Biopharmaceutical Sector

Weekly Update – May 27, 2024

STIFEL | Healthcare

Table of Contents

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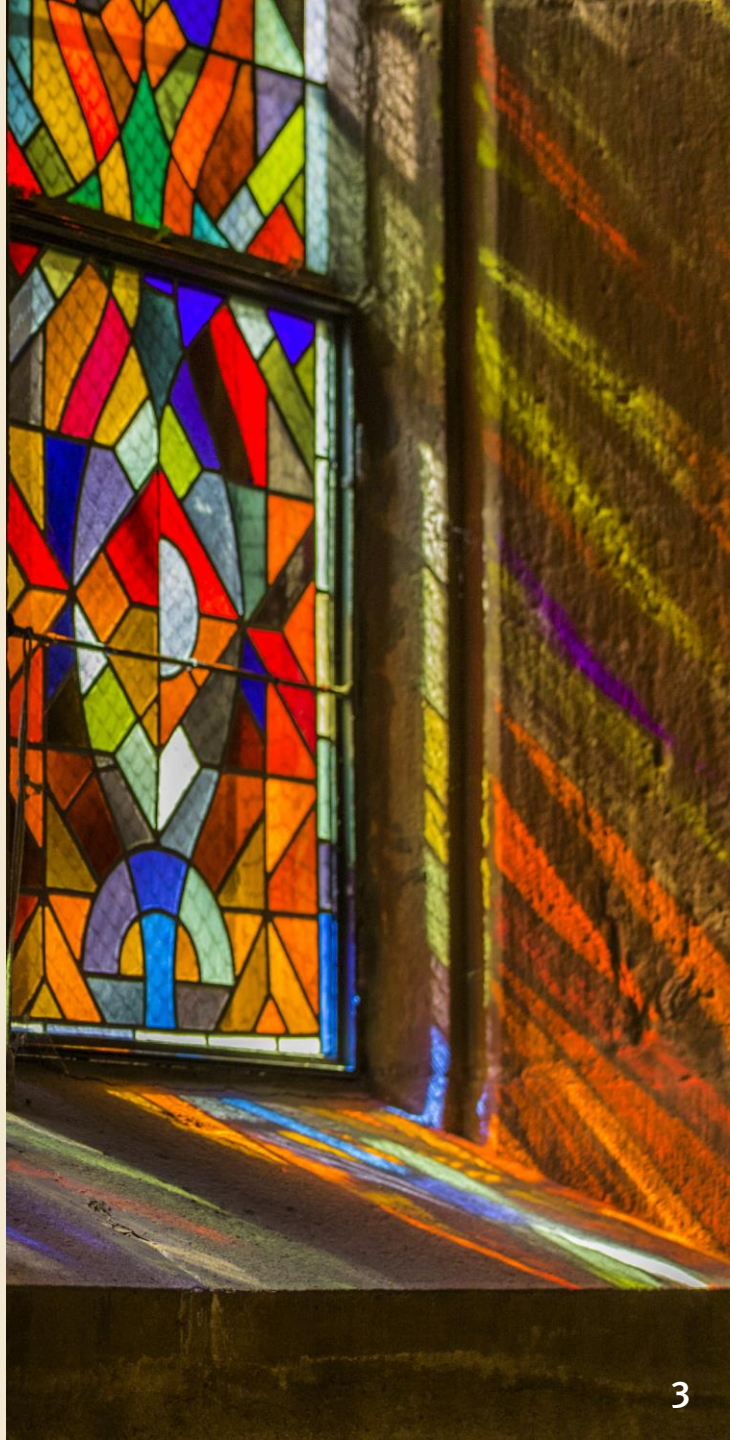
"Excitation" (Green Fluorescent Protein with *Aequorea Victoria*), Stained Glass made by Joel Kowit, On Exhibit at Harvard Medical School, 2024 (https://joel-kowit.squarespace.com/)

Accessing Past Issues

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

May 20, 2024 (Returning Capital)
May 13, 2024 (Brain, AlphaFold 3)
May 6, 2024 (Earnings, Obesity)
April 29, 2024 (M&A, Japan)
April 22, 2024 (Pharma Pricing)
April 15, 2024 (AI in Pharma)
April 8, 2024 (The Buyside)
April 1, 2024 (Biotech Balance Sheets)
March 25, 2024 (Women's Health)
March 18, 2024 (Inflammasome)
March 11, 2024 (IRA, Immunology)
March 4, 2024 (Biotech Employment)
Feb 26, 2024 (Biotech Strategy)
Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Jan 22, 2024 (AI in medicine)
Jan 15, 2024 (FDA Commissioner Priorities)
Jan 5, 2024 (Sector Outlookfor 2024)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 22, 2023 (Bullish on Biotech)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)



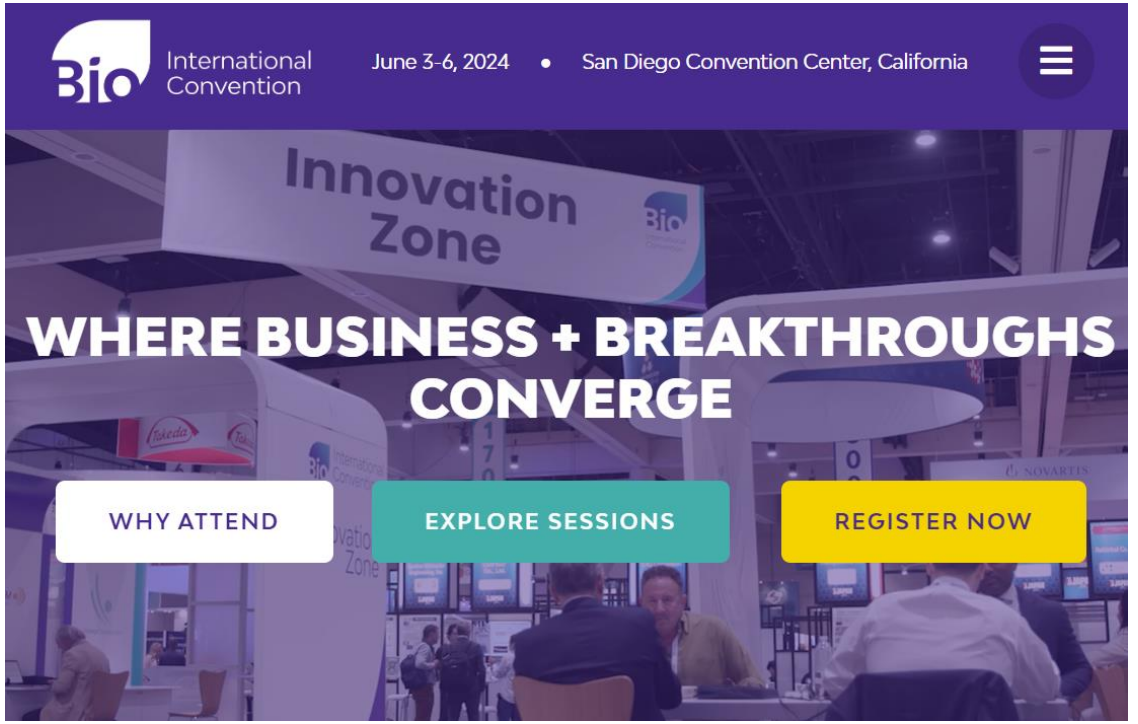
Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on May 24, 2024.

The next event will be on May 31, 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.

Also, Feel Free to Meet us At ASCO This Week

To meet us at ASCO please contact Natasha Yeung (yeungn@stifel.com) to set up a meeting.

Stifel will be hosting a cocktail event at the conference.

Macroeconomics Update

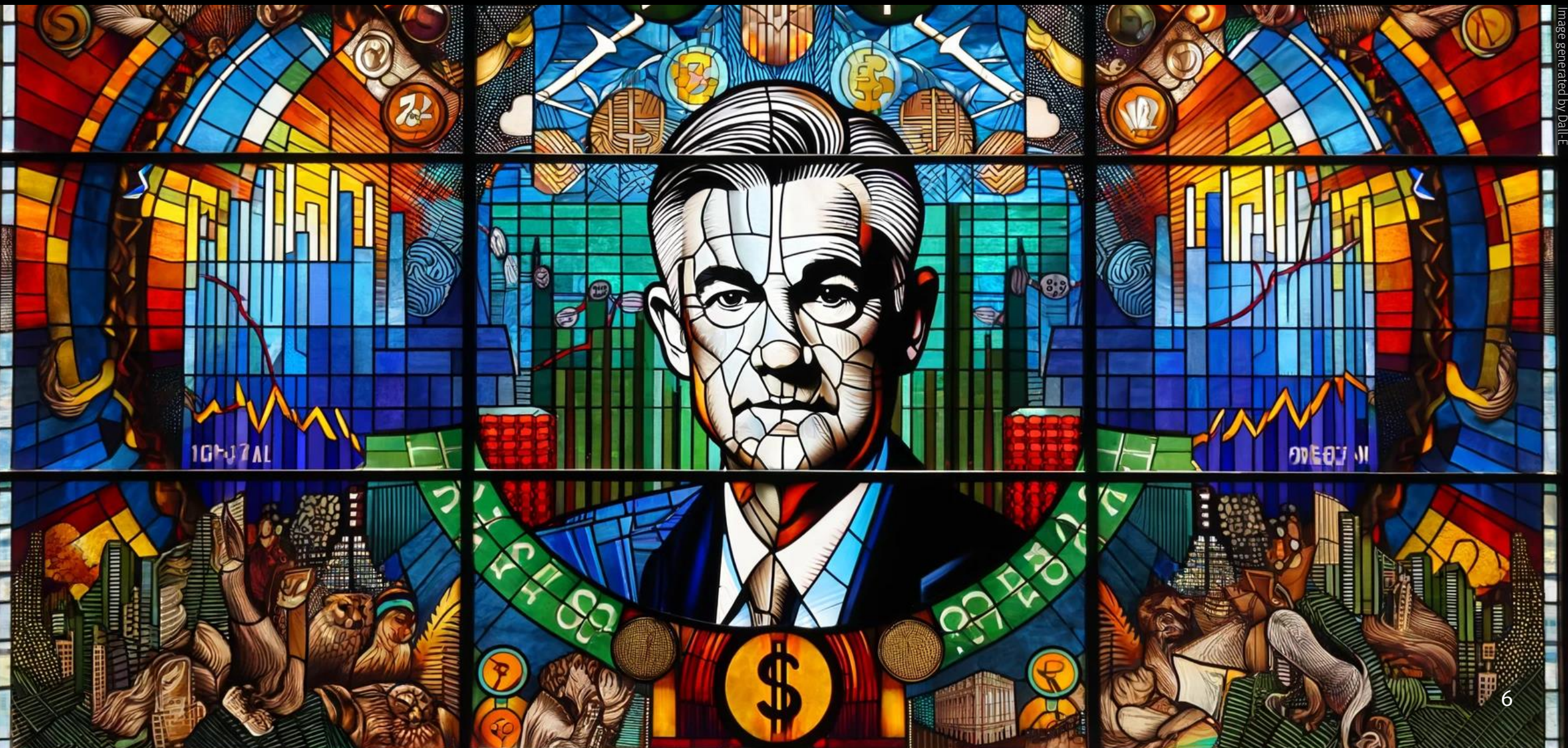


Image generated by Dall-E

Fed Officials Saw Longer Wait for Rate Cuts After Inflation Setbacks

Nick Timiraos and Paul Kiernan, *Wall Street Journal*, May 22, 2024 (excerpt)

Federal Reserve officials concluded at their most recent meeting they would need to hold interest rates at their current level for longer than they previously anticipated after a third straight disappointing inflation reading last month.

While officials continued to think interest rates were high enough to slow the economy and inflation, they signaled they were less certain over the degree to which rates would restrain activity and price pressures, according to minutes of the April 30-May 1 meeting, which were released Wednesday with a customary three-week delay.

Officials voted to hold their benchmark federal-funds rate steady in a range between 5.25% and 5.5%, the highest level in more than two decades. They have held rates at that level since July, when they concluded the most rapid series of interest-rate hikes in 40 years to combat high inflation.

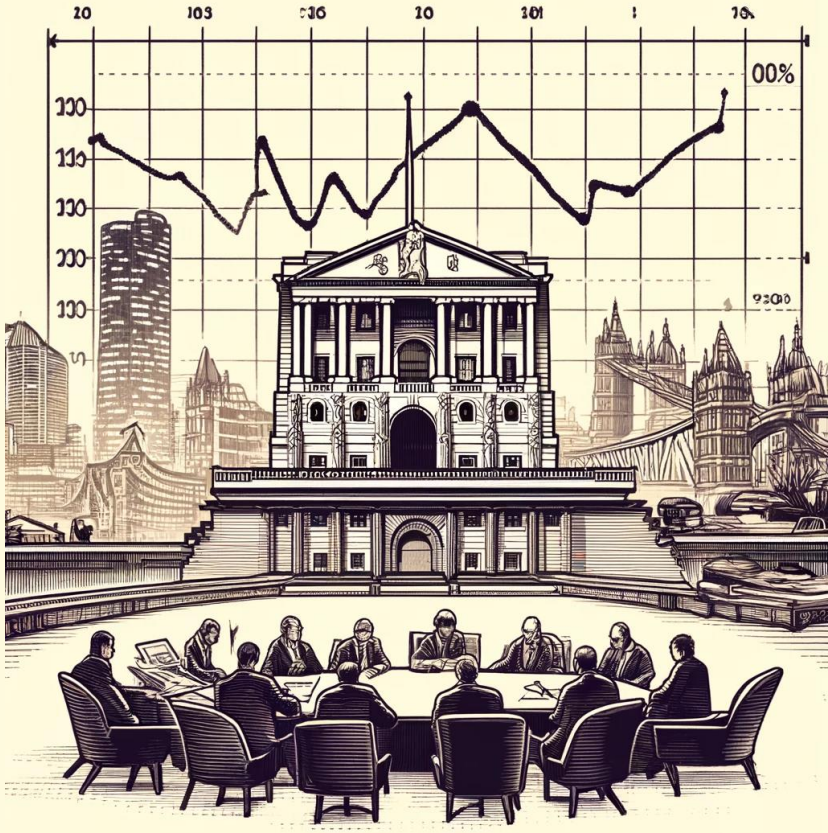
Price pressures slowed notably through the second half of last year, and Fed leaders in March had suggested they might be prepared to start cutting rates with one or two additional months of mild inflation.

But a run of data in the first quarter revealed simmering price pressures in the economy, and the Fed has been forced to table any deliberations about beginning rate cuts for the next few months unless the labor market weakens unexpectedly.

Source: https://www.wsj.com/economy/central-banking/fed-officials-saw-longer-wait-for-rate-cuts-after-inflation-setbacks-9c444903

New Data Shows U.K. Inflation Plummeting, in Contrast to the U.S.

Courtenay Brown, *Axios*, May 22, 2024 (excerpt)



The U.K. was once home to the developed world's worst inflation. Now, it's within striking distance of the central bank's 2% target.

Why it matters: It speaks to the different nature of inflation shocks on both sides of the Atlantic. Much of the rapid price increases in the U.K. resulted from soaring commodity costs after supplies from Russia were cut off — not strong demand, like in the U.S. Once the energy crisis subsided, inflation pressures started to ease notably.

By the numbers: The Consumer Prices Index rose by 2.3% in the 12 months through April — the smallest gain since the summer of 2021.

That is down from the 3.2% in March, a plunge driven by an energy price cut that resulted in the largest annual fall in electricity and gas costs on record.
The April data shows a plunge from the 3.2% in March, though economists thought it would actually drop further to 2.1%.

State of play: It comes as the Bank of England looks set to slash interest rates in the months ahead, though policymakers are trying to parse the stickiness of lingering inflationary pressures.

Source: https://www.axios.com/2024/05/22/inflation-uk-crisis

Yen Weakens to 157 Against Dollar, Touching 3-Week Low

Nikkei Asia, May 24, 2024 (excerpt)

TOKYO -- The yen weakened past 157 to the dollar on Thursday, reaching a three-week low after a U.S. purchasing managers index showed accelerated business activity.

The provisional reading for S&P Global's PMI survey beat market expectations, prompting dollar-buying among traders seeing a resilient U.S. economy.

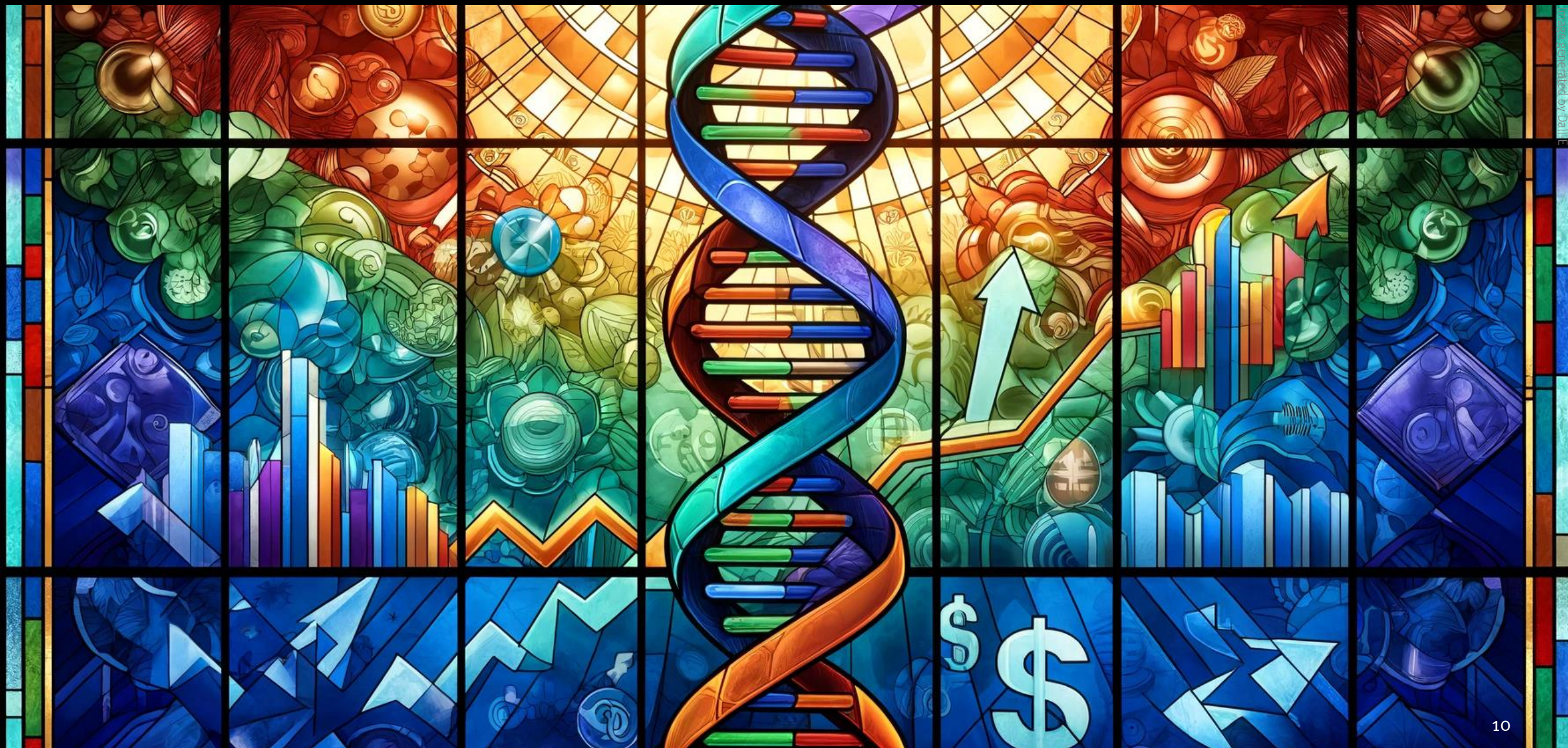
After the Japanese currency fell to the 160 range against the dollar on April 29, it surged on May 1 on large purchases believed to have been a market intervention. It strengthened to 151.80 at one point on May 3.

The yen has since trended weaker, partly on dollar-buying by Japanese importers. Yen sales apparently connected to carry trades also put downward pressure on the yen.

Source: https://asia.nikkei.com/Business/Markets/Currencies/Yen-weakens-to-157-against-dollar-touching-3-week-low

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

Biopharma Market Update



The XBI Closed at 88.83 Last Friday (May 14), Down 2.6% for the Week

The XBI fell last week after the Fed published minutes indicating hawkish sentiment on the FOMC. The XBI is flat for the year and has been directionless for many weeks. In contrast, our barometer of biotech value remains healthily positive for the year (up 14% YTD).

Biotech Stocks Down Last Week

Return: May 18 to May 24, 2024

Nasdaq Biotech Index: -0.3%
Arca XBI ETF: -2.58%
Stifel Global Biotech EV (adjusted): -4.2%*
S&P 500: +0.03%

Return: Dec 29, 2023 to May 24, 2024 (YTD)

Nasdaq Biotech Index: +1.4%
Arca XBI ETF: -0.5%
Stifel Global Biotech EV (adjusted): +14.1%*
S&P 500: +1.1%

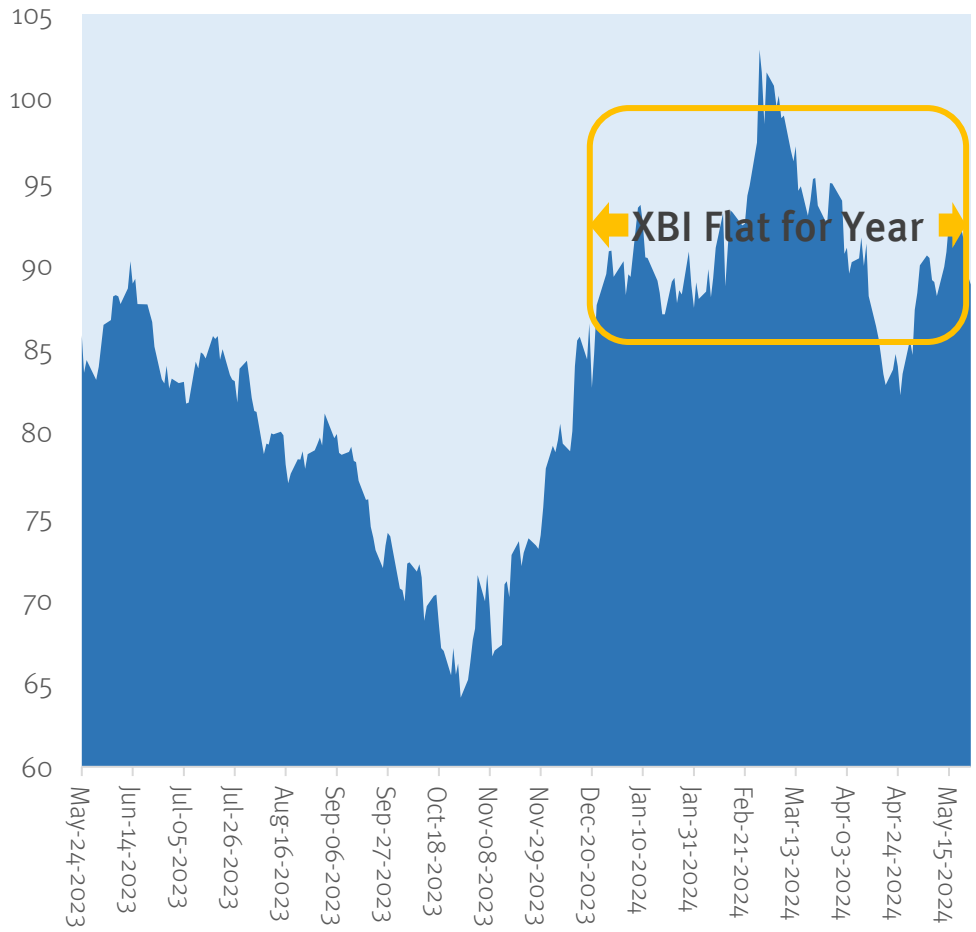
VIX Down Further

Jan 20, 2023: 19.9%
July 21, 2023: 13.6%
Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Mar 29, 2024: 13.0%
Apr 26, 2024: 15.0%
May 17, 2024: 12.0%
May 24, 2024: 11.93%

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%
Mar 29, 2024: 4.20%
Apr 26, 2024: 4.66%
May 17, 2024: 4.42%
May 24, 2024: 4.472%

XBI, May 24, 2023 to May 24, 2024



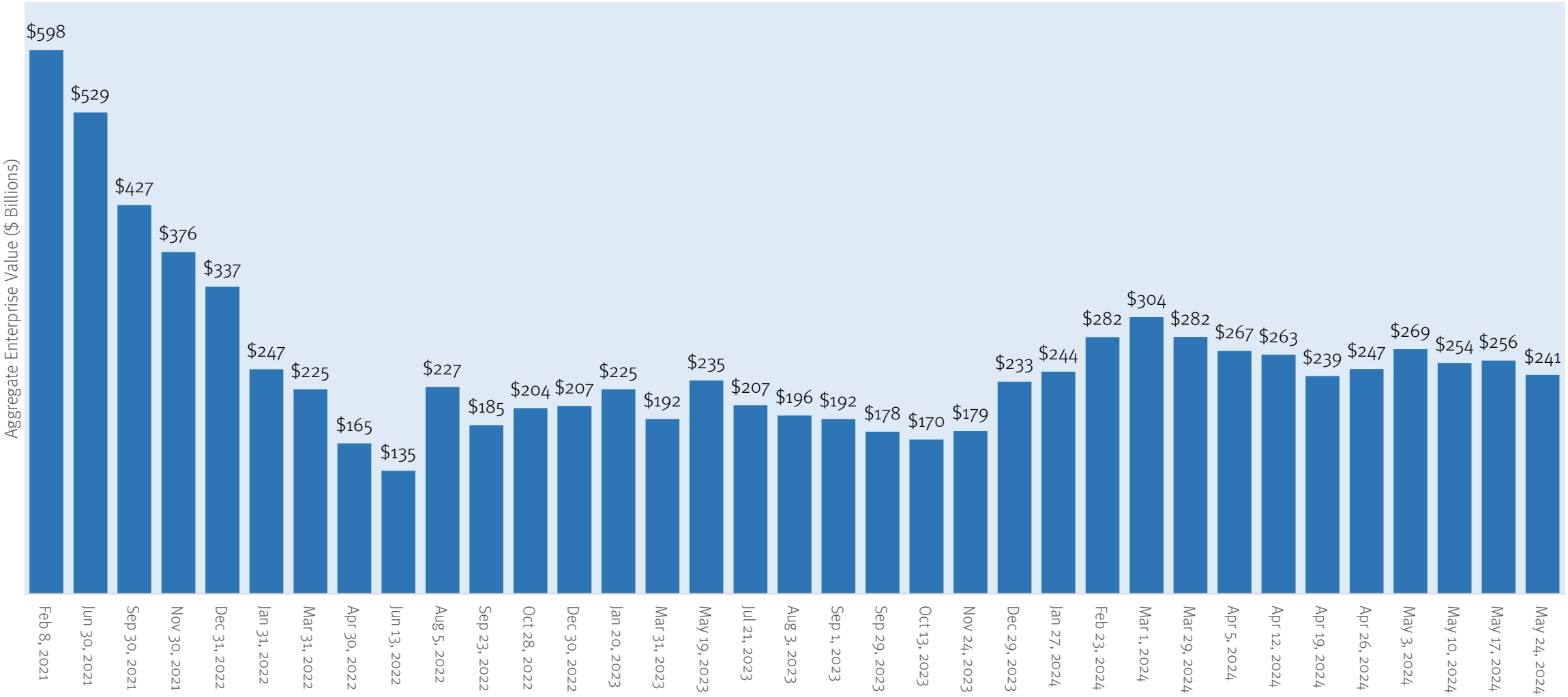
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Up 14% Year to Date

Biotech stocks were down 4.2% last week (on an exit/addition adjusted basis). If one adjusts for exits, total sector value is up 14.1% YTD.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to May 24, 2024 ($ Billions)



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

Biotech Exits This Year That are Added Back to Our Value Barometer

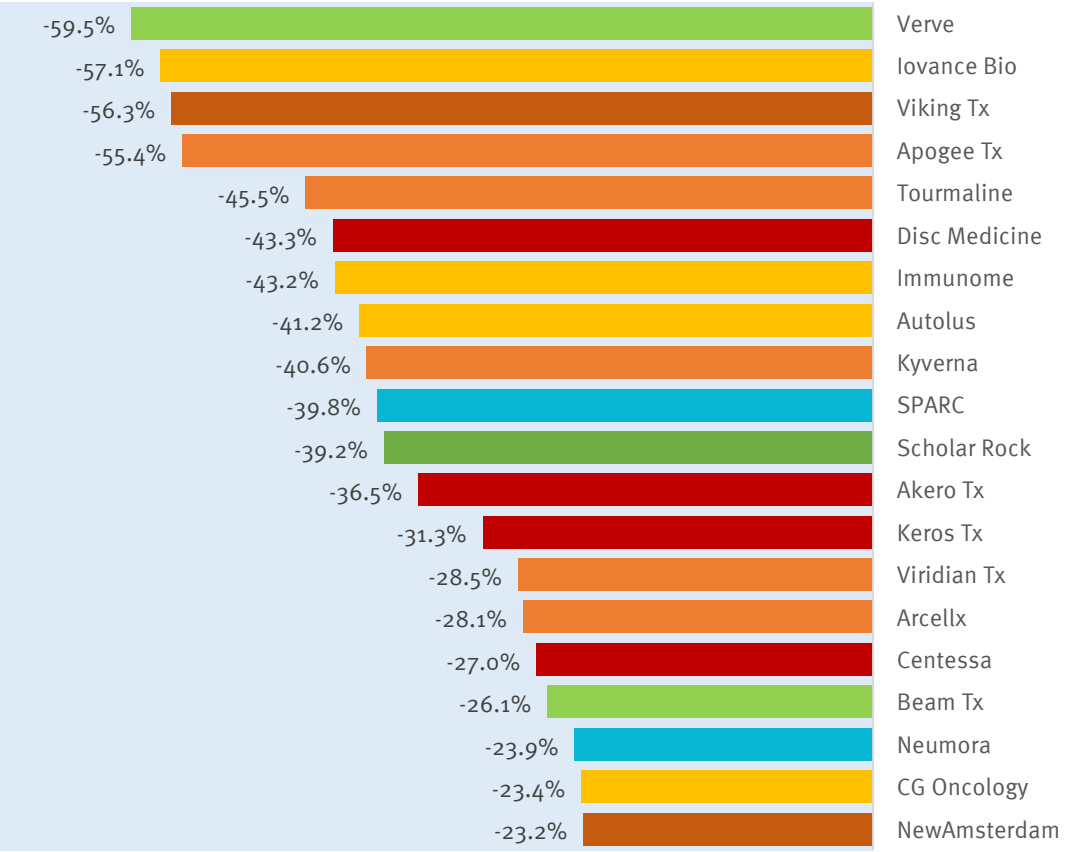
Company Name	Disposition	Net Effect on Value ($mm)
Gracell	Acquired	$969
Freeline	Acquired	$28
Cymabay	Acquired	$3,746
LianBio	Acquired	$515
Alpine Immune	Acquired	$4,900
Merrimack	Liquidated	$196
Karuna	Acquired	$11,336
RayzeBio	Acquired	$3,176
BaudaxBio	Liquidated	$18
Harpoon	Acquired	$680
	Total	$25,564

When you add back the $25.5bn of biotech exits, the Stifel Biotech Value Barometer is healthily positive for the year to date.

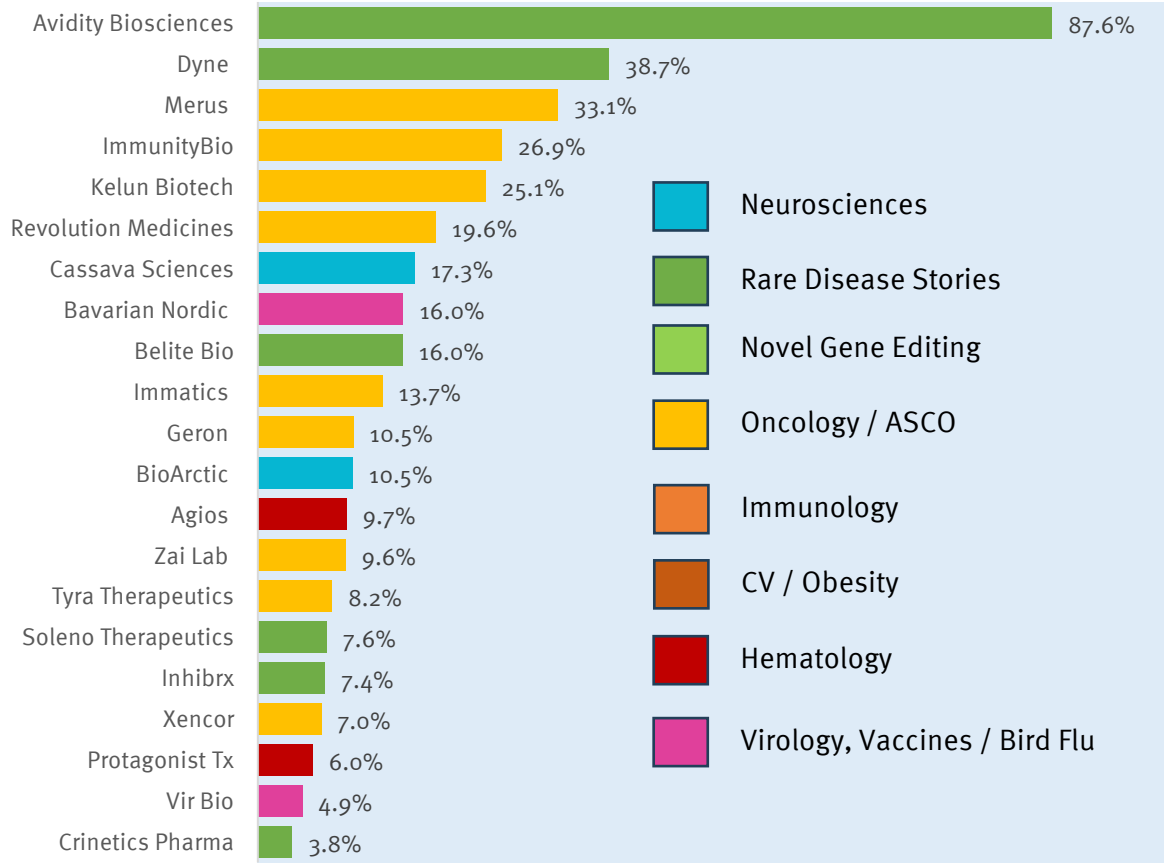
Biggest One Month Moves Among Larger Biotechs

We have seen several gene editing stories including Beam and Verve decline. Verve recently went on clinical hold. Cell-therapy based oncology has been weak while some oncology companies with other modalities going into ASCO have thrived. Merus had a great ASCO abstract on its bispecific last week and moved on that. Viking shares have come down due to competitive newsflow in the obesity field. Rare disease stories like Avidity have done well based on both data and a sense that the FDA's attitude is becoming more permissive. Avidity was awarded FDA Breakthrough Designation, for example. A short squeeze has helped Cassava.

Biggest Biotech Decliners Over Last Month by Percent Return



Biggest Biotech Gainers Over Last Month by Percent Return



Source: CapitalIQ and Stifel analysis. Companies for this analysis were selected from our list of global biotechs based on having a market cap of $1bn or more on April 24, 2024. Figures shown are one month percent change in market cap.

Cancer Biotech Stocks Are on the Move Ahead of ASCO

Josh Nathan-Kazis, *Barron's*, May 24, 2024 (excerpt)

The biggest weekend in cancer science is just a week away, which means that the research analysts who cover biopharma for Wall Street banks got very little sleep on Thursday night.

The American Society of Clinical Oncology is set to gather on May 31 in Chicago for its annual meeting, which runs through June 4 and draws not only research scientists and clinicians from around the world, but also a parade of biopharma companies, and the investors who track them.

Late Thursday, ASCO released most of the 5,000 summaries of research to be presented at the conference, including trial results from lots and lots of pharma and biotech names. While some closely watched data are not released until the day of the presentation, Wall Street always leaps on these early summaries, called abstracts, for insights on drug makers' oncology development programs.

From the time stamps on analyst reports that flooded healthcare investors' inboxes Thursday night through early Friday, it appears biotech analysts did not get much sleep.

Here are the stocks moving the most after the Thursday night data dump, and what to look out for at the conference next week.

Shares of the cancer-focused biotech Merus were up 30.4% Friday morning after the company released an abstract summarizing the results of a small trial of its experimental drug petosemtamab in combination with Merck's Keytruda in patients with head and neck squamous cell carcinoma.

Merus said that 60% of the 10 patients whose results were able to be evaluated by last November responded to the treatment.

American depositary receipts of Immunocore have tumbled since an abstract of the company's presentation on a trial of its drug brenetafusp in skin cancer posted late Thursday, but analysts argued through the night that the selloff was overdone. The Immunocore ADRs were down 11% Friday morning.

In the abstract, Immunocore reported on a 46-patient trial of brenetafusp. The company reported a response rate to the treatment of 13%, all of whom were only partial responders. That was the bad news. But in their notes, analysts said the good news outweighed the bad.

Source: https://www.barrons.com/articles/biotech-stocks-asco-wall-street-e692c4b9

Selected ASCO Share Price Movers

Company	24 May share price move	Trial	Note
Merus	+30%	NCT03526835	Petosemtamab + Keytruda, 60% ORR (incl 1 uPR) impresses in 1L head & neck cancer
Iovance	+1%	IOV-COM-202	Amtagvi + Keytruda, 65% ORR, 30% CR rate in 23 1L melanoma pts (per press release with Apr 2024 cutoff, vs Dec 2023 in abstract)
Genmab	-5%	NCT05117242	BioNTech-partnered acasunlimab disappoints in NSCLC, and shows liver toxicity
Tango	-5%	None	Company discontinues its USP1 inhibitor, as Roche's competing project also disappoints
Immunocore	-12%	NCT04262466	Anti-PRAME Immtac brenetafusp, 13% ORR in 31 post-checkpoint cutaneous melanoma pts
Candel	-15%	NCT04495153	Aglatimagene besadenovec + valacyclovir + CPI, mOS 20.2mth (0% ORR) in 44 (subgroup from 63 enrolled) post-CPI NSCLC pts
Verastem	-60%	Ramp-205	Avutometinib + defactinib + Abraxane + chemo, 75% ORR (incl 2 uPR) in 8 1L PDAC pts, but ovarian cancer approval pathway is narrowed to KRASm

Source: https://www.oncologypipeline.com/apexonco/asco-2024-abstract-movers-merus-convinces-now

Biotech Stocks are Rising Alongside Bird Flu Fears

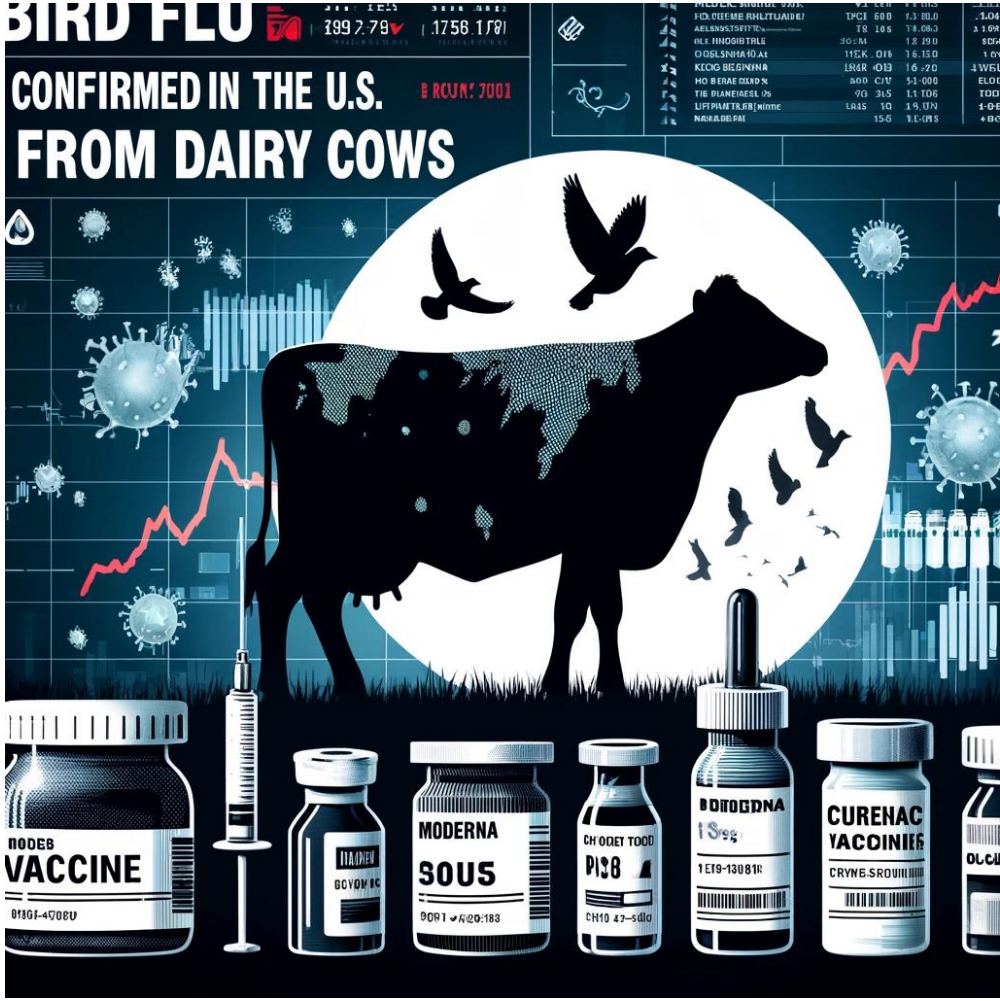
Caroline Anders, *Semafor*, May 23, 2024 (excerpt)

As the United States confirmed a second human case of bird flu from dairy cows on Wednesday, shares in biotech companies rose sharply. Vaccine makers, including Moderna, BioNTech, and CureVac, all saw double-digit stock increases, as investors bet they could cash in on a public health response should bird flu start spreading between people. COVID-19 offered a blueprint: Moderna and BioNTech both developed widely-used vaccines for the virus.

The virus is considered a pandemic threat because it often jumps between species, but less easily among humans. Risk to the public remains low, the US Centers for Disease Control and Prevention stressed, although bird flu has been spreading among cattle, and officials said people who work on farms should remain vigilant.

“It’s a familiar setup for industry veterans who have witnessed past trading frenzies at the first signs of an outbreak,” Bloomberg reported. But the scope of the outbreak is unclear, and officials have called for increased testing.

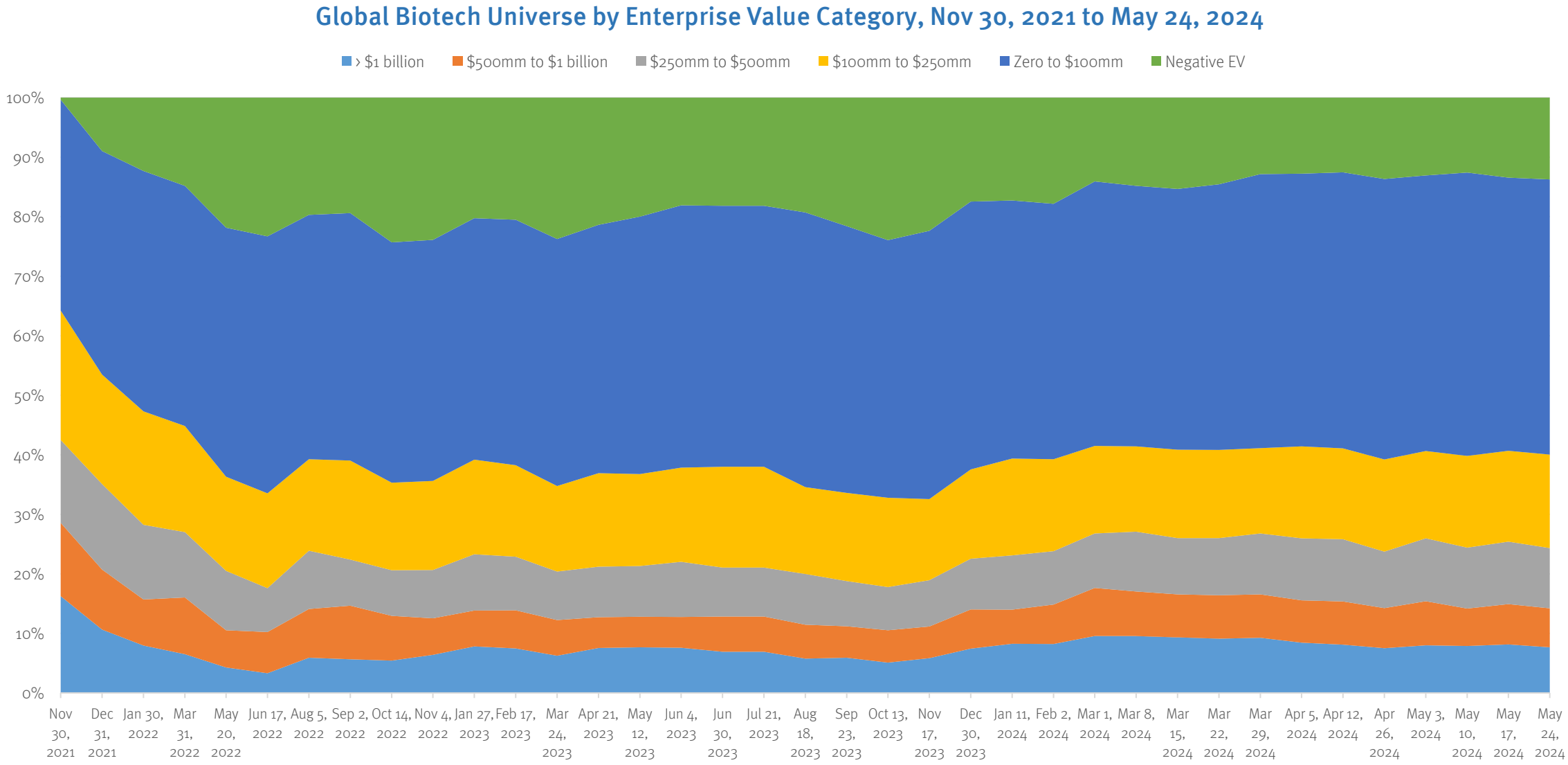
“We’re ahead of the game in terms of avian flu vaccine, compared to where we were with COVID,” an epidemiologist told Scientific American. US health authorities have a huge stockpile of vaccine doses that are effective against bird flu, and existing relationships with vaccine makers mean production could be increased quickly if needed.



Source: https://www.semafor.com/article/05/23/2024/biotech-stock-rising-bird-flu-fears-vaccines-moderna

Global Biotech Neighborhood Analysis

The population of companies worth more than $500mm has shrunk in recent weeks.



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

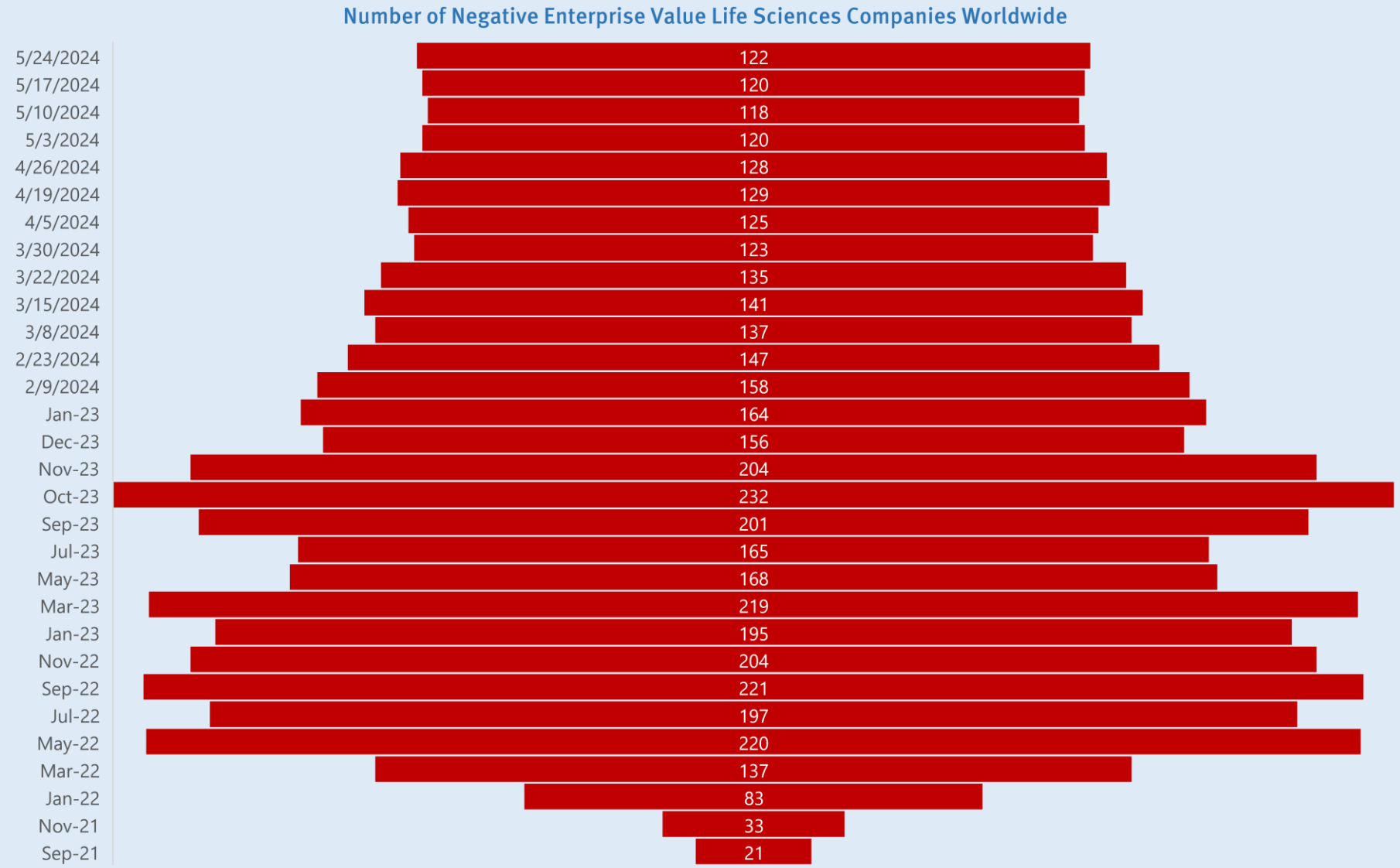
Life Sciences Sector Total Value Down 1.1% Last Week

All subsectors of the life sciences sector dropped in value last week. HCIT, CDMO's and biotech performed most poorly.

Sector	Firm Count	Enterprise Value (May 24, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$82,767	-1.3%	3.4%	4.8%
Biotech	791	$241,455	-4.2%	1.6%	-5.1%
CDMO	39	$141,649	-4.3%	-0.7%	-18.9%
Diagnostics	81	$265,621	-1.9%	1.1%	-0.8%
OTC	30	$25,937	-2.7%	-2.1%	-11.7%
Commercial Pharma	716	$6,334,456	-0.6%	4.8%	10.4%
Pharma Services	38	$184,468	-1.9%	-0.2%	-3.8%
Life Science Tools	51	$716,341	-1.9%	4.0%	4.2%
Devices	181	$1,687,635	-1.3%	2.6%	3.3%
HCIT	10	$17,662	-5.9%	2.7%	-23.3%
Total	**2018**	**$9,690,991**	**-1.1%**	**3.9%**	**7.5%**

Source: CapitalIQ and Stifel analysis

Small Increase Last Week in Count of Negative Enterprise Value Life Sciences Companies



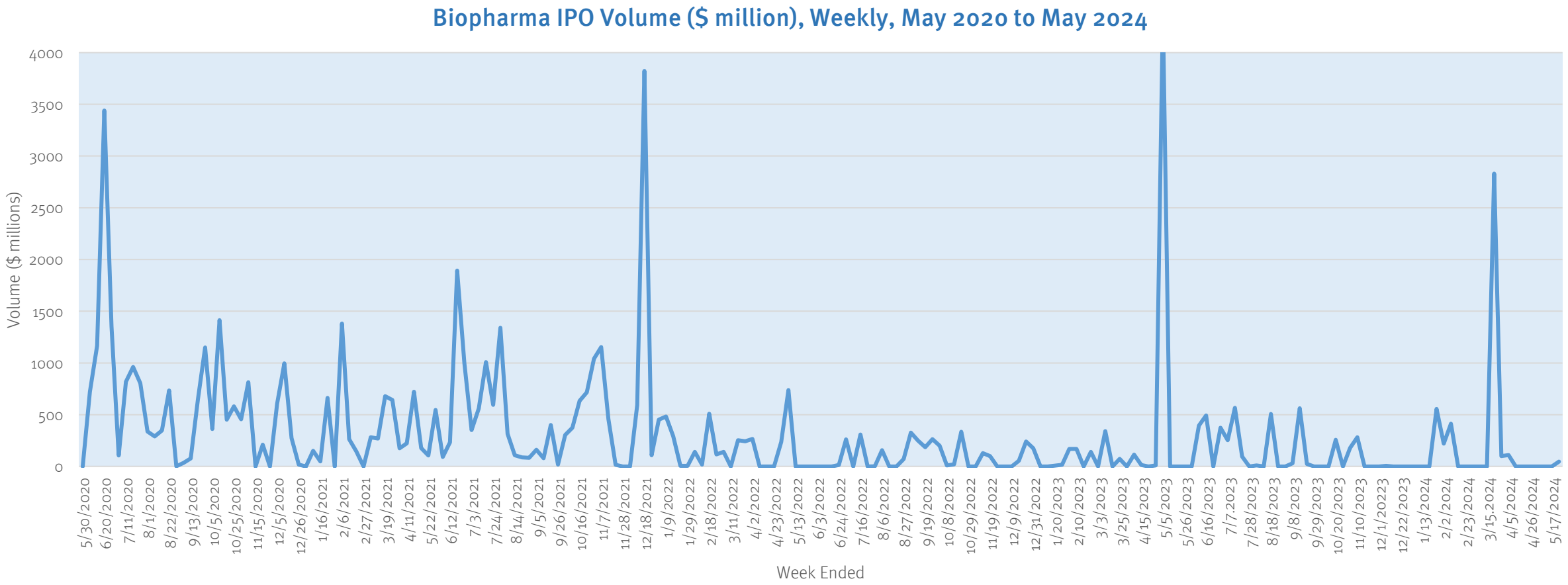
Source: CapitalIQ and Stifel analysis

Capital Markets Update

Image generated by Dall-E

Some IPO Activity in Asia Last Week

The IPO market remained inactive last week. The last company to go public in the U.S. or Europe debuted seven weeks ago. Sunho Biologics completed a successful $57 million IPO on the Hong Kong Stock Exchange last week.



Source: Data from CapitalIQ and Stifel research.

Solid Debut Last Week for Sunho Bio on HKEX

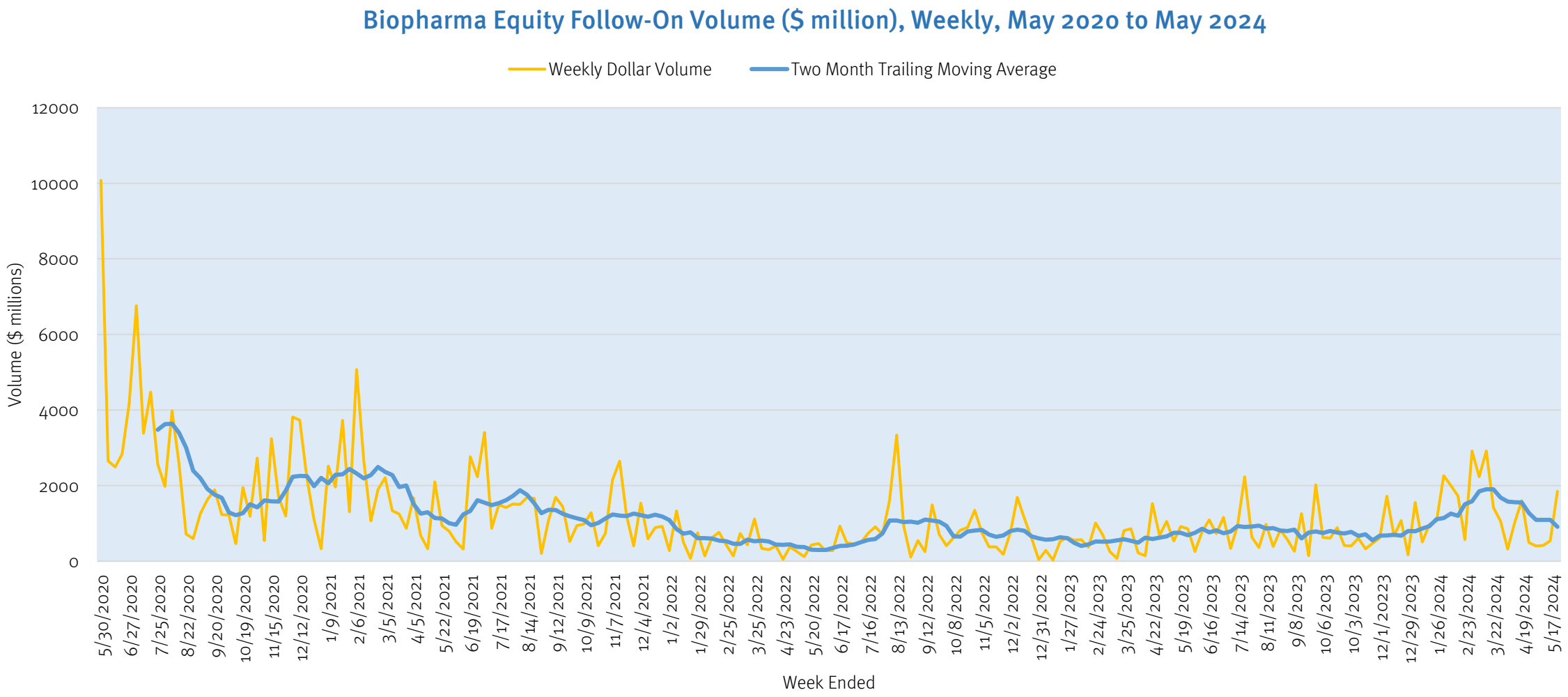
The Sunho Bio IPO was Hong Kong's largest pre-revenue biotech listing year to-date.

Sunho Biologics is a clinical stage biopharmaceutical company that focuses on the discovery, development, and commercialisation of biologics for the treatment of cancers and autoimmune diseases. It has three developed in-house core products and has initiated Phase II clinical trials for biliary tract carcinoma and completed a colorectal cancer to date Phase I clinical trial for advanced solid tumours. The company has nine pipeline products. In addition to its core products, three of these pipeline products are in the clinical stage, also focusing on the treatment of cancer.

Source: https://www2.deloitte.com/cn/en/pages/audit/articles/dtt-china-assists-listing-of-sunho-biologics-on-sehk.html

Follow-On Market Active Last Week

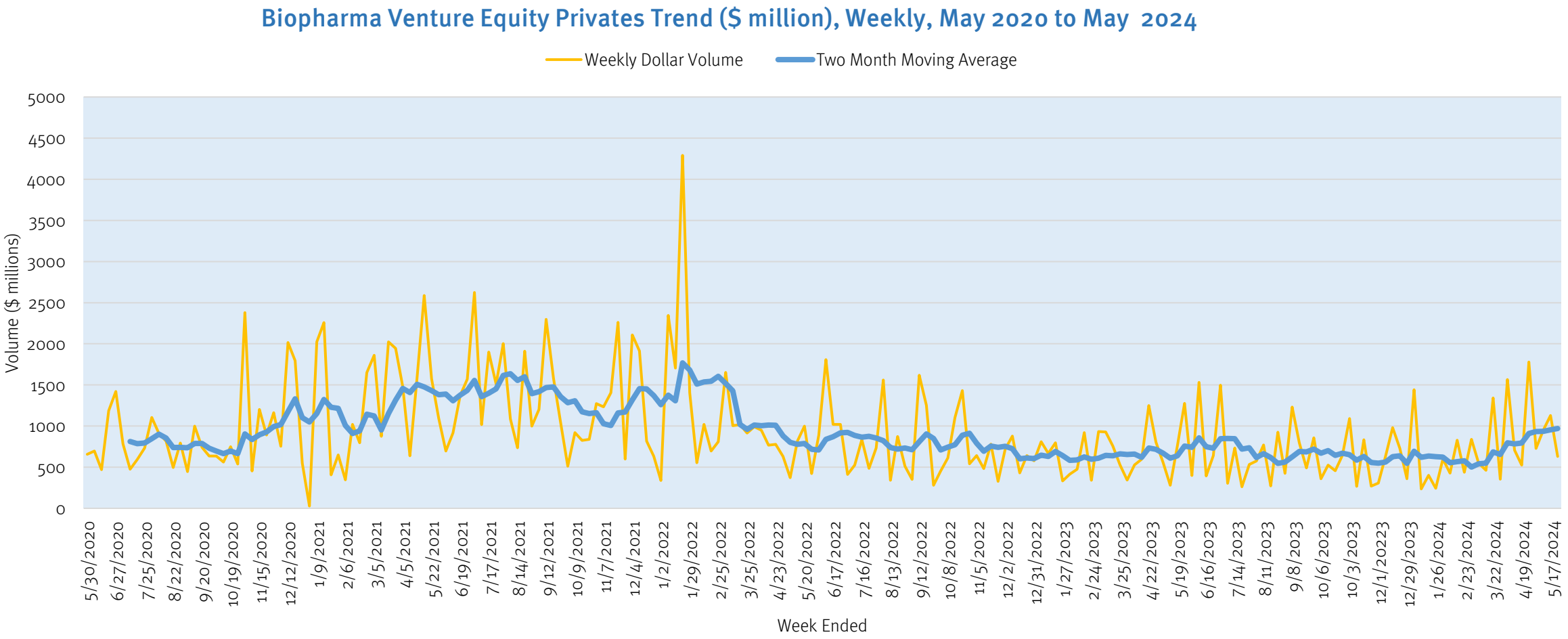
The follow-on market picked up quite a bit last week. A total of $1.7 billion was raised across 29 issues. The largest issues were by Bicycle ($556 million), Cytokinetics ($500 million) and Dyne ($325 million).



Source: Data from CapitalIQ.

Private Venture Equity Market Moderate Last Week

The venture private market was moderately active last week with $660 million raised by 23 issuers in this market. The largest issues were AltruBio ($225 million) and Pheon Therapeutics ($120 million).



Source: Data from CapitalIQ, Crunchbase.

AltruBio Secures up to $225M Series B Financing to Advance Novel Immune Checkpoint Enhancer Program

SAN FRANCISCO, May 21, 2024 (GLOBE NEWSWIRE): AltruBio Inc. ("AltruBio" or "the Company"), a clinical stage biotechnology company dedicated to the development of novel therapeutics for the treatment of immunological diseases with high unmet medical needs, today announced an oversubscribed Series B financing of up to $225 million. AltruBio plans to use the proceeds of the financing to advance the clinical development of the Company's first-in-class, novel immune checkpoint enhancer (ICE) PSGL-1 agonist antibody, ALTB-268. The funds will be used to support ongoing and planned Phase 2 clinical trials in ulcerative colitis (UC), one of many immunological disorders where the mechanism has been clinically validated.

The financing was led by BVF Partners LP with participation from new investors RA Capital Management, Cormorant Asset Management, and Soleus Capital, as well as existing investors aMoon Fund and Blackstone Multi-Asset Investing, with other new and existing investors joining the syndicate.

The Company's first-in-class, novel ICE agonist antibody, ALTB-268, is currently being studied in a Phase 2a exploratory biomarker study in patients with biologic refractory UC with an anticipated readout for its primary endpoint of clinical remission per modified Mayo score in 1H 2025. The company plans to initiate a global Phase 2b randomized, placebo-controlled clinical trial with a primary endpoint of clinical remission in both advanced therapy experienced and treatment naive patients with moderately to severely active UC. This study is anticipated to read out in 2H of 2026.

"Treatment options remain limited in many autoimmune conditions, including moderate to severe ulcerative colitis, and novel mechanisms are sorely needed," commented Gorjan Hrustanovic, Ph.D., Managing Director at BVF Partners LP. "We are excited to support AltruBio and their commitment to developing a potential first-in-class medicine across multiple autoimmune indications, starting with UC."

"We are honored to welcome this esteemed new group of investors, whose participation complements the support of our existing world-class investor group. Their collective backing not only affirms the potential of our program and company but also our mission of developing durable biologic therapies for patients suffering from autoimmune diseases"

Judy Chou
President and Chief Executive Officer, AltruBio

Source: https://www.blackstone.com/news/press/blackstone-life-sciences-launches-uniquity-bio-to-develop-novel-medicines-in-immunology-inflammation/

AltruBio Gathers Funds as Biotechs Aim for Next Blockbuster Anti-Inflammatory Therapy

Highly competitive sector heats up with large venture investments, acquisitions

Brian Gormley, *Wall Street Journal*, May 21, 2024 (excerpt)

Biotechnology startup AltruBio has secured fresh capital to develop a drug for ulcerative colitis as drugmakers compete to develop the next blockbuster therapy for this and other inflammatory diseases.

Immunological and inflammatory diseases are common and not all patients respond to existing treatments. The inflammatory bowel diseases ulcerative colitis and Crohn's disease, for example, affected an estimated three million U.S. adults in 2015, according to the Centers for Disease Control and Prevention.

Last year, drugmaker Merck acquired biotech company Prometheus Biosciences, for $10.8 billion, to secure a drug that could treat ulcerative colitis, Crohn's, and other diseases. In March, Mirador Therapeutics, a startup led by former Prometheus Chief Executive Mark McKenna, said it had raised more than $400 million in venture financing to develop precision medicines for immunological diseases.

Researchers are devising innovative antibody drugs and identifying new targets for them as they seek to bring the immune system into balance in patients with inflammatory disorders, said Dr. Raymond Kelleher, managing director of Cormorant Asset Management, which invested in Prometheus and AltruBio.

AltruBio takes aim at another target, a protein called PSGL-1, in an effort to rein-in T cells of the immune system involved in ulcerative colitis, a disease in which abnormal reactions in the immune system cause inflammation and ulcers in the inner lining of the large intestine, according to the National Institute of Diabetes and Digestive and Kidney Diseases.

When inflammatory diseases flare up, it is like a fire burning out of control, said AltruBio CEO Judy Chou. AltruBio seeks to douse the fire through its antibody treatment, which is designed to enhance PSGL-1's ability to tamp down overactive T cells, according to Chou.

"We think this could be a pipeline in a product," Kelleher said.

Source: https://www.wsj.com/articles/altrubio-gathers-funds-as-biotechs-aim-for-next-blockbuster-anti-inflammatory-therapy-12600b07

Pheon Therapeutics Announces $120m Series B Financing to Fund Development of its Differentiated ADC Pipeline

London UK, 21 May 2024: Pheon Therapeutics, a leading Antibody-Drug Conjugate (ADC) specialist developing next generation ADCs for a wide range of hard-to-treat cancers, today announces the completion of a $120m Series B financing to fund the development of its pipeline of differentiated ADCs. The financing was led by TCGX with participation from other new investors BVF Partners, Lightspeed and Perceptive Advisors, alongside existing investors Atlas Venture, Brandon Capital, Forbion, and Research Corporation Technologies.

The new financing will be used to further advance Pheon's differentiated ADC pipeline through clinical proof of concept. The first three assets are aimed at an undisclosed novel target which is highly overexpressed in a wide range of solid tumors. The first program has demonstrated an unprecedented preclinical therapeutic index while utilizing a DAR8 Topoisomerase-1 inhibitor linker-payload, whereas the next two ADCs utilize other linker-payload technologies to mine the broad potential of this target. The company expects to start its first Phase 1 clinical trial in 2024 and rapidly advance towards dose expansion cohorts. The capital will also enable the expansion of Pheon's suite of in-house technology platforms to generate optimized ADC constructs.

Cariad Chester, Managing Partner of TCGX, commented: "The recent clinical successes of optimized ADC constructs validate the promise of this therapeutic modality to treat solid tumors. Continued progress against cancer is predicated upon innovative approaches to new targets. Pheon has an exciting pipeline of first and best-in-class ADC programs and I look forward to working with the company as it enters into the next stage of growth and development."

PHEON THERAPEUTICS

"This raise is a critical step as we transition into a clinical-stage company. The proceeds will fund a robust clinical development pathway for our first three ADC assets, which are based on an exceptional novel target. We are excited to be working on these promising candidates and look forward to sharing their potential therapeutic benefits with patients."

Cyrus Mozayeni
Chief Executive Officer, Pheon Therapeutics

Source: https://pheontx.com/pheon-therapeutics-announces-120m-series-b-financing-to-fund-development-of-its-differentiated-adc-pipeline/

Health And Biotech Startups Now Get The Majority Of US Series A Funding

Joanna Glasner, *Crunchbase*, May 24, 2024 (excerpt)

This year is shaping up as the first we've seen in which biotech and healthcare startups receive a majority of U.S. Series A commitments.

So far in 2024, biotech and health companies have pulled in around $5.6 billion across 110 Series A rounds, per Crunchbase data. That accounts for 53% of all funding at the Series A stage, which is a closely watched barometer for the startup ecosystem.

The biotech sector's comparatively strong showing comes as overall Series A dealmaking looks on track to come in a bit above last year's totals. However, funding remains down from 2022 and much, much lower than in 2021, which was a record-breaking year for startup investment overall.

Notably, biotech and health companies aren't gobbling up a larger share of rounds. They account for less than a third of this year's Series A deals.

However, they are dominating in one subset of financings: the supergiant round.

Of the 10 largest Series A rounds this year, six are biotechs. This includes the largest financing, which went to Xaira Therapeutics, a San Francisco-based startup using AI for drug discovery and development. The company secured more than $1 billion of committed capital in April from lead investors Arch Venture Partners and Foresite Capital.

The second-largest Series A also went to a biotech, Mirador Therapeutics, which is focused on precision medicine for chronic inflammation and fibrotic disease. The San Diego company landed $400 million in a March round, also led by Arch.

The preponderance of biotech megadeals isn't limited to Series A rounds. A recent Crunchbase analysis of venture deals of $100 million or more this year found that 38 such financings went to biotech and healthcare companies, more than any other sector.

As biotech and healthcare companies scoop up a larger portion of Series A financing, there's a smaller slice going to startups in other sectors.

Given that so much of what remains is going to hot startups in generative AI, there appears to be even less to go around for those in other spaces.

This is worrisome given that there is a vast supply of seed-funded companies that raised capital when investment was hitting record highs. Many of those are at the stage where raising a Series A round would be the next logical step for founders. Whether investors agree remains to be seen.

Source: https://news.crunchbase.com/venture/series-a-funding-trends-health-biotech-data/

How Blackstone Bolted Past Rivals in Life Sciences

Jonathan Kandell, *Institutional Investor*, May 2024 (excerpt)

Some hospital visits can be good for your financial health, too, as Blackstone Group chairman and CEO Stephen Schwarzman discovered.

His epiphany came on the day he joined the board of NewYork-Presbyterian Hospital in 2016. As part of the VIP treatment for new trustees, two researchers gave presentations on the latest medical breakthroughs at the institution.

Schwarzman was wowed by the health benefits. But his other reaction was: This can be a hugely profitable business, and Blackstone should figure out how to become a major player.

Back at his mid-Manhattan headquarters during the weekly management committee meeting, Schwarzman had Blackstone map out a life-sciences strategy. Its goal was to marshal the firm's resources to help midwife the development of cutting-edge medications and biotechnology procedures.

The world is witnessing startling research and technological advances in medicines, developments with huge investment implications. Gene editing, mRNA, and artificial intelligence — to mention just a few — are speeding up the discovery and delivery of new drugs and raising the prospect of neutralizing deadly diseases even before a person exhibits symptoms.

But deep-pocketed alternative asset managers couldn't ask for a more promising life sciences landscape. And Blackstone has taken a clear lead over its peers in terms of fundraising and early returns from investments in new pharmaceuticals, including a cholesterol-lowering medication.

The firm's strategy is to focus on lower-risk, potential blockbuster products that consume hundreds of millions of dollars or more for clinical trials needed to gain Food and Drug Administration approval. It then takes in profits through royalties on the eventual sales if those products do well.

"We're financing the last mile of clinical development of pharmaceutical products," says Nicholas Galakatos, head of Blackstone Life Sciences, or BXLS. And measured in terms of FDA approval, the firm has a success rate far above the pharma industry average.

Blackstone's business model is well suited for life sciences. Its $1 trillion of assets under management are spread over more than 230 portfolio companies and massive holdings in real estate, credit, and private equity. And there's nothing to prevent BXLS from working with professionals in any area of the firm.

"We're able to come at life sciences from different directions," Blackstone president Jonathan Gray says.

Clarus founder Galakatos became head of the unit, renamed Blackstone Life Sciences. Today, BXLS has more than $8 billion in AUM. It has raised the largest amount of private money — totaling $6.2 billion — in life sciences. And it can rely on the parent firm to cover any additional financing needs.

Backed by Blackstone's scale and financial heft, Galakatos expanded the Phase III clinical development strategy pioneered at Clarus.

"We focus on products that have very significant potential in the marketplace and treating patients," he explains. "We're looking for products that can bring in at least $1 billion in peak annual sales."

The pharma industry's dearth of capital is creating plenty of opportunities to locate such potential blockbusters.

Demand for R&D investment by big pharma and biotech companies is about $300 billion a year, according to Evaluate Pharma, a data collector for the industry.

Source: https://www.institutionalinvestor.com/article/2d7csxixibte4rsch76yo/portfolio/how-blackstone-bolted-past-rivals-in-life-sciences

Invidia Capital Management Announces Healthcare Investment Firm Launch with Strategic Investment from GCM Grosvenor

NEW YORK and CHICAGO, May 21, 2024 (GLOBE NEWSWIRE) -- Invidia Capital Management, a healthcare investment firm founded by former Goldman Sachs partner Jo Natauri, has announced its launch with a strategic investment from GCM Grosvenor, a leading global alternative asset management solutions provider.

Natauri brings over 25 years of healthcare investing, operating, and investment banking experience to Invidia. She most recently served as Global Head of Private Healthcare Investing at Goldman Sachs, from which she departed in December 2023 after 17 years with the firm. Invidia has assembled an impressive team of senior advisors with deep knowledge and experience in the $4.5+ trillion healthcare sector. Since the firm's inception, Natauri has built a highly experienced team with expertise in operations, strategy, and deal execution. Jo has hired Vince Cuticello as Chief Administrative Officer and Chief Compliance Officer, Alice Kennon as Head of Operations and Capital Formation and six additional investment team members with experience at Goldman Sachs, TPG, KKR, Barclays, Partners Group, and Ontario Municipal Employees Retirement System.

Invidia will focus on upper-middle market investment opportunities where it believes that cost containment, quality, access, and innovation are well-positioned to address some of the most pressing global healthcare challenges and, consequently, where such assets are best poised for sustained, long-term growth.

"We are thrilled to unveil Invidia and our vision to build a differentiated healthcare investment platform that will offer comprehensive and thoughtful solutions to founders and management teams as they endeavor to grow their businesses and best serve their stakeholders. As the healthcare industry becomes increasingly complex, we believe we are well-positioned by virtue of our expertise, networks, and experience of investing in the sector to deliver unique value to our CEO partners and investors," Natauri announced. "We are fortunate to have GCM Grosvenor as a strategic partner at launch, given their track record of success in identifying and supporting world-class investment talent, and we are committed to making Invidia a leading force in healthcare innovation."

Jo Natauri, Head, Invidia Capital Management

Source: https://www.globenewswire.com/news-release/2024/05/21/2885694/0/en/Invidia-Capital-Management-Announces-Healthcare-Investment-Firm-Launch-with-Strategic-Investment-from-GCM-Grosvenor.html

Hedge Funds Hit by Lack of Private Equity Exits

Harriet Agnew, Will Louch and Costas Mourselas, FT, May 26, 2024 (excerpt)

Private equity's struggle to return money to clients is hitting hedge funds, which rely on the same pension plans, foundations and endowments for fundraising.

Hedge funds seeking to raise money from institutional investors are being rebuffed on the grounds that the institutions lack the cash to give them. The difficulty is at least in part due to a slowdown in distributions that investors have received from private equity funds. "The lower rate of distributions from private equity, [private] debt and venture funds is having a knock-on effect, leading some allocators to pause on new investments into illiquid funds and reduce new investments in more liquid hedge funds," said Michael Monforth, global head of capital advisory at JPMorgan Chase.

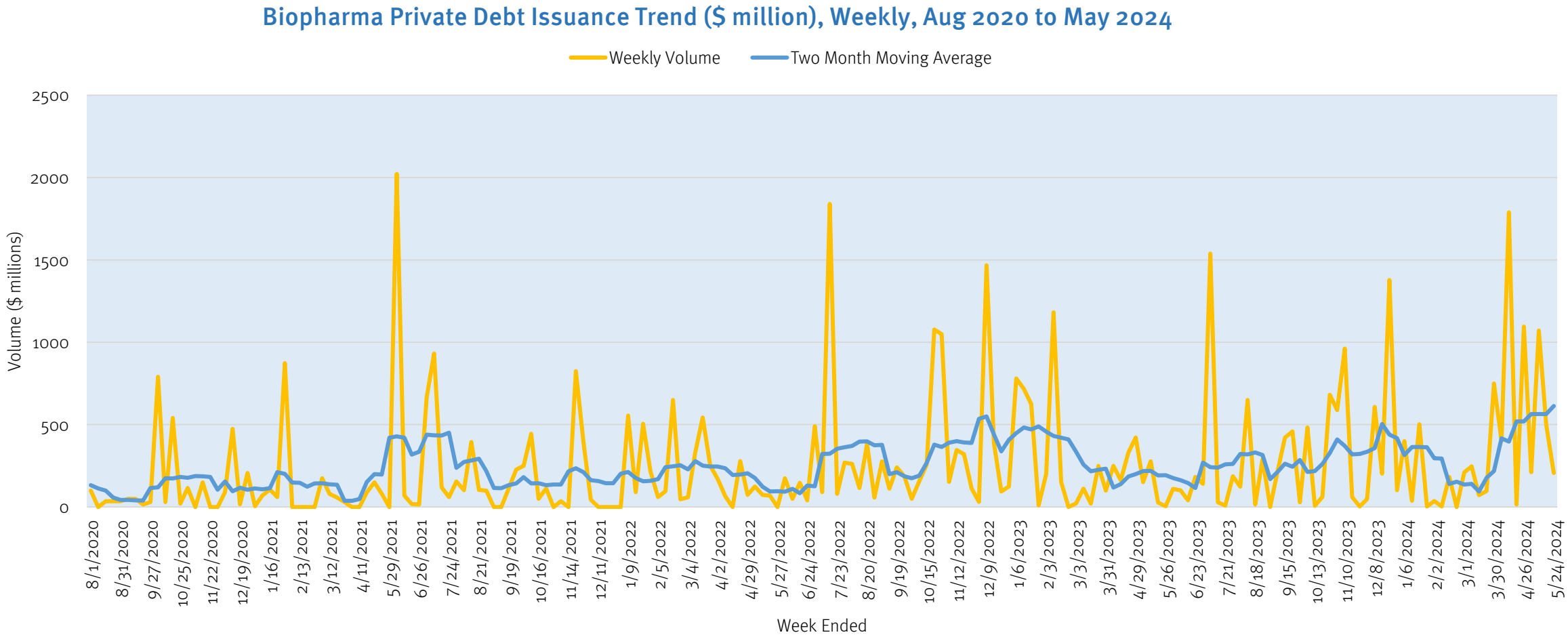
Buyout-backed exits fell to $345bn last year — their lowest level in a decade, according to Bain & Co's annual private equity report. This has left the private equity industry sitting on a record backlog of 28,000 companies worth more than $3tn, the Bain & Co report found, as a slowdown in dealmaking made it harder to return money to their backers.

"Private equity distributions have gone down, the IPO market has been very thin and M&A has been held back," said Nick Moakes, chief investment officer of the £36.8bn Wellcome Trust. "If you're not going to get bought and can't get listed, PE is scratching its head on how to do distributions."

Source: https://www.ft.com/content/62b1db7b-3e78-47ca-865e-02cc404915f0

Biopharma Private Debt Market Remained Active Last Week

The private debt market remained active last week with $206mm raised. The largest deal was a refinancing and restructuring of Cytokinetics' royalty obligations with Royalty Pharma with $200mm of net new capital raised.



Source: Data from CapitalIQ, Crunchbase, Stifel research.

Royalty Pharma and Cytokinetics Announce Expanded Strategic Funding Collaboration Totaling up to $575 Million to Support Commercial Launch of Aficamten and to Advance R&D Pipeline

SOUTH SAN FRANCISCO, Calif. and NEW YORK, May 22, 2024 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) and Royalty Pharma plc (Nasdaq: RPRX) today announced they have entered into a strategic funding collaboration providing capital to support the commercialization of aficamten and advance the company's expanding cardiovascular pipeline while diversifying access to capital as the company advances its muscle biology-directed specialty cardiology business.

"We have enjoyed a longstanding relationship with Royalty Pharma and this expanded strategic collaboration reinforces our shared conviction in the value of our cardiac myosin focused pipeline of drug candidates," said Robert I. Blum, Cytokinetics' President and Chief Executive Officer. "This diversified access to capital from a trusted partner supports our launch of aficamten while also fortifying our capital structure and lowering our cost of capital as we become a sustainable company. We believe this deal delivers on stated objectives of advancing our later-stage portfolio of potential medicines alongside our goal of increasing shareholder value."

"Both omecamtiv mecarbil and CK-586 represent strategic opportunities to expand our specialty cardiology pipeline in adjacent cardiovascular indications and help underserved patients," said Fady I. Malik, M.D., Ph.D., Cytokinetics' Executive Vice President of Research & Development. "Building on feedback from the FDA and EMA, we have designed a confirmatory Phase 3 clinical trial intended to replicate treatment effects previously observed with omecamtiv mecarbil among higher risk patients with heart failure with reduced ejection fraction. In addition, we look forward to advancing CK-586 to Phase 2 to further assess the pharmacology of cardiac myosin inhibition in sicker patients with heart failure with preserved ejection fraction."

The transaction includes funding for planned commercialization, development funding, royalty restructuring and revenue sharing and the purchase of Cytokinetics equity, together, affording Cytokinetics $250 million on closing and up to a total of $575 million to support the company's further maturation and corporate development.

Source: https://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-and-royalty-pharma-announce-expanded-strategic

Deal News

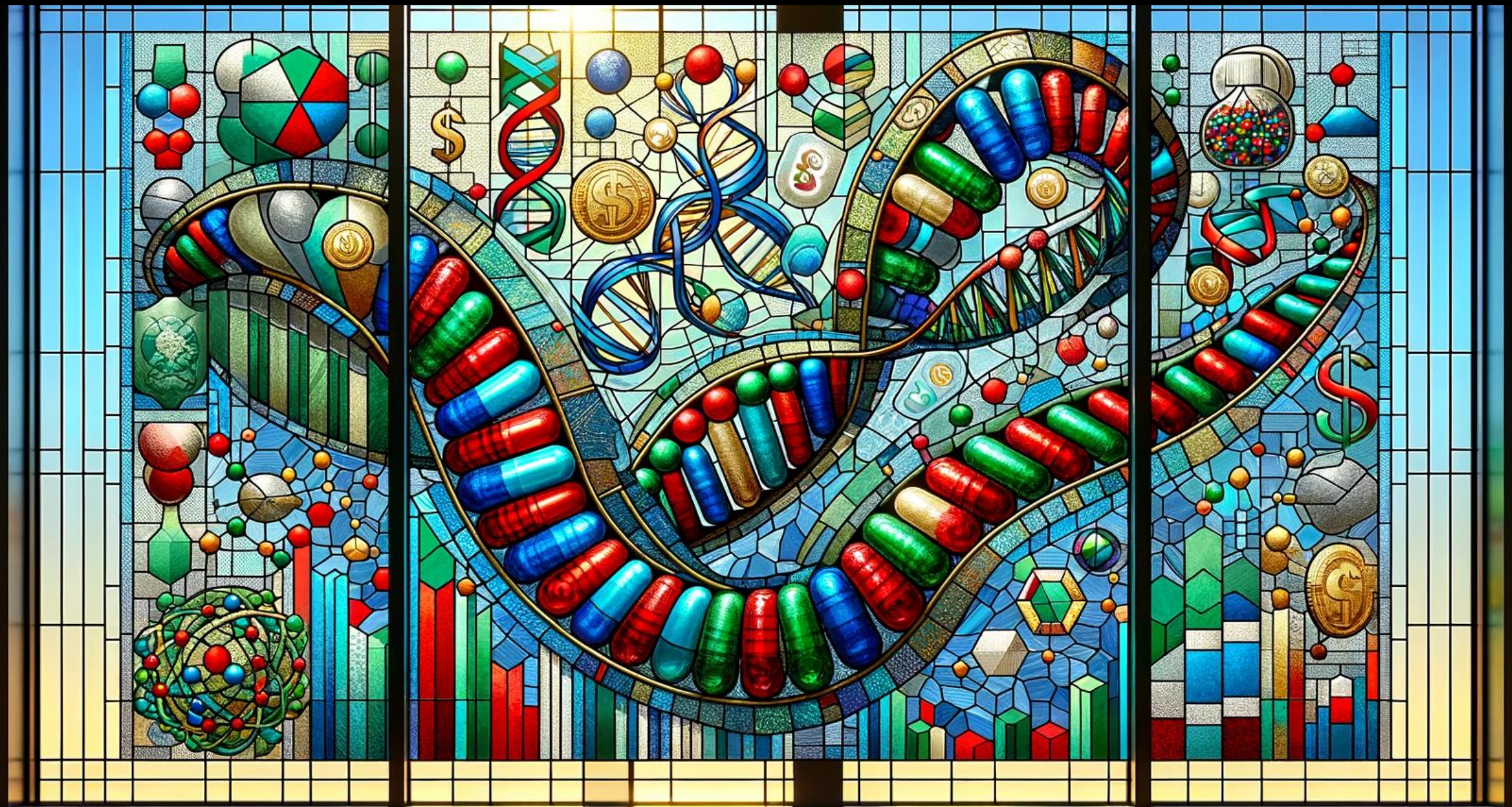
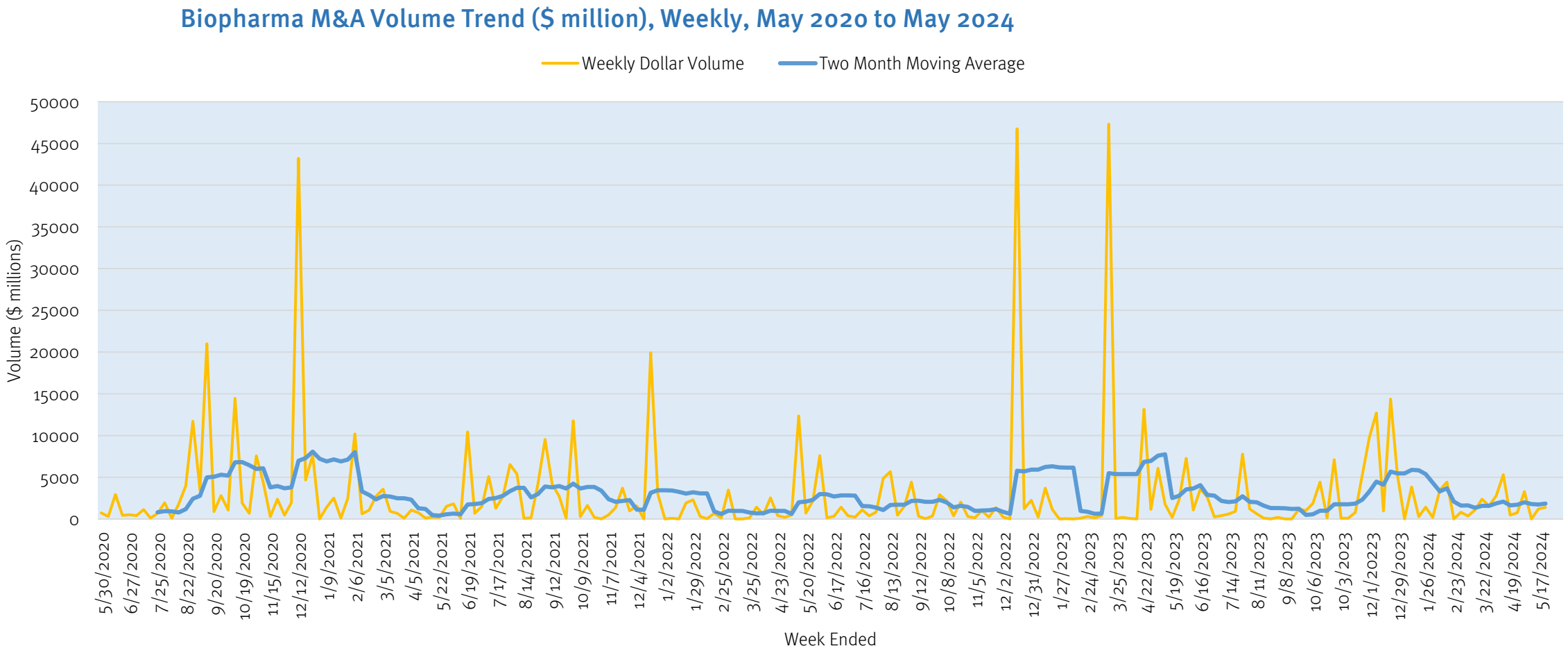


Image generated by Dall-E

Last Week Saw $1.7 Billion in M&A Volume

Last week saw Biogen buy Hi-Bio for $1.15 billion upfront, Flerie merge into Index Pharma in a deal worth $320 million and Orna Therapeutics acquire ReNAgade Therapeutics to form a new RNA therapeutics powerhouse.



Source: S&P, CapitalIQ

Biogen Acquires Hi-Bio

CAMBRIDGE, Mass. and SOUTH SAN FRANCISCO, Calif., May 22, 2024 (GLOBE NEWSWIRE). Biogen Inc. (Nasdaq: BIIB) and Human Immunology Biosciences (HI-Bio™), a privately-held clinical-stage biotechnology company focused on targeted therapies for patients with severe immune-mediated diseases (IMDs), today announced the companies have entered into a definitive agreement under which Biogen has agreed to acquire HI-Bio for $1.15 billion upfront and up to $650 million in potential milestone payments.

HI-Bio's lead asset, felzartamab, is a fully human anti-CD38 monoclonal antibody that has been shown in clinical studies to selectively deplete CD38+ cells including plasma cells and natural killer, or NK, cells which may allow for additional applications that improve clinical outcomes in a broad range of immune-mediated diseases.

Felzartamab has received Breakthrough Therapy Designation (BTD) and Orphan Drug Designation (ODD) from the U.S. Food and Drug Administration (FDA) for development in the treatment of primary membranous nephropathy (PMN) and has received ODD in the treatment of antibody-mediated rejection (AMR) in kidney transplant recipients. Phase 2 studies have been completed in PMN and AMR and remain ongoing in IgA nephropathy (IgAN), and HI-Bio has plans to advance each indication to Phase 3.

"We believe this late-stage asset, which has demonstrated impact on key biomarkers and clinical endpoints in three renal diseases with serious unmet needs, is a strategic addition to the Biogen portfolio as we continue to augment our pipeline and build on our expertise in immunology," said Priya Singhal, M.D., M.P.H., Head of Development at Biogen. "We look forward to welcoming HI-Bio employees into Biogen and, together, working to advance potential therapies for patients with rare immune diseases with high unmet need."

Financial Details and Terms of the Transaction

Under the terms of the agreement, Biogen will make an upfront payment to HI-Bio of $1.15 billion. HI-Bio's stockholders would also be eligible for payments of up to an additional $650 million, for a total potential deal value of up to $1.8 billion, should the felzartamab programs achieve certain development milestones. The acquisition of HI-Bio is not expected to impact Biogen's previously issued 2024 guidance. Biogen expects to finance the acquisition with cash and may also draw on its revolving credit agreement. The transaction is subject to customary closing conditions, including receipt of necessary regulatory approvals and is currently anticipated to close in the third quarter of 2024.

This deal is a direct hit on Biogen's sweet spot: a biologic leveraging advanced immunology in rare kidney disease.

If felzartamab gets approved in any of the three rare kidney fields where it's being developed, it should pay off quite well for Biogen.

The price seems eminently reasonable given the stage of development.

Obviously, this will not be the first CD38 mAb on the market, but the clinical development is quite distinct from that pursued by other market participants.

Source: https://investors.biogen.com/news-releases/news-release-details/biogen-bolsters-late-stage-pipeline-expands-immunology-portfolio

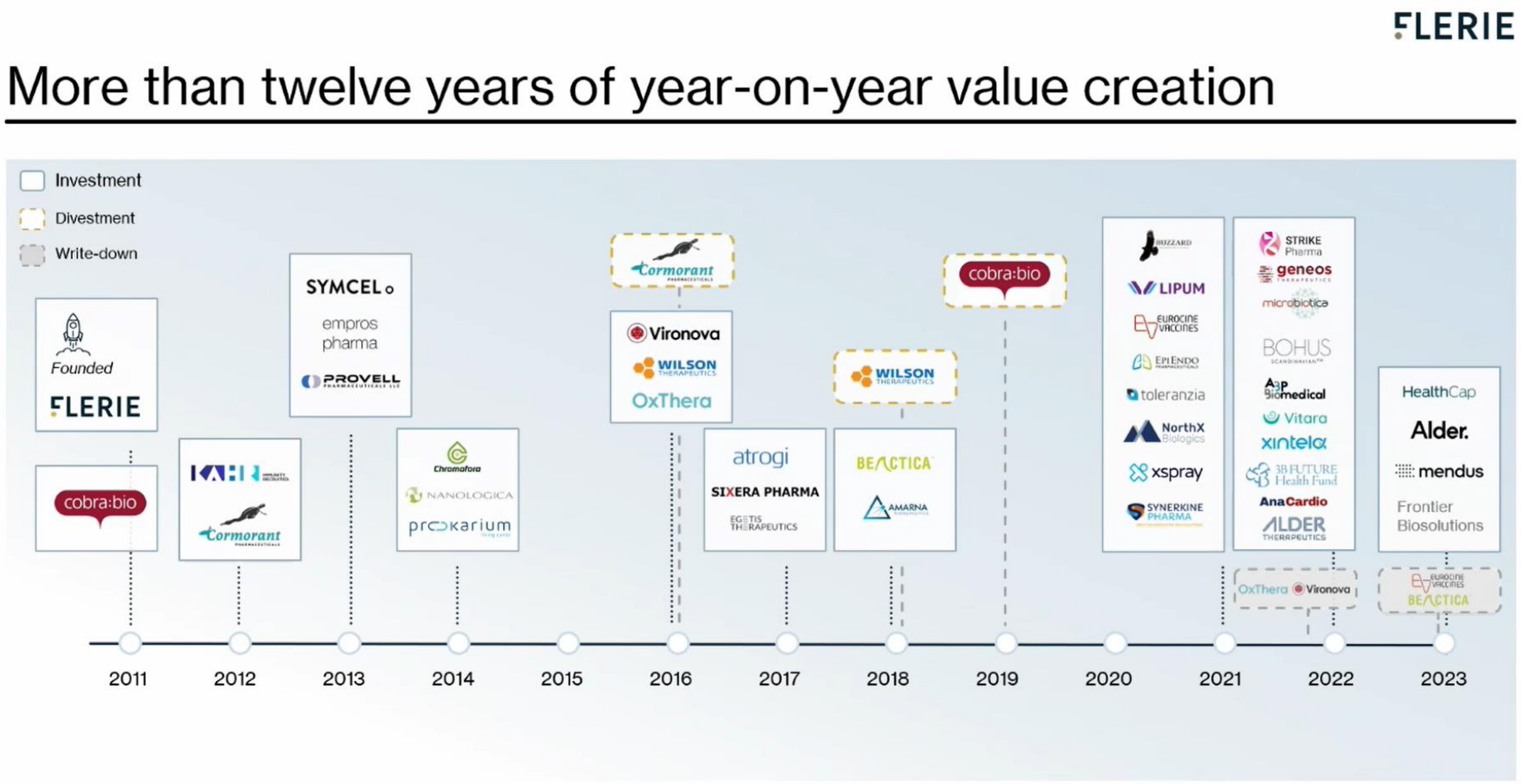
Healthcare Investor Flerie Reverse Merges into Index Pharmaceuticals in Deal Worth $320 Million

May 20, 2024. The transaction in brief:

- InDex Pharmaceuticals has entered into an agreement with the shareholders of Flerie Invest AB ("Flerie") to acquire all shares in Flerie through an issue in kind of 6,073,952,948 new shares in the Company. Through the Transaction, Flerie will become a wholly-owned subsidiary of InDex Pharmaceuticals and Flerie's shareholders will initially hold approximately 91.9 per cent of the total number of shares and votes in the Company, prior to the completion of the Capital Raise. As a result of the Transaction, the Company will change its name to Flerie AB ("New Flerie").
- Flerie is valued at approximately SEK 3,073 million in the Transaction, based on reported net asset value as of 31 March 2024 with a discount of 10 per cent. InDex Pharmaceuticals is valued at approximately SEK 269 million, corresponding to the Company's estimated cash position after closing costs with a premium of 20 per cent, which entails a subscription price of approximately SEK 0.506 per Consideration Share.
- As part of the Transaction and the continued financing of New Flerie, a number of institutional investors, including the Company's existing shareholders the Fourth Swedish National Pension Fund, HBM Healthcare Investments, Linc AB and SEB Stiftelsen, have undertaken to subscribe for new shares in the Company in a directed share issue (the "Capital Raise"). Through the Capital Raise, the Company will raise in aggregate approximately MSEK 520 before transaction costs.
- HBM Healthcare Investments, Linc AB, SEB Stiftelsen and S-E Bankens Utvecklingsstiftelse, who together represent approximately 27.9 per cent of the shares and votes in InDex Pharmaceuticals, have undertaken to vote in favour of the Transaction and related resolutions at the EGMs. Furthermore, the Fourth Swedish National Pension Fund, representing approximately 9.8 per cent of the shares and votes in the Company, has expressed its intention to vote in favour of the Transaction and related resolutions at the EGMs.
- The completion of the Transaction is, among other things, conditional upon resolutions at the EGMs and that the Company receives approval for continued listing on Nasdaq First North Growth Market.

Source: https://www.indexpharma.com/en/index-pharmaceuticals-has-entered-into-a-conditional-agreement-regarding-a-reverse-merger-with-flerie. Image generated by Dall-E.

Index Transaction Leverages Excellent Track Record of Flerie in Value Creation



Flerie has been the powerhouse family office of Thomas Eldered of Sweden.

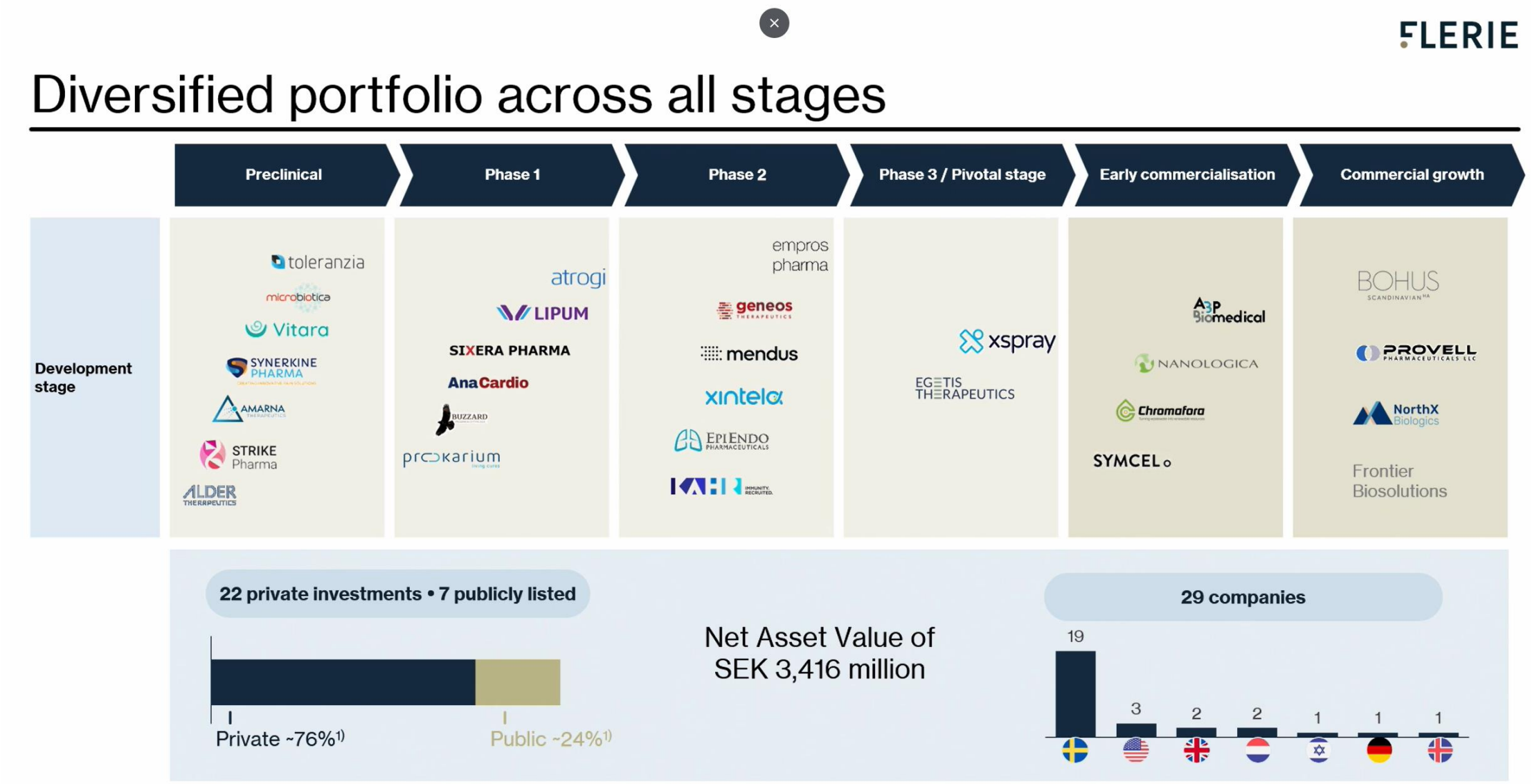
Mr. Eldered has had many good exits and roll-ups over time including the buildout of Recipharm. Flerie sold Cormorant Pharmaceuticals to BMS in 2016 and Cobra Biologics to Cognate Bioservices in early 2020. Flerie was also an investor in Wilson. He has built out an excellent team run by Dr Ted Fjällman.

It's quite a bold move to take a family office company with a portfolio of holdings public. We haven't seen something like this before.

The portfolio quality looks good to us and we expect that the new Flerie will thrive on the stock exchanges in Sweden.

Source: https://www.redeye.se/events/1004277/investor-update-index-pharmaceuticals-2-2

Flerie Portfolio is Highly Diversified



Source: https://www.redeye.se/events/1004277/investor-update-index-pharmaceuticals-2-2

Orna Therapeutics Announces Strategic Acquisition of ReNAgade Therapeutics to Solidify Leadership in Circular RNA Therapies

WATERTOWN and CAMBRIDGE, Mass., May 23, 2024 /PRNewswire/. Orna Therapeutics, a biotechnology company dedicated to designing and delivering a new class of fully engineered circular RNA therapeutics (oRNA®), today announced its acquisition of ReNAgade Therapeutics, a pioneer in unlocking the potential of RNA therapeutics that demonstrated industry-leading delivery to multiple extra-hepatic cells in non-human primate (NHP) models over the past 18 months.

Amit D. Munshi, Chief Executive Officer of ReNAgade, will succeed Tom Barnes, Ph.D., to lead Orna as Chief Executive Officer.

An industry veteran of more than 30 years, Mr. Munshi is former President and CEO of Arena Pharmaceuticals Inc., which he built from a $300 million market cap into a late clinical stage company before its acquisition for $6.7 billion by Pfizer. Dr. Barnes will retain his position on Orna's Board of Directors and serve as chair of its Scientific Advisory Board. "Orna remains singularly focused on developing the right tools and technologies and building the right company to power an entirely new class of RNA-based medicines," said Dr. Barnes, founding Chief Executive Officer of Orna Therapeutics. "The combination of technologies positions Orna to advance best-in-class panCAR in vivo CAR RNA therapies and expand existing gene editing delivery solutions with circular RNA to address the massive unmet need in multiple diseases."

"Both Orna and ReNAgade were founded on our bold vision to push the boundaries of RNA medicine," said Ansbert Gadicke, M.D., Managing Partner of MPM BioImpact. "The fusion of these industry leaders in circular RNA and delivery will transform the landscape of RNA therapeutics and accelerate clinical milestones leading to greater impact for patients living with cancer and autoimmune diseases. The combined company is supported by a substantial financial position enabling these milestones.“

Built by MPM BioImpact, both Orna and ReNAgade bring significant financing. Orna launched with $100 million in Series A financing in February 2021, subsequently announcing in August 2022 a $221 million Series B in addition to a strategic partnership. ReNAgade launched in May 2023 with $300 million Series A financing. The combined company will have a robust pipeline with panCAR programs in oncology and autoimmune disease, vaccine programs partnered with Merck, and genetic disease programs.

Source: https://www.prnewswire.com/news-releases/orna-therapeutics-announces-strategic-acquisition-of-renagade-therapeutics-to-solidify-leadership-in-circular-rna-therapies-302153347.html

ORNA™ + ReNAgade THERAPEUTICS = Highly Synergistic Combination

The merger between Renegade Therapeutics and Orna Therapeutics makes strategic sense due to the complementary nature of their technologies and the potential for significant advancements in RNA medicine. The strengthened company is well positioned for either an IPO or exit in due course given the obvious complementarities.

Renegade Therapeutics brings to the table its proprietary delivery technologies, including novel lipid nanoparticles (LNPs), which enable the delivery of RNA medicines to previously inaccessible tissues and cells. This capability is crucial for expanding the potential addressable disease market for RNA therapies

On the other hand, Orna Therapeutics specializes in circular RNA technology, which offers a stable and efficient means of encoding therapeutic proteins. Combining Orna's circular RNA technology with Renegade's advanced delivery systems creates a powerful, integrated platform that can deliver, code, edit, and insert RNA-based therapies. This merger is expected to overcome significant limitations in RNA therapeutics by ensuring effective delivery and stability of RNA medicines.

The combined company brings substantial financial support, exemplified by Renegade's $300 million Series A funding round led by MPM BioImpact and F2 Ventures. The backing of these prominent investors not only validates the technological promise of the merger but also provides the necessary resources to drive innovation and bring new RNA therapies to market. The two companies are also located relatively closely to each other, facilitating integration.

"RNA-centric approaches are poised to eclipse traditional cell therapy-based methods and reshape the future of medicine. This strategic acquisition unifies Orna's and ReNAgade's strengths and capabilities under one roof, expanding technological synergies and multiplying the companies' depth and breadth of expertise to drive a unique RNA therapeutic-focused R&D engine. Orna will now advance an industry-leading approach combining the Company's circular RNA expression technology with ReNAgade's broad portfolio of LNP-based RNA delivery systems and comprehensive editing programs to solve the most pressing challenges in drug development."

Amit Munshi

Chief Executive Officer, Orna Therapeutics

Source of quotation from Mr. Munshi: https://www.prnewswire.com/news-releases/orna-therapeutics-announces-strategic-acquisition-of-renagade-therapeutics-to-solidify-leadership-in-circular-rna-therapies-302153347.html

Western Companies Drive Chinese Biotech Licensing Deal Blitz

Eleanor Olcott and Xueqiao Wang, *Financial Times*, May 26, 2024 (excerpt)

Western pharmaceutical companies and investors are driving a record number of licensing deals with Chinese drugmakers that have insufficient capital to fund late-stage drug development and global expansion. Merck, GSK and AstraZeneca have all signed licensing deals in a wave of biotech investment that hit a record $44.1bn last year. The momentum has been sustained in 2024, with $9.8bn worth of biotech licensing deals signed in the first quarter.

Most of the deals involve US or European pharmaceutical companies licensing Chinese-made drugs for a low price and then providing the capital needed for more development, clinical trials and commercialisation. Some of the deals are to license the rights to sell within China.

"It's a form of venture capital investment," said Chen Chen. New investors are coming to the sector. "One of the most interesting developments is the entry of private equity, seeking Chinese assets for internationalisation with the hope of exiting to large pharmaceutical companies within one to three years," said Helen Chen of LEK. This month, Shanghai-listed Jiangsu Hengrui Pharmaceuticals said it sold the overseas licence for a portfolio of weight loss drugs to Hercules CM NewCo, a company formed by a consortium of investors including Bain Capital Life Sciences, the US buyout group's pharma arm. It has licensed three drug candidates for $110mn, with later payments upon hitting regulatory targets and royalties if the product is rolled out to the public. Hengrui also received a 20 per cent stake in Hercules.

Hengrui struck a less favourable deal in August to sell the global rights for its adult asthma treatment to Aiolos Bio, then known as One Bio, for an initial upfront payment of $21.5mn, with up to $1bn more if it gains approval overseas.

In October, Aiolos raised $245mn from a group of backers including Bain Capital Life Sciences and venture capital firms Atlas Venture, Forbion and Sofinnova.

Months later, GSK announced it had acquired Aiolos for an upfront payment of $1bn, with a further $400mn to be paid after clearing regulatory milestones. GSK will also pay Hengrui if the drug hits certain milestones and royalties if it commercialises.

The deal has prompted criticism within the Chinese pharmaceutical industry, where some are calling for more government support.

"Why is China selling its own innovative drugs so cheaply to foreigners?" said one Chinese biotech start-up executive who sold their drug licensing rights after struggling to raise capital from investors. "Beijing should help good enterprises to develop promising products and not just let them be sold to foreign companies."

Source: https://www.ft.com/content/b5683319-9662-4bc9-95dd-60c9e20788c1

Industry News

Image of historical figures in medicine generated by Dall-E

Injectable Weight Loss Drugs: Who Uses Them, and Do They Work?

Dan Witters and Ellyn Maese, *Gallup News*, May 21, 2024 (excerpt)

WASHINGTON, D.C. -- Six percent of U.S. adults, representing an estimated 15.5 million people, report having used injectable diabetes medicine to reduce weight, including 3% who are currently using such medicine specifically for this purpose. Current or past usage runs slightly higher among women, those with health insurance and those aged 40 to 64.

This analysis is part of the Gallup National Health and Well-Being Index. The results are based on a web survey of 5,577 U.S. adults, conducted March 4-9, 2024, using Gallup's probability-based panel encompassing all 50 states and the District of Columbia.

Since the U.S. Food and Drug Administration approved the Eli Lilly drug Wegovy for weight loss in 2021, the use of diabetic drugs containing semaglutide has rapidly gained popularity among those hoping to lose weight. Other options have since come on the market, including Zepbound (tirzepatide), which received FDA approval in November 2023.

Reported effectiveness among users of injectable weight loss drugs indicates that a substantial number of Americans -- about 10 million -- believe they have benefited from the injections. Evidence of lower rates of obesity and other chronic conditions among past users relative to current users may corroborate these reports.

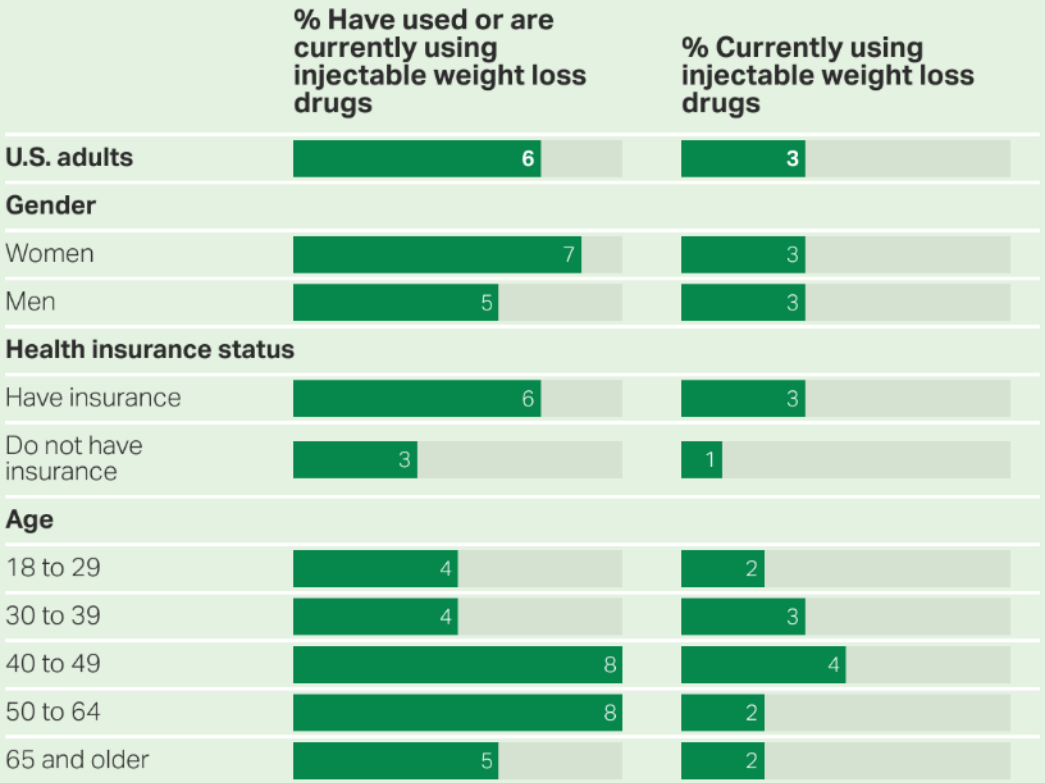
However, lower levels of self-reported effectiveness among older adults and past users, as well as lower rates of use among uninsured Americans, suggest a need for further exploration of patterns of access and benefit across various subgroups.

Source: https://news.gallup.com/poll/644861/injectable-weight-loss-drugs-uses-work.aspx

U.S. Adults Who Have Used or Currently Use Injectable Weight Loss Drugs

Have you or a family member ever taken an injection for weight loss, such as semaglutide (brand names Ozempic and Wegovy) or liraglutide (brand name Saxenda)?

Are you currently taking injections for weight loss, such as semaglutide (brand names Ozempic and Wegovy) or liraglutide (band name Saxenda)?



March 4-9, 2024

GALLUP

Evaluations of Effectiveness of Injectable Weight Loss Drugs, by Age

Based on your experience using an injectable weight loss drug, how effective would you describe the drug in helping you lose weight?

	U.S. adults %	18 to 49 %	50 to 64 %	65 and older %
Extremely effective + Effective	**64**	**70**	**67**	**48**
Extremely effective	30	34	34	18
Effective	34	36	33	30
Only a little effective	20	14	19	33
Not at all effective	11	9	10	14
Don't know	5	6	3	5
Only a little effective + Not at all effective	**31**	**23**	**29**	**47**

March 4-9, 2024

GALLUP

Users of Injectable Weight Loss Drugs Carry Heavier Disease Burden

Health condition	Currently using injections %	Have previously used, but not currently %	Have never used %
Obese	71	64	36
Currently have or are being treated for high blood pressure	53	39	30
Currently have or are being treated for high cholesterol	46	42	26
Diagnosed with diabetes	46	36	10

March 4-9, 2024

GALLUP

Source: Source: https://news.gallup.com/poll/644861/injectable-weight-loss-drugs-uses-work.aspx

Young Women are Frequent Users of GLP-1 Agonists

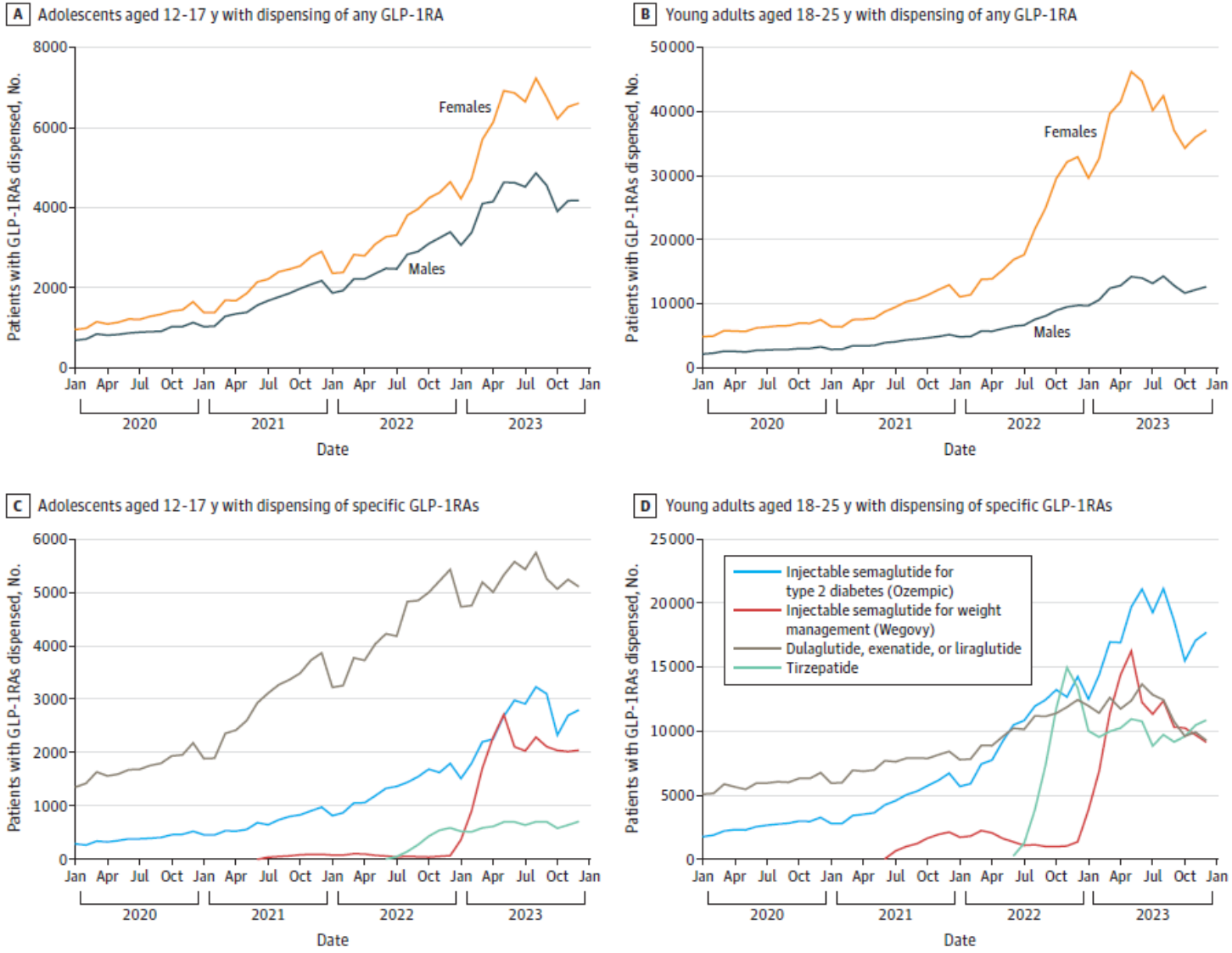
Lee JM, Sharifi M, Oshman L, Griauzde DH, Chua KP. Dispensing of Glucagon-Like Peptide-1 Receptor Agonists to Adolescents and Young Adults, 2020-2023. *JAMA*, May 22, 2024:e247112.

This study uses data from US retail pharmacies to assess national GLP-1RA dispensing to adolescents and young adults from 2020-2023.

Between 2020 and 2023, the number of adolescents and young adults with GLP-1RA dispensing increased substantially. In contrast, the number with dispensing of other drugs decreased. Increases in GLP-1RA dispensing were greatest for females, highlighting the importance of educating patients and prescribers on sex-specific safety risks

Source: https://pubmed.ncbi.nlm.nih.gov/38776113/

Figure. Monthly Number of US Adolescents and Young Adults With ≥1 Dispensed Prescription for Any Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) and Specific Medications, January 2020-December 2023



Tirzepatide is only approved in adults, but off-label use in adolescents is possible. Due to low numbers, dispensing of the oral formulation of semaglutide approved for type 2 diabetes is not shown.

jama.com

JAMA Published online May 22, 2024

Lilly Increases Manufacturing Investment to $9 Billion at Newest Indiana Site to Boost API Production for Tirzepatide and Pipeline Medicines

Eli Lilly Press Release, May 24, 2024 (excerpt)

Eli Lilly and Company (NYSE: LLY) announced today that it has more than doubled its investment in its Lebanon, Indiana, manufacturing site with a new $5.3 billion commitment, increasing the company's total investment in this site from $3.7 billion to $9 billion. This expansion will enhance Lilly's capacity to manufacture active pharmaceutical ingredients (API) for Zepbound® (tirzepatide) injection and Mounjaro® (tirzepatide) injection so that more adults with chronic diseases like obesity and type 2 diabetes may benefit from these important treatments.

Since 2020, Lilly has committed more than $16 billion to develop new manufacturing sites in the U.S. and Europe. New locations outside Indiana include Research Triangle Park and Concord, North Carolina; Limerick, Ireland; and Alzey, Germany. Separately, the company has invested an additional $1.2 billion to update existing manufacturing facilities in Indianapolis and recently acquired an injectable manufacturing facility in Pleasant Prairie, Wisconsin, from Nexus Pharmaceuticals. Together, these manufacturing investments total more than $18 billion.

"Today's announcement tops the largest manufacturing investment in our company's history and, we believe, represents the single largest investment in synthetic medicine API manufacturing in U.S. history," said David A. Ricks, Lilly's chair and CEO. "This multi-site campus will make our latest medicines, including Zepbound and Mounjaro, support pipeline growth and leverage the latest technology and automation for maximum efficiency, safety and quality control. Importantly, we are investing in our home state of Indiana, creating high-wage, advanced manufacturing, engineering and science jobs for hundreds of current and future Hoosier families.“

Lilly embarked on a significant manufacturing expansion in 2020, driven by the research results for tirzepatide. The company made this strategic investment decision at risk so that upon the approval of Mounjaro (2022) and Zepbound (2023), it could make these medicines available to adults living with type 2 diabetes and obesity, respectively. Since then, the strong demand for these medicines – the only approved treatments activating two incretin hormone receptors, GIP and GLP-1 – underscores the urgent unmet need for treatments in both type 2 diabetes and obesity.

As part of this additional investment in the Lebanon site, located within Indiana's LEAP Research and Innovation District, Lilly expects to add 200 full-time jobs for highly skilled workers such as engineers, scientists, operating personnel and lab technicians, resulting in an estimated 900 full-time employees when the facility is fully operational. Additionally, there will be more than 5,000 construction jobs during the site's development.

Source: https://investor.lilly.com/news-releases/news-release-details/lilly-increases-manufacturing-investment-9-billion-newest

Lilly LEAP Lebanon, IN site

Source: https://www.prnewswire.com/news-releases/lilly-increases-manufacturing-investment-to-9-billion-at-newest-indiana-site-to-boost-api-production-for-tirzepatide-and-pipeline-medicines-302155135.html

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

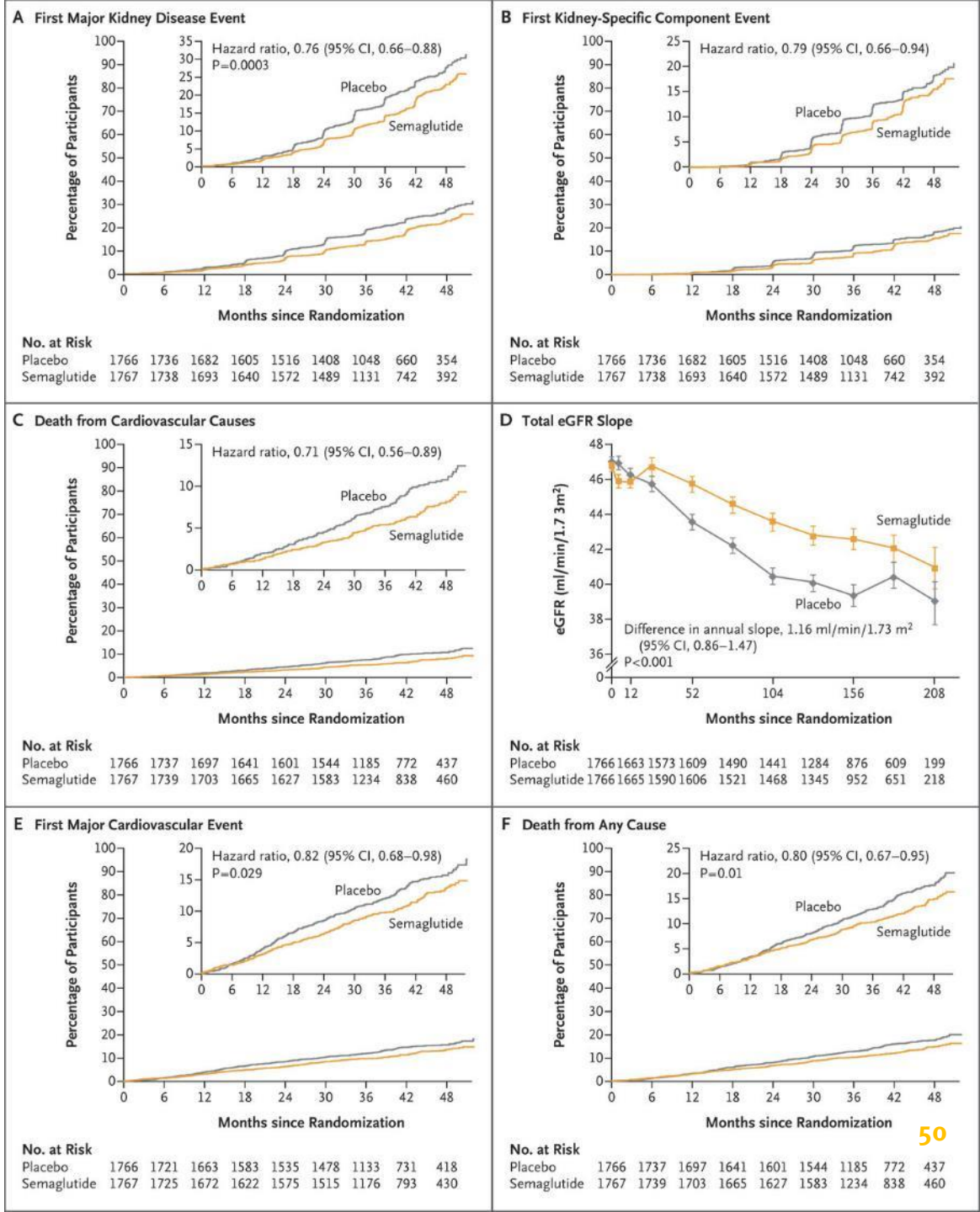
Perkovic et.al., *New England Journal of Medicine*, May 24, 2024 (excerpt)

Patients with type 2 diabetes and chronic kidney disease are at high risk for kidney failure, cardiovascular events, and death. Whether treatment with semaglutide would mitigate these risks is unknown.

Among the 3533 participants who underwent randomization (1767 in the semaglutide group and 1766 in the placebo group), median follow-up was 3.4 years, after early trial cessation was recommended at a prespecified interim analysis. The risk of a primary-outcome event was 24% lower in the semaglutide group than in the placebo group (331 vs. 410 first events; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.88; P=0.0003). Results were similar for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79; 95% CI, 0.66 to 0.94) and for death from cardiovascular causes (hazard ratio, 0.71; 95% CI, 0.56 to 0.89). The results for all confirmatory secondary outcomes favored semaglutide: the mean annual eGFR slope was less steep (indicating a slower decrease) by 1.16 ml per minute per 1.73 m2 in the semaglutide group (P<0.001), the risk of major cardiovascular events 18% lower (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P=0.029), and the risk of death from any cause 20% lower (hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P=0.01). Serious adverse events were reported in a lower percentage of participants in the semaglutide group than in the placebo group (49.6% vs. 53.8%).

Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2403347



BMI Status and Weight Trajectories Across Females' Reproductive Years and Risk of Adverse Pregnancy Outcomes: a Prospective Cohort Study

Arvizu et.al., *American Journal of Clinical Nutrition*, May 20, 2024 (excerpt)

Study population

The Nurses' Health Study II (NHSII) is an ongoing prospective cohort that enrolled 116,429 female nurses aged 25 to 42 y in 1989. Participants complete questionnaires with information on lifestyle and medical conditions every 2 y. The response rate for each questionnaire cycle is ›85%. In 2009, when most participants had reached menopause, females were asked to recall their lifetime pregnancy history.

Results

Between 1989 and 2009, we followed 16,241 females and their 25,386 pregnancies. The median (IQR) age in 1989 was 30.0 (28.0–33.0), with a mean (SD) age at first in-study pregnancy of 33.7 (4.1) y. Prepregnancy weight status was reported on average 1.5 (0.5) y before pregnancy. The average time between the 18th birthday and each pregnancy, baseline and each pregnancy, and between pregnancies was 16.3 (4.0) y, 6.1 (3.0) y, and 2.9 (1.6) y with a corresponding weight change of 6.4 (9.1), 3.1

Discussion

In this population-based study of 25,386 pregnancies from 16,241 females with follow-up throughout their reproductive years, we found that weight status and weight trajectories were strongly associated with risk of APOs. Females who gained weight throughout their adult life (mean 16 y) had higher risks of APOs (including HDP, GDM, preterm birth, and stillbirth); interpregnancy weight change (mean 3 y) was only related to a higher risk of HDP.

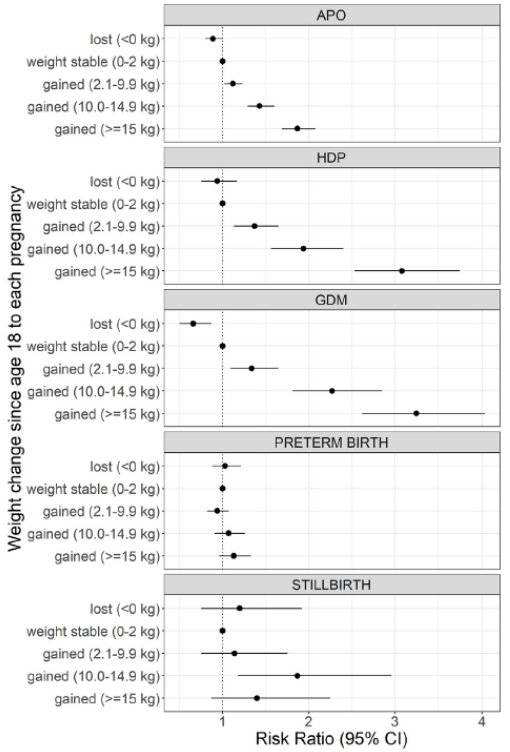


FIGURE 1. Weight change from age 18 y to each pregnancy and risk of APO (n = 25,201 pregnancies, n = 16,132 females). The RRs and 95% CIs were estimated by employing generalized estimated equations log-binomial model with exchangeable correlation matrix to account for repeated pregnancies per woman. Models were adjusted for age at pregnancy, marital status, race, prepregnancy physical activity, smoking status, multivitamin use, history of infertility, year of pregnancy, parity, height, and BMI at age 18 years. APO, adverse pregnancy outcome; CI, confidence interval; GDM, gestational diabetes; HDP, hypertensive disorders of pregnancy; RRs, relative risks.

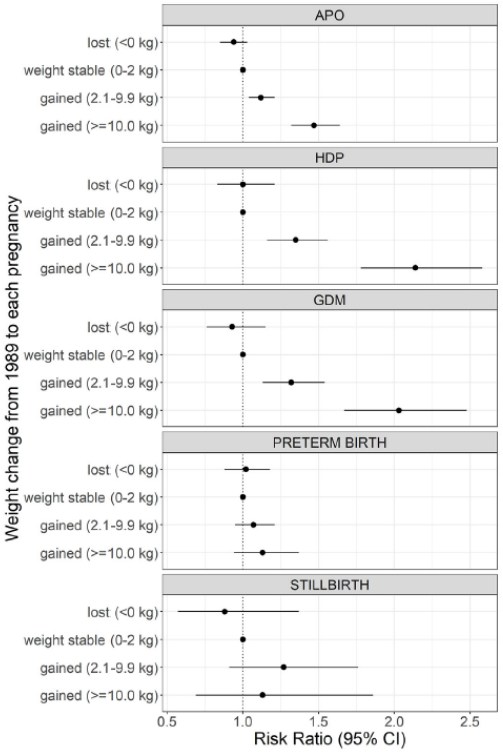
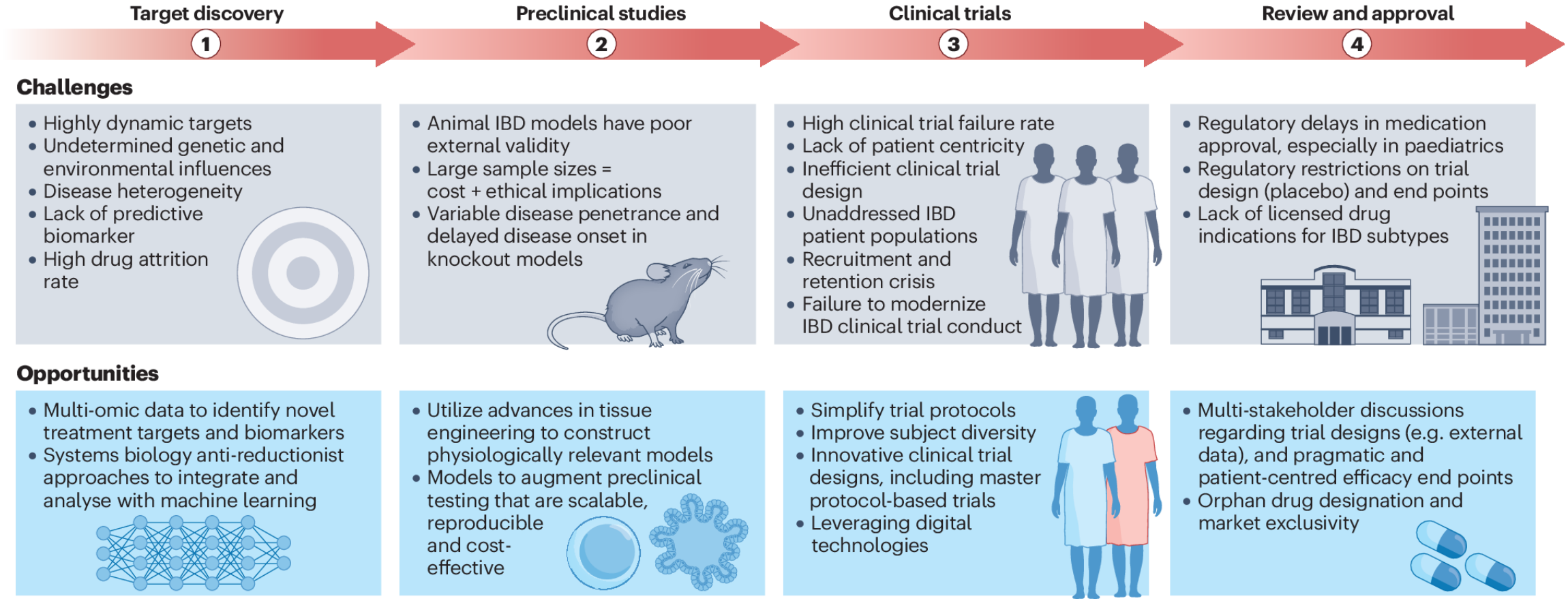


FIGURE 2. Weight changes from baseline (1989) to each pregnancy and risk of APO (n = 17,754 pregnancies, n = 11,966 females). The RRs and 95% CIs were estimated by employing generalized estimated equations log-binomial model with exchangeable correlation matrix to account for repeated pregnancies per woman. Models were adjusted for age at pregnancy, marital status, race, prepregnancy physical activity, smoking status, multivitamin use, history of infertility, year of pregnancy, parity, height, and BMI at baseline. APO, adverse pregnancy outcome; CI, confidence interval; GDM, gestational diabetes; HDP, hypertensive disorders of pregnancy; RRs, relative risks.

Source: https://ajcn.nutrition.org/article/S0002-9165(24)00460-X

Challenges and Opportunities for IBD Drug Development

Honap, S., Jairath, V., Danese, S. et al. Navigating the complexities of drug development for inflammatory bowel disease. *Nat Rev Drug Discov*, May 24, 2024.



Source: https://www.nature.com/articles/s41573-024-00953-0

IBD Drug Pipeline

Honap, S., Jairath, V., Danese, S. et al. Navigating the complexities of drug development for inflammatory bowel disease. *Nat Rev Drug Discov*, May 24, 2024.

Drug class	Drug/company	Drug target	Molecule/mechanism of action	Disease	Development phase
Anti-IL-23	Guselkumab (CNTO-1959)/Janssen	p19 subunit of IL-23	Humanized IgG1λ monoclonal antibody p19 antagonist	Ulcerative colitis/Crohn's disease	Phase III
	Mirikizumab (LY3074828)/Eli Lilly	p19 subunit of IL-23	Humanized IgG4 monoclonal antibody p19 antagonist	Crohn's disease	Phase III
	Risankizumab (ABBV-066)/AbbVie	p19 subunit of IL-23	Humanized IgG1 monoclonal antibody p19 antagonist	Ulcerative colitis	Pre-registration
Anti-DHODH	Vidofludimus (IMU-838)/Immunic Therapeutics	DHODH	Oral inhibitor of DHODH, a key mitochondrial enzyme of pyrimidine de novo biosynthesis, to induce apoptosis of activated immune cells	Ulcerative colitis	Phase II
Anti-integrin	MORF-057/Morphic Therapeutic	α4β7 integrin	Oral small-molecule inhibitor	Ulcerative colitis	Phase II
microRNA-124 upregulator	Obefazimod (ABX464)/Abivax	Immune cells	Oral small molecule that modulates inflammation by upregulating miR-124 to modulate transcription	Ulcerative colitis	Phase III
Anti-TL1A	PRA009 (MK-7240)/Merck	TL1A	Humanized IgG1 monoclonal antibody to inhibit TL1A, which regulates pro-inflammatory cytokines and fibrosis	Ulcerative colitis	Phase III
	RVT-3101 (PF06480605)/Roche	TL1A	Humanized IgG1 monoclonal antibody to inhibit TL1A, which regulates pro-inflammatory cytokines and fibrosis	Ulcerative colitis/Crohn's disease	Phase II
IL-2 therapy	Efavaleukin alfa/Amgen	Regulatory T cells	IL-2 mutein Fc fusion protein that decreases binding to IL-2Rβ and increases dependence on IL-2Rα (CD25) to expand regulatory T cells	Ulcerative colitis	Phase II
S1PR modulator	VTX002/Ventyx Biosciences	S1P1	Oral S1PR modulator	Ulcerative colitis	Phase II
JAK inhibitor	Deucravacitinib (BMS-986165)/Bristol Myers Squibb	Tyrosine kinase 2	Oral selective JAK inhibitor	Crohn's disease	Phase II
	Brepocitinib (PF-06700841)/Roivant Sciences	JAK1/TYK2	Oral selective JAK inhibitor	Ulcerative colitis/Crohn's disease	Phase II
	Ritlecitinib (PF-06651600)/Pfizer	JAK3/TEC	Oral selective JAK inhibitor	Ulcerative colitis	Phase II
	Ivarmacitinib (SHR0302)/Reistone Biopharma	JAK3/TEC	Oral selective JAK inhibitor	Ulcerative colitis/Crohn's disease	Phase III/II

Source: https://www.nature.com/articles/s41573-024-00953-0

How Genentech uses AI to Make Drug-Finding More Efficient

Ron Leuty, *San Francisco Business Times*, May 23, 2024 (excerpt)

Aviv Regev didn't move from the East Coast to the West Coast, uproot her family during the heart of the Covid-19 pandemic and exit a long academic career to mess around. As head of Genentech Research and Early Development — the signature drug discovery engine of Roche's South San Francisco-based North American biotech business — Regev is charged with piloting Genentech's journey into artificial intelligence.

For Genentech, which 48 years ago launched the molecular biology revolution and changed how drugs are discovered and developed, the push into AI has a similar game-changing feel, Regev said. And it's starting to deliver results. "If it's AI on the top or AI on the side, it's not going to make a difference," Regev said. As an example, Regev said, Genentech in 2021 trained an algorithm to screen for billions of potential bacteria-killing antibiotics. It found a 60-fold better hit rate of potential antibiotics than it found in 2017 from traditional screens with the same data.

"We have to think beyond our imagination," Regev said. "The algorithm is imagining scaffolds that weren't seen before."

Aiding Genentech's AI drive, too, is its August 2021 acquisition of Prescient Design — a New York AI company founded by computational biology and computer science faculty members at New York University and the Flatiron Institute — that's become an engine for discovery of antibodies and other potential drugs. Genentech also inked a collaboration deal in November with Nvidia Corp., the Santa Clara-based AI computing company that has jumpstarted its drug-development business through partnerships.

"The power is blowing us away," Regev said about Genentech's evolving focus on AI. "It is exceeding our rosy expectations."

Source: https://www.bizjournals.com/sanfrancisco/news/2024/05/23/genentech-ai-drug-discovery.html


Aviv Regev, Head Genentech Research and Early Development

Post-Trial Monitoring of a Randomised Controlled Trial of Intensive Glycaemic Control in Type 2 Diabetes Extended From 10 Years to 24 Years

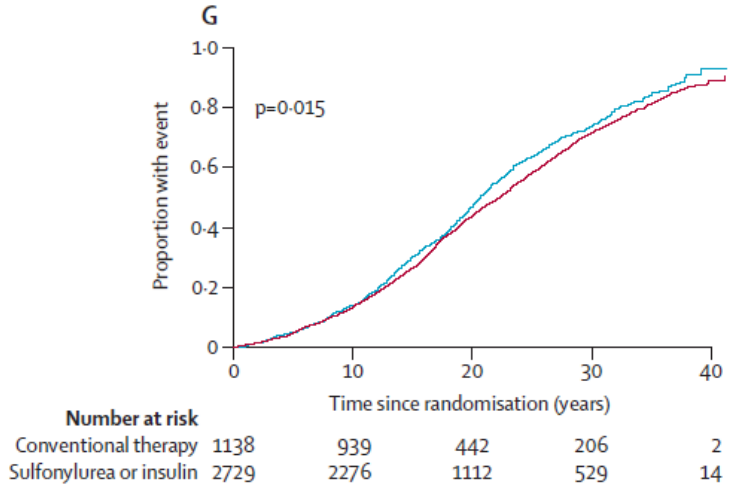
Adler et.al., *Lancet*, May 17, 2024 (excerpt)

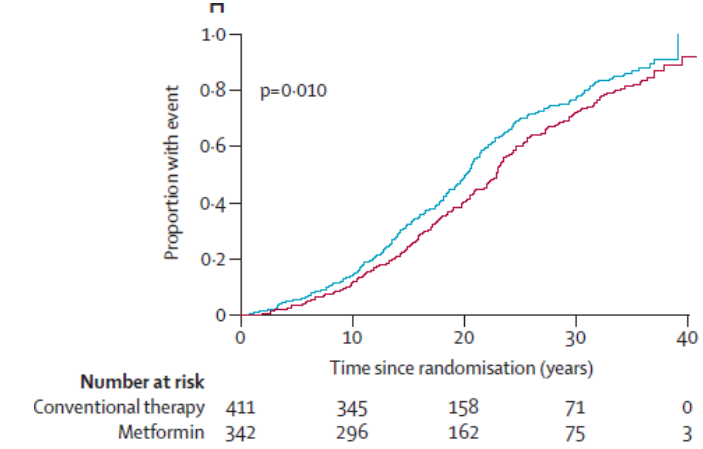
The 20-year UK Prospective Diabetes Study showed major clinical benefits for people with newly diagnosed type 2 diabetes randomly allocated to intensive glycaemic control with sulfonylurea or insulin therapy or metformin therapy, compared with conventional glycaemic control. 10-year post-trial follow-up identified enduring and emerging glycaemic and metformin legacy treatment effects. We aimed to determine whether these effects would wane by extending follow-up for another 14 years.

Between Oct 1, 2007, and Sept 30, 2021, 1489 (97·6%) of 1525 participants could be linked to routinely collected NHS administrative data. Their mean age at baseline was 50·2 years (SD 8·0), and 41·3% were female. The mean age of those still alive as of Sept 30, 2021, was 79·9 years (SD 8·0). Individual follow-up from baseline ranged from 0 to 42 years, median 17·5 years (IQR 12·3–26·8). Overall follow-up increased by 21%, from 66 972 to 80 724 person-years. For up to 24 years after trial end, the glycaemic and metformin legacy effects showed no sign of waning. Early intensive glycaemic control with sulfonylurea or insulin therapy, compared with conventional glycaemic control, showed overall relative risk reductions of 10% (95% CI 2–17; p=0·015) for death from any cause, 17% (6–26; p=0·002) for myocardial infarction, and 26% (14–36; p<0·0001) for microvascular disease. Corresponding absolute risk reductions were 2·7%, 3·3%, and 3·5%, respectively. Early intensive glycaemic control with metformin therapy, compared with conventional glycaemic control, showed overall relative risk reductions of 20% (95% CI 5–32; p=0·010) for death from any cause and 31% (12–46; p=0·003) for myocardial infarction. Corresponding absolute risk reductions were 4·9% and 6·2%, respectively. No significant risk reductions during or after the trial for stroke or peripheral vascular disease were observed for both intensive glycaemic control groups, and no significant risk reduction for microvascular disease was observed for metformin therapy.

Early intensive glycaemic control with sulfonylurea or insulin, or with metformin, compared with conventional glycaemic control, appears to confer a near-lifelong reduced risk of death and myocardial infarction. Achieving near normoglycaemia immediately following diagnosis might be essential to minimise the lifetime risk of diabetes-related complications to the greatest extent possible.

All Cause Mortality Improved Most by Metformin

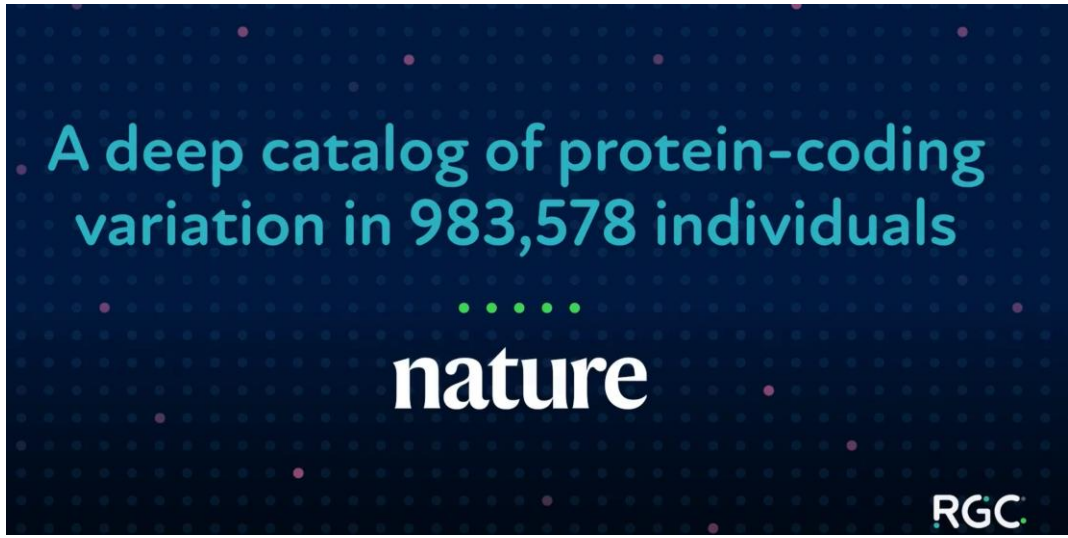




Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)00537-3/fulltext

A Deep Catalogue of Protein-Coding Variation in 983,578 Individuals

Kathie Sun et.al., Regeneron Genetics Center, *Nature*, May 20, 2024



Rare coding variants that significantly impact function provide insights into the biology of a gene. However, ascertaining their frequency requires large sample sizes. Here, we present a catalogue of human protein-coding variation, derived from exome sequencing of 983,578 individuals across diverse populations. 23% of the Regeneron Genetics Center Million Exome data (RGC-ME) comes from non-European individuals of African, East Asian, Indigenous American, Middle Eastern, and South Asian ancestry. This catalogue includes over 10.4 million missense and 1.1 million predicted loss-of-function (pLOF) variants. We identify individuals with rare biallelic pLOF variants in 4,848 genes, 1,751 of which have not been previously reported. From precise quantitative estimates of selection against heterozygous loss-of-function, we identify 3,988 loss-of-function intolerant genes, including 86 that were previously assessed as tolerant and 1,153 lacking established disease annotation. We also define regions of missense depletion at high resolution. Notably, 1,482 genes have regions depleted of missense variants despite being tolerant to pLOF variants. Finally, we estimate that 3% of individuals have a clinically actionable genetic variant, and that 11,773 variants reported in ClinVar with unknown significance are likely to be deleterious cryptic splice sites. To facilitate variant interpretation and genetics-informed precision medicine, we make this important resource of coding variation from the RGC-ME accessible via a public variant allele frequency browser.

Source: https://www.nature.com/articles/s41586-024-07556-0

Does Sleep Really Clean the Brain? Maybe Not, New Paper Argues

Sara Reardon, *Science*, May 24, 2024 (excerpt)

We all need sleep, but no one really knows why. For the past 10 years, a prevailing theory has been that a key function of sleep is to wash waste products and toxins from the brain via a series of tiny channels called the glymphatic system. Sleep problems can disrupt this process, the theory's proponents say, perhaps raising the risk of Alzheimer's disease and other brain disorders.

Mouse experiments seem to support the idea. But in recent years, several groups of scientists have challenged some aspects of the theory. Now, a new study has found that the mouse brain clears small dye molecules more efficiently while the animal is awake than when it is asleep or under anesthesia. A glymphatic system might still cleanse the brain, the researchers say, but sleep actually slows this cleansing down.

Other researchers are stumped as to how to explain the opposing results, and several declined to comment on the record for fear of entering a heated debate. A few see the new findings as a serious blow to the sleep clearance theory, but others say the new paper's methods are too different from those of the earlier work to credibly challenge it. "When you criticize a concept that has been there for some time, then your design should be even better," says Per Kristian Eide of the University of Oslo.

In the original mouse experiments, neuroscientist Maiken Nedergaard at the University of Rochester and her team injected a dye into the cisterna magna, a fluid-filled pocket at the back of the neck, which sits just outside the brain and supplies it with cerebrospinal fluid (CSF). They used a two-photon microscope to measure the influx of the dye to the brain and its spread through the organ. The influx increased when mice were asleep or under anesthesia compared with when they were awake, allowing the dye to penetrate through the brain. That led the researchers to conclude that more fluid was flowing through the brain and draining into blood or lymphatic vessels. Nicholas Franks, an anesthesia researcher at Imperial College London and senior author of the new paper, didn't set out to disprove this popular hypothesis. "I really liked this sort of theory of sleep," he says, "as a basic housekeeping mechanism that keeps the brain healthy and fully functional." But he questioned whether the influx of dye was a reliable proxy for efflux, which he says would be impossible to measure directly by tracking every blood or lymphatic vessel or potential exit point from the brain.

He likens the brain to a leaky bucket, where the water level is the amount of dye that penetrates it. That level will rise when water is poured into the bucket faster—if the brain pulls more CSF in during sleep. But it will also rise if the hole at the bottom shrinks—if efflux slows. And it's difficult to distinguish the two.

Source: https://www.science.org/content/article/does-sleep-really-clean-brain-maybe-not-new-paper-argues

Testing Theory of Mind in Large Language Models and Humans

Strachan, J.W.A., Albergo, D., Borghini, G. et al., *Nature Human Behavior*, May 20, 2024. (excerpt)

At the core of what defines us as humans is the concept of theory of mind: the ability to track other people's mental states. The recent development of large language models (LLMs) such as ChatGPT has led to intense debate about the possibility that these models exhibit behaviour that is indistinguishable from human behaviour in theory of mind tasks. Here we compare human and LLM performance on a comprehensive battery of measurements that aim to measure different theory of mind abilities, from understanding false beliefs to interpreting indirect requests and recognizing irony and faux pas. We tested two families of LLMs (GPT and LLaMA2) repeatedly against these measures and compared their performance with those from a sample of 1,907 human participants. Across the battery of theory of mind tests, we found that GPT-4 models performed at, or even sometimes above, human levels at identifying indirect requests, false beliefs and misdirection, but struggled with detecting faux pas. Faux pas, however, was the only test where LLaMA2 outperformed humans. Follow-up manipulations of the belief likelihood revealed that the superiority of LLaMA2 was illusory, possibly reflecting a bias towards attributing ignorance. By contrast, the poor performance of GPT originated from a hyperconservative approach towards committing to conclusions rather than from a genuine failure of inference. These findings not only demonstrate that LLMs exhibit behaviour that is consistent with the outputs of mentalistic inference in humans but also highlight the importance of systematic testing to ensure a non-superficial comparison between human and artificial intelligences.

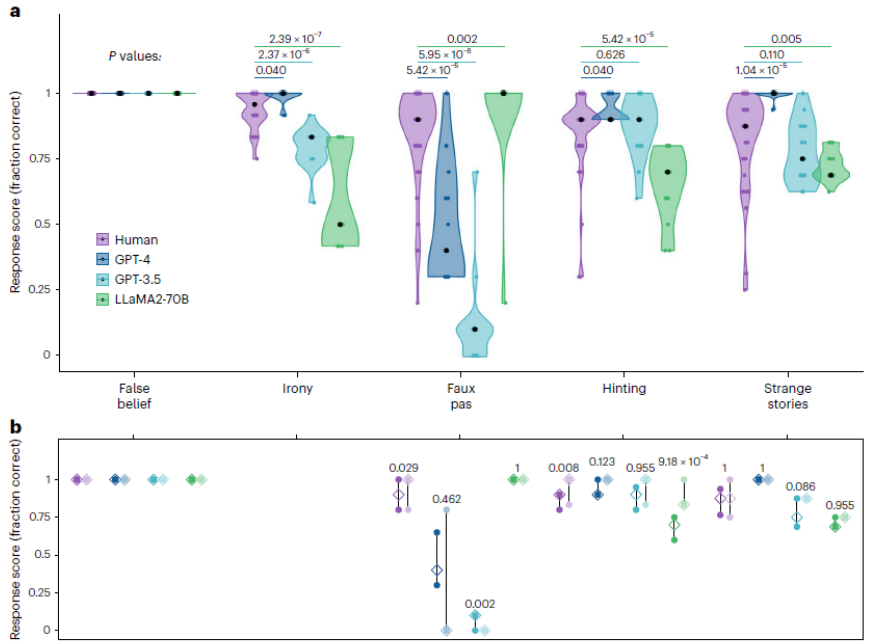


Fig. 1 | Performance of human (purple), GPT-4 (dark blue), GPT-3.5 (light blue) and LLaMA2-70B (green) on the battery of theory of mind tests. a, Original test items for each test showing the distribution of test scores for individual sessions and participants. Coloured dots show the average response score across all test items for each individual test session (LLMs) or participant (humans). Black dots indicate the median for each condition. *P* values were computed from Holm-corrected Wilcoxon two-way tests comparing LLM scores ($n = 15$ LLM observations) against human scores (irony, $N = 50$ human participants; faux pas, $N = 51$ human participants; hinting, $N = 48$ human participants; strange stories, $N = 50$ human participants). Tests are ordered in descending order of human performance. **b**, Interquartile ranges of the average scores on the original published items (dark colours) and novel items (pale colours) across each test (for LLMs, $n = 15$ LLM observations; for humans, false belief, $N = 49$ human participants; faux pas, $N = 51$ human participants; hinting, $N = 48$ human participants; strange stories, $N = 50$ human participants). Empty diamonds indicate the median scores, and filled circles indicate the upper and lower bounds of the interquartile range. *P* values shown are from Holm-corrected Wilcoxon two-way tests comparing performance on original items against the novel items generated as controls for this study.

Source: https://www.nature.com/articles/s41562-024-01882-z

NUDCD3 Deficiency Can Cause SCID and Omenn Syndrome

Chen R, et.al., *Science Immunology*, May 24, 2024 (excerpt)

Inborn errors of T cell development present a pediatric emergency in which timely curative therapy is informed by molecular diagnosis. In 11 affected patients across four consanguineous kindreds, we detected homozygosity for a single deleterious missense variant in the gene NudC domain-containing 3 (NUDCD3). Two infants had severe combined immunodeficiency with the complete absence of T and B cells (T -B- SCID), whereas nine showed classical features of Omenn syndrome (OS). Restricted antigen receptor gene usage by residual T lymphocytes suggested impaired V(D)J recombination. Patient cells showed reduced expression of NUDCD3 protein and diminished ability to support RAG-mediated recombination in vitro, which was associated with pathologic sequestration of RAG1 in the nucleoli. Although impaired V(D)J recombination in a mouse model bearing the homologous variant led to milder immunologic abnormalities, NUDCD3 is absolutely required for healthy T and B cell development in humans.

Source: https://www.science.org/doi/10.1126/sciimmunol.ade5705

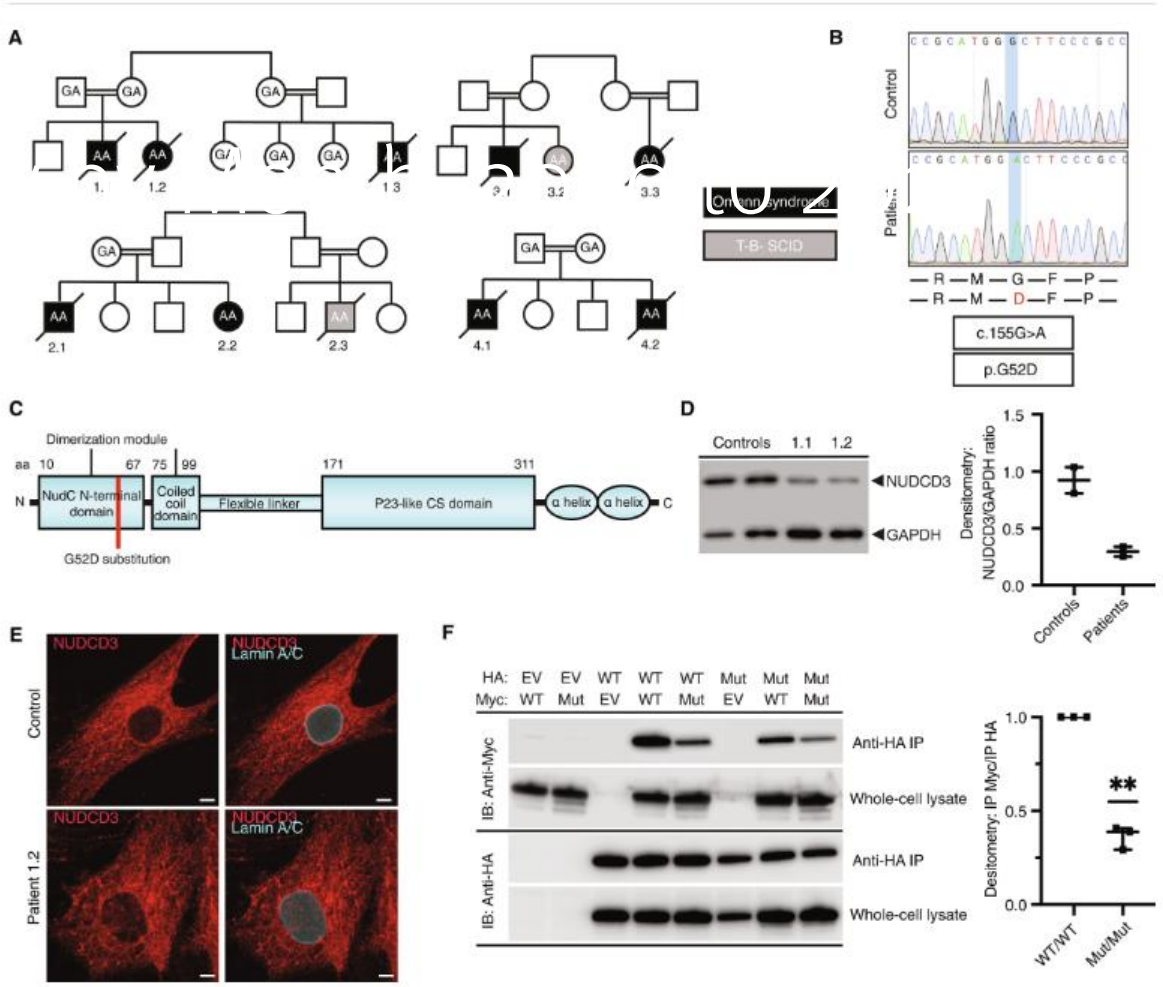


Fig. 1. An autosomal recessive variant in *NUDCD3* causes SCID/OS.
(**A**) Pedigrees showing patients affected by OS (black) and T$^-$B$^-$ SCID (gray) with letters indicating genotype. (**B**) Representative Sanger sequencing chromatogram of patient as compared with reference. (**C**) Schematic representation of NUDCD3 protein domains with the location of the G52D substitution highlighted in red. (**D**) Immunoblot showing reduced protein expression of NUDCD3 in primary patient dermal fibroblasts compared with controls (top) with corresponding densitometry analysis (bottom) (n = 2, normalized NUDCD3/GAPDH ratio; each data point represents average from each individual). (**E**) Comparable distribution of NUDCD3 (red) in representative immunofluorescence micrographs of healthy control and patient fibroblasts costained with nuclear membrane marker lamin A/C (cyan). Scale bars, 5 μm. (**F**) Impaired dimerization of NUDCD3^{G52D} by comparison with NUDCD3^{WT} upon coimmunoprecipitation with alternatively tagged NUDCD3^{WT} or NUDCD3^{G52D} in HEK293T cells transfected with plasmids encoding corresponding proteins (EV, empty vector; WT, wild type; Mut, G52D variant; IB, immunoblot) (top) and quantified by densitometry (below) (Myc IP/HA IP, ratio to WT/WT, n = 3, one-sample t test. Statistical significance was defined as $^{**}P < 0.01$).

AstraZeneca Investor Day

AstraZeneca Aims to Double Revenues to $80bn by 2030

Julia Kollewe, *The Guardian*, May 21, 2024 (excerpt)

Britain's biggest drugmaker, AstraZeneca, has set out a bold ambition to reach $80bn (£63bn) in revenues by 2030 from treatments for cancer, rare diseases and other conditions, by launching 20 major new medicines before the end of the decade.

As the company presented its growth plans to shareholders at its labs and corporate headquarters in Cambridge, England, its chief executive, Pascal Soriot, said 12 of the 20 new drugs would have the potential to generate more than $5bn in annual revenues at their peak, including five cancer treatments.

The Anglo-Swedish pharmaceutical company made revenues of $45.8bn last year, achieving a year early the goal it had set out as part of its defence against a £70bn hostile takeover approach from US rival Pfizer in 2014.

"Today AstraZeneca announces a new era of growth," Soriot said. "The breadth of our portfolio together with continued investment in innovation supports sustained growth well past the end of the decade."

He added that the firm's strong position in emerging markets would be vital to achieving its growth targets. It is the largest drugmaker by sales in China and has a major research and development centre in Shanghai.

With Soriot at the helm, AstraZeneca has revamped its drugs pipeline and developed a strong portfolio of cancer, cardiovascular, metabolic, respiratory and rare disease medicines.

However, its share price growth has been sluggish in the past year, slowing to just under 2%. Its best-selling diabetes pill, Farxiga, starts to lose patent protection from next year, and revenues in the industry will also come under pressure from reforms that will enable the US government to negotiate drug prices for the first time.

We were very impressed by AZ's presentation to investors last week and note that their revenue goal is well above analyst consensus for 2030 ($69 billion).

AZ stock barely moved last week despite the inspiring presentation. However, the Investor Day was well advertised, and AZ shares rose significantly in the lead up to the meeting.

Source: https://www.theguardian.com/business/article/2024/may/21/astrazeneca-revenues-uk-drugmaker-medicines

AstraZeneca: A Wise and Strategic Dealmaker

Pascal Soriot joined AstraZeneca in 2012 – a very tough time for the company as it was facing a series of major patent expiries with a so-so pipeline. In 2014 Pfizer came calling with an offer to buy the company for $100 billion. Today, AZ is worth $250 billion and has a massively better portfolio and pipeline as highlighted in last week's investor day materials.

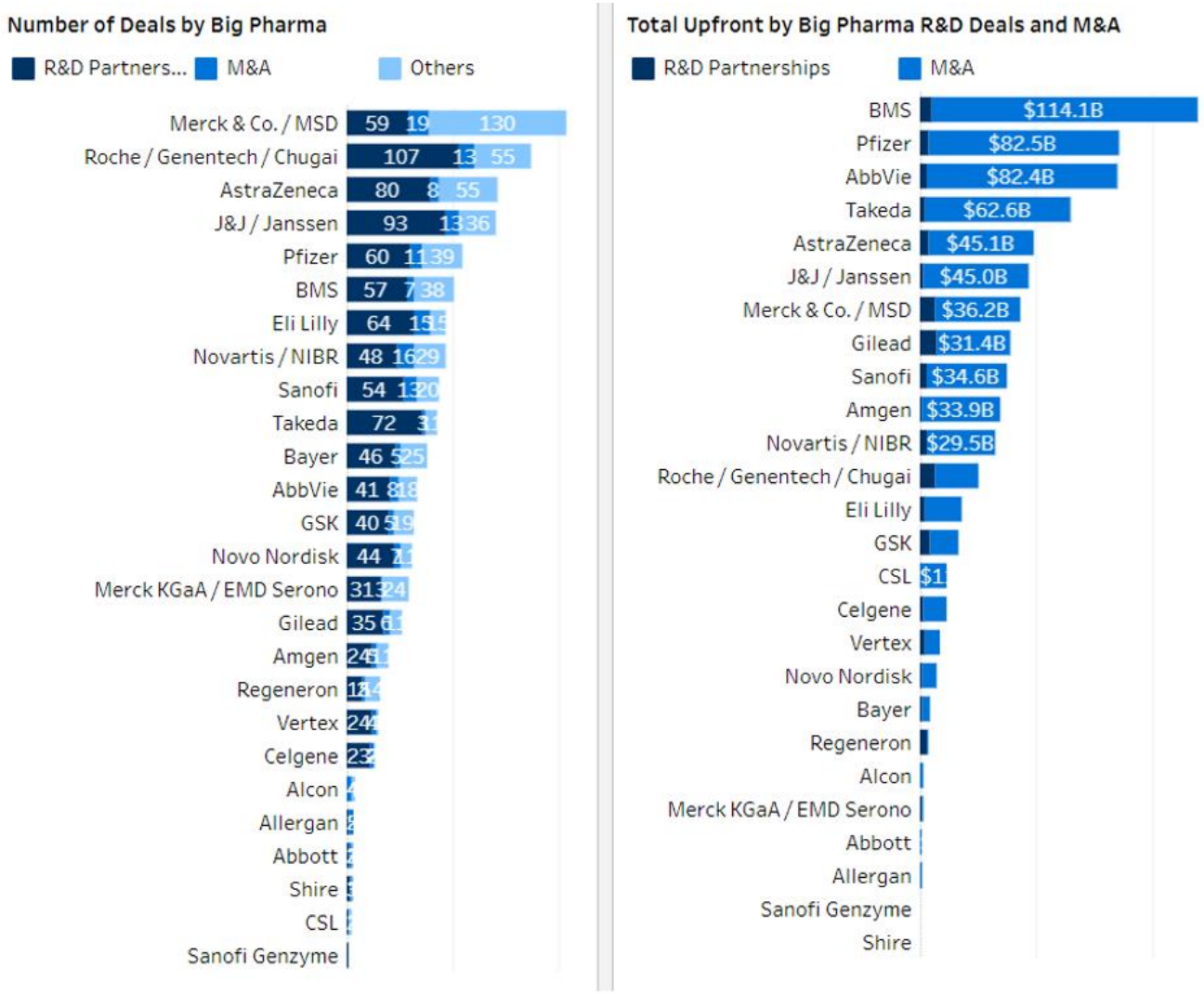
The chart at right shows that AZ has not been a big user of M&A – making eight deals since 2018 but a huge user of partnerships and other methods. AZ ranks #3 in terms of number of deals but #5 in terms of dollars spent.

It's big M&A move was its buy of Alexion which allowed it to create a whole new business to add on to its oncology and biopharmaceuticals business area.

AZ has been very strategic in using partnerships where possible to build out portfolios in areas like oncology and, instead, has relied on M&A for add-on's in cardiometabolic (Cincor), CAR-t (Gracell) and vaccines (Icosavax).

The next question is whether AZ can get to $80bn by 2030. Despite the lack of market reaction to last week's presentation, we don't doubt that they can. The presentation materials, overall, were impressive showing particularly well thought out and deep portfolios in oncology, rare disease, cardiometabolic and respiratory. The emerging portfolios in vaccines and immunology are also notable.

Large Pharma Dealmaking Activity, Jan 2018 to May 2024



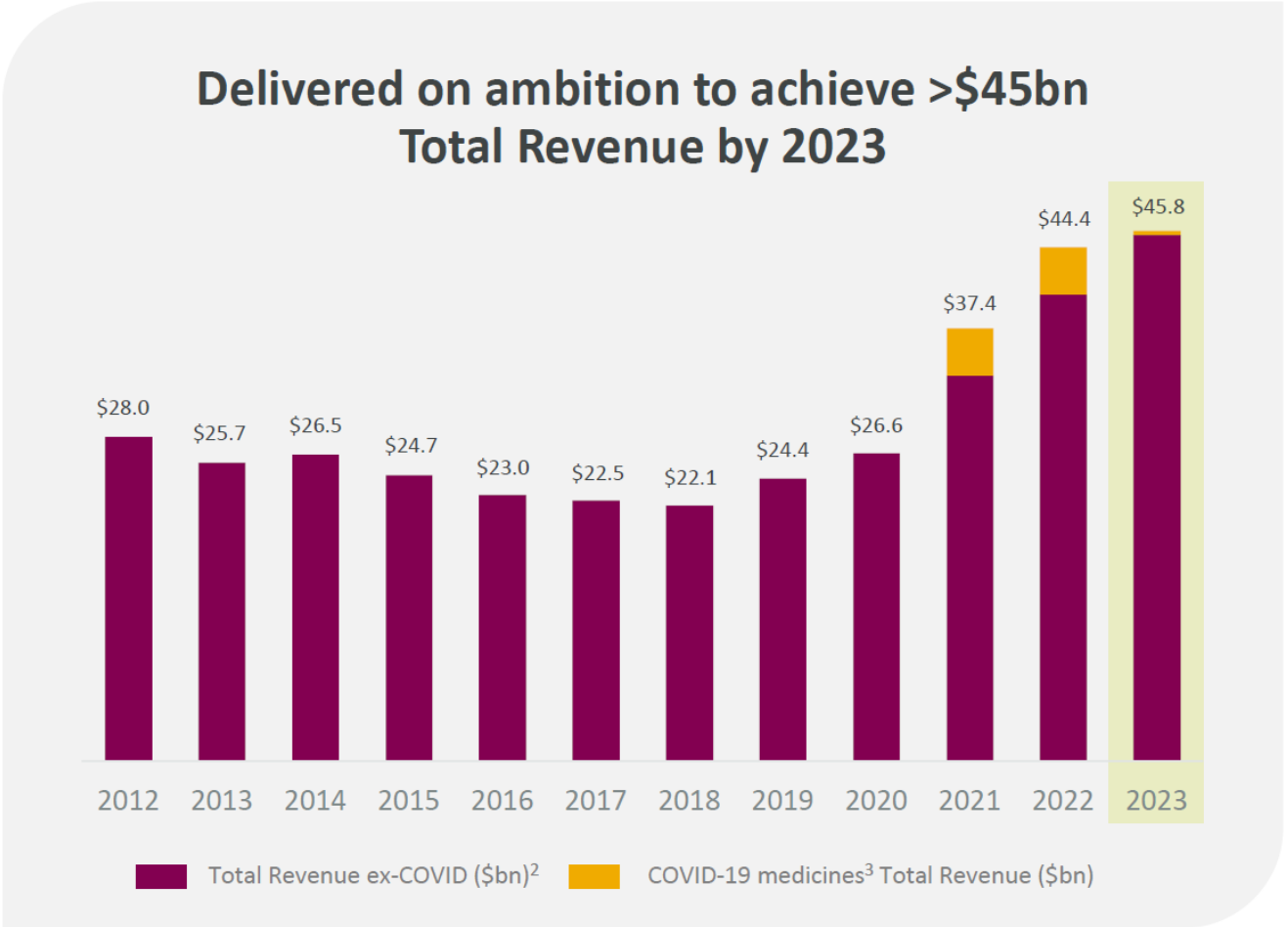
Source: DealForma

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

We delivered on our Total Revenue ambition set in 2014

"From **2017 to 2023** AstraZeneca is targeting strong and consistent revenue growth leading to annual revenues of greater than **$45 billion by 2023**"

Press release issued 06 May 2014[1]



1. AstraZeneca Company Statement, 06 May 2014. 2. Total Revenues ex-COVID from 2021 onwards. 3. *Vaxzevria, Evusheld, sipavibart*. Acronym definitions can be found in Glossary.

Source https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

Now we have a new ambition to deliver
$80bn in Total Revenue by 2030 with sustained growth thereafter

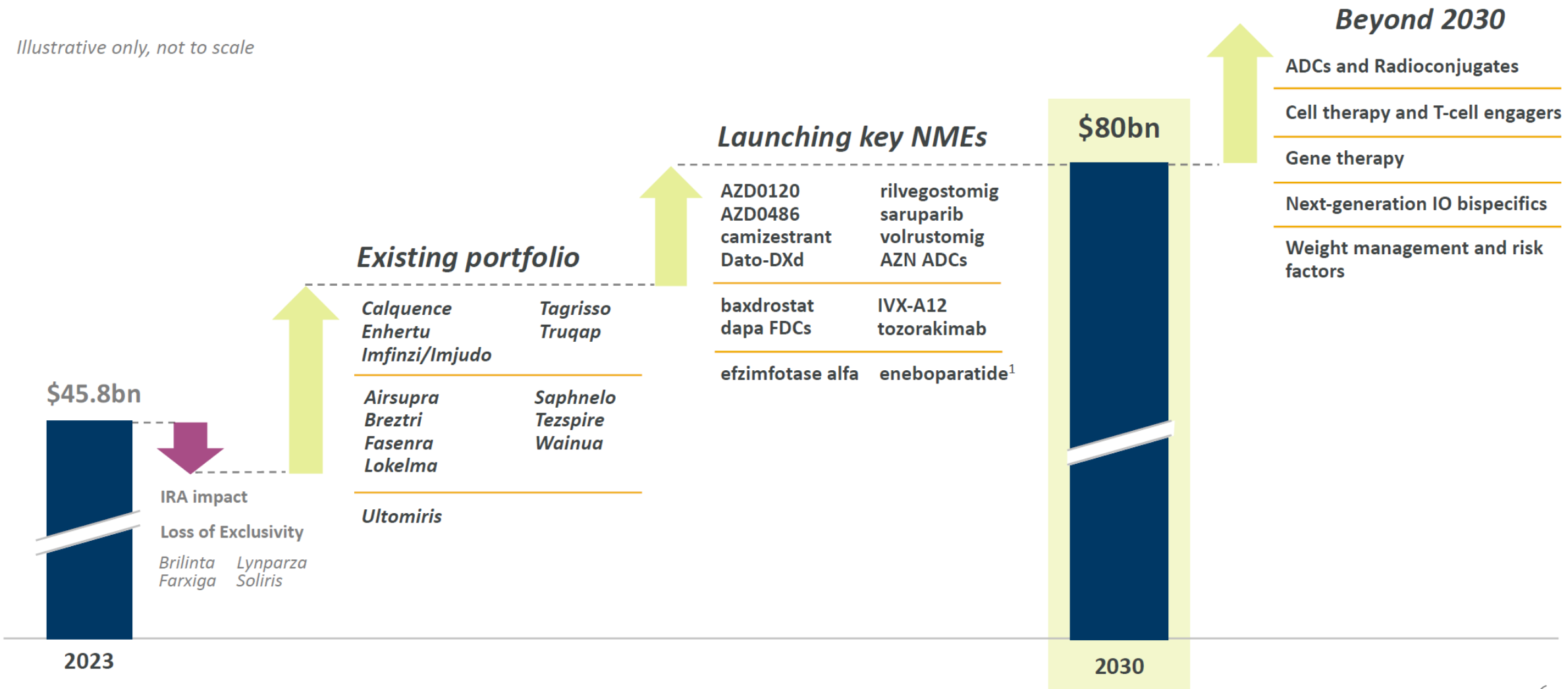
On track to deliver **mid-30s% Core operating margin by 2026**

Beyond 2026, Core operating margin will be influenced by portfolio evolution, and the Company will **target at least mid-30s%**

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

Ambition – $80bn Total Revenue by 2030 and sustained 2030+ growth

Working on "today, tomorrow and the day after"



Note: Ambition to achieve $80bn in Total Revenue by 2030 is risk-adjusted, based on latest long-range plan – see 'Forward looking statements' slide for forward looking statement..
Medicines and assets listed reflect key contributors to 2030 Total Revenue ambition; however, this list is not exhaustive. Medicines and assets listed in alphabetical order and sorted by therapy area.
1. Amolyt Pharma acquisition remains subject to customary external clearances; all clinical development plans mentioned herein subject to deal closure.
Collaboration partners: Daiichi Sankyo (*Enhertu*, Dato-DXd), Amgen (*Tezspire*), Ionis (*Wainua*), Compugen (rilvegostomig), Merck & Co., Inc. (*Lynparza)*. Acronym definitions can be found in Glossary.

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

40+ Phase III trial readouts expected by end of 2025

~$20bn potential revenue in 2030 (non-risk adjusted) from major 2024/2025 readouts[1] and launches to date in 2024

Major 2024 readouts

Truqap
CAPItello-281 | d*PTEN* mHSPC

Dato-DXd
TROPION-Breast02 | TNBC

Tezspire
WAYPOINT | CRwNP

Major 2025 readouts

Dato-DXd
AVANZAR | 1L NSCLC

camizestrant
SERENA-6 | *ESR1*m HR+ mBC

anselamimab
301/2 | AL amyloidosis

Enhertu
DB09 | HER2+ mBC

baxdrostat
BaxHTN | uHTN

eneboparatide[1]
CALYPSO | hypoparathyroidism

Enhertu
DB11 | HER2+ mBC

Breztri
KALOS/LOGOS | asthma

Ultomiris
TM-313 | HSCT-TMA

Calquence
AMPLIFY | 1L CLL

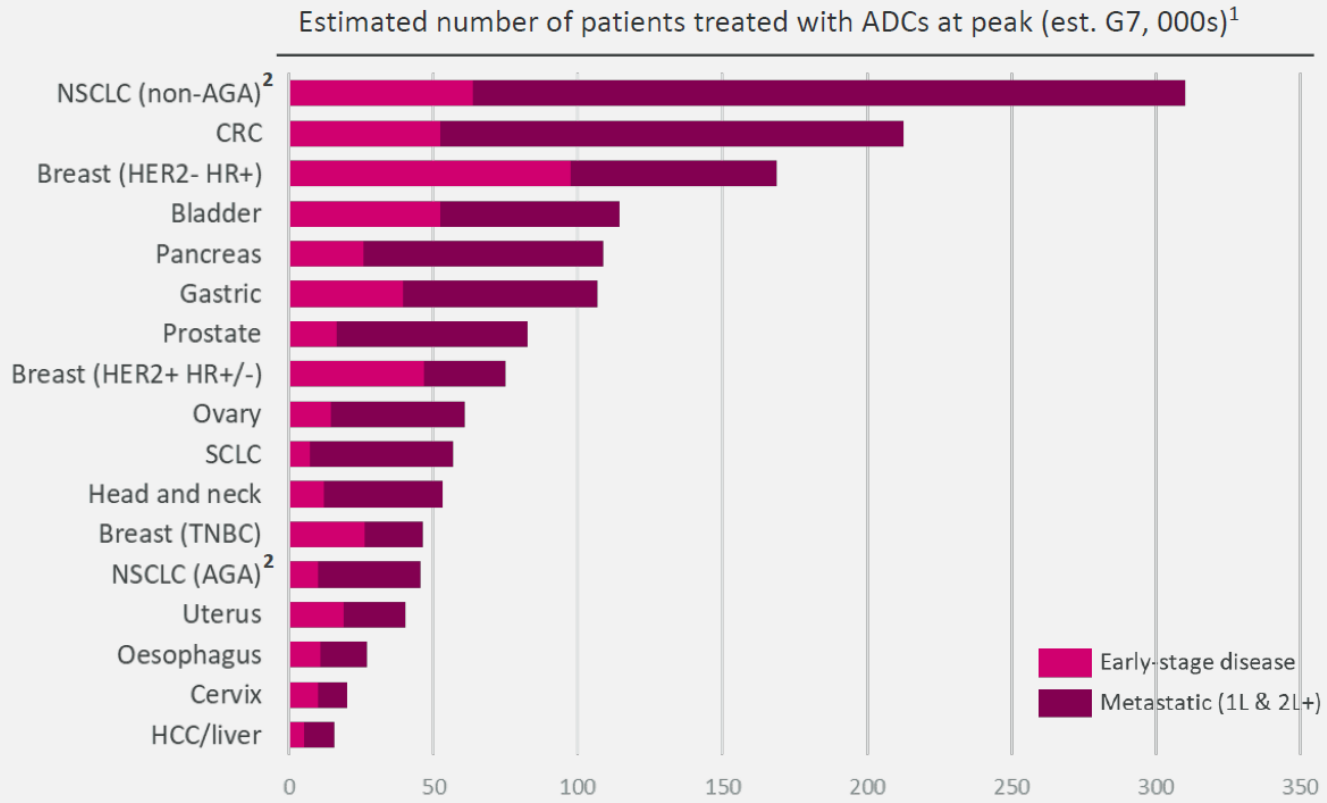
Fasenra
RESOLUTE | COPD

1. 2024/2025 readouts include those listed within prior slide and anticipated readouts listed on this slide. 2. Amolyt Pharma acquisition remains subject to customary external clearances; all clinical development plans mentioned herein subject to deal closure. Acronym definitions can be found in Glossary.
Collaboration partners: Daiichi Sankyo (*Enhertu*, Dato-DXd), Amgen (*Tezspire*).

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

We are leading the ADC revolution to replace systemic chemotherapy

Significant potential ADC opportunity across multiple tumours



AstraZeneca robust ADC portfolio with proven execution

Strong foundation in ADCs

Daiichi-Sankyo

Six clinical-stage internal ADCs

B7H4 • CLDN18.2 • CD123
EGFR/cMET • GPRC5D • FRα

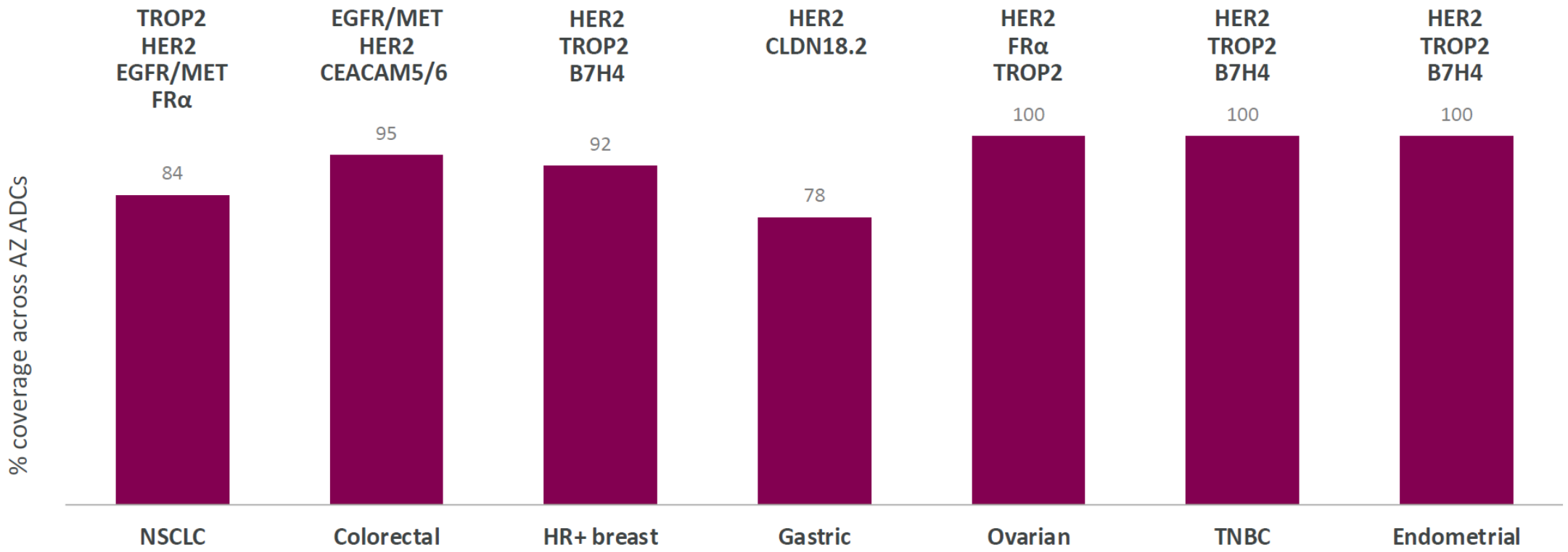
Combination opportunities

with IO and DDR

1. AZ internal estimates. G7 proportion of patients treated with Chemotherapy CancerMPact®, Cerner Enviza. 2. AGA actionable genomic alterations in NSCLC (e.g. *EGFR, ALK, ROS1, RET, MET, NTRK, BRAF*). Acronym definitions can be found in Glossary.

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

Vision to establish at least 2-3 foundational ADCs in major tumours with >80% coverage

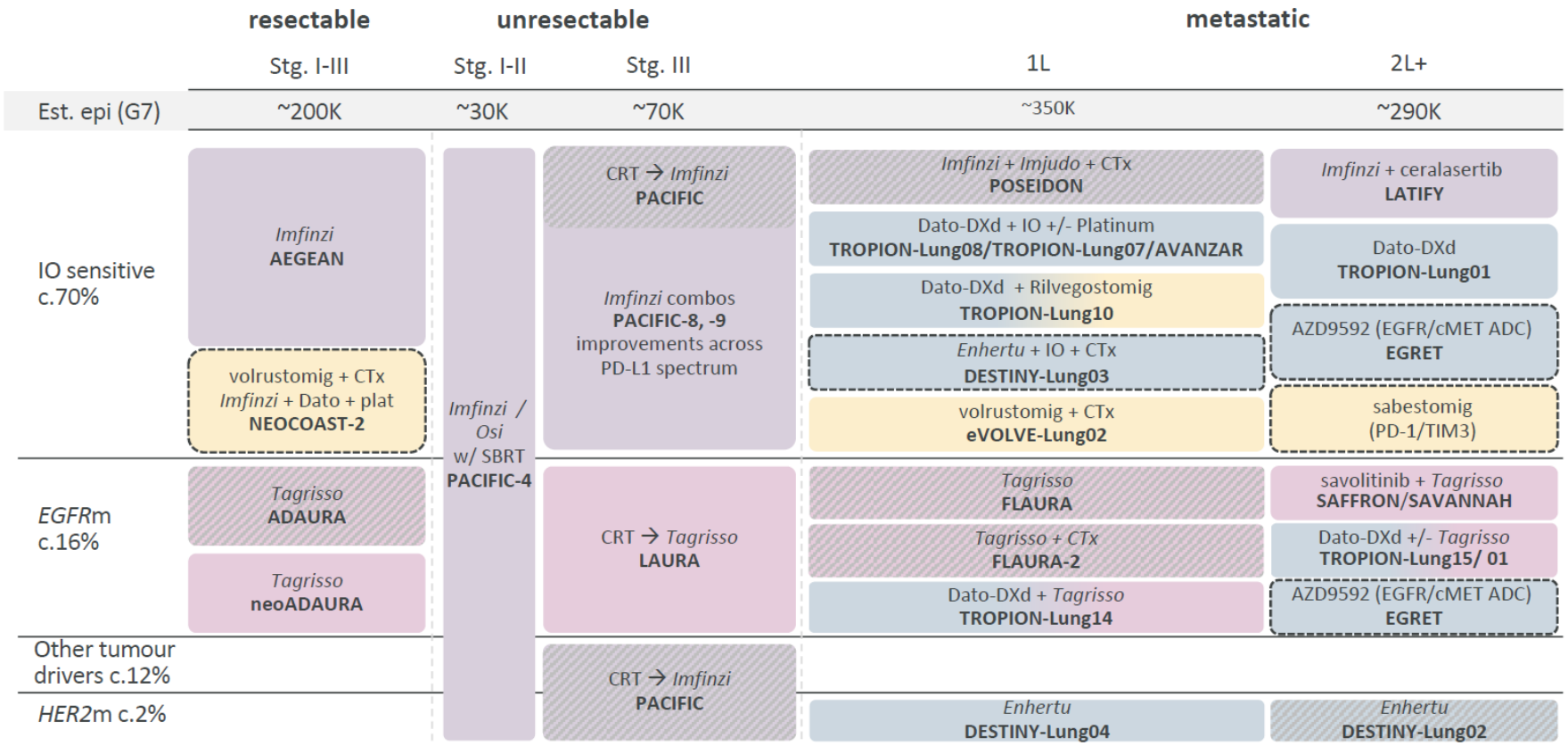


	NSCLC	Colorectal	HR+ breast	Gastric	Ovarian	TNBC	Endometrial
Future potential G7 patients treated with ADCs	310k	213k	169k	107k	61k	47k	40k

31 AZ internal translational data. 1. Coverage inclusive of other targets in development. Acronym definitions can be found in Glossary.

AstraZeneca in lung cancer

Ambition for >50% of lung cancer patients to be eligible for AZN medicine by 2030



Leading the future of lung cancer treatment

- Establishing *Tagrisso* as backbone TKI in *EGFR*m
- *Imfinzi* leading IO in unresectable
- Advancing best-in-class ADCs to replace systemic chemotherapy
- Delivering next-wave bispecifics to improve on PD-(L)1
- Developing novel combinations, including IO & *Tagrisso* + ADCs
- Investing behind new technologies and platforms, including cell therapy and testing/screening

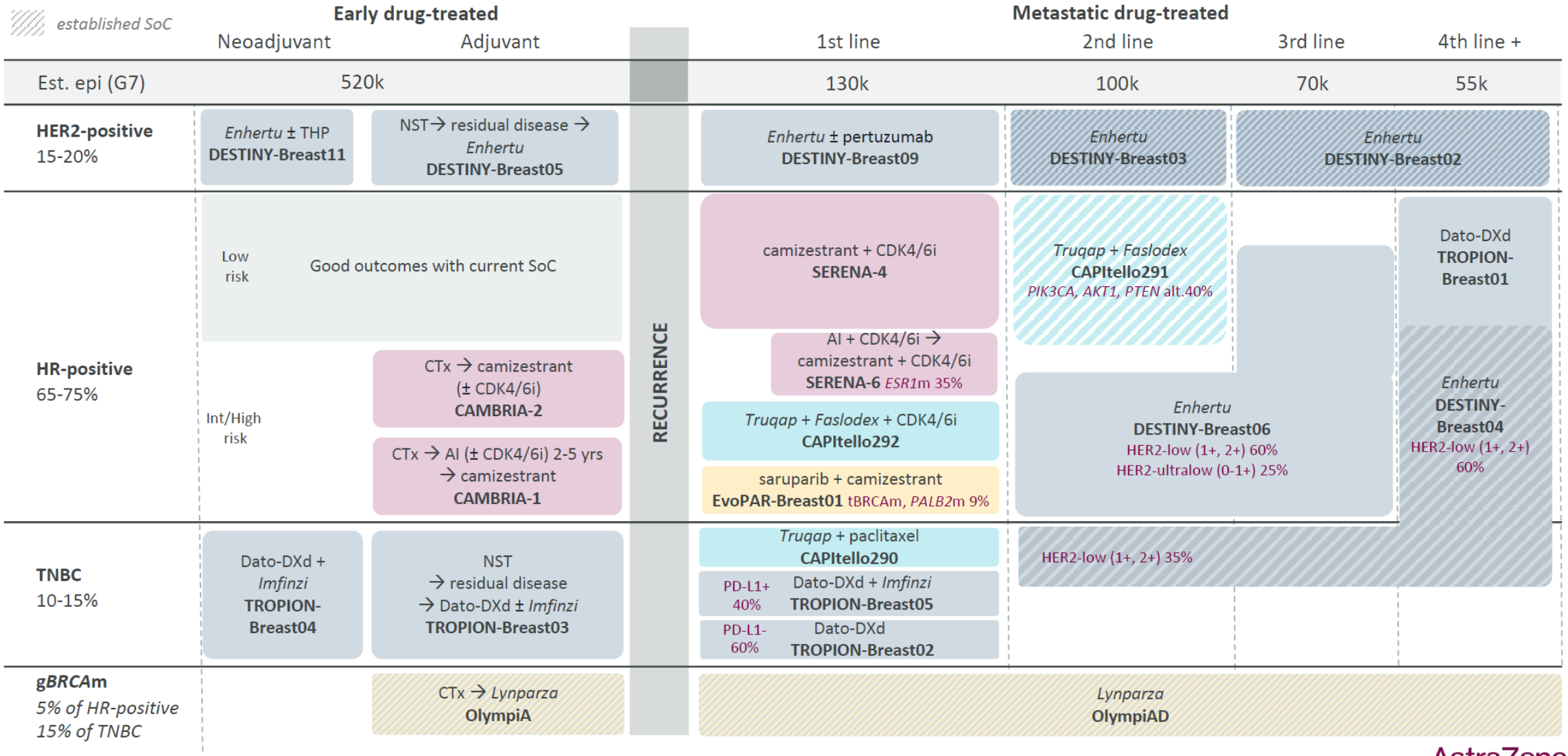
All numbers are approximate. Illustrative settings and populations, not to scale. Acronym definitions can be found in Glossary.
Collaboration partners: Daiichi Sankyo (*Enhertu*, Dato-DXd), Compugen (rilvegostomig).

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

AstraZeneca in breast cancer

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

Ambition to eliminate breast cancer as a cause of death

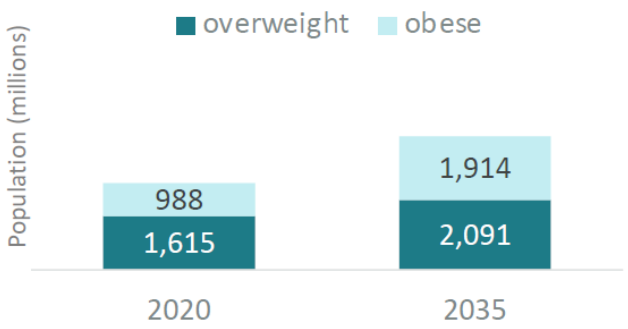


All numbers are approximate. Illustrative settings and populations, not to scale. All numbers for epi are drug-treated. Acronym definitions can be found in Glossary.
Collaboration partners: Daiichi Sankyo (*Enhertu*, Dato-DXd).

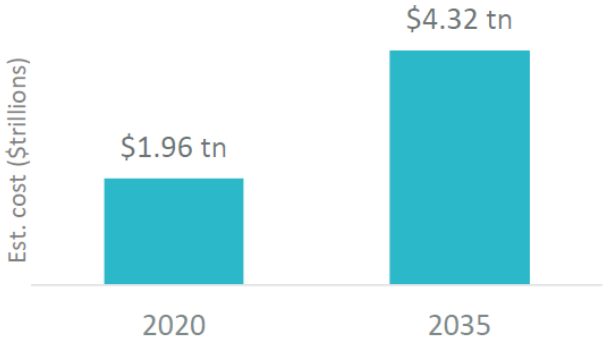
Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

Going beyond obesity to improve quality of weight loss and manage comorbidities

>50% of global population will be overweight or obese by 2035[1]

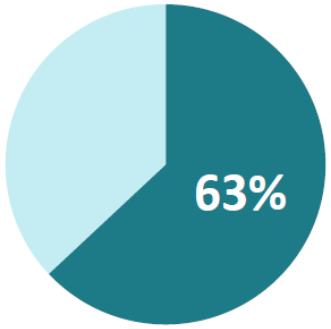


Obesity estimated to cost the economy **3% of global GDP**[1]

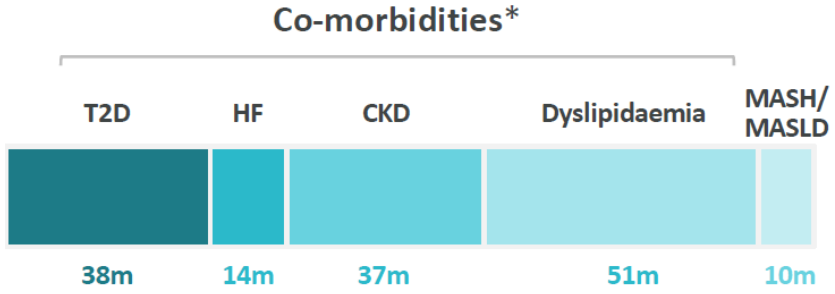


63% of comorbidities to be targeted by our oral and injectable combinations[2]

48.2m patients have no co-morbidity



82.2m patients have ≥1 co-morbidity

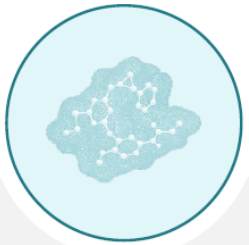


1. World Obesity Atlas 2023. Excludes children under 5 years. 2. TriNetX (US EHR data), November 2020. Obesity defined as ICD10 codes E66.0, E66.1 , E66.2 , E66.8 , E66.9; T2D defined by ICD10 code E11; CKD defined by eGFR levels between 15 and 75 (CKD stages 2-4); heart failure defined by ICD10 code 150; NASH/NAFLD defined by ICD10 codes K75.81 and K76.0; dyslipidaemia defined by LDL>70. *% adds up to more than 82.2m as many patients have several co-morbidities. Acronym definitions can be found in Glossary.

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

$5bn+*

Three high potential assets progressing to Phase IIb

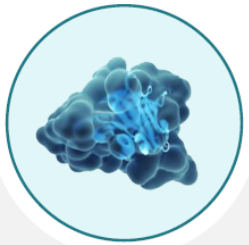


AZD5004

oGLP-1

- Small molecule
- Strong target engagement
- Once-daily dosing
- Combinations across obesity, weight management, and type-2 diabetes

Two Phase IIb trials planned in 2024

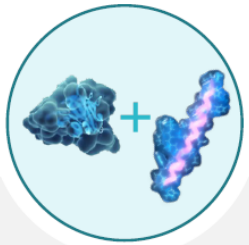


AZD6234

long-acting amylin

- Selective amylin agonist
- Once-weekly dosing
- Adjunct for additional fat-specific weight loss
- Replacement therapy for incretin intolerance

Phase IIb trial planned in 2024



AZD6234 + AZD9550

long-acting amylin + GLP-1/glucagon

- Triple peptide agonists
- Once-weekly dosing
- Fat-specific weight loss
- Organ protection

Phase IIb trial planning underway

*Peak Year Revenue potential, non-risk adjusted for franchise; includes several medicines with multi-blockbuster potential. Acronym definitions can be found in Glossary.
Collaboration partner: Eccogene (AZD5004)

AstraZeneca Joins Obesity Biotech SixPeaks at Basecamp with $80M for Buyout Option

Annalee Armstrong, *FierceBiotech*, May 22, 2024 (excerpt)

The obesity business is cutthroat these days. AstraZeneca is taking no chances on missing out on the next big thing. The U.K. pharma is one of the first investors in a new biotech emerging today with $110 million to develop new therapies for healthy weight loss.

Based in Switzerland, the aptly named SixPeaks Bio broke stealth Wednesday, announcing $30 million in series A funding. The financing round was led by founding investor Versant Ventures, a venture capital company with $5.5 billion under management for biotech company building.

AstraZeneca also participated in the series A, but beyond that, has committed $80 million in capital, both upfront and in near-term payments. That extra bump of support provides the U.K. pharma with an option to acquire SixPeaks down the road once the biotech reaches an investigational new drug filing.

SixPeaks came to be in 2022 out of Versant's Ridgeline Discovery Engine in the Basel Technology Park. The company is creating an activin IIA/B receptor antibody that aims to spur weight loss while preserving skeletal muscle mass.

AstraZeneca has been a late entrant to the obesity space, well behind Novo and Lilly which both have approved—and very successful—therapies. But AstraZeneca has a few stakes in the climb beyond this new SixPeaks collaboration, including a phase 1 amylin analogue called AZD-6234, which kicked off a trial in the fourth quarter of 2022.

Source: https://www.fiercebiotech.com/biotech/astrazeneca-climbs-front-line-80m-new-weight-loss-biotech-sixpeaks

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

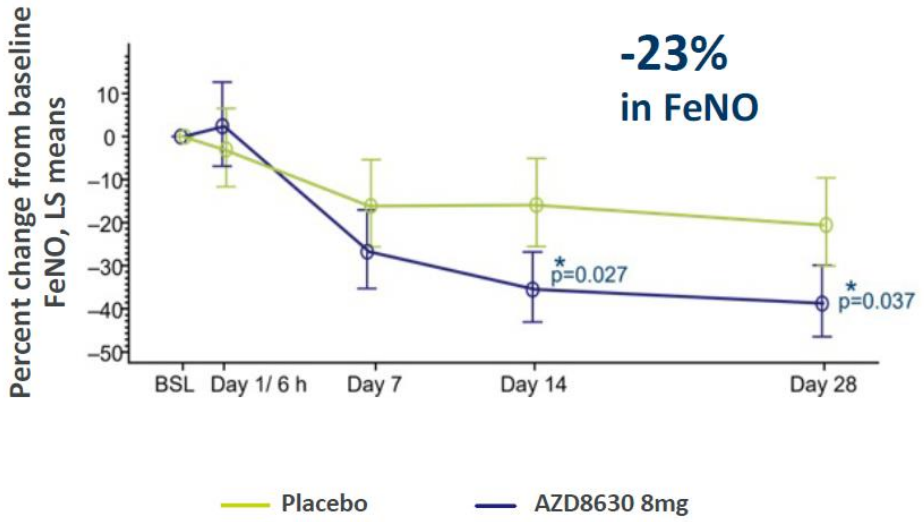
AZD8630 (inhaled anti-TSLP) – potential to extend *Tezspire* franchise beyond severe asthma with first-ever inhaled biologic

Further biologics-penetration expansion beyond systemic biologics

New population beyond those served by *Tezspire* in severe asthma, **potential additional 8.9m patients**[1]

Franchise expansion potential beyond *Tezspire* loss of exclusivity

AZD8630 Phase Ib data[2] – reduced FeNo consistent with *Tezspire*



ATS 2024

Comparable to 25% reduction in *Tezspire* Phase IIb PATHWAY trial[3] in asthma at same timepoint (28 days)

AZD8630 Phase II planned in 2024

1. In G8 markets; source: IQVIA/AstraZeneca analysis. 2. Doffman S, et al. "Phase 1 safety and efficacy of AZD8630/AMG 104 inhaled anti-TSLP in healthy volunteers and patients with asthma on medium-high dose inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) with elevated baseline fractional exhaled nitric oxide (FeNO)," American Thoracic Society International Conference 2024. 3. Corren et al, "Tezepelumab in Adults with Uncontrolled Asthma" (PATHWAY), *New England Journal of Medicine*, 2017. Acronym definitions can be found in Glossary.
Collaboration partner: Amgen.

Source: https://www.astrazeneca.com/investor-relations/astrazeneca-investor-day.html

BioPharmaceuticals – delivering on our strategy to unlock the next phase of growth

2023

$18.4bn
BioPharmaceuticals Total Revenue

Five blockbuster medicines

Fasenra
farxiga
Symbicort
BRILINTA
CRESTOR

2030

New indications and NMEs

Potential **~10** new blockbusters

WAINUA
BREZTRI AEROSPHERE
TEZSPIRE™
LOKELMA™
Saphnelo™
AIRSUPRA™

baxdrostat **tozorakimab** **IVX-A12**

dapa combinations

2030+

New modalities and novel combinations

Amyloidosis combinations

Weight management and dyslipidaemia combinations

Expanding modalities in respiratory care

Auto-immune disease
cell therapy, T-cell engagers, CAR-Treg

Is AstraZeneca's $80B Revenue Goal By 2030 a Bridge Too Far?

Greg Slabodkin, *Biospace*, May 24, 2024 (excerpt)

At Tuesday's Investor Day 2024 event, AstraZeneca laid out an ambitious plan to reach $80 billion in total revenue by 2030—up from $45.8 billion in 2023—and to launch 20 new medicines by the end of the decade. CEO Pascal Soriot declared it's a "new era of growth" for the U.K.-based company that he contends will be achieved through its existing portfolio, as well as 20 new therapies, "many with the potential to generate more than $5 billion in peak year revenues."

Why should we believe AstraZeneca can meet this lofty goal of nearly doubling sales? In a presentation to investors on Tuesday, Soriot said the company has a track record of success—specifically, by delivering last year on its ambitious $45 billion revenue goal set a decade ago, up from $22.1 billion in 2018.

However, as Bloomberg Television anchor Guy Johnson pointed out in Tuesday's interview with CFO Aradhana Sarin, AstraZeneca's $80 billion revenue target by 2030 implies 7% to 8% topline growth over that period and "the market doesn't see you generating those sort of numbers, or hasn't up until now." Johnson then very directly asked, "What is the market missing about the potential this company has that will get it to those kinds of growth rates?"

Sarin acknowledged it's a "bold ambition" for AstraZeneca to reach by the end of the decade. At the same time, the CFO boasted that "the breadth and scope of our medicines is truly incredible," noting that currently oncology represents approximately 40% of the company's business with the expectation that cancer drugs will generate "very strong double-digit growth."

In an interview Tuesday with CNBC, Sarin said AstraZeneca's goal in oncology is to have medicines that can potentially treat half of all cancers by 2030. Ultimately, she said, the company is looking to replace chemotherapy with antibody-drug conjugates (ADCs) and to replace radiation therapy with radiopharmaceuticals. "It will take time, but we think we have the technologies today to start replacing them," Sarin told CNBC. "We already have drugs filed with the FDA, for example, to replace chemotherapy in certain areas."

Source: https://www.biospace.com/article/is-astrazeneca-s-80b-revenue-goal-by-2030-a-bridge-too-far-/

Disclosure

STIFEL | Healthcare

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