGG treatment is to stabilize or shrink the tumor without further disrupting the child's and family's life. Historically, there has been no standard of care for children with pLGG who have relapsed. We are excited to welcome a new targeted treatment option with once-weekly oral dosing designed specifically for these kids and their families."

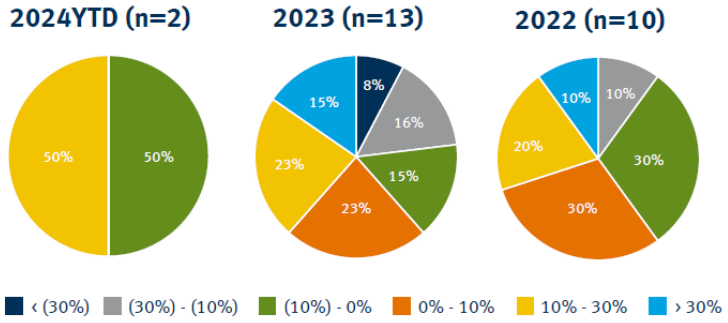
Source: https://ir.dayonebio.com/news-releases/news-release-details/day-ones-ojemdatm-tovorafenib-receives-us-fda-accelerated

Stock Price Performance of Biotechs Around First FDA Approval Events

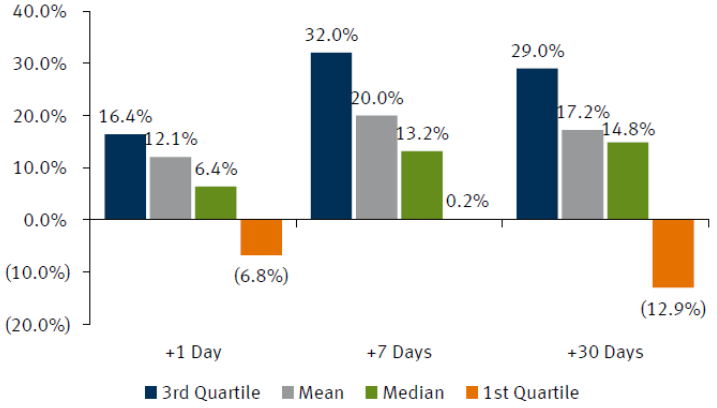
Average Stock Price Performance from 6 Months Pre-Approval to 6 Months Post-Approval



+1 Day Stock Price Performance Following FDA Approval



Stock Price Performance Following FDA Approval



Summary of Stock Price Performance for Biopharma Companies With First FDA Approval 2022-2024YTD

Approval Date[1]	Company	Product	At Approval		Stock Performance[3]		
			Equity Value	Enterprise Value[2]	-30 Days	FDA Appr.	+30 Days
3/14/2024	Madrigal Pharmaceuticals	Rezdiffra	$4,846	$4,327	23.6%	38.9%	20.9%
2/16/2024	Iovance Biotherapeutics	Lifileucel	$2,526	$2,247	5.2%	31.4%	88.9%
11/27/2023	Springworks Therapeutics	Ogsiveo	$1,300	$877	(18.1%)	(25.1%)	48.4%
11/15/2023	CorMedix	DefenCath	$172	$85	(33.0%)	(39.6%)	(25.3%)
10/30/2023	Phathom Pharmaceuticals	Vonoprazan	$492	$418	13.2%	(19.1%)	(24.2%)
9/11/2023	BioLineRX	Aphexda	$129	$107	151.3%	267.2%	139.0%
7/25/2023	Tarsus Pharmaceuticals	Xdemvy	$643	$490	26.6%	54.7%	7.2%
7/21/2023	Verrica Pharmaceuticals	Ycanth	$313	$258	33.3%	79.6%	11.6%
5/26/2023	Lexicon Pharmaceuticals	Inpefa	$603	$547	13.1%	49.3%	8.5%
5/19/2023	Krystal Biotech	Vyjuvek	$2,256	$1,906	1.4%	13.0%	51.1%
5/1/2023	Avadel Pharmaceuticals	Lumryz	$676	$692	41.7%	66.6%	143.9%
4/26/2023	Seres Therapeutics	Vowst	$807	$750	(15.5%)	(2.9%)	(15.0%)
4/17/2023	Gamida Cell	Omisirge	$91	$132	(2.6%)	(35.6%)	19.0%
2/28/2023	Reata Pharmaceuticals	Skyclarys	$1,142	$755	55.1%	26.6%	291.9%
2/17/2023	Travere Therapeutics	Filspari	$1,144	$1,078	(26.2%)	(35.8%)	(18.9%)
11/17/2022	Provention Bio	Tzield	$522	$337	37.6%	82.3%	113.9%
9/29/2022	Amylyx Pharmaceuticals	Relyvrio	$1,767	$1,560	65.0%	102.2%	137.0%
9/8/2022	Revance Therapeutics	Daxxify	$1,521	$1,675	5.4%	39.5%	60.2%
8/19/2022	Axsome Therapeutics	Auvelity	$1,710	$1,732	52.6%	43.5%	50.9%
7/29/2022	Arcutis Biotherapeutics	Zoryve	$1,251	$1,043	40.1%	65.4%	46.8%
5/24/2022	Roivant Sciences	Vtama	$2,526	$884	(44.7%)	(51.3%)	(37.2%)
4/6/2022	BioXcel Therapeutics	Igalmi	$556	$356	(49.7%)	(36.9%)	(57.8%)
3/18/2022	Marinus Pharmaceuticals	Ztalmy	$318	$240	(14.6%)	(28.8%)	(45.1%)
2/17/2022	Agios Pharmaceuticals	Pyrukynd	$1,687	$764	(22.5%)	(28.8%)	(33.2%)
1/26/2022	Immunocore Holdings	Kimmtrak	$962	$641	(10.7%)	(36.5%)	(25.6%)

Summary Statistics

3rd Quartile	$1,687	$1,078	37.6%	54.7%	60.2%
Mean	$1,198	$956	13.1%	24.8%	38.3%
Median	$962	$750	5.4%	26.6%	19.0%
1st Quartile	$522	$356	(15.5%)	(28.8%)	(24.2%)

Source: FactSet and company filings as of April 19, 2024.
Note: Includes public biopharma companies who received their first FDA approval for their lead product candidate since 2022.

Ipsen, Skyhawk Ink Potential $1.8B Deal to Target RNA in Neuro Diseases

Tristan Manalac, *Biospace*, April 22, 2024 (excerpt)

Ipsen and Skyhawk Therapeutics on Monday announced they have entered into an exclusive worldwide collaboration agreement to develop novel small molecule drugs against RNA targets in rare neurological conditions.

The companies did not reveal the specific financial breakdown of the deal but said that Ipsen is committing up to $1.8 billion, which includes the upfront payment as well as development, regulatory and commercial milestones. Skyhawk will also be entitled to tiered royalties on products that come out of the partnership.

The agreement will allow Ipsen to "explore the potential for modifying RNA expression across rare and debilitating neurological conditions," Steve Glyman, head of Ipsen's neuroscience R&D, said in a statement, adding that the company's "expertise in movement disorders" will be bolstered by Skyhawk's novel technology which is "at the cutting-edge of research."

At the center of Monday's deal is Skyhawk's proprietary platform, which combines four complementary data sets to discover and design small molecule drugs against RNA molecules that are upstream of disease-causing proteins. According to the biotech's website, this approach could potentially yield treatments for "thousands" of previously undruggable targets.

The first component of Skyhawk's platform is SKYSTAR, which combs through public and proprietary data, taking into account structural, bioinformatic and computation biology information to identify high-value RNA targets. SKYSEQ, a multiplex screening system, then tests several of these potential targets and looks through Skyhawk's repository called SKYLIBRARY for RNA-targeting compounds likely to have therapeutic effects.

The partners did not disclose what specific disease targets they will go after but Skyhawk CSO Sergey Paushkin in a statement did say noted that they will work on "rare neurological diseases for which there are no approved therapeutics."

Source: https://www.biospace.com/article/ipsen-skyhawk-ink-potential-1-8b-deal-to-target-rna-in-neuro-diseases/

Alzheimer's Drug Leqembi Falls Short of Blockbuster Status in Faltering US Rollout

Oliver Barnes, *Financial Times*, April 22, 2024 (excerpt)

Every fortnight, retired business owner Carolyn Davis drives more than 300 miles from her home in Florida's Pensacola Beach to a hospital in Atlanta, Georgia, for an hour-long infusion of a novel medicine that promises to slow the progression of Alzheimer's disease. After four years plagued by acute memory loss since her diagnosis, Davis credits Leqembi — which last year became the first fully approved treatment in the US for Alzheimer's, the most common type of dementia — with restoring a sense of normality."

I used to forget the tiniest everyday things: I'd put eggs on to boil, I'd forget. Papers were stacked four feet high on my desk," said Davis, 74. Since commencing the fortnightly infusions last November, her cognition scores have improved 20 per cent.

Leqembi, jointly developed by Japan's Eisai and US-based Biogen after hundreds of other Alzheimer's treatments flopped in clinical trials, has improved the lives of Davis and thousands of other Americans. But the rollout of the drug is stuttering.

Eisai, which is leading on Leqembi's launch, had set a target of getting 10,000 US patients on to the therapy by the end of March. Instead, only about 5,600 patients had been approved for treatment by early April, according to a registry by the Centers for Medicare & Medicaid Services shared with the Financial Times.

A combination of the heavy lifting required to deliver the treatment, high costs and concerns over its efficacy and side effects means Leqembi has fallen short of expectations, according to 10 US-based doctors interviewed by the FT."

There's not the clear-cut clinical evidence like physicians wanted, the products don't stop the disease like the patients wanted, they're never going to be as big a blockbuster as industry wanted and they don't necessarily save money for Medicare [the federal health insurance scheme]," said Robert Przybelski, a geriatrician at UW Health in Madison, Wisconsin, where about 25 patients have been treated with the drug.

Source: https://www.ft.com/content/1e02c10c-f7c4-48e9-a6a4-774531b56350

Deloitte Report on Pharma R&D Returns Released Last Week

Our analysis over the past 14 years has shown a steady decline in productivity between 2010 and 2019, a short-lived improvement due to the impact of the COVID-19 assets in 2020 and 2021, followed by a dip in 2022, and in the 2023 cycle, we are beginning to see signs of some improvement. This year's modelling, based on a dataset which includes an expanded scope of assets and line extensions, calculates that the IRR has risen to 4.1 per cent from 1.2 per cent last year, which was the lowest point for the cohort since our analysis began.

IRR depends on both efficiency (cycle times and costs) and value creation (risk-adjusted forecast sales), each of which has multiple parameters that can improve outcomes. It is therefore important to understand both the trends in costs to develop an asset from discovery to launch and also the risk-adjusted forecast revenue of the assets in the pipeline.

The average R&D cost to progress an asset from discovery to launch has remained flat for 2022-2023 at $2,284 million per asset, reflecting an expanded range of assets and line extensions in the analysis this year.

The cohort's average forecast peak sales per pipeline asset fell from $389 million in 2022 to $362 million in 2023. Reflecting the successful approval of high value assets which we have observed year-on-year, the total revenue for our cohort continues to trend upwards without interruption with reported top 20 pharma R&D sales increasing by 9.6 per cent in 2023.

Improving productivity in biopharma R&D will never be easy given the need to balance efficiency (cost) and value creation (sales), each of which depends on multiple factors that can influence the drivers of change. This year, regulatory changes, the impending and unprecedented scale of the loss of exclusivity of high value assets for many companies in our cohort, inflationary pressures, the rapid pace of scientific and technological advances and rising protocol design complexity are all placing significant pressures on the current R&D operating model but are also creating new opportunities to improve R&D productivity.

Deloitte.

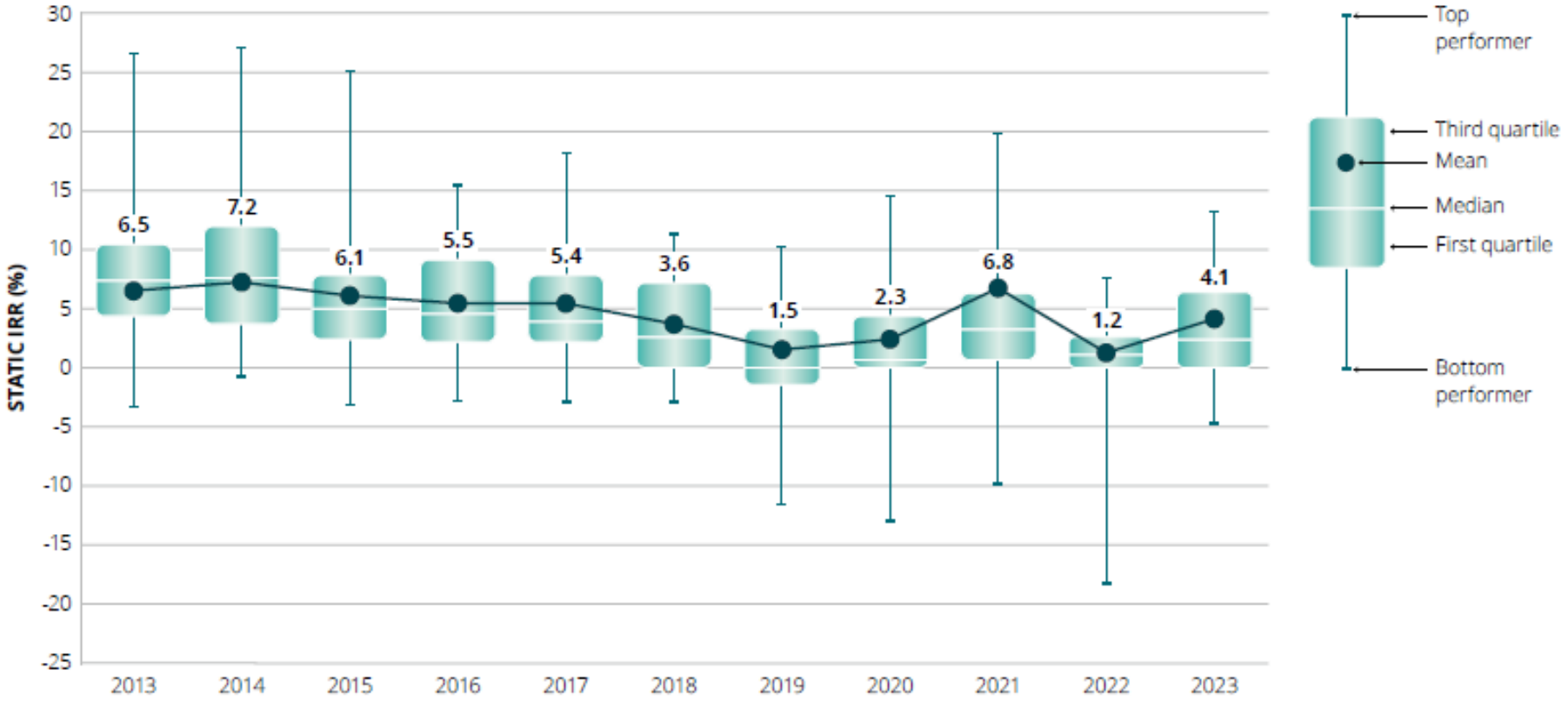
Unleash AI's potential
Measuring the return from pharmaceutical innovation – 14th edition

April 2024

Source: https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/measuring-return-from-pharmaceutical-innovation.html

Deloitte: Pharma R&D Returns Improving But Still Way Below Cost of Capital

Figure 1. Return on late-stage pipeline, 2013-2023



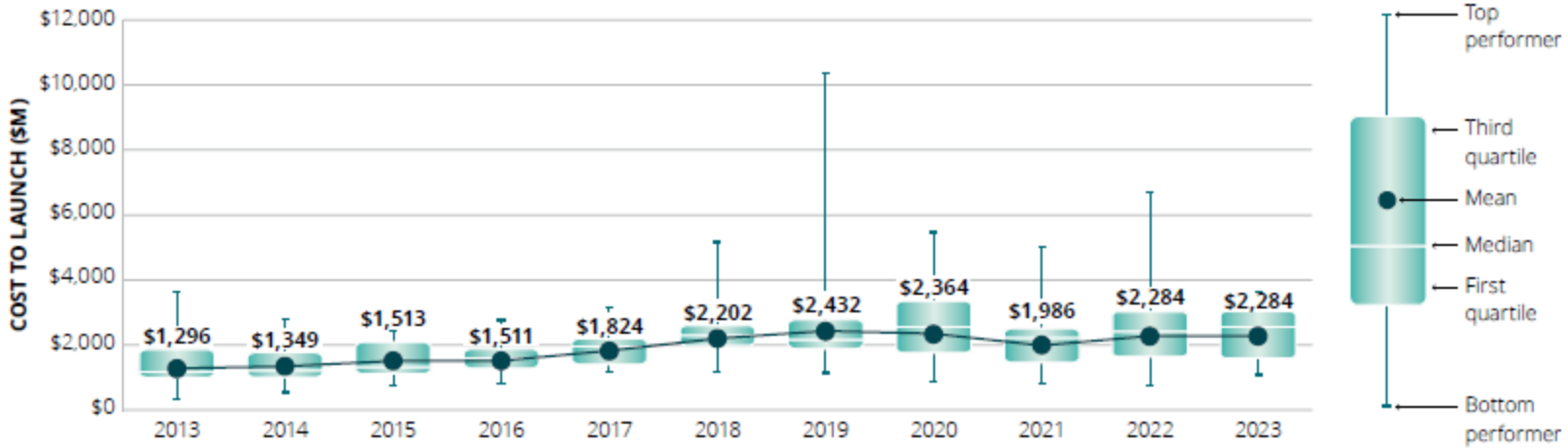
Note: 2013-2022 calculated from GlobalData dataset, 2023 data point calculated from Evaluate dataset
Source: Deloitte analysis, 2024.

Source: https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/measuring-return-from-pharmaceutical-innovation.html

While the total R&D expenditure has increased, the average cost to develop a pipeline asset is unchanged

Figure 2 shows that the average R&D cost to progress an asset from discovery to launch has remained flat for 2022-2023 at $2,284 million per asset. However, this plateau results from the larger number of assets in the 2023 portfolio due to the increase in the scope of assets and line extensions.

Figure 2. Average R&D cost to develop an asset from discovery to launch, 2013-2023

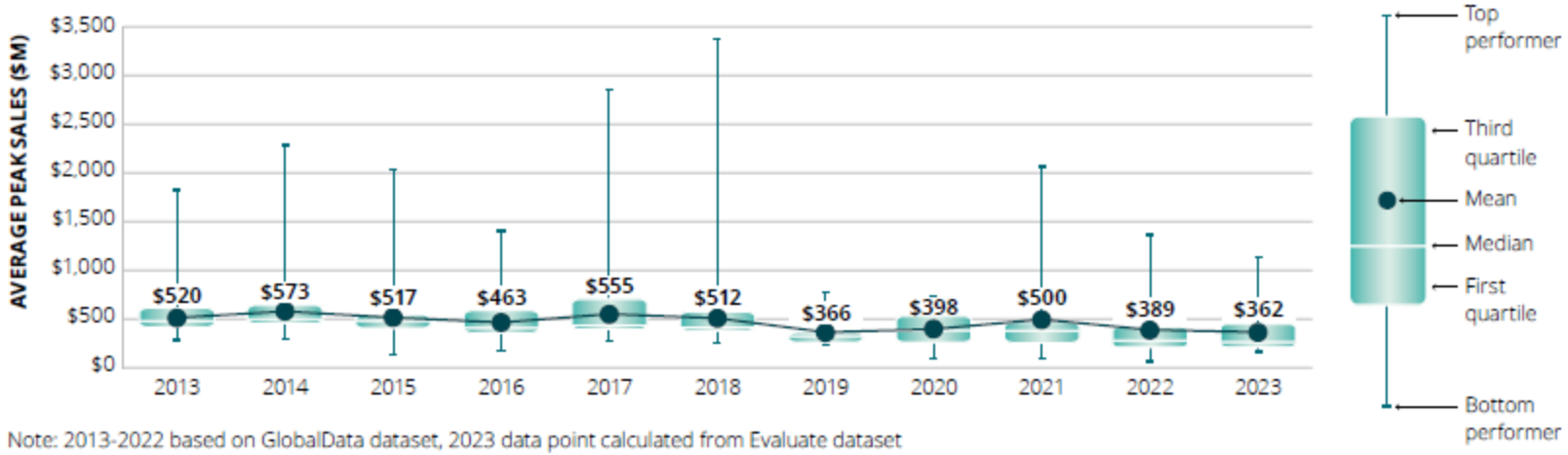


Note: 2013-2022 based on GlobalData dataset, 2023 data point calculated from Evaluate dataset
Source: Deloitte analysis, 2024.

The average forecast peak sales per asset has decreased

In 2023 only one of the companies in our analysis is predicted to achieve forecast peak sales per asset of more than $1 billion. The cohort's average forecast peak sales per pipeline asset decreased from $389 million in 2022 to $362 million in 2023, as shown in Figure 3.

Figure 3. Average forecast peak sales per pipeline asset, 2013-2023

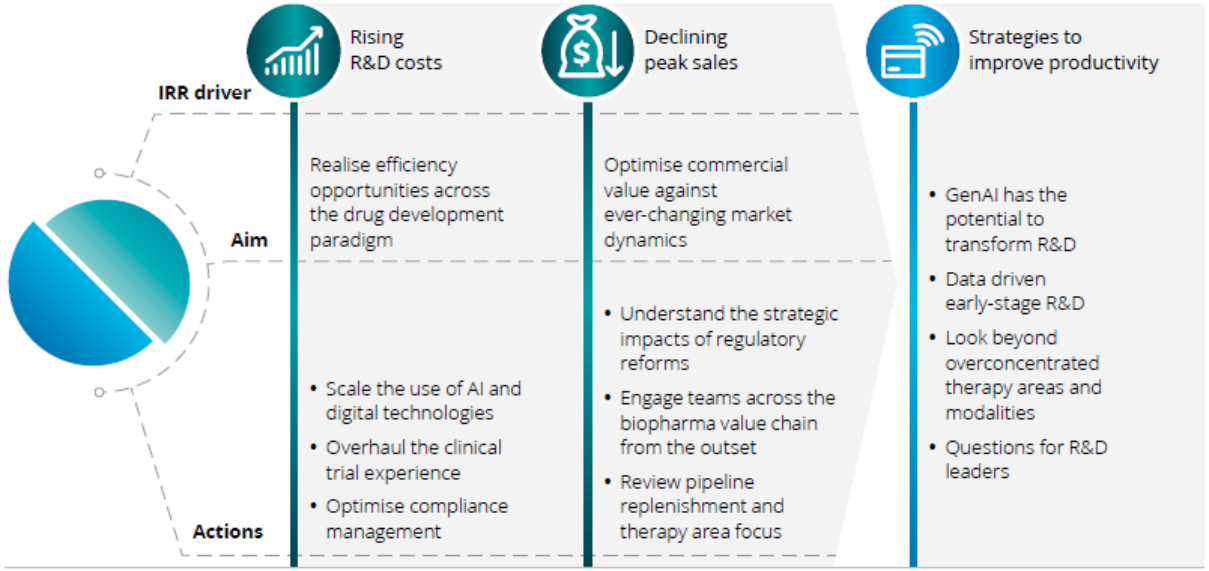


Note: 2013-2022 based on GlobalData dataset, 2023 data point calculated from Evaluate dataset
Source: Deloitte analysis, 2024.

Source: https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/measuring-return-from-pharmaceutical-innovation.html

Deloitte: Opportunities to Improve R&D Productivity

Figure 4. Opportunities to tackle the drivers of IRR and improve productivity



Source: Deloitte analysis, 2024.

Figure 8. Strategic applications of AI across the R&D value chain

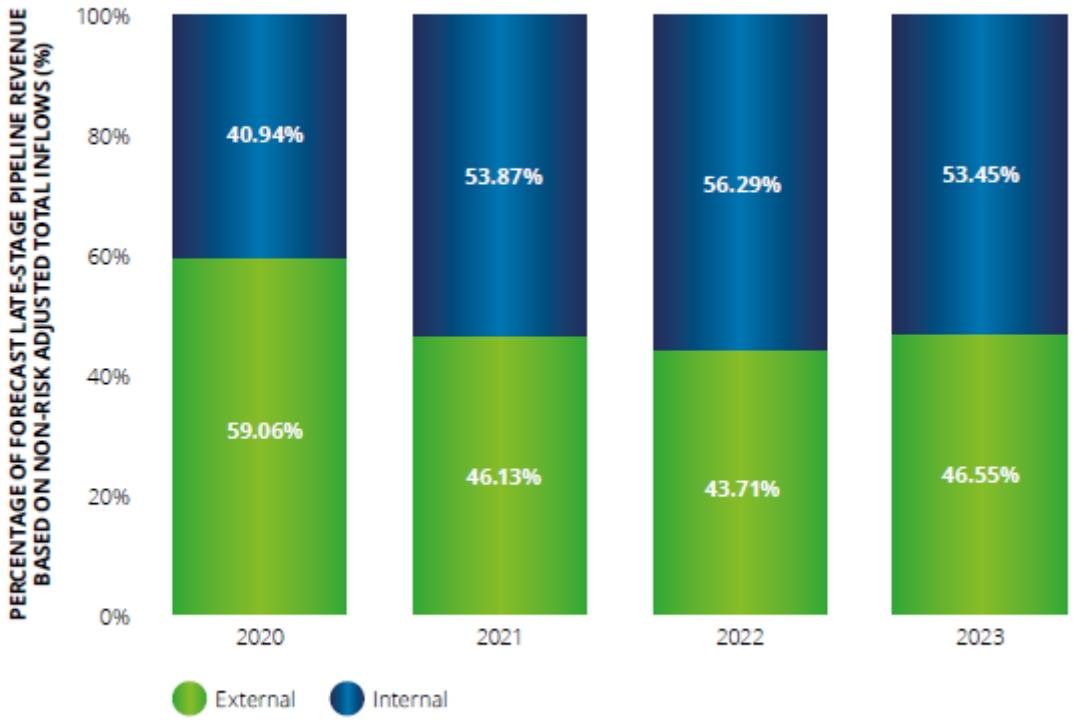
	Role of AI	Value levers
Drug repurposing	Perform meta-analysis of clinical trial and research data to generate high quality hypothesis for drug repurposing	• Reduced pre-clinical costs • Reduced time to market • Higher NDAs
AI-driven drug discovery	Optimise target and biomarker identification and shortlisting candidates while assessing toxicity and therapeutic efficacy	• Improved clinical success rate • Lower failure rates • Higher number of NDAS
Rapid design and startup	Automated protocol generation, drafting of study documents (consent form, agreements) and regulatory submissions	• Lower average protocol authoring time • Lower average time to first enrollment
Digital data flow	Collate and standardise trial data elements to create analysis-ready data sets and to auto-populate tables and charts in trial artifacts (e.g., case report forms)	• Reduced total time per phase • On-time database lock • Faster documentation creation
Regulatory intel and submission excellence	Identify regulatory requirements across geographies, generate drafts of dossiers, and understand competitor regulatory strategy	• Higher regulatory success
Participant experiences	Enhancing participant experiences with stategic nudges to revolutionise recruitment and retention strategies	• Reduced drop out rate • Faster recruitment • Lower terminations for insufficient recruitment

Source: Deloitte analysis, 2024.

Source: https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/measuring-return-from-pharmaceutical-innovation.html

Deloitte: Roughly 50% of Late-Stage Pharma Pipeline Externally Sourced

Figure 6. Proportion of late-stage pipeline forecast sourced from internal and external sources, 2020-23

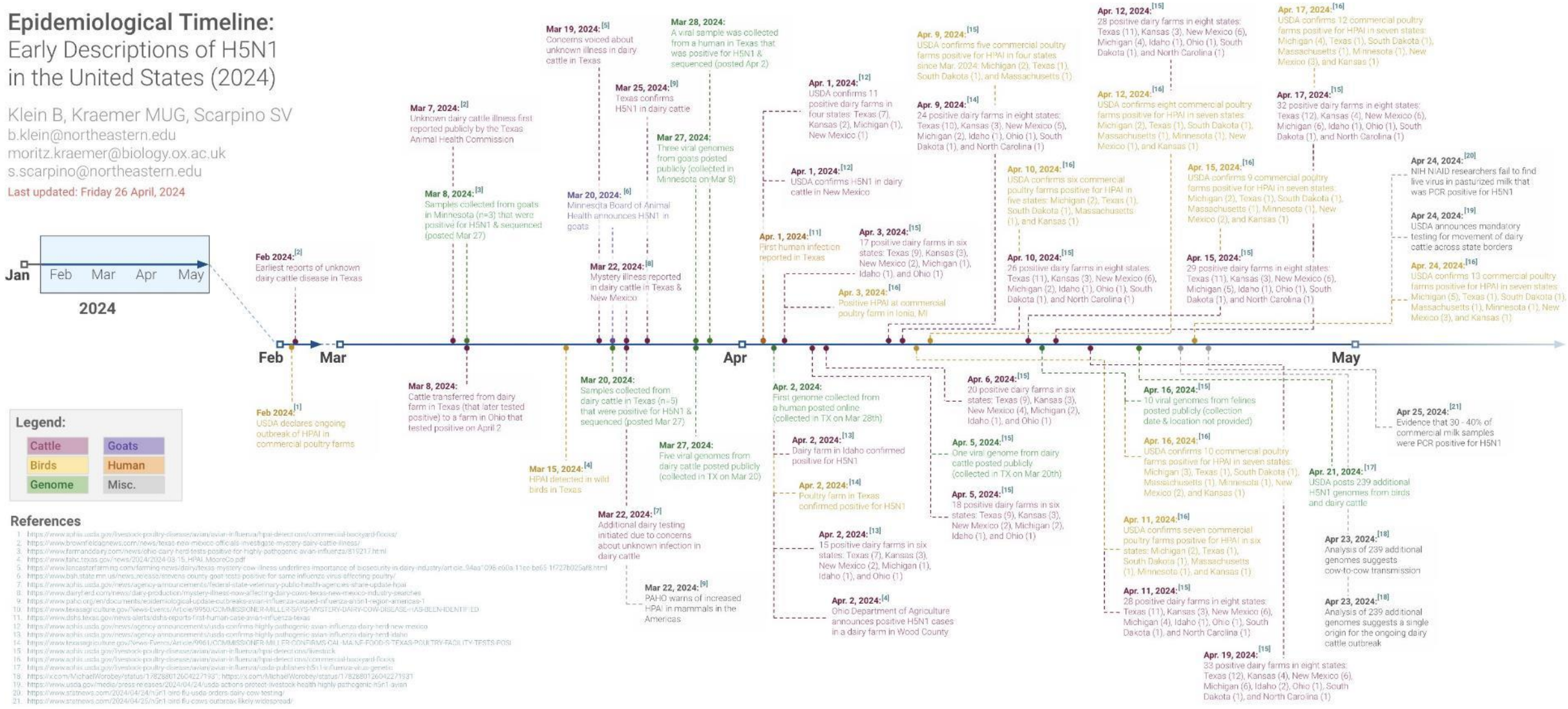


Source: Deloitte analysis, 2024.

We have looked at the composition of the cohort's pipeline with our new dataset back to 2020. For these companies, the proportion of expected revenue from internally sourced assets has remained relatively steady since 2021, at just over half the proportion of forecast revenue 50 per cent, see Figure 6.

Source: https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/measuring-return-from-pharmaceutical-innovation.html

Bird Flu H5N1 Spreading Widely in Dairy Cows



Source: https://twitter.com/svscarpino/status/1783926319991976250/photo/1

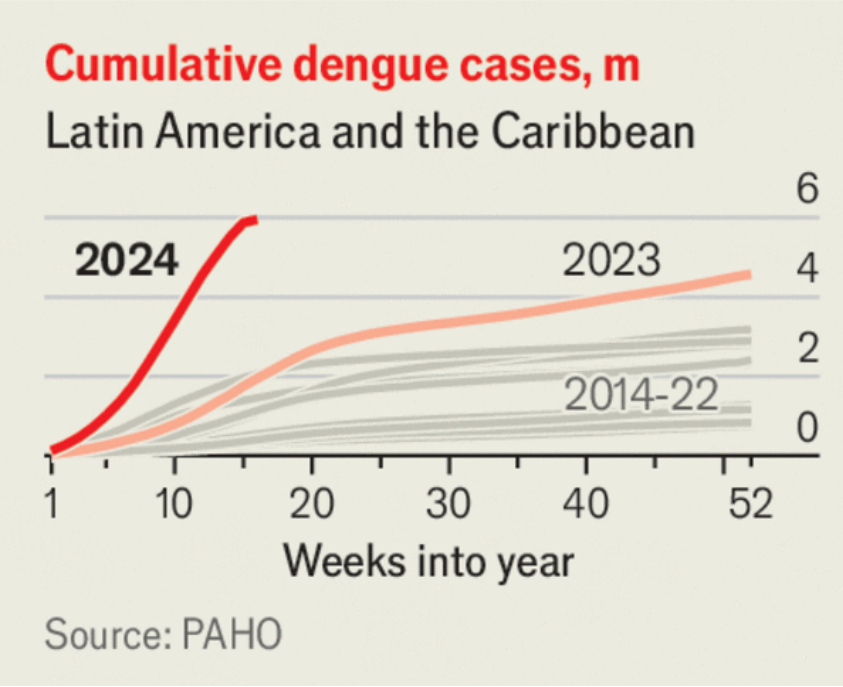
Dengue Fever on the Rise

***Economist*, April 25, 2024**

Unlike her stealthy, malaria-spreading cousin, the female *Aedes aegypti* signals her approach with an exasperating drone. Her bite is far worse than her buzz. If she carries a flavivirus pathogen, her victim can be infected with dengue fever. Most infections pass without symptoms, but an unfortunate few are racked with “breakbone fever”, which causes severe joint pain, haemorrhage and, occasionally, death. The after-effects, which are poorly understood, include fatigue and cognitive impairment. Aedes is so plentiful that the United States Centres for Disease Control and Prevention reckons 100m people around the world fall sick with dengue every year.

The number of people contracting dengue has risen dramatically. In 2000 about 20,000 people died of it, according to the World Health Organisation (who). This year at least 40,000 will perish. By contrast, between 2000 and 2022, deaths from malaria declined by 30%, the who says.

The suffering is likely to rise further and spread beyond the tropics. Aedes mosquitoes are sensitive to small changes in temperature and their range has been expanding as the planet warms. Anopheles, the species that spreads malaria, is already established in most of the world. Aedes is not. Modelling suggests that, on current trends of climate change, Aedes will spread into large parts of southern Europe and the United States, putting another 2bn people at risk of getting dengue.



Source: https://www.economist.com/leaders/2024/04/25/as-the-planet-warms-watch-out-for-dengue-fever

Science is Closing in on the Frailties of Old Age

Camilla Cavendish, *Financial Times*, April 26, 2024 (excerpt)

Do you fancy becoming immortal? Me neither. Silicon Valley titans who lust after "escape velocity from death" leave me cold. But most of us would love to stay younger for longer — preferably without Botox. A stream of breakthroughs suggests that the science of ageing is now at an inflection point.

Already, our perceptions of old age are changing. People who packed out concert halls in their youth to hear the Beatles sing "will you still need me . . . when I'm 64?" now think that old age starts at 74. According to a big German study, those in middle or older age today have an elevated idea of "old" compared to previous generations. This mirrors increases in life expectancy, especially for the better-off half of the population in rich countries. The big prize now is to improve the final decade for everyone — rich and poor.

Few of us want to live forever, even if it was on offer; but we'd give a great deal to avoid a grim descent into the twilight zone of crippling frailty. Ever since I interviewed scientists for a book about ageing, I am regularly asked for my advice on what substances to take, including "off-label". Everyone wants a longevity short-cut. American men in high-powered jobs are especially keen to experiment with products, including supplements, which are available in the US not Europe.

I myself am taking one of them, with no visible results — but then they wouldn't be visible. Given the amount of snake-oil in this market, it's safer to wait for formally licensed products. But that is now the big question: will regulators agree to consider ageing as a "treatable" condition? While conventional medicine treats one disease at a time, scientists since the 1990s have been making discoveries that suggest we could target the biology that underlies ageing itself. They have created worms and mice that live longer, and stay vibrant for longer, by targeting particular genes. Cynthia Kenyon, the biologist who found that partially disabling a single gene could double the lifespan of roundworms, described to me the awe she felt watching the modified worms wiggling around almost until death, skipping the prolonged doddery stage she observed in their normal worm friends. A steady flow of discoveries is driving the emerging field of geroscience.

Many focus on stemming the decline in the body's ability to repair DNA. Some molecular biologists are working on NAD (nicotinamide adenine dinucleotide), an enzyme central to metabolism that declines as we get older. Others, like the Australian-American David Sinclair believe that epigenetic noise is a major cause of ageing, confusing signals in the body. Sinclair and colleagues at Life Biosciences have partially restored sight to mice and monkeys.

Part of the aim of the metformin trial is to persuade the US Food and Drug Administration to approve ageing as an "indication", to signify that it can be "treated". It is struggling to raise enough funding for clinical trials, because metformin is a generic drug, so offers insufficient profit to pharmaceutical companies. The turning point may come through dogs, not humans. The wonderfully named Dog Aging Project, which has sequenced the genomes of more than 7,000 pets provided by keen owners, is conducting a clinical trial to see whether rapamycin can extend the longevity and health of our furry friends. Last year Loyal, a veterinary medicine company, announced that it had met the FDA's "reasonable expectation of effectiveness" test for a drug it is developing to lengthen canine lives.

Source: https://www.ft.com/content/bb0a8eb7-227a-400a-919a-ab7dd2f20f0b

Star Scientist's Claim of 'Reverse Aging' Draws Hail of Criticism

Alex Janin, Dominique Mosbergen and Amy Dockser Marcus, *Wall Street Journal*, April 27, 2024 (excerpt)

Harvard geneticist David Sinclair, who has said his "biological age" is roughly a decade younger than his actual one, has put forward his largely unlined face as a spokesman for the longevity movement. The 54-year-old has built his brand on the idea that aging is a treatable disease. The notion has proven so seductive that legions of acolytes follow his online postings about his research and the cocktails of supplements he consumes to stave off the inevitable.

His social-media accounts are a platform for assertions that his work is pushing nearer to a fountain of youth. He claimed last year that a gene therapy invented in his Harvard lab and being developed by a company he co-founded, Life Biosciences, had reversed aging and restored vision in monkeys. "Next up: age reversal in humans," he wrote on X and Instagram.

On Feb. 29, in the eyes of many other scientists working to unlock the mysteries of aging, he went too far. The response was swift and harsh. The Academy for Health and Lifespan Research, a group of about 60 scientists that Sinclair co-founded and led, was hit with a cascade of resignations by members outraged by his claims. One scientist who quit referred to Sinclair on X as a "snake oil salesman."

The search for eternal youth has fueled a longevity industry that attracted roughly $43 billion in global investment in the past decade, according to research and media company Longevity.Technology. Companies including Altos Labs and Alphabet's Calico Life Sciences are studying potential mechanisms and treatments for aspects of aging.

Companies are exploring techniques such as rejuvenating cells, with an aim to reverse diseases and restore cell functions that can diminish with age. Dr. Shinya Yamanaka and John B. Gurdon won a Nobel Prize in 2012 for their pioneering work in cell reprogramming.

Some longevity researchers caution that rejuvenating some cells isn't the same thing as reversing aging in people. "Reversal of aging is a term I stay away from. The evidence in humans isn't there," said Dr. Bruce Yankner, a professor of genetics and neurology at Harvard and co-director of the Paul F. Glenn Center for Biology of Aging Research.

Dr. Danielle Belardo, a cardiologist in Los Angeles, said she gets requests for off-label metformin from patients who have read Sinclair's 2019 bestseller, "Lifespan: Why We Age—And Why We Don't Have To." She said she encourages patients to stop using supplements, including resveratrol, that Sinclair and other longevity influencers have said they take. "At best, it's wasted money," she said.

Source: https://www.wsj.com/health/wellness/david-sinclair-longevity-aging-criticism-645fddc5

T-Cell Engager for Refractory RA

Bucci, L., Hagen, M., Rothe, T. et al, "Bispecific T cell engager therapy for refractory rheumatoid arthritis," *Nature Medicine*, April 26, 2024

Bispecific T cell engagers (BiTEs) kill B cells by engaging T cells. BiTEs are highly effective in acute lymphoblastic leukemia. Here we treated six patients with multidrug-resistant rheumatoid arthritis (RA) with the CD19xCD3 BiTE blinatumomab under compassionate use. Low doses of blinatumomab led to B cell depletion and concomitant decrease of T cells, documenting their engager function. Treatment was safe, with brief increase in body temperature and acute phase proteins during first infusion but no signs of clinically relevant cytokine-release syndrome. Blinatumomab led to a rapid decline in RA clinical disease activity in all patients, improved synovitis in ultrasound and FAPI-PET-CT and reduced autoantibodies. **High-dimensional flow cytometry analysis of B cells documented an immune reset with depletion of activated memory B cells, which were replaced by nonclass-switched IgD-positive naïve B cells. Together, these data suggest the feasibility and potential for BiTEs to treat RA.** This approach warrants further exploration on other B-cell-mediated autoimmune diseases.

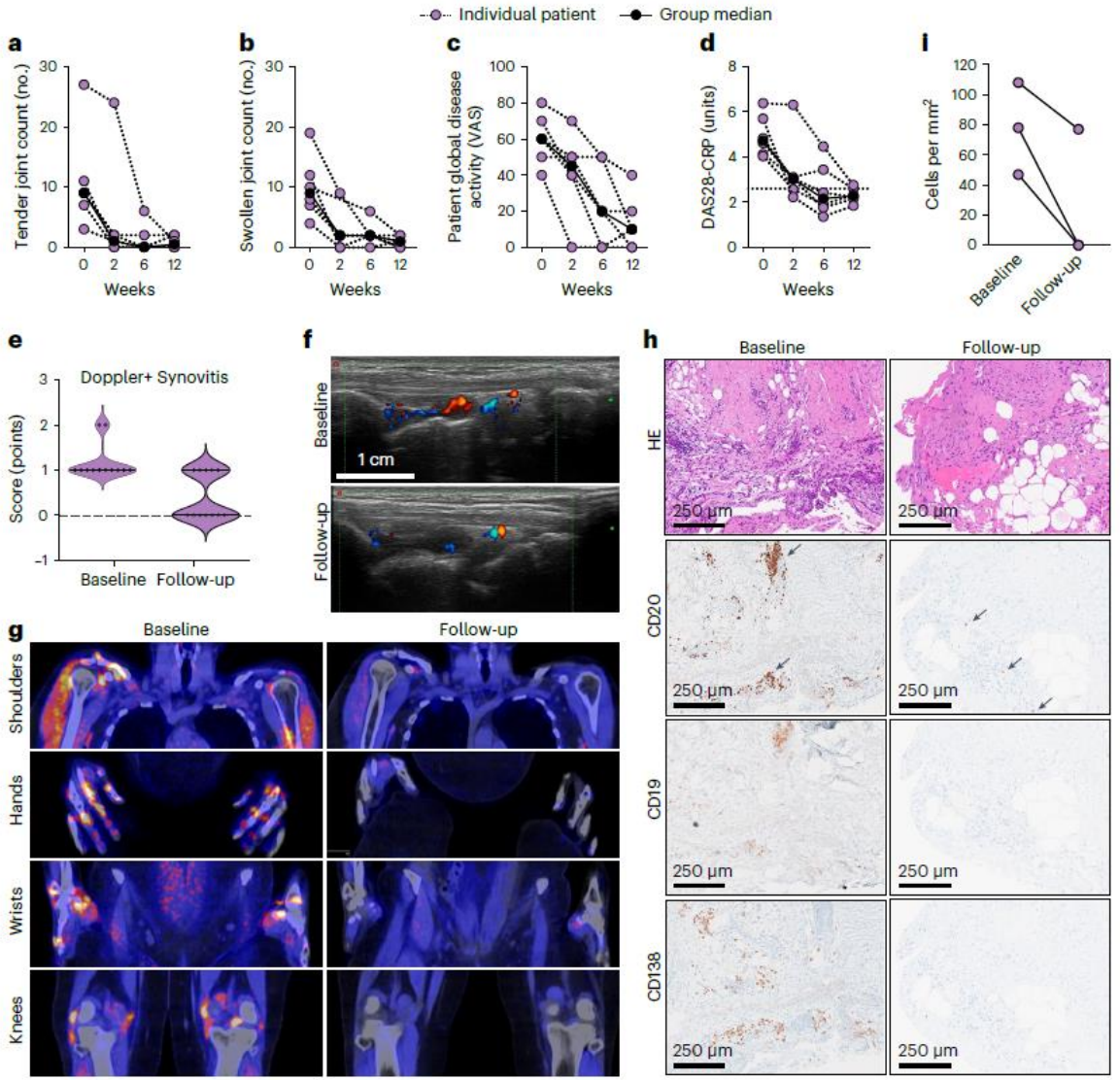


Fig. 3 | Clinical efficacy of blinatumomab therapy in RA. a–d, Effects of blinatumomab on tender joint count (**a**), swollen joint count (**b**), patient global disease activity (VAS, 0–100) (**c**) and DAS28 (**d**). Dotted horizontal line in **d** shows cut-off for remission (2.6); $n = 6$ individual patients. **e**, Quantification of PD before (baseline) and after (follow-up) therapy with blinatumomab; $n = 12$ joints from $n = 6$ individual patients. **f**, Example of decrease in PD signal in the wrist before and after blinatumomab (patient 5). **g**, Example of FAPI-PET-CT before and 3 months after therapy with blinatumomab (patient 2). **h**, Example of immunohistochemistry of synovial tissue of wrist joint biopsies before blinatumomab and 3 months after blinatumomab (patient 6). Staining with hematoxylin eosin (HE) and CD19⁺ B cells, CD20⁺ B cells and CD138⁺ plasmablasts/plasma cells is shown. All pictures were taken at ×200 magnification using the software ndpView (Hamamatsu). **i**, All five sections of synovial biopsies of patients 1 (proximal interphalangeal joint), 4 and 6 (both wrist joints) were examined for the presence of CD19⁺CD20⁺ B cells before blinatumomab and 3 months after blinatumomab.

Source: https://www.nature.com/articles/s41591-024-02964-1

UCSF Study: Possible to Predict Onset of MS Many Years Ahead of Time in a Subset of Patients

Zamecnik CR, An autoantibody signature predictive for multiple sclerosis. *Nat Med*. April 19, 2024.

Although B cells are implicated in multiple sclerosis (MS) pathophysiology, a predictive or diagnostic autoantibody remains elusive. In this study, the Department of Defense Serum Repository (DoDSR), a cohort of over 10 million individuals, was used to generate whole-proteome autoantibody profiles of hundreds of patients with MS (PwMS) years before and subsequently after MS onset. This analysis defines a unique cluster in approximately 10% of PwMS who share an autoantibody signature against a common motif that has similarity with many human pathogens. These patients exhibit antibody reactivity years before developing MS symptoms and have higher levels of serum neurofilament light (sNfL) compared to other PwMS. Furthermore, this profile is preserved over time, providing molecular evidence for an immunologically active preclinical period years before clinical onset. This autoantibody reactivity was validated in samples from a separate incident MS cohort in both cerebrospinal fluid and serum, where it is highly specific for patients eventually diagnosed with MS. This signature is a starting point for further immunological characterization of this MS patient subset and may be clinically useful as an antigen-specific biomarker for high-risk patients with clinically or radiologically isolated neuroinflammatory syndromes.

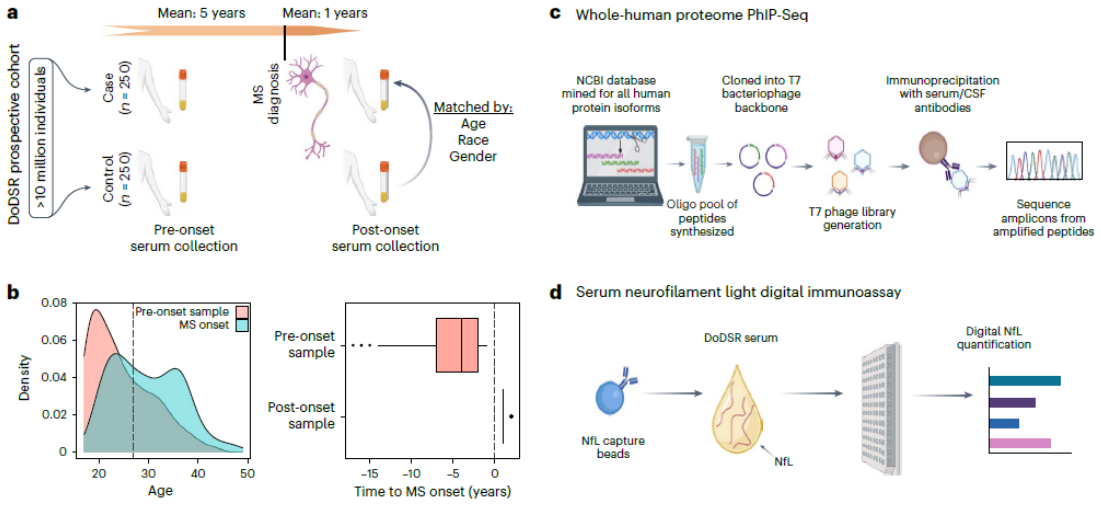


Fig. 1 | Overview of MS biomarker study. a, Schematic of DoDSR cohort and collection. **b**, Age and time to symptom onset for MS cases (data are presented as median values; box edges are 1st and 3rd quartiles; and whiskers represent 1.5× interquartile range; $n = 250$ for each group). **c**,**d**, Molecular biomarker assays performed on DoDSR cohort of longitudinal sera. NCBI, National Center for Biotechnology Information.

Source: https://pubmed.ncbi.nlm.nih.gov/38641750/

Antibody Highly Effective in Preventing Malaria

Kayentao et.al., *N Engl J Med* April 26, 2024;390:1549-1559

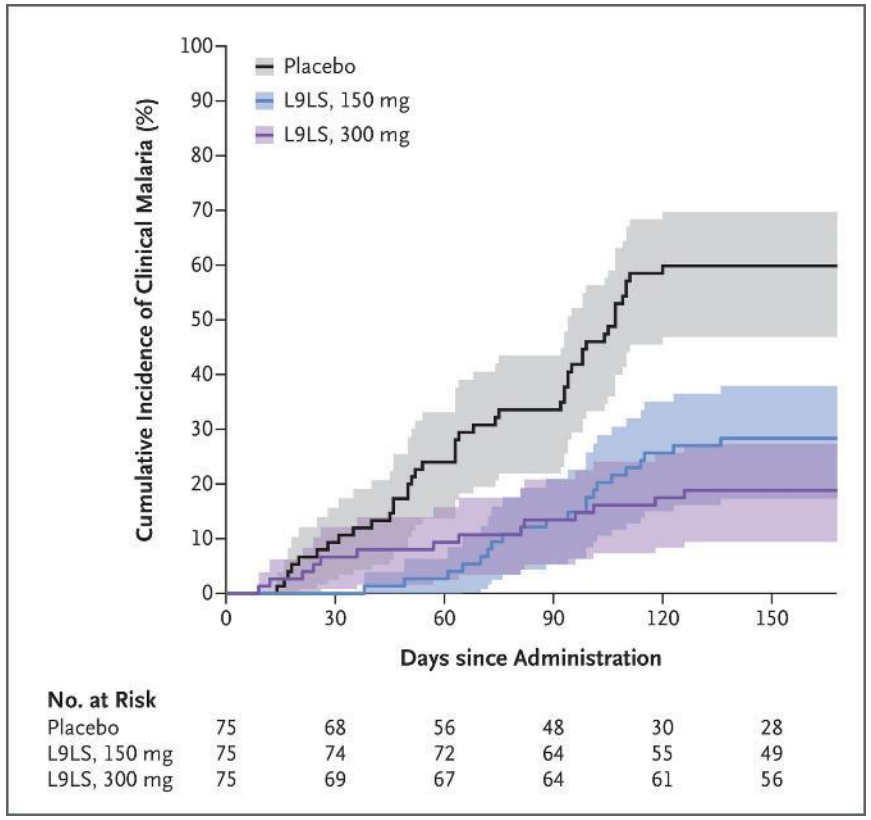
Subcutaneous administration of the monoclonal antibody L9LS protected adults against controlled *Plasmodium falciparum* infection in a phase 1 trial. Whether a monoclonal antibody administered subcutaneously can protect children from P. falciparum infection in a region where this organism is endemic is unclear. We conducted a phase 2 trial in Mali to assess the safety and efficacy of subcutaneous administration of L9LS in children 6 to 10 years of age over a 6-month malaria season. In part A of the trial, safety was assessed at three dose levels in adults, followed by assessment at two dose levels in children. In part B of the trial, children were randomly assigned, in a 1:1:1 ratio, to receive 150 mg of L9LS, 300 mg of L9LS, or placebo. The primary efficacy end point, assessed in a time-to-event analysis, was the first P. falciparum infection, as detected on blood smear performed at least every 2 weeks for 24 weeks. A secondary efficacy end point was the first episode of clinical malaria, as assessed in a time-to-event analysis.

RESULTS

No safety concerns were identified in the dose-escalation part of the trial (part A). In part B, 225 children underwent randomization, with 75 children assigned to each group. No safety concerns were identified in part B. P. falciparum infection occurred in 36 participants (48%) in the 150-mg group, in 30 (40%) in the 300-mg group, and in 61 (81%) in the placebo group. The efficacy of L9LS against P. falciparum infection, as compared with placebo, was 66% (adjusted confidence interval [95% CI], 45 to 79) with the 150-mg dose and 70% (adjusted 95% CI, 50 to 82) with the 300-mg dose (P<0.001 for both comparisons). Efficacy against clinical malaria was 67% (adjusted 95% CI, 39 to 82) with the 150-mg dose and 77% (adjusted 95% CI, 55 to 89) with the 300-mg dose (P<0.001 for both comparisons).

CONCLUSIONS

Subcutaneous administration of L9LS to children was protective against P. falciparum infection and clinical malaria over a period of 6 months. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT05304611.)



Shown is the cumulative incidence of the first clinical malaria episode due to P. falciparum infection during a 6-month malaria season after a single subcutaneous injection of 150 mg of L9LS, 300 mg of L9LS, or placebo. The prespecified definition of clinical malaria that was used in this analysis was an illness accompanied by a measured axillary temperature of at least 37.5°C or a history of fever (subjective or objective) in the previous 24 hours and P. falciparum asexual parasitemia of more than 5000 parasites per cubic millimeter as detected on microscopic examination of thick blood smears (definition 1).

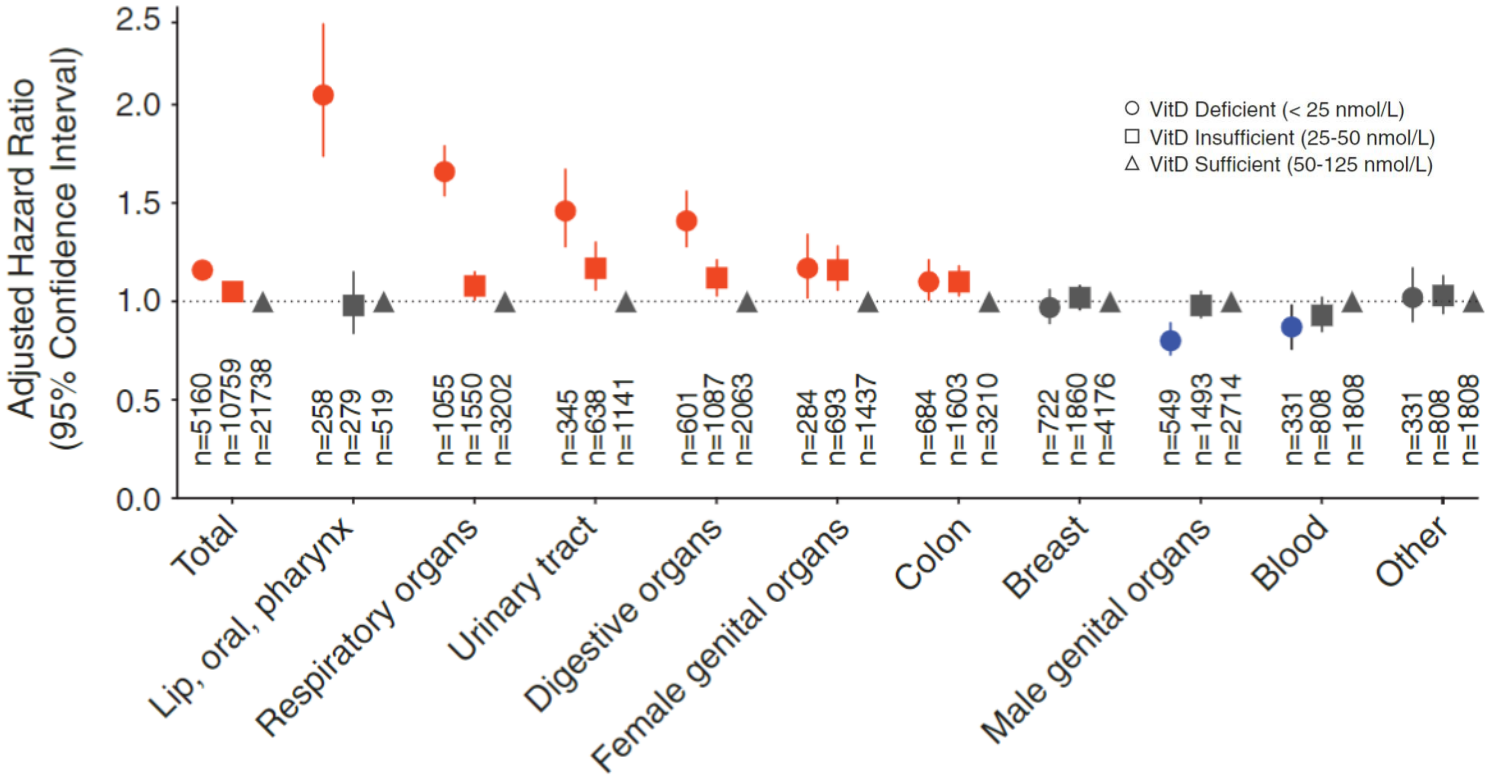
Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2312775

Vitamin D Deficiency is Linked to Death from Cancer

Giampazolias E., et.al., "Vitamin D regulates microbiome-dependent cancer immunity," *Science*. Apr 26, 2024;384(6694):428-437.

A role for vitamin D in immune modulation and in cancer has been suggested. In this work, we report that mice with increased availability of vitamin D display greater immune-dependent resistance to transplantable cancers and augmented responses to checkpoint blockade immunotherapies. Similarly, in humans, vitamin D–induced genes correlate with improved responses to immune checkpoint inhibitor treatment as well as with immunity to cancer and increased overall survival. In mice, resistance is attributable to the activity of vitamin D on intestinal epithelial cells, which alters microbiome composition in favor of Bacteroides fragilis, which positively regulates cancer immunity. Our findings indicate a previously unappreciated connection between vitamin D, microbial commensal communities, and immune responses to cancer. Collectively, they highlight vitamin D levels as a potential determinant of cancer immunity and immunotherapy success.

Risk of Death from Cancer 20% Higher Among Vitamin D Deficient Persons



Source: https://www.science.org/doi/10.1126/science.adh7954

Vitamin Deficiency Well Known to Increase Cancer Risk

Gupta D, Vashi PG, Trukova K, Lis CG, Lammersfeld CA. Prevalence of serum vitamin D deficiency and insufficiency in cancer: Review of the epidemiological literature. *Exp Ther Med.* March 2011 Mar;2(2):181-193.

Vitamin D deficiency has been found to be associated with a variety of cancers, including prostate, multiple myeloma, colorectal and breast cancer. Certain studies have shown vitamin D levels to have an inverse relation with cancer mortality while others have considered it a potential risk factor. Higher vitamin D concentrations are associated with a 3-fold decreased risk for pancreatic cancer (highest vs. lowest quintile, ›26.2 vs. ‹12.8 ng/ml).

Grant demonstrated that much of the geographic variation in cancer mortality rates in the US can be attributed to variations in solar UV-B radiation exposure. Clearly, improving vitamin D status appears vital to overall health, particularly in non-summer months. The evidence that higher 25(OH)D levels through increased sunlight exposure or dietary supplement intake inhibit colorectal carcinogenesis is substantial. The biologic evidence for an anti-cancer role of 25(OH)D is also strong for prostate cancer, but the epidemiologic data have not been supportive. The above data indicate that vitamin D influences cancer prevalence, risk and survival and hence the need to assess vitamin D levels in cancer.

Sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3440651/, https://www.sciencedirect.com/science/article/pii/S0960076023000638.

Gerbenn Seraphin, Sandra Rieger, Martin Hewison, Enrico Capobianco, Thomas S. Lisse, "The impact of vitamin D on cancer: A mini review," *The Journal of Steroid Biochemistry and Molecular Biology*, Volume 231, July 2023.

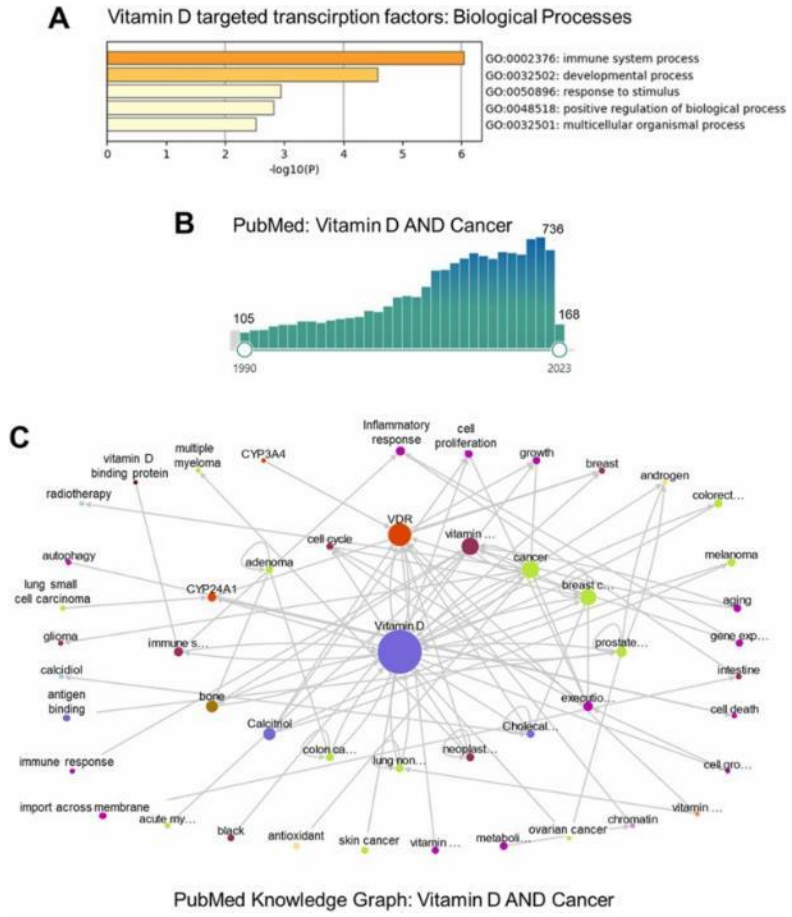
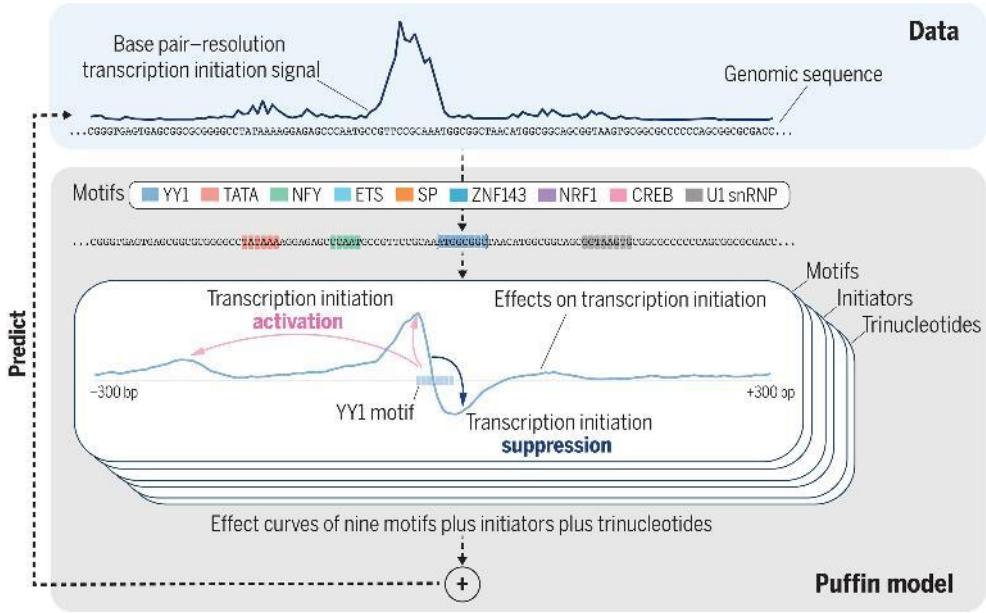


Fig. 1. Recent advances in vitamin D cancer research. (A) Top-level Gene Ontology of Biological Processes regulated by vitamin D-targeted transcription factors: BCL6, NFE2, POU4F2, ELF4, IRF5, MAFF, MYCL, NFXL1, TFEC, MAMLD, PPARGC1B, SRA1, ZBTB46 (source Metascape.org) [43].(B) A rapid increase in the number of published articles on vitamin D and cancer in PubMed between 1990 and 2023. (C) PubMed knowledge graph was used to assess vitamin D and cancer relationships in approximately 904 of the most recently accessed PubMed articles.

What Sequence Patterns Define a Genetic Promoter?

Dudnyk K, Cai D, Shi C, Xu J, Zhou J., "Sequence basis of transcription initiation in the human genome," *Science*, Apr 26, 2024 (excerpt)

With this approach, we developed an explainable machine-learning model, Puffin, and showed that a small set of sequence patterns and simple rules are sufficient to explain most human promoters. These sequence patterns have different activating or repressive effects on transcription initiation depending on their position and strand relative to the transcription start site. We identified three types of sequence patterns: motifs, initiators, and trinucleotides. Motifs are the main contributors to transcription initiation, initiators fine-tune the local preference of transcription start sites, and trinucleotides capture the residual dependencies. The effects of individual sequence patterns at each base-pair location were combined additively at the log scale. Although most motifs identified by Puffin match known transcription factor motifs, the position- and strand-specific effects of these motifs on transcription initiation had not been previously characterized. We uncovered both motifs with directional effects and motifs with bidirectional effects. Directional motifs such as TATA and YY1 have strong activating effects on transcriptional initiation signals, preferentially on one strand, whereas bidirectional motifs such as NFY, ETS, SP, ZNF143, NRF1, and CREB activate transcription initiation on both strands toward opposite directions. Each motif has distinct strand- and position-specific effects, and they likely reflect the underlying mechanisms of transcription activation. We validated the Puffin model with various experimental data, including verifying the effects of depleting transcription factors NF-Y and YY1 on transcription initiation signals from data. We also developed a new CRISPR-Cap assay to assess the impact of sequence perturbations on transcription initiation signals in the native genome, and we verified that the sequence perturbation effects aligned with model predictions.



A unified model that explains the sequence basis of transcription initiation in the human genome.

Puffin predicts transcription initiation signals by first detecting sequence patterns that appear in the DNA sequence and then applying the effects of every sequence pattern on the transcription initiation signal. The model includes three types of sequence patterns: motifs, initiators, and trinucleotides. Strand-specific base pair–resolution transcription initiation signals are predicted by combining motif effects additively in log scale and then transforming to output scale. bp, base pairs.

Source: https://pubmed.ncbi.nlm.nih.gov/38662817/

Super-Resolution Microscopy Becoming More Accessible

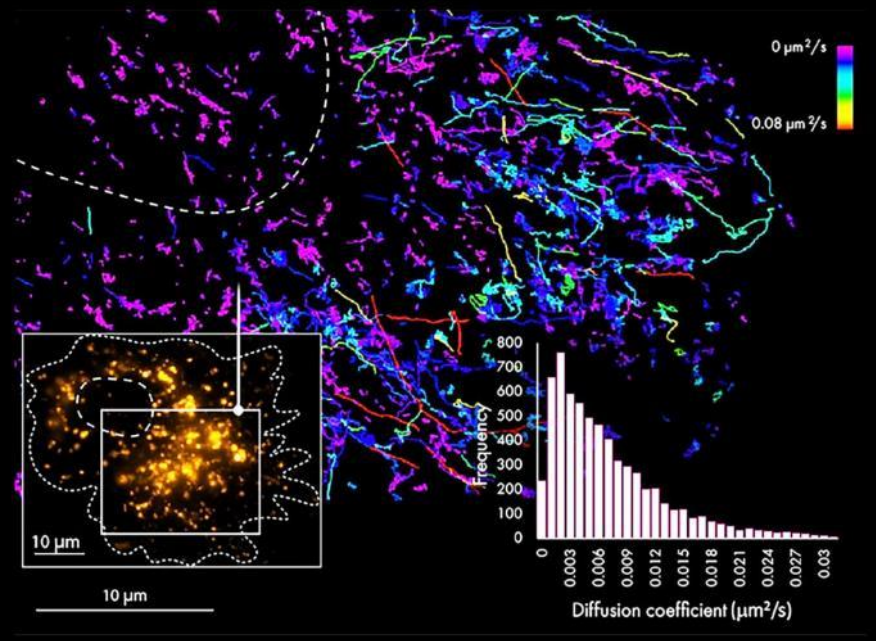
Julianna LeMieux, *Genetic Engineering & Biotechnology News*, April 9, 2024 (excerpt)

A decade ago, the Nobel Prize in Chemistry was awarded to a trio of researchers for the development of super-resolved fluorescence microscopy. The announcement at the time stated that the researchers' work had "brought optical microscopy into the nanodimension." Indeed, their work broke the diffraction-limited resolution barrier. In conventional light microscopy, the diffraction limit, or the physical limit for the maximum resolution, is 200 nm.

One of the two techniques recognized by the prize was single-molecule localization microscopy (SMLM). Actually, SMLM is a group of techniques. It includes stochastic optical reconstruction microscopy (STORM), DNA-based point accumulation for imaging in nanoscale topography (DNA-PAINT), and photoactivated localization microscopy (PALM). The three approaches vary in how they carry out the random activation of a subset of fluorescent molecules—the cornerstone of SMLM. The data analysis leads to the resolution of structures at the nanoscale level.

SMLM was developed by two of the Nobel Prize winners, Eric Betzig, PhD, and William E. Moerner, PhD. Betzig is a senior fellow at the Janelia Research Campus, a professor of molecular and cell biology and a Howard Hughes Medical Institute Investigator at the University of California, Berkeley. Moerner is a professor of chemistry and a professor of applied physics at Stanford University. What does it take to bring SMLM to non-microscopists? Jell suggests removing barriers such as the need for a darkroom, temperature control, a special table, or a technician to tweak or align the instrument. In ONI's instrument, the nanoimager, a microscope floats within an enclosure with stable optics that are easy to maintain. The company has swapped out commercially available lasers for ones that it has designed in house, and it has built flow cells to allow multiple lanes on a single chip.

Jell suggests that SMLM will push microscopy to overcome assumptions. For example, that microscopy is only qualitative. SMLM doesn't just produce images. It also generates data. In a sense, the images are data. The rows and rows of points that constitute an image are actually coordinate-based datasets that can be used not only to pinpoint the 3D position of molecules, but also to determine how proteins interact.



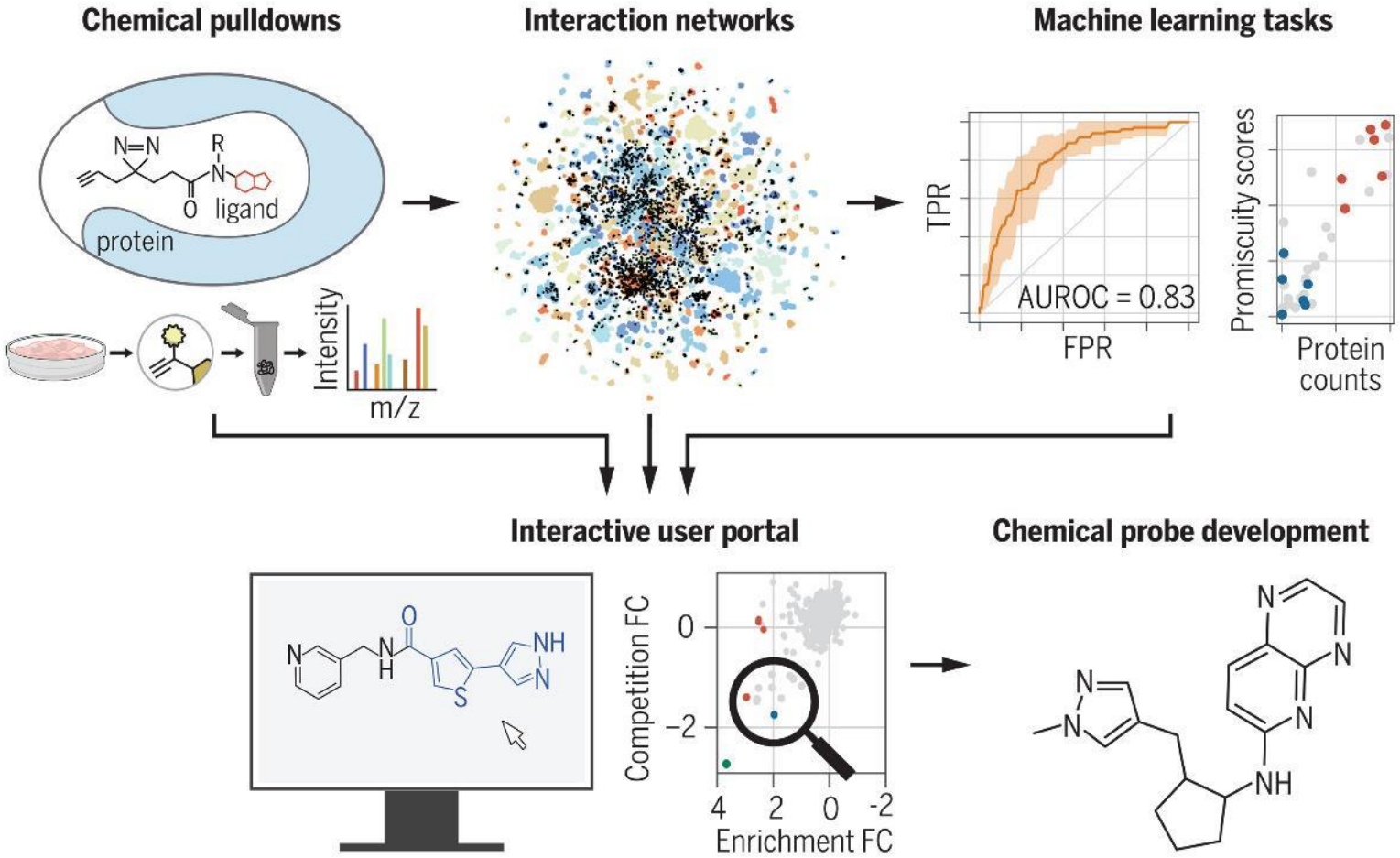
This image summarizes a study in which single-particle tracking technology from ONI was used to analyze the internalization of extracellular vesicles in living Burkitt's lymphoma cells. The image, from Maria Panagopoulou, PhD, and Margaret Paterson, PhD, in the laboratory of Christopher D. Gregory, PhD, at the University of Edinburgh, measured, tracked, and extracted information on diffusion coefficients to illuminate intercellular communication processes.

Source: https://www.genengnews.com/topics/drug-discovery/super-resolution-microscopy-can-be-super-accessible/

Large-Scale Chemoproteomics Expedites Ligand Discovery and Predicts Ligand Behavior in Cells

Offensperger F et.al., "Large-scale chemoproteomics expedites ligand discovery and predicts ligand behavior in cells," *Science*, April 26, 2024;384(6694).

Chemical modulation of proteins enables a mechanistic understanding of biology and represents the foundation of most therapeutics. However, despite decades of research, 80% of the human proteome lacks functional ligands. Chemical proteomics has advanced fragment-based ligand discovery toward cellular systems, but throughput limitations have stymied the scalable identification of fragment-protein interactions. We report proteome-wide maps of protein-binding propensity for 407 structurally diverse small-molecule fragments. We verified that identified interactions can be advanced to active chemical probes of E3 ubiquitin ligases, transporters, and kinases. Integrating machine learning binary classifiers further enabled interpretable predictions of fragment behavior in cells. The resulting resource of fragment-protein interactions and predictive models will help to elucidate principles of molecular recognition and expedite ligand discovery efforts for hitherto undrugged proteins.



Schematic representation of the ligand discovery approach. Chemoproteomics was used to assess 407 small-molecule fragments. Hundreds of fragment-protein interactions were identified as starting points for probe development. System-level analyses coupled to machine learning enabled prediction of fragment binding and behavior in living cells. An interactive web resource has been provided for data exploration, which also allows the generation and application of bespoke predictive models.

Source: https://www.science.org/doi/10.1126/science.adk5864

A Shortcut for Drug Discovery: Novel Method Predicts on a Large Scale how Small Molecules Interact with Proteins

CEMM Press Release, April 23, 2024 (excerpt)

For most human proteins, there are no small molecules known to bind them chemically (so called “ligands”). Ligands frequently represent important starting points for drug development but this knowledge gap critically hampers the development of novel medicines. Researchers at CeMM, in a collaboration with Pfizer, have now leveraged and scaled a method to measure the binding activity of hundreds of small molecules against thousands of human proteins. This large-scale study revealed tens of thousands of ligand-protein interactions that can now be explored for the development of chemical tools and therapeutics. Moreover, powered by machine learning and artificial intelligence, it allows unbiased predictions of how small molecules interact with all proteins present in living human cells. These groundbreaking results have been published in the journal *Science*, and all generated data and models are freely available for the scientific community.

The majority of all drugs are small molecules that influence the activity of proteins. These small molecules – if well understood - are also invaluable tools to characterize the behavior of proteins and to do basic biological research. Given these essential roles, it is surprising that for more than 80 percent of all proteins, no small-molecule binders have been identified so far. This hinders the development of novel drugs and therapeutic strategies, but likewise prevents novel biological insights into health and disease.

To close this gap, researchers at CeMM in collaboration with Pfizer have expanded and scaled an experimental platform that enables them to measure how hundreds of small molecules with various chemical structures interact with all expressed proteins in living cells. This yielded a rich catalog of tens of thousands of ligand-protein interactions than can now be further optimized to represent starting points for further therapeutic development. In their study, the team led by CeMM PI Georg Winter has exemplified this by developing small-molecule binders of cellular transporters, components of the cellular degradation machinery and to understudied proteins involved in cellular signal transduction. Moreover, taking advantage of the large dataset, machine learning and artificial intelligence models were developed that can predict how additional small molecules interact with proteins expressed in living human cells.

Georg Winter, CeMM-PI and last author of the study

Source: https://cemm.at/news/n/a-shortcut-for-drug-discovery-novel-method-predicts-on-a-large-scale-how-small-molecules-interact-with-proteins

State of Japan Biotech

Nxera – the new name for Japan biotech Sosei Heptares

Why Japan Lacks a Vibrant Biotech Industry

Kessel, M., Vickrey, C., *Nature Biotechnology*, April 22, 2024 (excerpt)

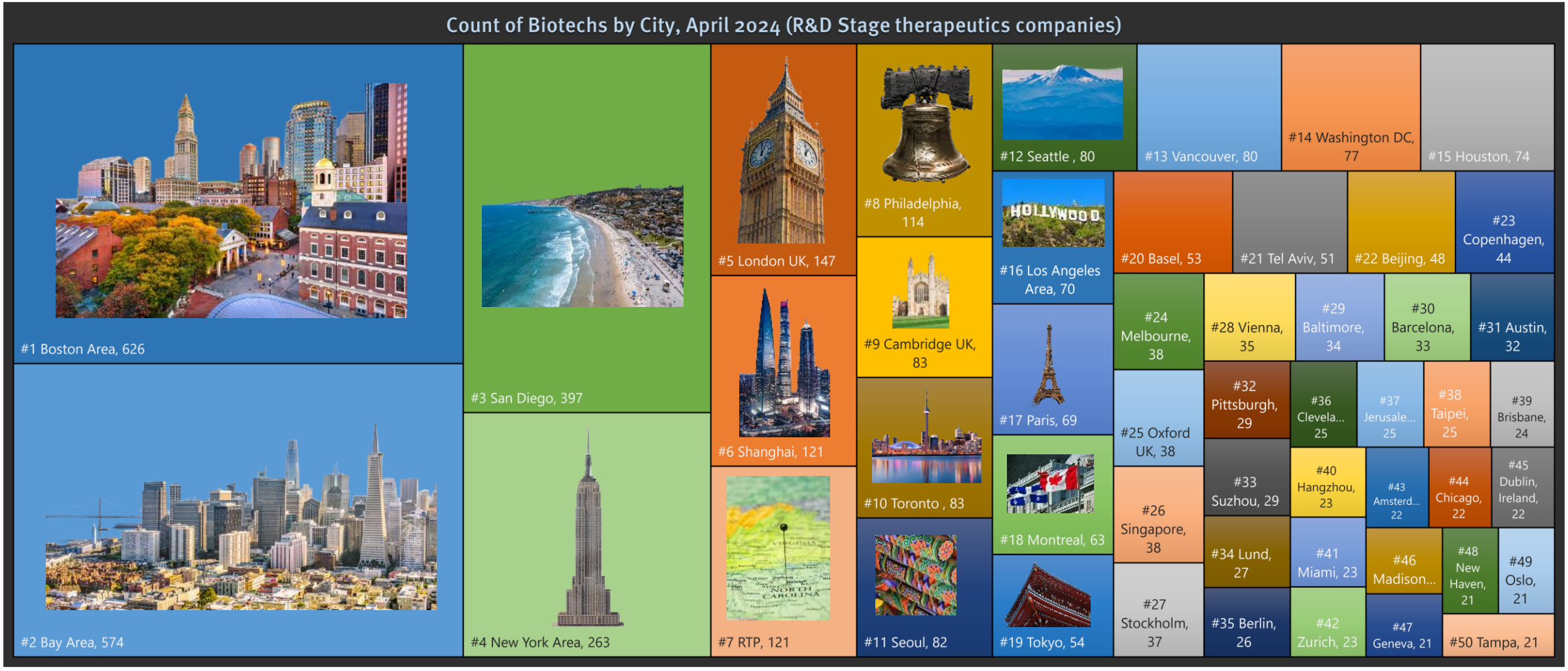
Recent analysis of the biopharmaceutical industry in Japan has emphasized that the lack of a thriving biotech ecosystem in that country is largely due to tight controls on drug pricing. However, this is only one part of the explanation, and any strategy to promote Japanese biotech must acknowledge the full complexity of the problem. Japan has long punched above its weight in innovative research in biochemistry and medicinal chemistry despite relative government underinvestment compared with the United States and Europe. In the United States, 363 new drugs were approved by the Food and Drug Administration between 2011 and 2021. The leading country of origin of these approvals was the United States, with 223 drugs, but Japan was the second-leading country of origin, with 33 drugs. Drugs first developed in Japan include statins (Sankyo) and the cancer immunotherapy Opdivo (nivolumab; Ono Pharmaceutical), based on the discovery of programmed death inhibitor proteins by Nobel prize recipient Tasuku Honjo. In the field of biotechnology, Japanese successes include BioWa (acquired by Kirin), a producer of monoclonal antibodies, and Chugai Pharmaceutical, which has the largest bioreactor capacity in Japan and has been fed a steady stream of new drugs from its majority owner Roche.

Yet Japan lacks a home-grown biotech ecosystem. Even the discovery of induced pluripotent stem cells by Kyoto University researcher Shinya Yamanaka has not translated into Japanese leadership in cell therapies. Several factors beyond drug price controls are involved. Although many Japanese pharmaceutical companies have corporate venture capital arms and invest in biotech startups, these investments are mostly in the United States and other regions outside Japan. The same is true of Japanese venture capital investing as a whole. In 2022, this sector invested 120 times more in the United States than in Japan. Japan has simply failed to develop a startup ecosystem, especially in biotech. According to the Global Startup Ecosystem Report 2021 from Startup Genome, Tokyo ranked ninth in the world as a startup hub, below other cities in East Asia, including Beijing and Shanghai.

Source: https://www.nature.com/articles/s41587-024-02227-x

How Does Japan Rank in Biotech Anyway?

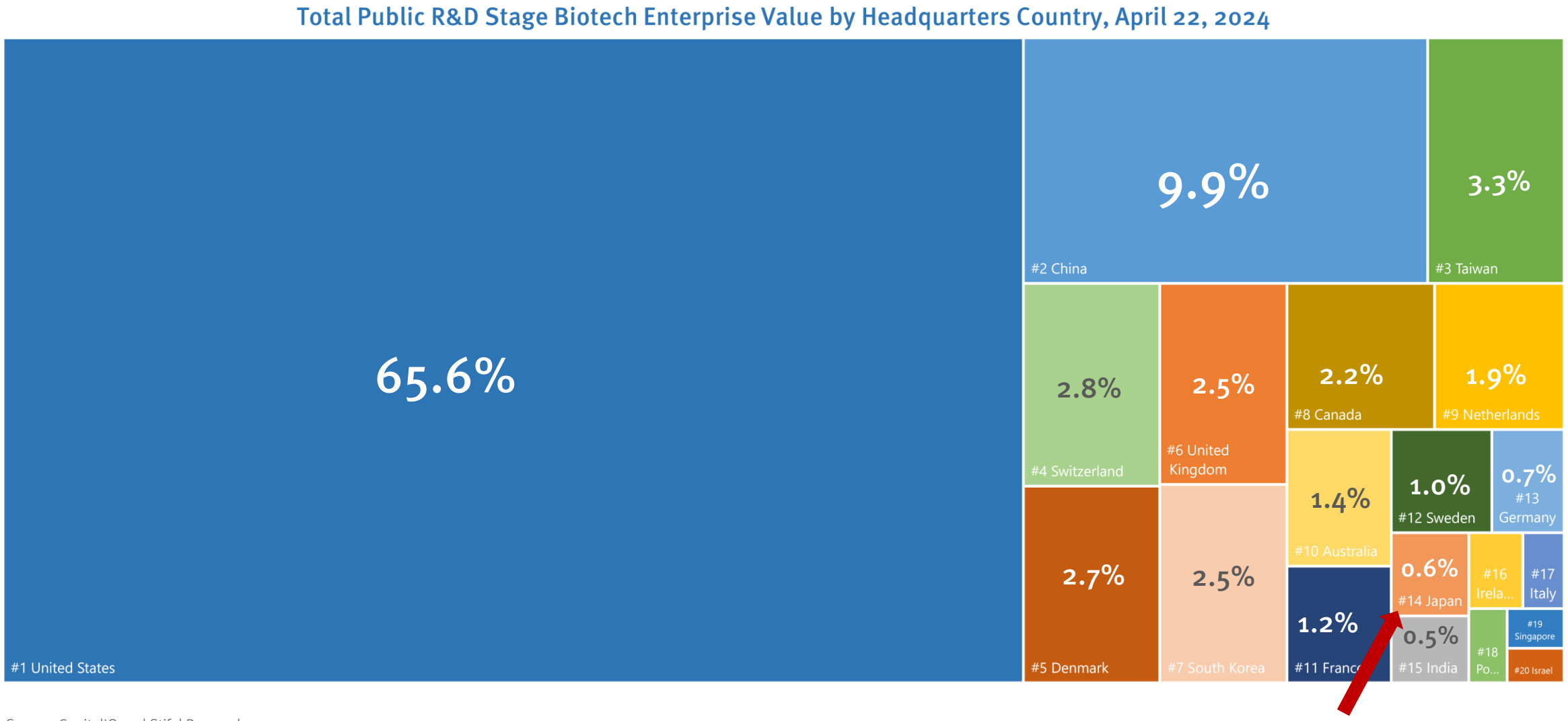
Tokyo is Japan's largest city for biotechs and is ranked #19 for number of R&D-stage therapeutics companies. The Boston area leads with 626 biotech companies according to DealForma. The Bay Area is close behind.



Source: DealForma and Stifel Research

Japan a Relatively Small Piece of Global Biotech Value Pie

Japan is ranked #14 by value of publicly traded R&D stage therapeutics companies (biotechs). The U.S. has a dominant position at present.



Source: CapitalIQ and Stifel Research

Comments from Taro Inaba on Japan Biotech

I took a look at the *Nature Medicine* article. Here is my comment on the current Japanese biotech industry. The lack of growth in the size of the Japanese biotech industry can be attributed to several key factors, including:

1. Traditional lifetime employment practices in large corporations, where individuals prioritize job stability.

2. A shortage of industry-experienced professionals, particularly in academia, due to segmented career paths and limited workforce mobility.

3. Biases in the Japanese market favoring platform-type start-ups over product-oriented companies, resulting in institutional investors devaluing product-based start-ups with persistent financial losses.

4. Limited financial reserves among individual professionals, stemming from Japan's compensation system, which poses challenges for entrepreneurs seeking self, family, or friend funding to launch new businesses especially in the biotech area where more seed capital is needed to launch a new company compared to the other industries.

5. Additionally, academia, notably universities, faces constraints in budget and resources to develop industry-viable intellectual property portfolios, leading to groundbreaking inventions not being patented effectively.

However, the landscape is evolving rapidly, particularly with government initiatives aimed at bolstering the drug discovery ecosystem through organizations like AMED and significant funding. Japan, with its continuous generation of attractive inventions in academia, established history in the pharmaceutical industry, and abundance of key expertise in drug discovery and development, is poised to advance its biotech sector in the near term. Collaborative efforts between the government, venture capitalists especially those active in company creation, and academia hold the potential to cultivate a robust ecosystem for biotech innovation in Japan.

Taro Inaba
Managing Partner
Remiges Ventures
Tokyo, Japan

See: https://remigesventures.com/team/taro-inaba/

Takeda, Astellas and Sumitomo Mitsui Banking to Establish Joint Venture Company for Incubation of Early Drug Discovery Programs in Japan

TOKYO, April 22, 2024 /PRNewswire/ -- Takeda Pharmaceutical Company Limited (TSE: 4502/NYSE: TAK, President and CEO; Christophe Weber, "Takeda"), Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas"), and Sumitomo Mitsui Banking Corporation (President & CEO: Akihiro Fukutome, "SMBC") today announced that the three companies signed a master agreement on April 22, 2024, to establish a joint venture company. The new company will be dedicated to the incubation of early drug discovery programs, primarily originating from Japan and toward the creation of innovative therapeutics.

Background

Japan, as one of the world's leaders in drug discovery and development, is home to both world-class academic institutions conducting innovative basic research in drug discovery and global pharmaceutical companies, with extensive expertise in early drug research and development. Both possess a wealth of early drug discovery programs with breakthrough potential. However, in recent years, advancing academic discoveries from bench to bedside, known colloquially as the "valley of death", has presented a major challenge when it comes to unleashing the full potential of innovative technologies and seed assets originating in Japan. In response to this challenge, the three companies have been engaged in discussions to establish a joint venture company that will seamlessly cover the entire drug discovery process, spanning early drug discovery research through the inception of drug discovery startups.

The joint venture company will focus on the following three aspects:

1. Advancing innovative drug discovery programs primarily originating in Japan into the global market.
2. Incubating globally competitive drug discovery technology and fostering entrepreneurship.
3. Unleashing the potential of drug discovery ecosystem in Japan through the creation of high caliber start-ups

Name	To be determined
CEO	Toshio Fujimoto, MD, MBA*
Location	Shonan Health Innovation Park (Fujisawa, Kanagawa, Japan)
Capital	Approximately 600 million yen (including capital reserve)
Capital Structure	Takeda 33.4%, Astellas 33.4%, SMBC 33.2%
Establishment	Mid-2024
Business	Incubation of early discovery programs to develop innovative therapeutics primarily originated from Japan

In addition to establishing the joint venture company, Takeda and Astellas will provide support to the joint venture company leveraging their expertise gained from global drug discovery research and development, aiming to accelerate open innovation in early-stage drug discovery, and toward the creation of start-up companies for the benefit of society. The joint venture company plans to begin incubation activities by collaboratively working with academia, pharmaceutical companies, and start-up companies across Japan to enable access to potentially transformative early drug discovery programs.

Source: https://www.prnewswire.com/news-releases/takeda-astellas-and-sumitomo-mitsui-banking-announce-master-agreement-to-establish-joint-venture-company-for-incubation-of-early-drug-discovery-programs-302123110.html

Japan is a Global Bio-Innovation Dynamo

Japan is the #2 Source of Drug Discoveries in the World

1. Akira Endo discovers first statin in 1970s
2. Lupron discovered in Japan
3. Tacrolimus discovered in Japan
4. Pioglitazone discovered in Japan
5. PD-1 discovered in Japan
6. Yamanaka factors discovered in Japan
7. Daiichi-Sankyo breakthroughs from Japan

Source: https://www.jstage.jst.go.jp/article/bpb/46/5/46_b23-00107/_html/-char/en

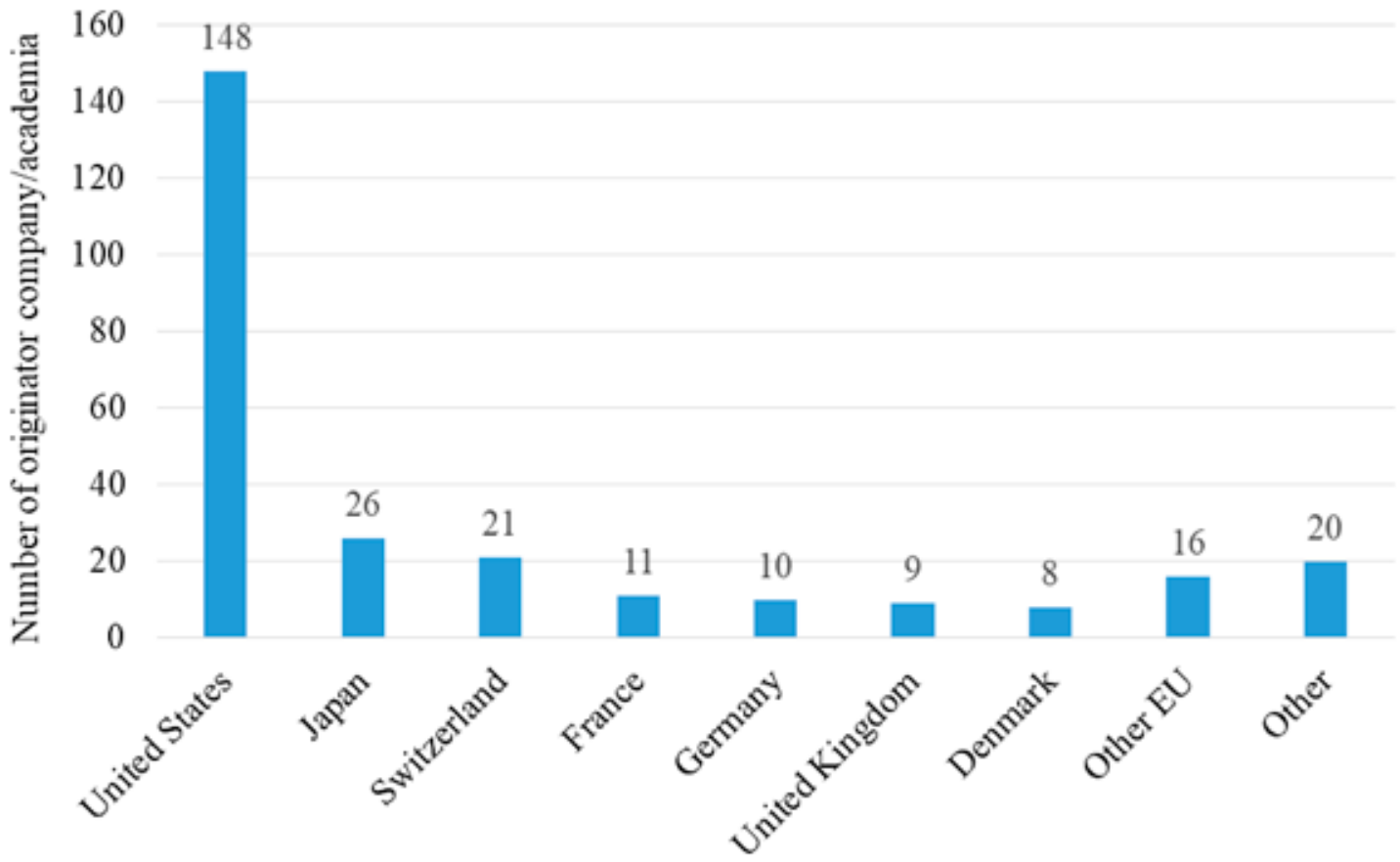
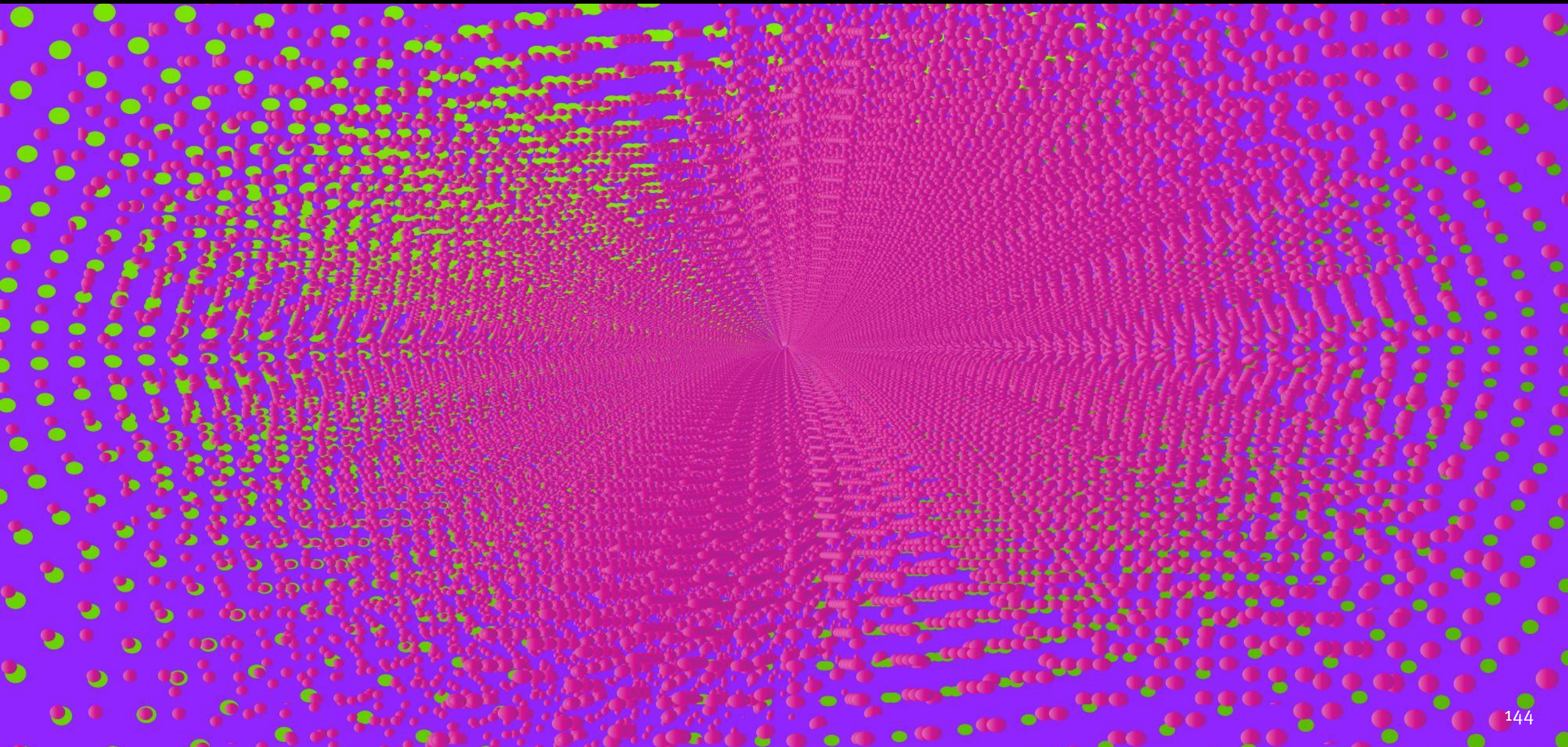


Fig. 1. Location of Firm/Academia That Created New Drugs Approved by the FDA from 2017 to 2022
Each column represents the number of originator companies or academic institutions of the drugs that were approved by the FDA from 2017 to 2022 in each country/region in which the originator companies or academic institutions are located.

Snapshots from a Stifel April ’24 Trip to Japan

From top left around the clock: Cherry blossoms on a Tokyo street, Camelia blossom, Pocari Sweat (our favorite drink with local soccer team), “be careful” sign for bikers, tuna sashimi, strawberry mochi and the Imperial Palace, Tokyo

Werner Helicase Inhibitor Update

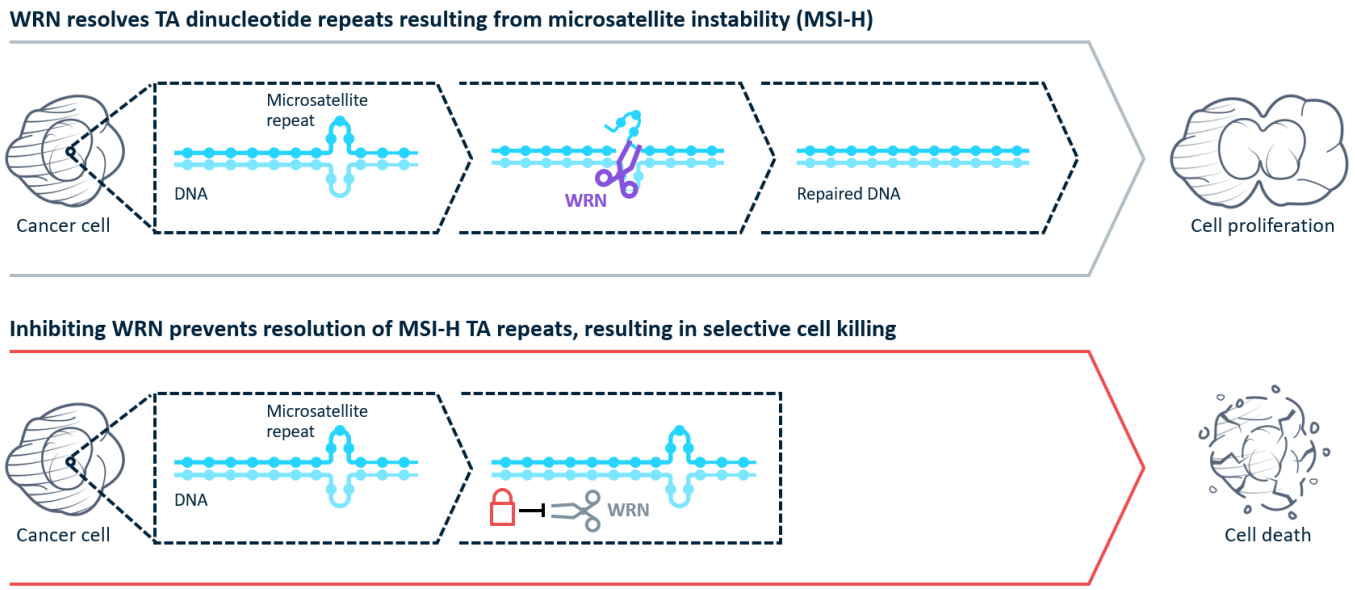


Werner Helicase Inhibitors and Microsatellite Instability (MSI)

MSI is a change in the DNA content of a tumor cell in which the number of repeats of microsatellites, short repeated sequences of DNA, differ as cells divide. High MSI is present in many solid tumor cancers, and tumors are routinely assessed for MSI status in multiple diagnostic profiling tests.

Werner protein is a RecQ family enzyme involved in the maintenance of genome integrity. Germline loss of function mutations in Werner protein lead to premature aging and pre-disposition to cancer.

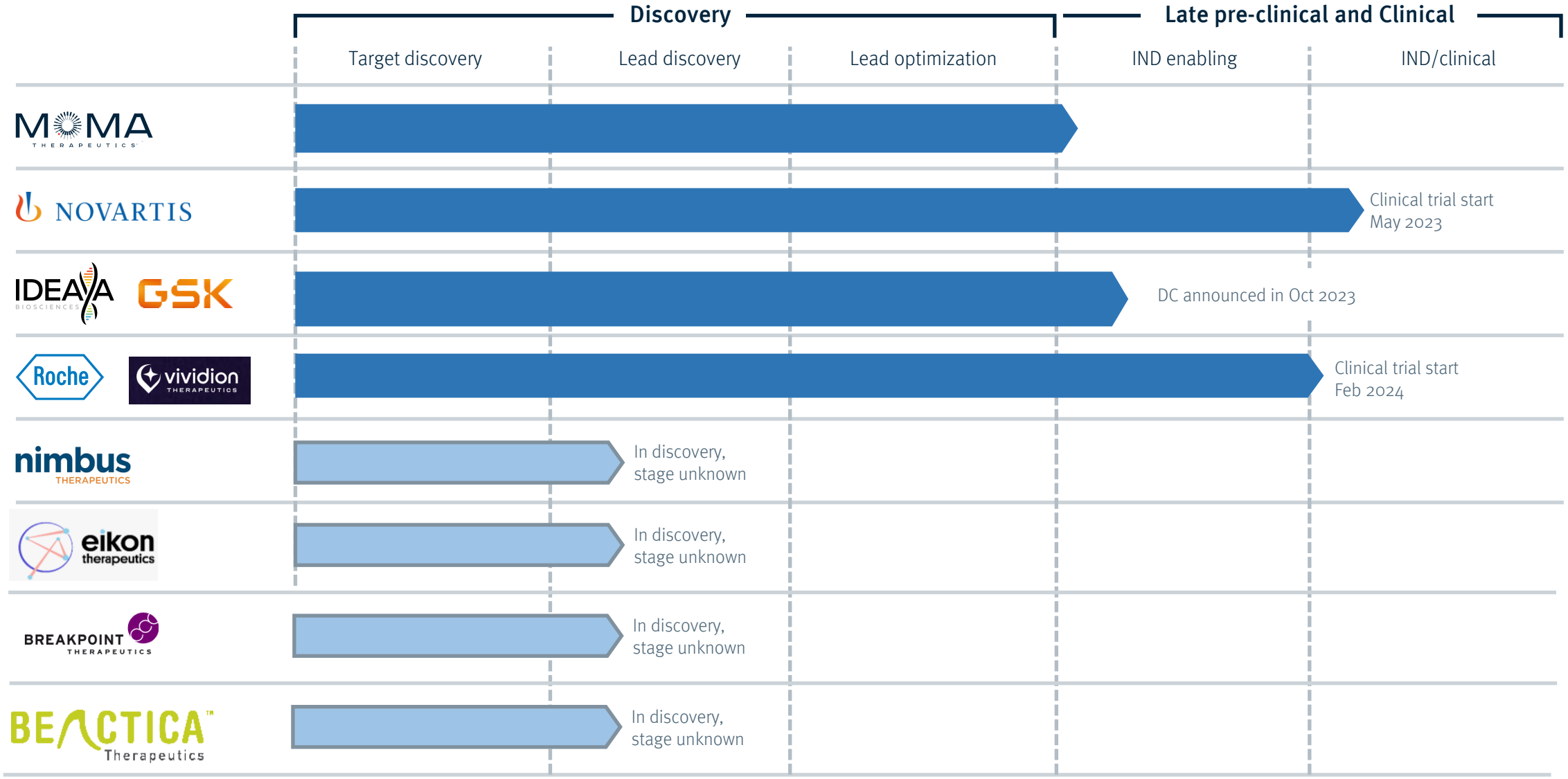
Werner protein has two functional domains, and the helicase functional domain of Werner protein is responsible for this synthetic lethal interaction in MSI-high cells. See Ideaya's paper "*Werner Syndrome Helicase is Required for the Survival of Cancer Cells with Microsattelite Instability*," Vol. 13, pp. 488-497 (Mar 2019).



We touch on the role of Werner Helicase inhibitors because of the publication of two reports on drug discoveries in this area in *Nature* last week.

Sources: Ideaya Website and Moma Therapeutics Corporate Presentation, April 2024

Werner Helicase Inhibitor Pipeline



Sources: Stifel research and Moma Therapeutics Corporate Presentation, April 2024

Novartis: Discovery of WRN Inhibitor HRO761 with Synthetic Lethality in MSI Cancers

Ferretti S et.al., "Discovery of WRN inhibitor HRO761 with synthetic lethality in MSI cancers," *Nature* April 24, 2024

The Werner syndrome RecQ helicase WRN was identified as a synthetic lethal target in cancer cells with microsatellite instability (MSI) by several genetic screens1-6. Despite advances in treatment with immune checkpoint inhibitors7-10, there is an unmet need in the treatment of MSI cancers11-14. Here we report the structural, biochemical, cellular and pharmacological characterization of the clinical-stage WRN helicase inhibitor HRO761, which was identified through an innovative hit-finding and lead-optimization strategy. HRO761 is a potent, selective, allosteric WRN inhibitor that binds at the interface of the D1 and D2 helicase domains, locking WRN in an inactive conformation. Pharmacological inhibition by HRO761 recapitulated the phenotype observed by WRN genetic suppression, leading to DNA damage and inhibition of tumour cell growth selectively in MSI cells in a p53-independent manner. Moreover, HRO761 led to WRN degradation in MSI cells but not in microsatellite-stable cells. Oral treatment with HRO761 resulted in dose-dependent in vivo DNA damage induction and tumour growth inhibition in MSI cell- and patient-derived xenograft models. These findings represent preclinical pharmacological validation of WRN as a therapeutic target in MSI cancers. A clinical trial with HRO761 (NCT05838768) is ongoing to assess the safety, tolerability and preliminary anti-tumour activity in patients with MSI colorectal cancer and other MSI solid tumours.

Source: https://pubmed.ncbi.nlm.nih.gov/38658754/

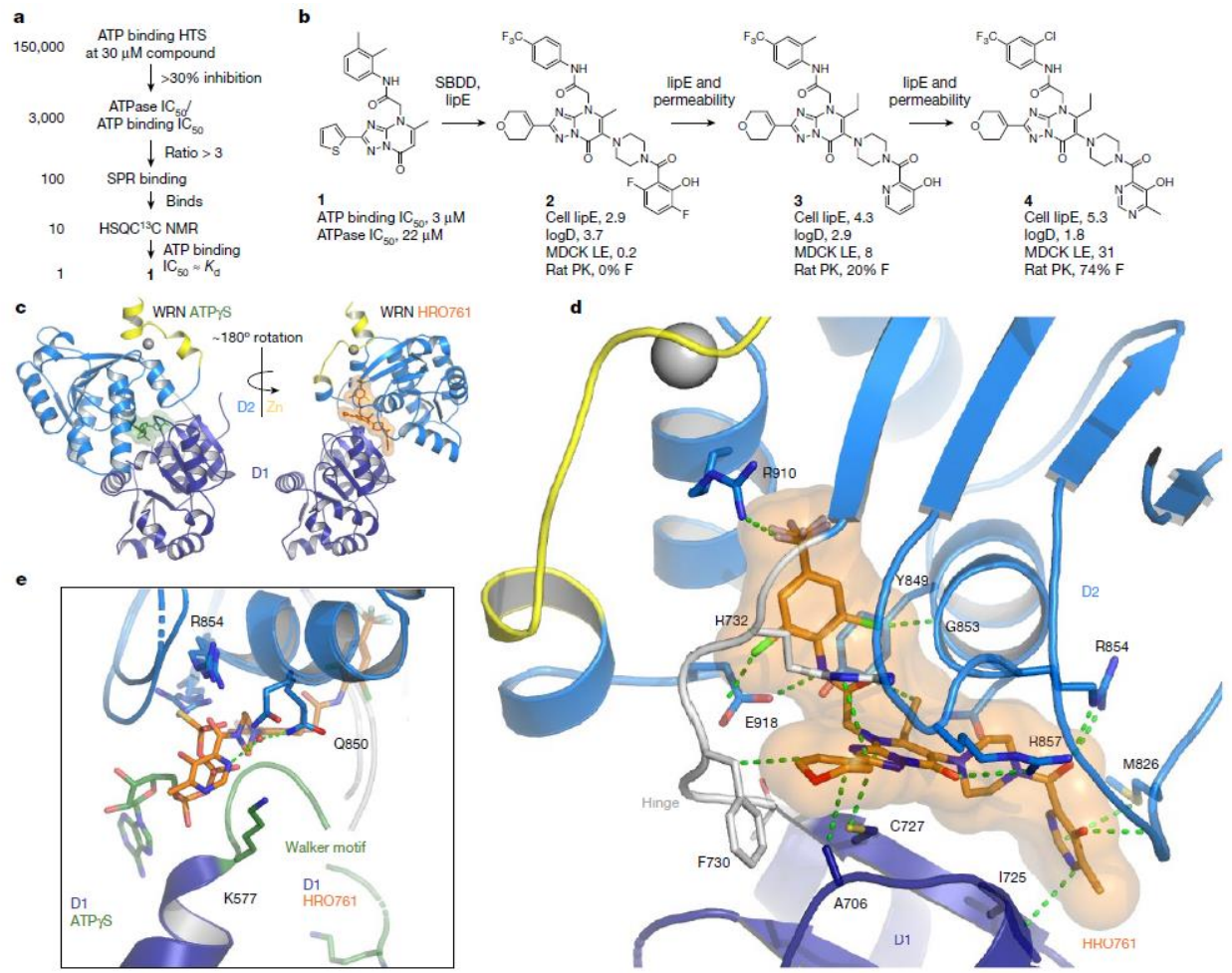


Fig. 1 | Identification and structural basis of HRO761, an allosteric WRN inhibitor. a, Screening funnel with hit count on the left and progression criteria on the right leading to the identification of hit **1**. HTS, high-throughput screening; K_d, dissociation constant; NMR, nuclear magnetic resonance; SPR, surface plasmon resonance. **b**, The structure of hit **1** and medicinal chemistry optimization to clinical candidate **4**, HRO761, with key profiling data of compounds **2**–**4** (cell lipE calculated from SW48 proliferation GI_{50} and the distribution coefficient between 1-octanol and water at pH 7.4 (logD), apparent permeability in low-efflux Madin–Darby canine kidney cells (MDCK LE P_{app}, 10^{-6} cm s^{-1}), oral bioavailability (F) and structure based drug design (SBDD)). **c**, HRO761 is an allosteric inhibitor of the WRN helicase binding at the D1–D2 interface in a novel conformation involving a 180° rotation of the D1 and D2 domains relative to ATPγS-bound WRN (ligands are shown as sticks with transparent surface). **d**, Owing to the overlap with the D2 ATP half-site, the HRO761-binding site is unusually polar and rich in arginine residues. HRO761 makes extensive polar interactions and engages key residues of the flexible hinge (Thr728-Gly-Phe-Asp-Arg). **e**, Overlay of the D2 domains of ATPγS- and HRO761-bound WRN showing that HRO761 displaces the Walker motif (green) and its catalytic residue Lys577 through mimicry of the ATP γ-phosphate, including coordination of the hydrolytic water by Gln850.

Vividion Also Reports in *Nature* Last Week on Discovery of a Werner Helicase Inhibitor

Chemoproteomic discovery of a covalent allosteric inhibitor of WRN helicase

https://doi.org/10.1038/s41586-024-07318-y

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Check for updates

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WRN helicase is a promising target for treatment of cancers with microsatellite instability (MSI) due to its essential role in resolving deleterious non-canonical DNA structures that accumulate in cells with faulty mismatch repair mechanisms[1–5]. Currently there are no approved drugs directly targeting human DNA or RNA helicases, in part owing to the challenging nature of developing potent and selective compounds to this class of proteins. Here we describe the chemoproteomics-enabled discovery of a clinical-stage, covalent allosteric inhibitor of WRN, VVD-133214. This compound selectively engages a cysteine (C727) located in a region of the helicase domain subject to interdomain movement during DNA unwinding. VVD-133214 binds WRN protein cooperatively with nucleotide and stabilizes compact conformations lacking the dynamic flexibility necessary for proper helicase function, resulting in widespread double-stranded DNA breaks, nuclear swelling and cell death in MSI-high (MSI-H), but not in microsatellite-stable, cells. The compound was well tolerated in mice and led to robust tumour regression in multiple MSI-H colorectal cancer cell lines and patient-derived xenograft models. Our work shows an allosteric approach for inhibition of WRN function that circumvents competition from an endogenous ATP cofactor in cancer cells, and designates VVD-133214 as a promising drug candidate for patients with MSI-H cancers.

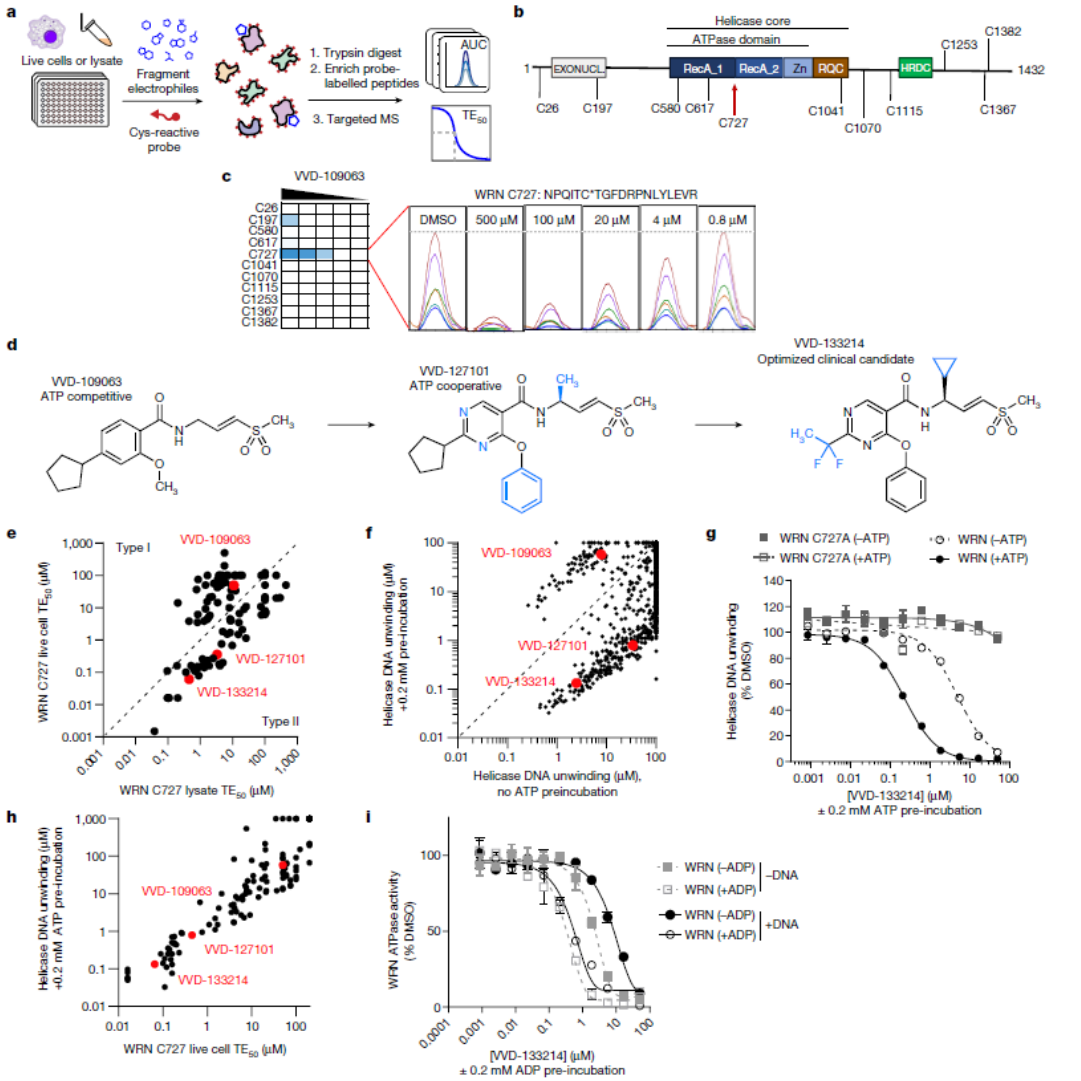
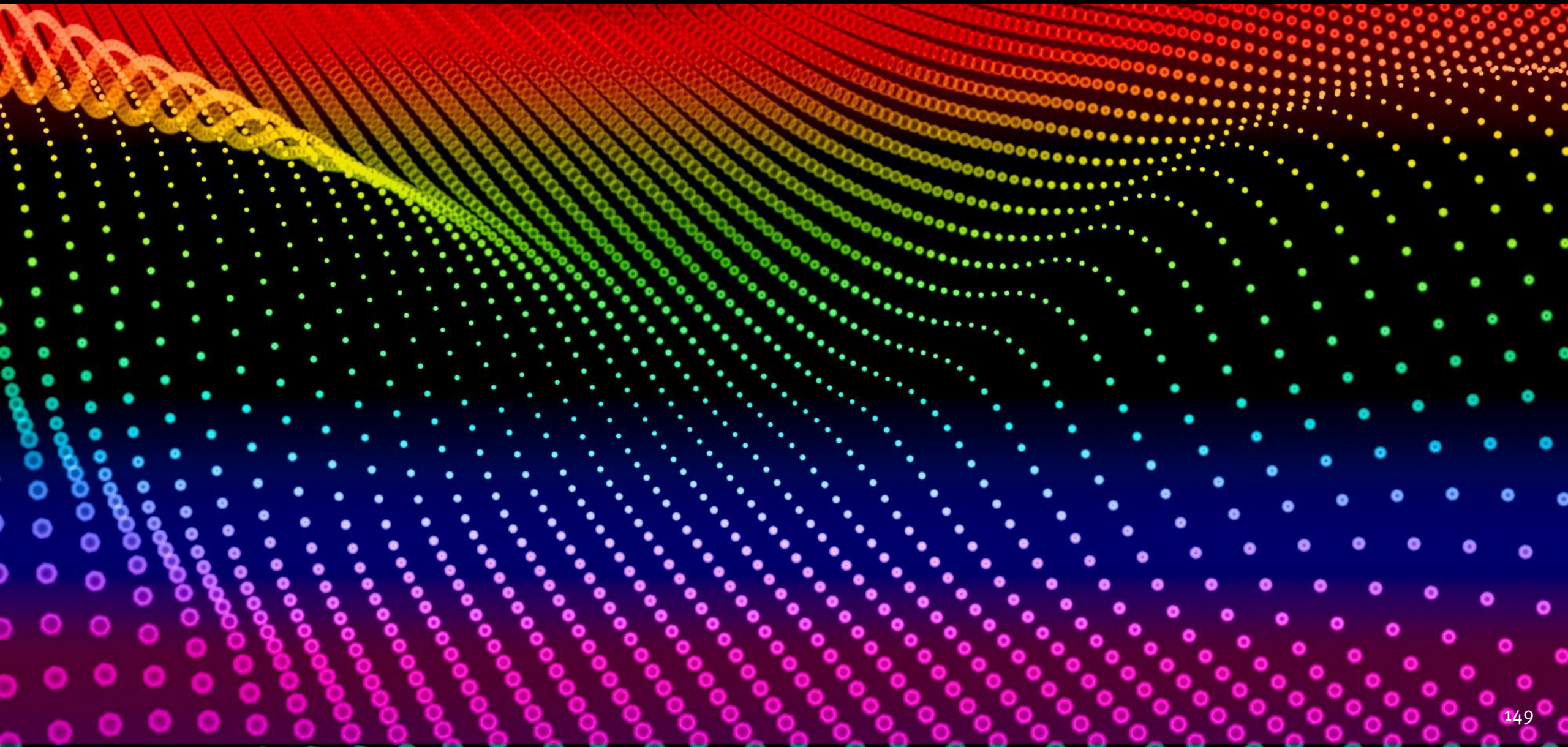


Fig. 1 | Discovery of a covalent WRN inhibitor, VVD-133214, using chemoproteomics. a, General protocol for chemoproteomics-based inhibitor discovery: live cells or cell lysates are treated with DMSO or inhibitors in a 96-well plate. Inhibitor binding prevents cysteine residues from reacting with the probe, and probe-enriched peptides are measured using label-free parallel reaction monitoring mass spectrometry (MS). Target engagement (TE) is calculated by comparison of areas under the curve (AUCs) of inhibitor-treated and control wells and can be curve-fitted to determine TE_{50} values. **b**, Location of probe-accessible cysteines (C) on WRN subjected to chemoproteomics screening. **c**, Discovery of VVD-109063 as a WRN C727 binder with an approximate TE_{50} of 10 µM in lysates and good selectivity for C727. **d**, Progression of WRN C727 series from the initial VVD-109063 hit to the more advanced ATP-cooperative compounds VVD-127101 and VVD-133214. **e**, Comparison of TE_{50} in lysates versus live cells demonstrates distinct populations of compounds showing either reduced or enhanced potency in live cells relative to lysates. **f**, Comparison of WRN helicase ($hWRN^{519-1227}$) DNA unwinding activity with or without 0.2 mM ATP during the compound preincubation period demonstrated two distinct populations showing either competitive activity (for example, VVD-109063) or cooperative inhibitory activity (for example, VVD-127101 and VVD-133214). **g**, Inhibition of $hWRN^{519-1227}$ (wild type (WT) and C727A) by VVD-133214 with or without ATP during the compound preincubation period. **h**, Correlation between live cell WRN C727 engagement and biochemical $hWRN^{519-1227}$ helicase activity plus 0.2 mM ATP during the compound preincubation period. **i**, ATPase activity of $hWRN^{519-1227}$ in the presence of VVD-133214 with or without ADP preincubation and DNA substrate. IC_{50} derived from $n = 2$ biologically independent samples and presented as means ± s.e.m.

Source: https://www.nature.com/articles/s41586-024-07318-y

GPR75 Modulators Update



GWAS Study by Regeneron Discovers Importance of GPR75 Target in Obesity

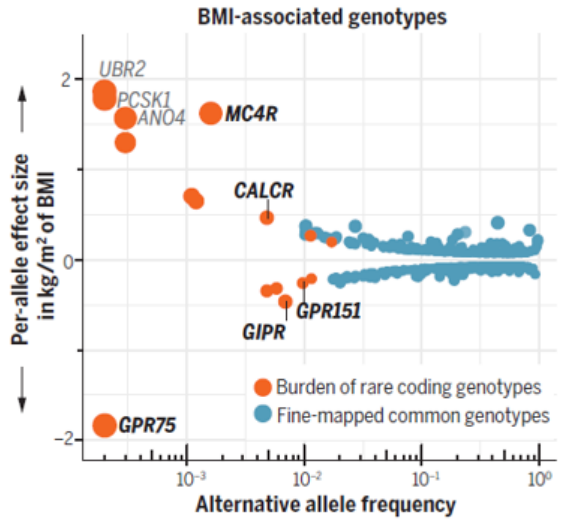
Akbari *et al.*, *Science* **373**, 73 (2021) 2 July 2021

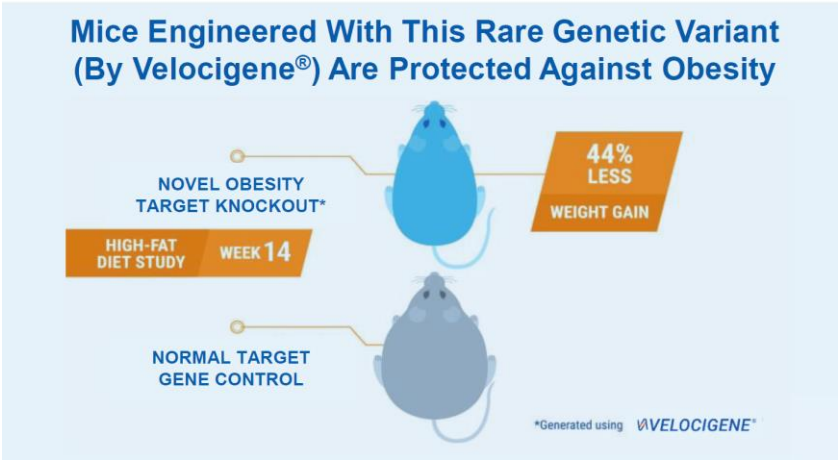
RESEARCH ARTICLE SUMMARY

HUMAN GENOMICS

Sequencing of 640,000 exomes identifies *GPR75* variants associated with protection from obesity

Parsa Akbari†, Ankit Gilani†, Olukayode Sosina†, Jack A. Kosmicki, Lori Khrimian, Yi-Ya Fang, Trikaldarshi Persaud, Victor Garcia, Dylan Sun, Alexander Li, Joelle Mbatchou, Adam E. Locke, Christian Benner, Niek Verweij, Nan Lin, Sakib Hossain, Kevin Agostinucci, Jonathan V. Pascale, Ercument Dirice, Michael Dunn, Regeneron Genetics Center, DiscovEHR Collaboration, William E. Kraus, Svati H. Shah, Yii-Der I. Chen, Jerome I. Rotter, Daniel J. Rader, Olle Melander, Christopher D. Still, Tooraj Mirshahi, David J. Carey, Jaime Berumen-Campos, Pablo Kuri-Morales, Jesus Alegre-Díaz, Jason M. Torres, Jonathan R. Emberson, Rory Collins, Suganthi Balasubramanian, Alicia Hawes, Marcus Jones, Brian Zambrowicz, Andrew J. Murphy, Charles Paulding, Giovanni Coppola, John D. Overton, Jeffrey G. Reid, Alan R. Shuldiner, Michael Cantor, Hyun M. Kang, Goncalo R. Abecasis, Katia Karalis, Aris N. Economides, Jonathan Marchini, George D. Yancopoulos, Mark W. Sleeman, Judith Altarejos, Giusy Della Gatta, Roberto Tapia-Conyer‡, Michal L. Schwartzman‡, Aris Baras‡*, Manuel A. R. Ferreira‡, Luca A. Lotta‡*





Murtaza et.al., Biochimie, April 2022:

The metabolic syndrome is a plethora of related disorders that are frequently associated with morbidity and mortality in addition to economic burden. While various treatment options are available, the need to understand the pathology and find new targets still remains.

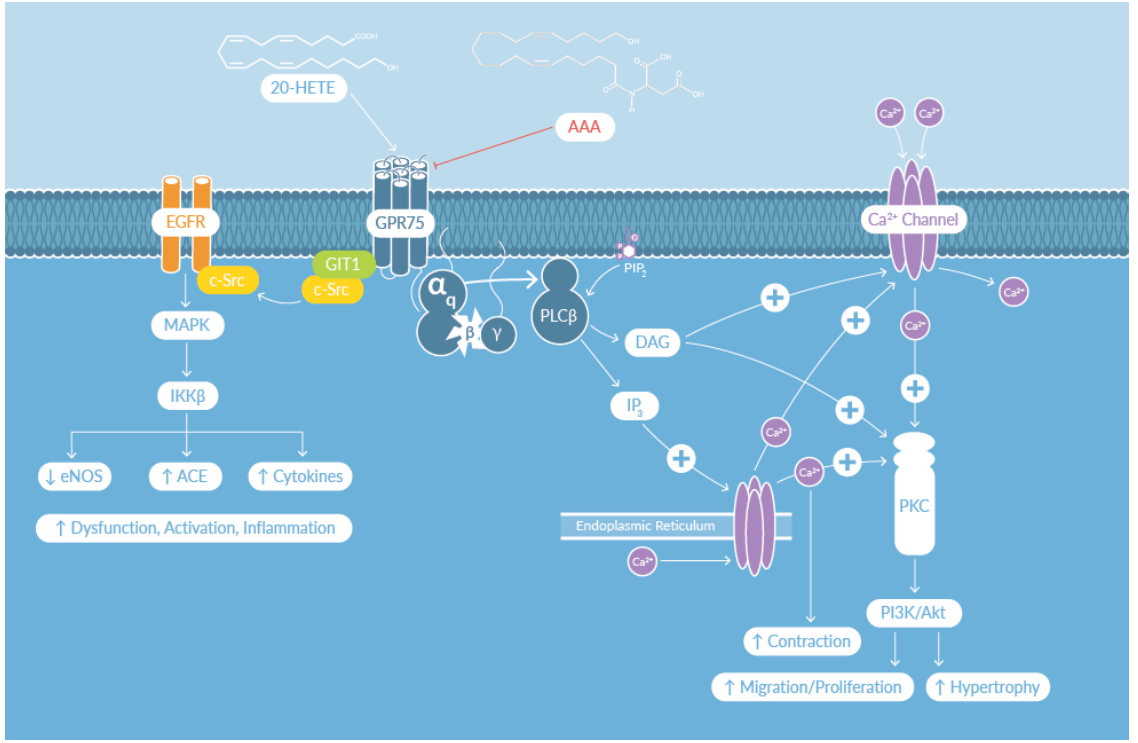
Recent data have suggested GPR75 as one such exciting target that has shown to a highly druggable potential. In this review, we have discussed the recent findings on GPR75 in terms of its expression and signaling and the way it could be a novel target in diseases associated with metabolic syndrome including obesity, dyslipidemia, diabetes, cardiovascular disease, and cerebrovascular disease. In addition, the opportunities and challenges related with the druggable potential of GPR75 have also been highlighted in this review.

Sources: https://www.science.org/doi/10.1126/science.abf8683, https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-genetics-center-discovers-gpr75-gene-mutations-protect, https://www.sciencedirect.com/science/article/abs/pii/S0300908422000141

GPR75 Binds to 20-HETE and CCL5/RANTES

Fan F, Roman RJ. GPR75 Identified as the First 20-HETE Receptor: A Chemokine Receptor Adopted by a New Family. *Circ Res*. 2017 May 26;120(11):1696-1698.

G protein-coupled receptor 75 (GPR75) has been identified as a 20-HETE receptor. It signals through Gq/phospholipase C (PLC)/protein kinase C (PKC) and c-Src/EGFR pathways (fig below). Previously GPR75 was deorphanized as an inflammatory chemokine receptor when CCL5/RANTES was identified as its ligand. Through GPR75, RANTES was shown to activate MAPK signaling to protect hippocampal HT22 cells from amyloid-β-induced cell death and to stimulate insulin secretion in pancreatic islet cells. Now it has been established that 20-HETE, a member of the cytochrome (CYP) P450-derived eicosanoids, acts through the same receptor to elicit vascular effects.



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5766006/

Functional Relationship Between GPR75 and 20-Hete

Pascale JV et.al.. Uncovering the signalling, structure and function of the 20-HETE-GPR75 pairing: Identifying the chemokine CCL5 as a negative regulator of GPR75. *Br J Pharmacol.* 2021 Sep;178(18):3813-3828.

SPR confirmed 20-HETE binding to GPR75 with an estimated KD of 1.56 × 10-10 M. In GPR75-transfected HTLA cells, 20-HETE stimulated intracellular Ca2+ levels, IP-1 accumulation and β-arrestin recruitment, all of which were negated by known 20-HETE functional antagonists. Computational modelling of the putative ligand-binding pocket and mutation of Thr212 within the putative 20-HETE binding site abolished 20-HETE's ability to stimulate GPR75 activation. Knockdown of GPR75 in human endothelial cells nullified 20-HETE-stimulated intracellular Ca2+ . The chemokine CCL5, a suggested GPR75 ligand, binds to GPR75 (KD of 5.85 × 10-10 M) yet fails to activate GPR75; however, it inhibited 20-HETE's ability to activate GPR75 signalling.

Source: https://bpspubs.onlinelibrary.wiley.com/doi/epdf/10.1111/bph.15525

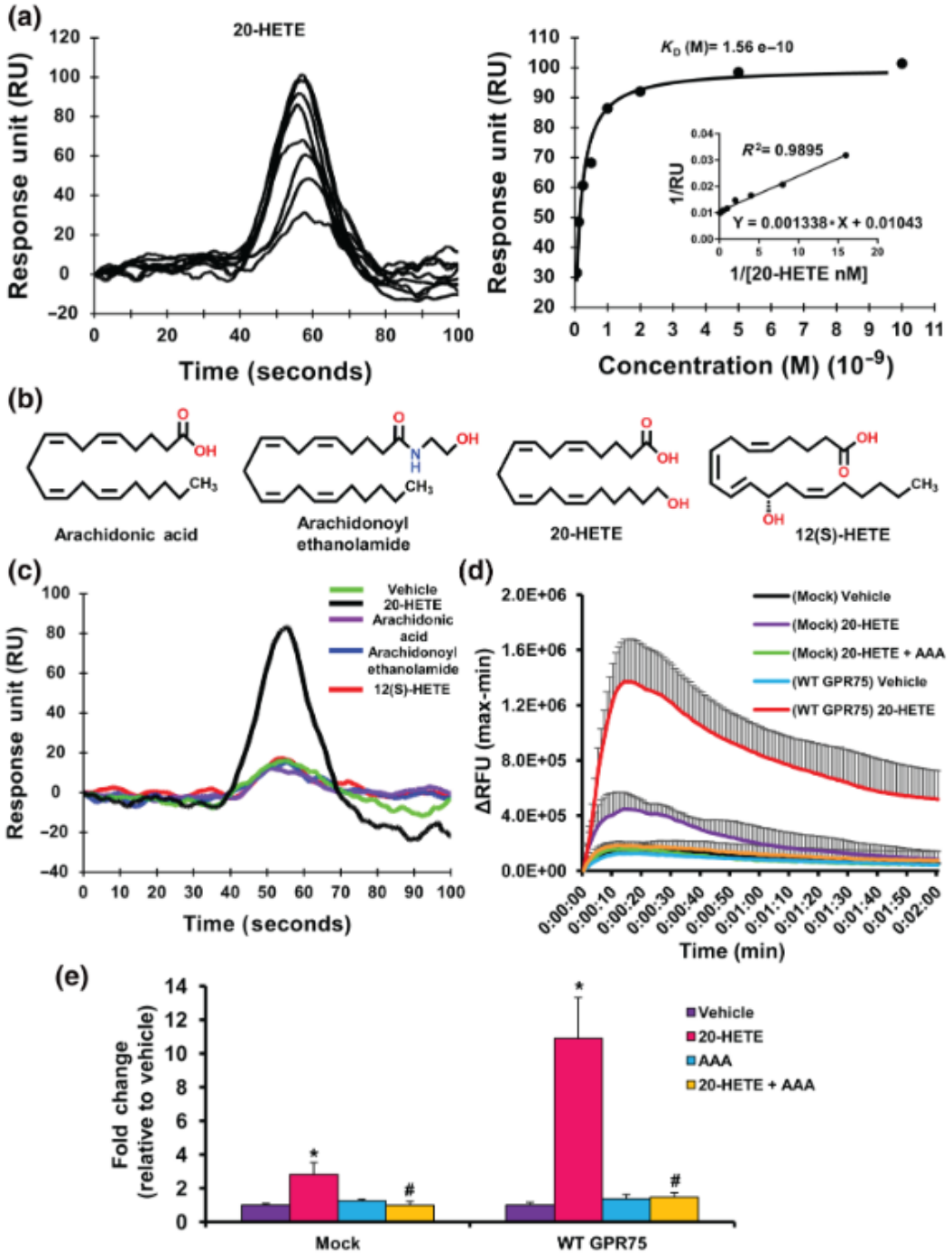


FIGURE 1 20-HETE binds to GPR75. (a) Surface plasmon resonance (SPR) analysis of 20-HETE-GPR75 binding, depicting the sensogram (normalized to vehicle (HBSS containing 1% ethanol) (left) of human recombinant GPR75 immobilized to the SPR sensor surface followed by 20-HETE injections (0.0625, 0.125, 0.25, 0.5, 1, 2, 5 and 10 nM) injected at a flow rate of 20 μl min^{-1} and affinity analysis (right). (b) Structures of arachidonic acid, arachidonoyl ethanolamide, 20-HETE and 12(*S*)-HETE. (c) SPR sensogram of human recombinant GPR75 immobilized to the SPR sensor surface followed by injections of vehicle (HBSS containing 1% ethanol), arachidonic acid, arachidonoyl ethanolamide, 12(*S*)-HETE and 20-HETE (1 nM) injected at a flow rate of 20 μl min^{-1}; 20-HETE increases intracellular calcium (iCa^{2+}) via GPR75. (d) FLIPR Calcium 6 assays of mock- or *GPR75*-transfected HTLA cells treated with vehicle (ethanol), 20-HETE (1 nM) and co-treatment of 20-HETE (1 nM) with AAA (1 nM), a 20-HETE receptor antagonist, showing post-treatment live calcium traces (2 min) or (e) peak treatment response expressed as fold change relative to vehicle-treated cells. Data shown are means ± SEM; $n = 6$. $^{*}P < 0.05$, significantly different from vehicle (ethanol), $^{\#}P < 0.05$, significantly different from 20-HETE

Chinese Team Solves for GPR75 Structure using Cryo-EM in 2022

Zilin LV, et.al., "Cryo-EM complex structure of 1 active GPR75 with a nanobody," *BioRxiv*, Aug 18, 2022

Although there has been enormous progress in the last half-century in the drug discovery targeting obesity and associated co-morbidities, the clinical treatment of obesity remains tremendously challenging. GPR75 is an orphan receptor and is suggested to be a potential novel target for the control of obesity and related metabolic disorders. Inhibition of the GPR75 signaling pathway by small molecules, antibodies, or genetic manipulations may provide a therapeutic strategy for obesity. Here, we report the active-like Cryo-EM structure of human GPR75 with an intracellular nanobody, which reveals the receptor activation mechanism. The extensive interaction network required to achieve the active structure helps explain the allosteric coupling between the orthosteric pocket and the G-protein coupling domain. The well-defined orthosteric ligand binding pocket of human GPR75 provides a structural basis for anti-obesity drug discovery.

Source: https://www.biorxiv.org/content/10.1101/2022.08.18.503988v1.full

Figure legends

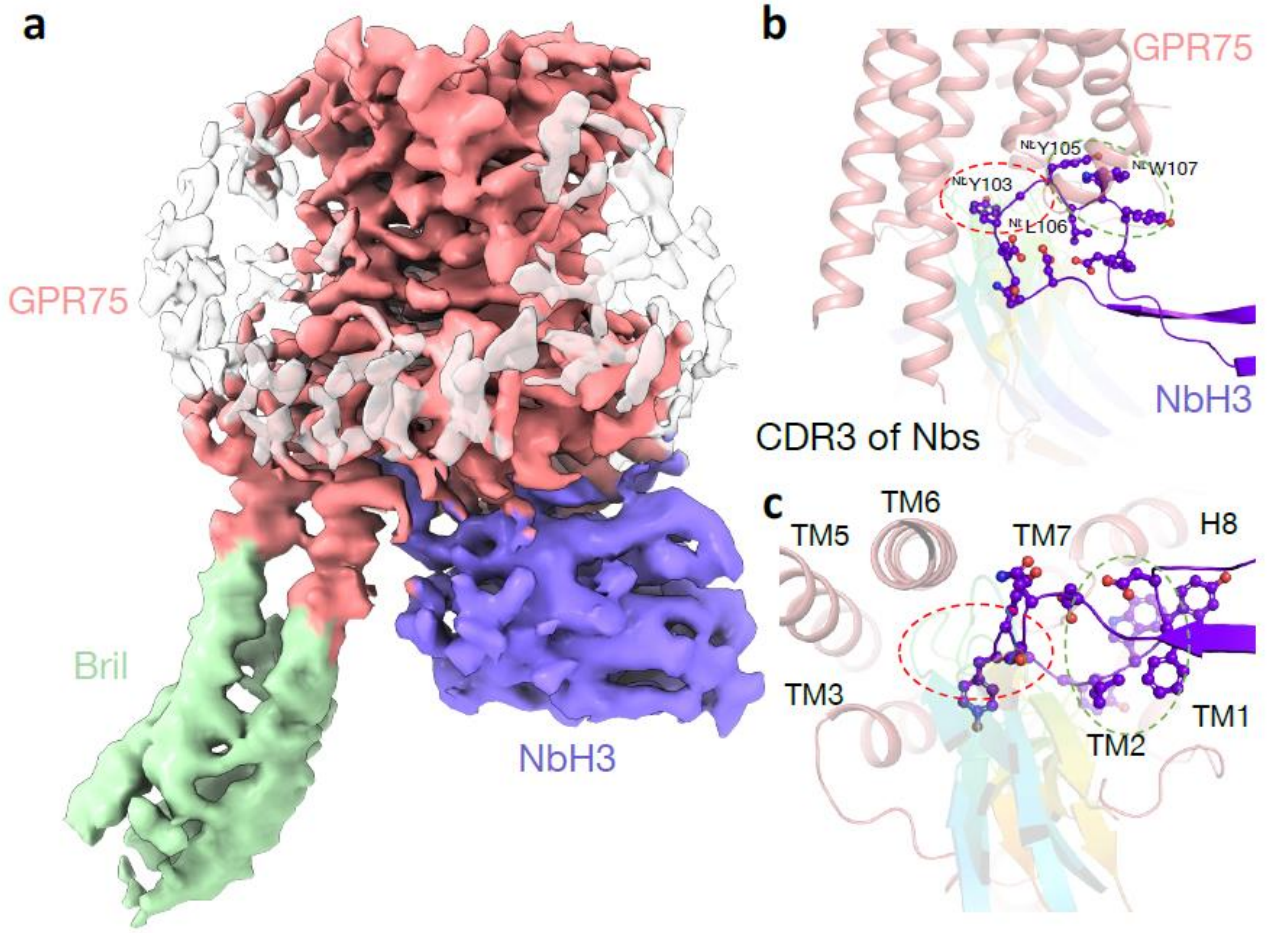


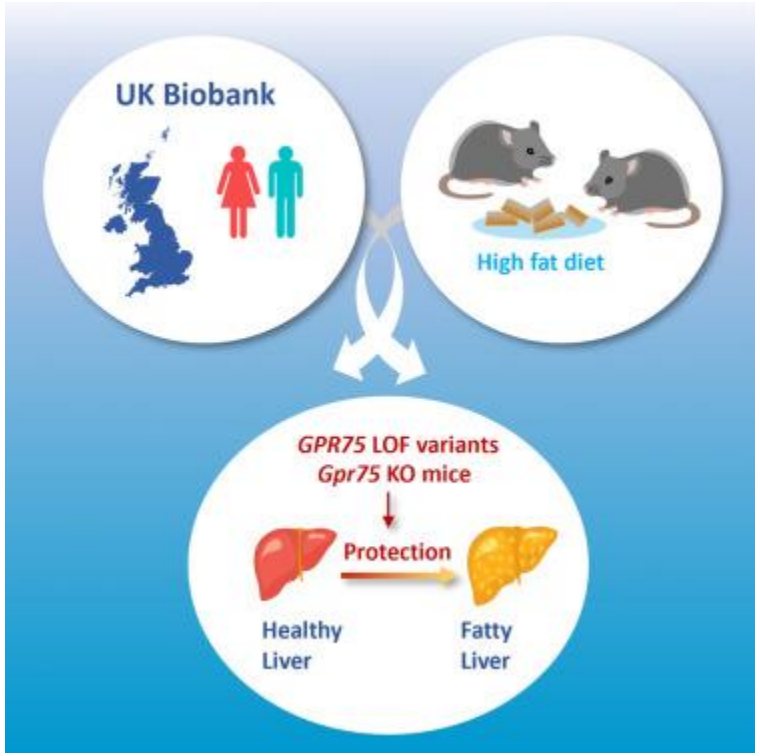
Fig. 1 The overall structure of GPR75-NbH3.

(a). Orthogonal view of the density map for the GPR75 (salmon) - NbH3 (nitrogen) nanobody complex. The fused bril domain is shown in lime green. (b, c) The CDR3 loop of NbH3 occupied two epitopes, one is the classical epitope shared by a number of GPCR nanobodies (indicated as red dash circle), and the other is a unique epitope formed by ICL1, TM7, and H8 (indicated as green dash circle). The CDR3 of several GPCR-specific nanobodies (PDB ID: 6O3C, 6OS2, 6MXT, 5WB1, 4MQT, 5JQH, 3P0G, 3VG9) is shown as a rainbow cartoon, and residues in NbH3 mediating directly interaction are shown as sticks and spheres.

Recent Paper in *Cell Metabolism* Identifies GPR75 as Key Protein in NAFLD

Leeson-Payne A. et.al., "Loss of GPR75 protects against non-alcoholic fatty liver disease and body fat accumulation," *Cell Metabolism*, May 7, 2024

Approximately 1 in 4 people worldwide have non-alcoholic fatty liver disease (NAFLD); however, there are currently no medications to treat this condition. This study investigated the role of adiposity-associated orphan G protein-coupled receptor 75 (GPR75) in liver lipid accumulation. We profiled *Gpr75* expression and report that it is most abundant in the brain. Next, we generated the first single-cell-level analysis of *Gpr75* and identified a subpopulation co-expressed with key appetite-regulating hypothalamic neurons. CRISPR-Cas9-deleted *Gpr75* mice fed a palatable western diet high in fat adjusted caloric intake to remain in energy balance, thereby preventing NAFLD. Consistent with mouse results, analysis of whole-exome sequencing data from 428,719 individuals (UK Biobank) revealed that variants in *GPR75* are associated with a reduced likelihood of hepatic steatosis. Here, we provide a significant advance in understanding of the expression and function of GPR75, demonstrating that it is a promising pharmaceutical target for NAFLD treatment.



Source: https://www.cell.com/cell-metabolism/abstract/S1550-4131(24)00120-7

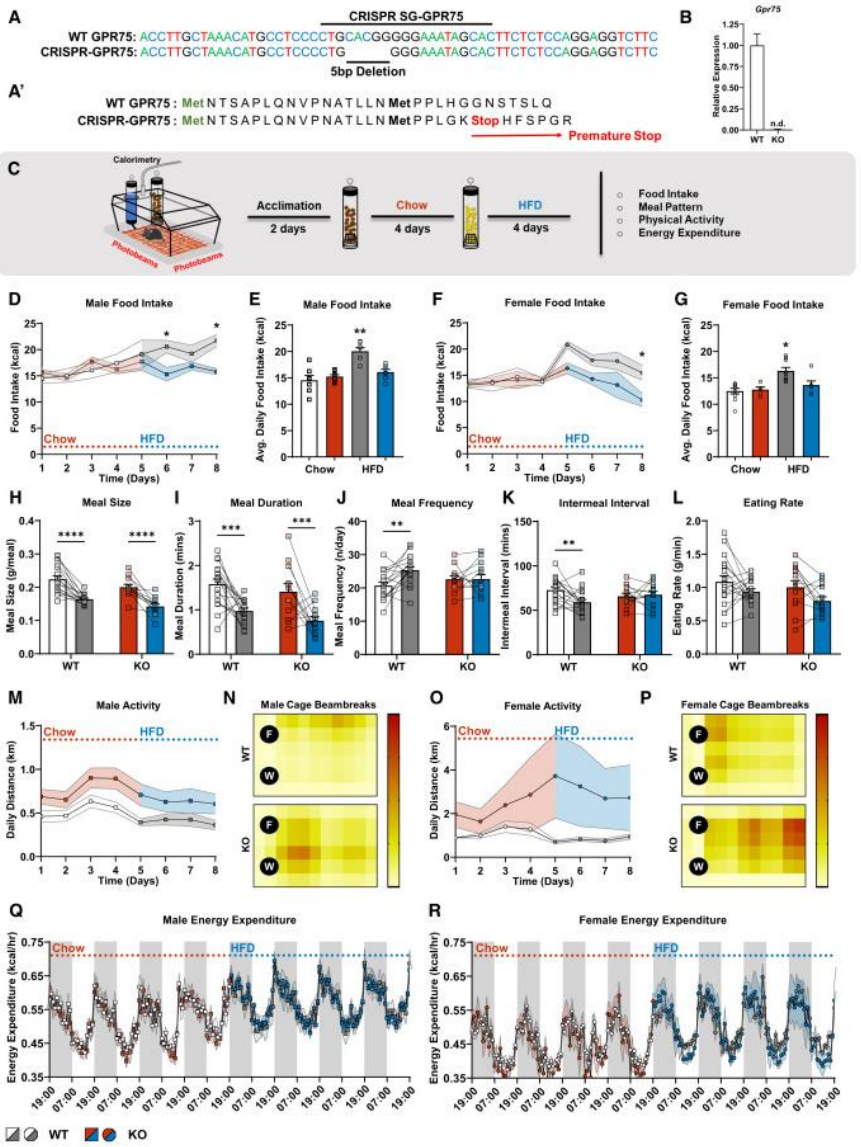


Figure 2 *Gpr75* knockout mice show reduced food intake and higher activity on high-fat diet

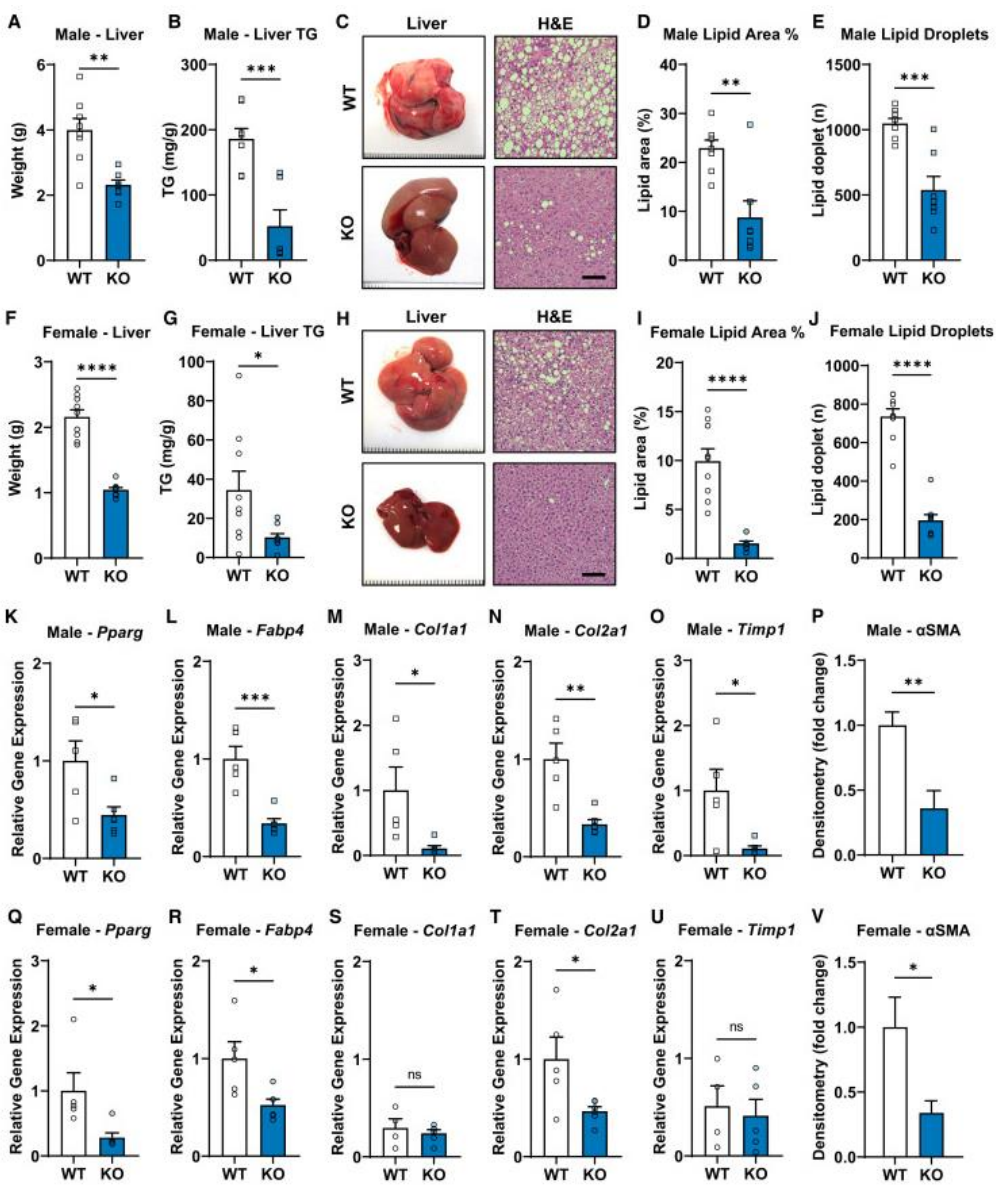


Figure 4 *Gpr75* knockout mice are protected from fatty liver

Source: https://www.cell.com/cell-metabolism/abstract/S1550-4131(24)00120-7

GPR75 Drug Pipeline

Hit-to-Lead Stage

ConfometRx Research Foundation

Lead to IND Stage

Alnylam / Regeneron
AstraZeneca / Regeneron
Orion Biotechnology
Shulmu Biosciences

Phase 1

Taisho (20-Hete inhibitor, abandoned)

Regeneron is pursuing three modalities to target GPR75:

- *siRNA collaboration with Alnylam*
- *Small molecule collaboration with AstraZeneca*
- *Antibody approach*

Disclosure

STIFEL | Healthcare

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