Biopharmaceutical Sector

Weekly Update – May 20, 2024

© 2024. All rights on original content reserved. Securities in the United States are offered through Stifel, Nicolas & Company, Member FINRA/SIPC. In Europe such services are offered through Stifel Nicolas Europe Limited, which is authorized and regulated by the UK Financial Conduct Authority.

STIFEL | Healthcare

Table of Contents

STIFEL | Healthcare

787 7th Avenue, New York NY 10019, +1 (212) 887-7777
web: www.stifel.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 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 Outlook for 2024)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 22, 2023 (Bullish on Biotech)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

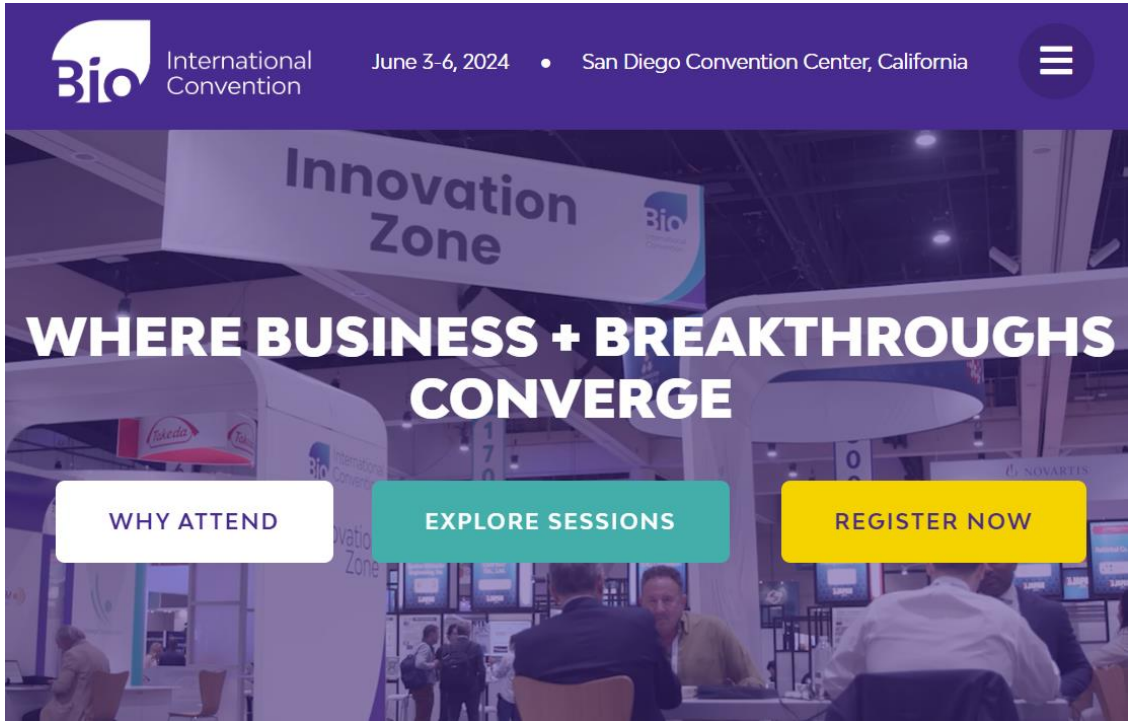
Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on May 17, 2024.

The next event will be on May 24, 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/

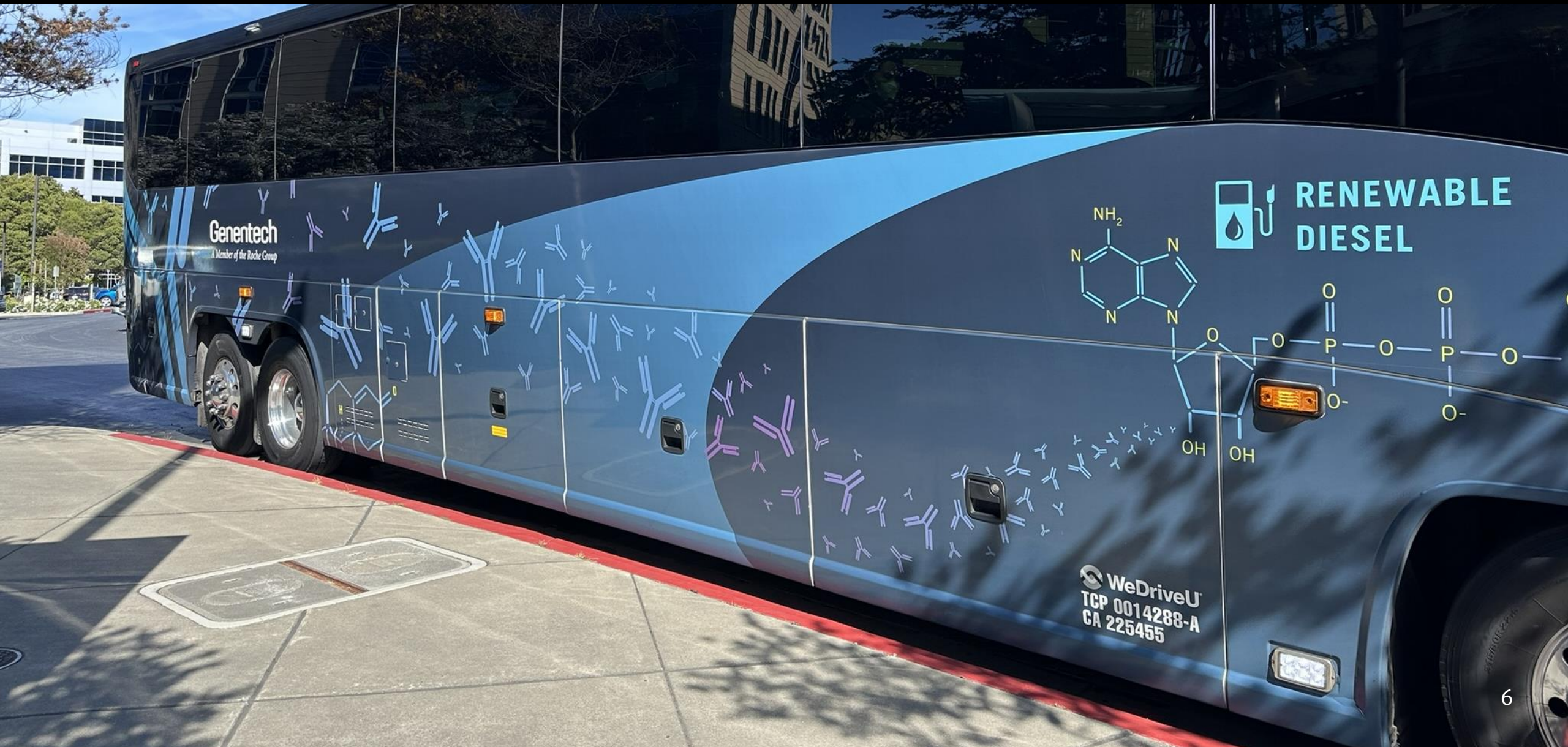
We will also be at ASCO from May 31 to June 2nd. Happy to meet up there as well.

Also, Feel Free to Meet us At ASCO in Two Weeks

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



US Stocks Close at Record High on Slower Pace of Inflation

James Politi, Martha Muir and Kate Duguid, *Financial Times*, May 15, 2024 (excerpt)

US stocks closed at a record high after data showed inflation had fallen slightly to 3.4 per cent in April, prompting traders to increase their bets on Federal Reserve's interest rate cuts this year.

The consumer price index data released by the US labour department on Wednesday was in line with economists' expectations. It compared with March's rate of 3.5 per cent and ended a four-month streak in which inflation outstripped expectations.

"It is something of a relief that for the first time this year, CPI did not come in higher than forecast," said Eric Winograd, senior economist for fixed income at AllianceBernstein.

US stocks set new peaks on the news while government bond yields fell. The S&P 500 closed 1.2 per cent higher, chalking up its first record closing high since late March and leaving the blue-chip index 11.3 per cent higher this year. The tech-heavy Nasdaq Composite climbed 1.4 per cent for its second record in as many days.

The two-year Treasury yield, which moves with interest rate expectations, initially dropped to 4.71 per cent — its lowest level since early April. It later retraced some of that to be 0.09 percentage points lower at 4.73 per cent in late-afternoon trading.

Source: https://www.ft.com/content/ef0028e6-ec29-4521-80fa-2cb6531adb39

Treasury Yields are Little Changed as Investors Weigh State of the Economy

Lisa Kailai Han and Sophie Kiderlin, *CNBC*, May 17, 2024 (excerpt)

Investors weighed the state of the U.S. economy and the path ahead for monetary policy after the latest economic data and comments from Federal Reserve officials.

Data released Thursday showed that import prices soared 0.9%, far higher than the 0.3% Dow Jones estimate, while the latest weekly initial jobless claims figures were broadly in line with expectations.

This comes after several key inflation readings earlier in the week. April's consumer price index came in 0.3% higher from the previous month and rose 3.4% from a year earlier. The monthly figure was just below forecasts, while the annual reading was in line with expectations.

Atlanta Fed President Raphael Bostic on Thursday said that he was pleased with the progress on inflation in April, but that the central bank should stay "patient and vigilant" and was "not there yet."

Fed officials in recent weeks have indicated caution when it comes to monetary policy plans, especially regarding interest rate cuts. Policymakers have widely suggested that they were still waiting for more evidence that inflation is easing sustainably, and that this may take some time. Additional remarks from central bank officials are expected Friday and throughout the coming week.

Earlier in the week, the producer price index for April had reflected an increase of 0.5% on a monthly basis in April, which was above previous expectations.

Source: https://www.cnbc.com/2024/05/17/us-treasurys-investors-weigh-state-of-the-economy.html

Biopharma Market Update

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

The XBI Closed at 91.18 Last Friday (May 17), Up 3.4% for the Week

The XBI was up last week in the presence of improved CPI inflation data. The S&P 500 rose. The XBI is now up for the year (again). The Stifel global biotech market barometer rose by 1%.

Biotech Stocks Up Last Week

Return: May 11 to May 17, 2024

Nasdaq Biotech Index: +2.4%
Arca XBI ETF: +3.4%
Stifel Global Biotech EV (adjusted): +1%*
S&P 500: +1.5%

Return: Dec 29, 2023 to May 17, 2024 (YTD)

Nasdaq Biotech Index: +1.4%
Arca XBI ETF: +2.1%
Stifel Global Biotech EV (adjusted): +19.0%*
S&P 500: +11.2%

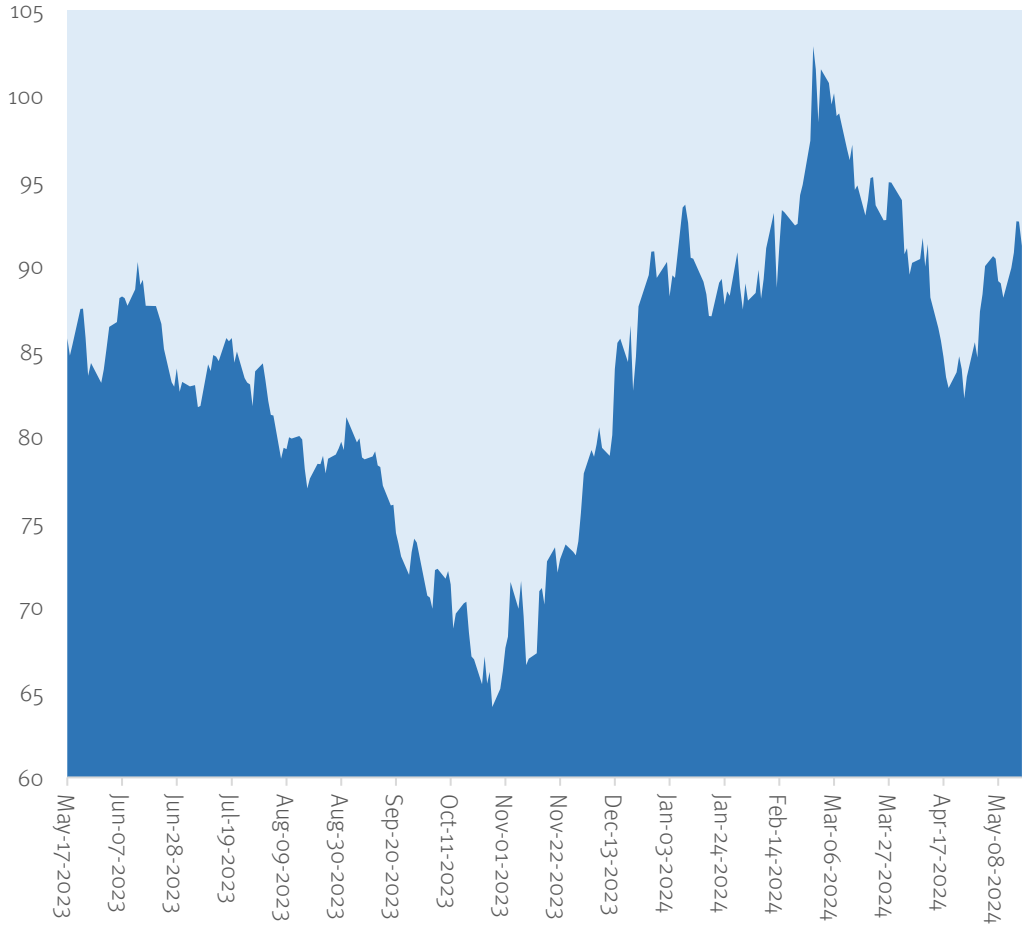
VIX Down Further

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 10, 2024: 12.6%
May 17, 2024: 12.0%

10-Year Treasury Yield Down

Jan 20, 2023: 3.48%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Mar 29, 2024: 4.20%
Apr 26, 2024: 4.66%
May 10, 2024: 4.5%
May 17, 2024: 4.42%

XBI, May 17, 2023 to May 17, 2024



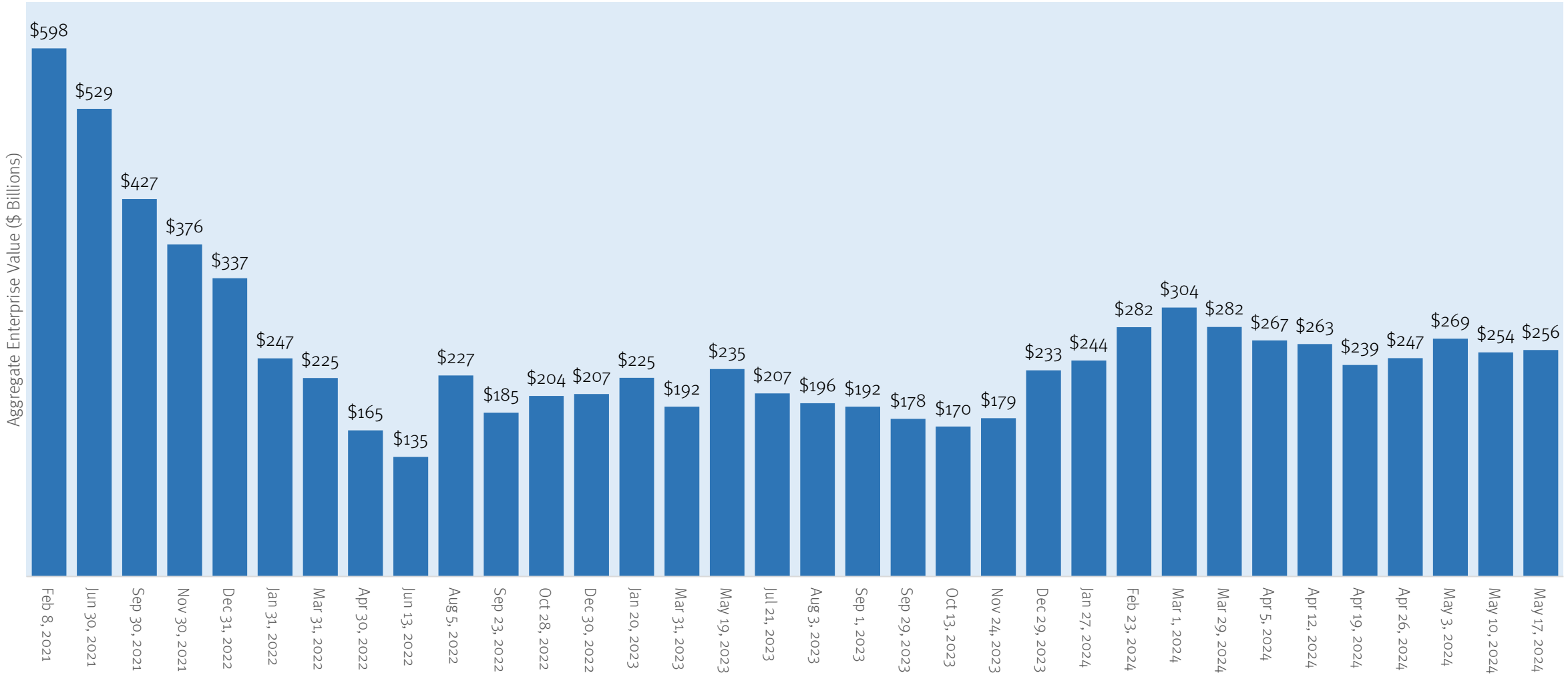
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Up 1% Last Week

Biotech stocks were up slightly last week. On an exit/addition adjusted basis biotech is up 19% for the year.

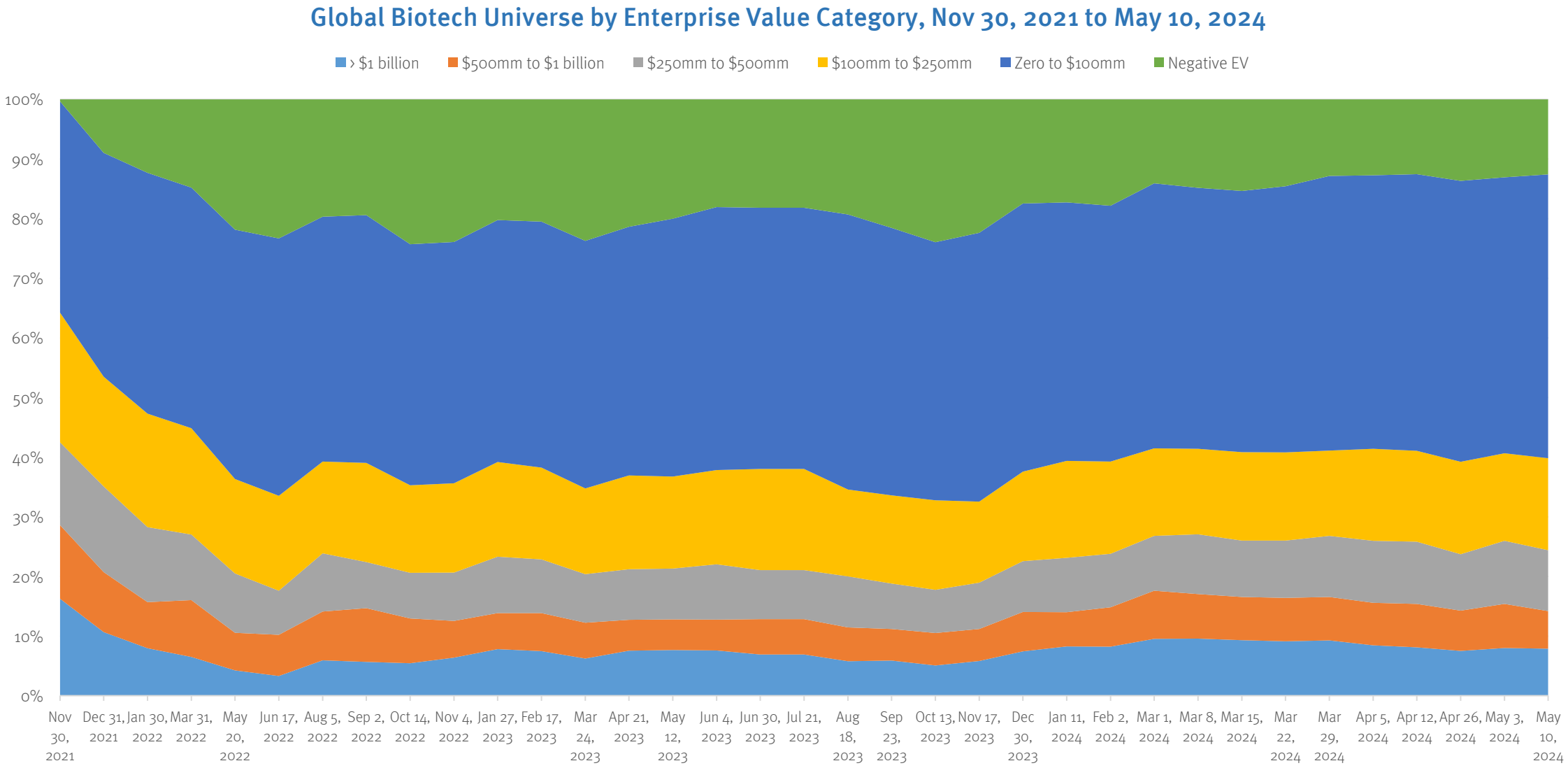
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to May 17, 2024 ($ Billions)



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

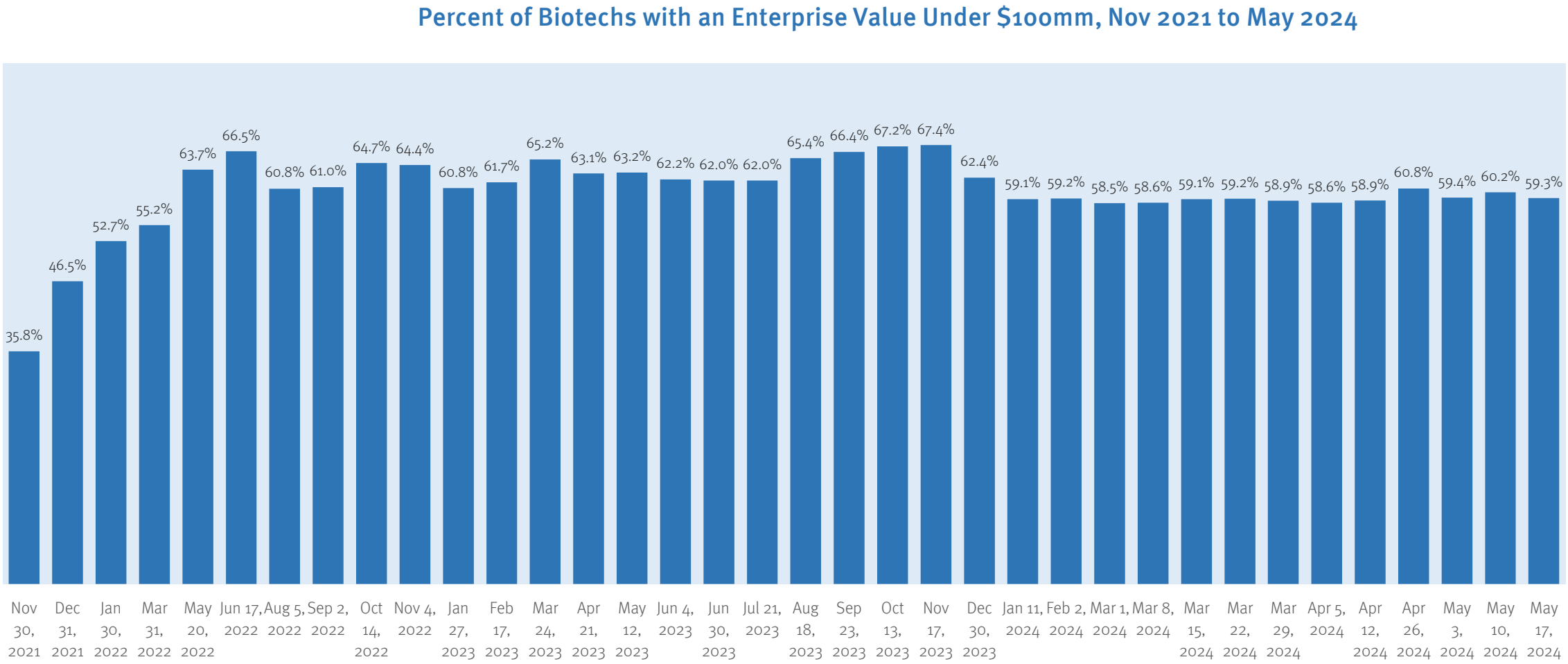
Global Biotech Neighborhood Analysis

The population of companies worth $250mm or more shrunk in the last week.



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

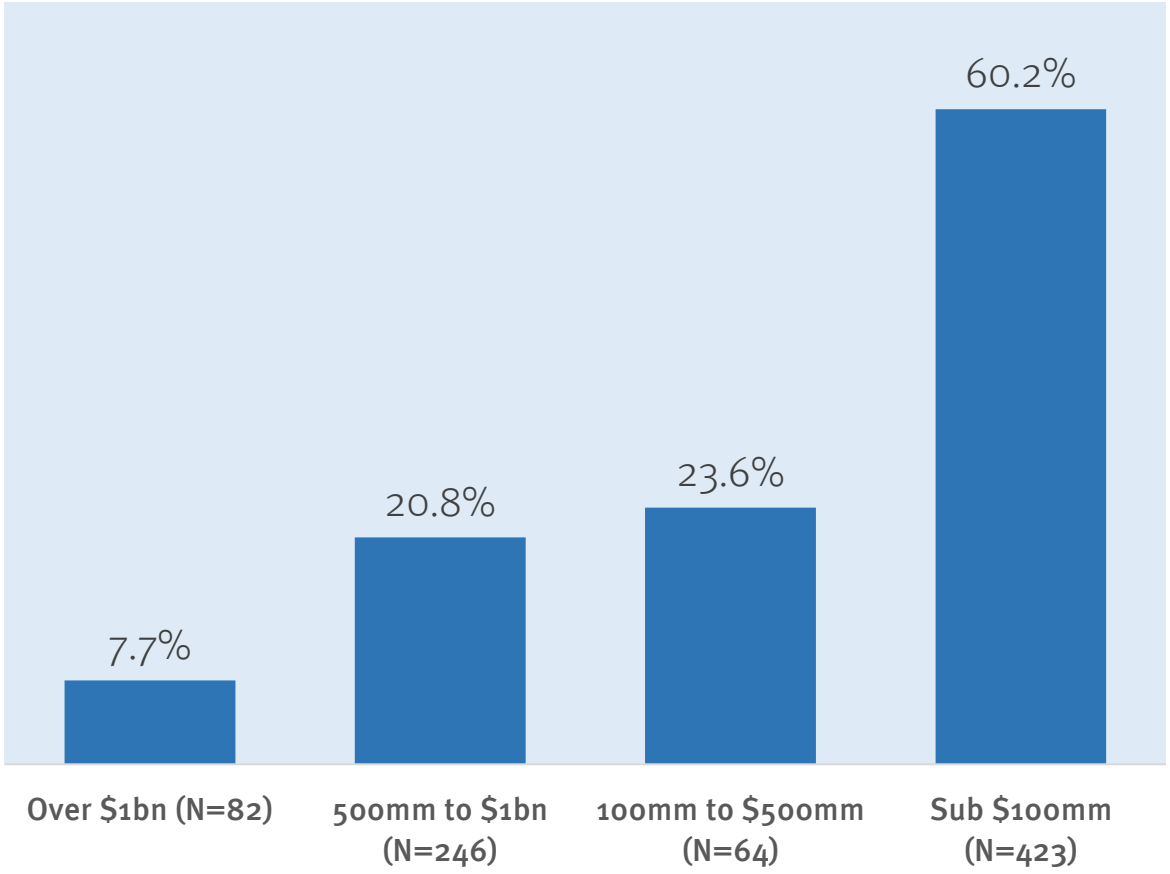
Population of Sub $100mm Biotechs Steady at 59% of Total



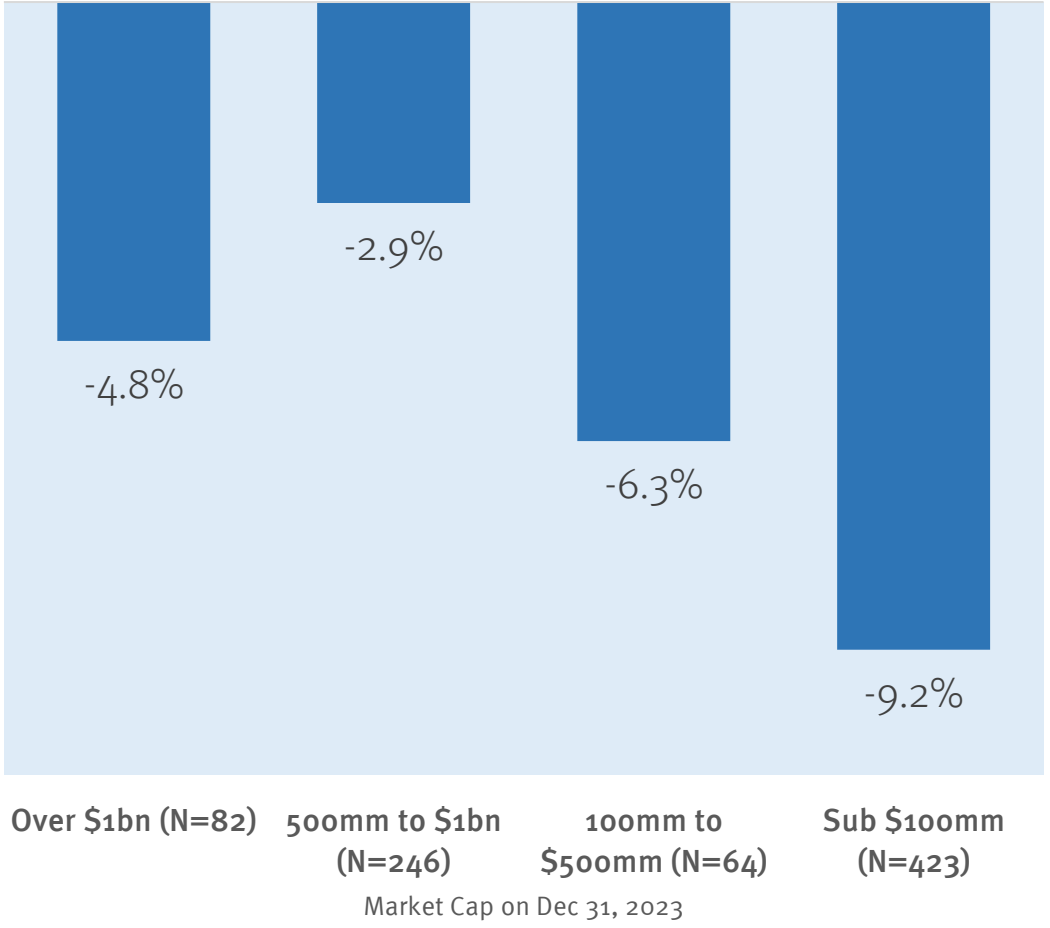
Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

MicroCaps Have Performed Best for the Year But Worst for the Current Quarter

Change in Global Biotech Valuations, Dec 31, 2023 to May 17, 2024
(Percent Change in Value of Company Group, N=815)



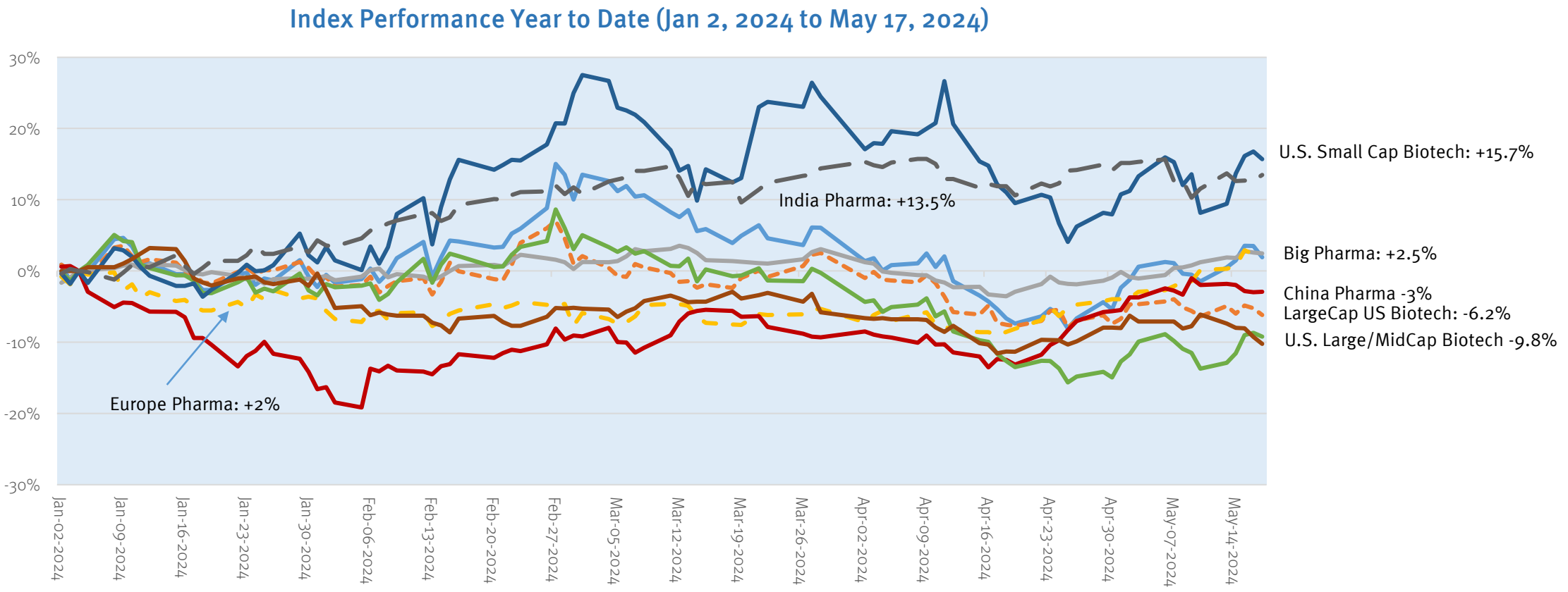
Change in Global Biotech Valuations, Mar 31, 2024 to May 17, 2024
(Percent Change in Value of Company Group, N=811)



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

Small Cap Biotech and India Pharma Shine in 2024

The best performing biopharma subsectors are U.S. small cap biotech and India pharma. The worst performing sectors are large / mid-cap biotech and large-cap biotech. China biopharma was down 20% in early Feb but has come back since then.



Notes: These data are from S&P CapitalIQ and are compiled into equal-weighted indices. Big pharma includes PFE, LLY, MRK, ABBV, NOVO B, ROG, JNJ, AMGN, AZN, NOVN and SAN. China Pharma includes 600276, 1093, 2186, BGNE, 000963, 600196, 000538, 600518, 002422, 000597, 3692 and ZLAB. India Pharma includes SUNPHARMA, 500257, AUROPHARMA, CIPLA, MANKIND, GLENMARK, 500124, ZYDUSLIFE. Europe Pharma includes Merck KGAA, IPN, HLUN A, BAYN, REC, SOBI, ALM, FRE, ORNBV, UCB, GRF. Japan Pharma includes Takeda, Daiichi-Sankyo, Chugai, Astellas, Eisai. Otsuka Holdings, Shionogi, Ono, Kyowa Kirin, Nippon Shinyaku, Santen and Sumitomo Pharma. Large / midcap biotech includes VRTX, ARGX, ALNY, BMRN, INCY, NBIX, OGN, IONS, EXEL, ALKS, ITCI, HRMY, INDV, BPMC, MRTX, SAGE, IDIA, APLS. US Small/midcap pharma includes SUPN, EGRX, CPRX, PCRX, IRWD, JAZZ, COLL, BHC, BLCO, ARQT, HLS, ASRT, OPTN, GTHX, ANIK, HROW, PHAT, ESPR, CALTX, AMARIN, OPK, LQDA, RIGL, EYPT, MRNS, ALIM, TRVN. LargeCap biotech includes KRTX, MDGL, CERE, CYTK, ARWR, PCVX, DNLI, VIR, CRSP, PRTA, BEAM, AKRO, IMVT, VRNA, VTYX, SWTX, SNDX and Microcap biotech includes LCTX, GLSI, GRPH, CYDY, OMER, SVRA, THRD, EVLO, TCRT, CMRX, TSHA, DTIL, OVID, TNYA, VXRT, CUE, XFOR, ATHA, TRVI, CTXR, SELB, CRMD, MTNB, AKBA.

Life Sciences Sector Total Value Up 1.6% Last Week

Performance was mixed across the life sciences sector last week as HCIT, OTC, diagnostics, devices, tools and biotech rose while API and pharma services dropped.

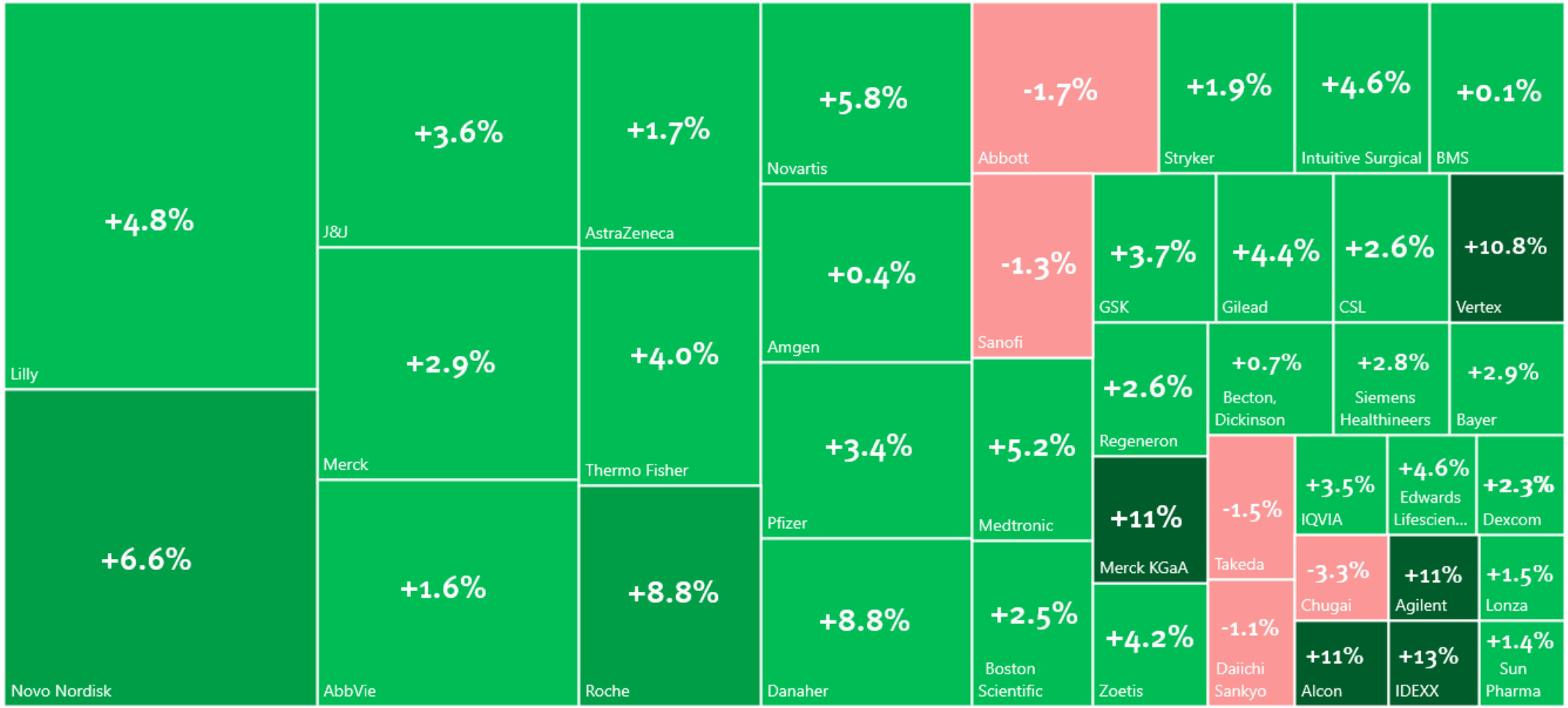
Sector	Firm Count	Enterprise Value (May 17, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$83,581	-0.9%	8.1%	7.8%
Biotech	793	$255,927	1.0%	5.4%	-5.1%
CDMO	39	$148,259	0.9%	3.8%	-16.2%
Diagnostics	81	$270,809	2.2%	5.2%	-0.7%
OTC	30	$26,644	-2.9%	2.0%	-10.3%
Commercial Pharma	716	$6,369,404	1.6%	7.1%	8.6%
Pharma Services	38	$187,985	-0.6%	1.6%	-3.7%
Tools	51	$729,834	1.8%	9.5%	5.2%
Devices	181	$1,709,487	2.0%	5.5%	0.2%
HCIT	10	$18,763	7.6%	9.2%	-20.4%
Total	**2020**	**$9,794,692**	**1.6%**	**6.7%**	**6.1%**

Source: CapitalIQ and Stifel analysis

35 of the Top 40 Life Sciences Players Up in Last Two Weeks

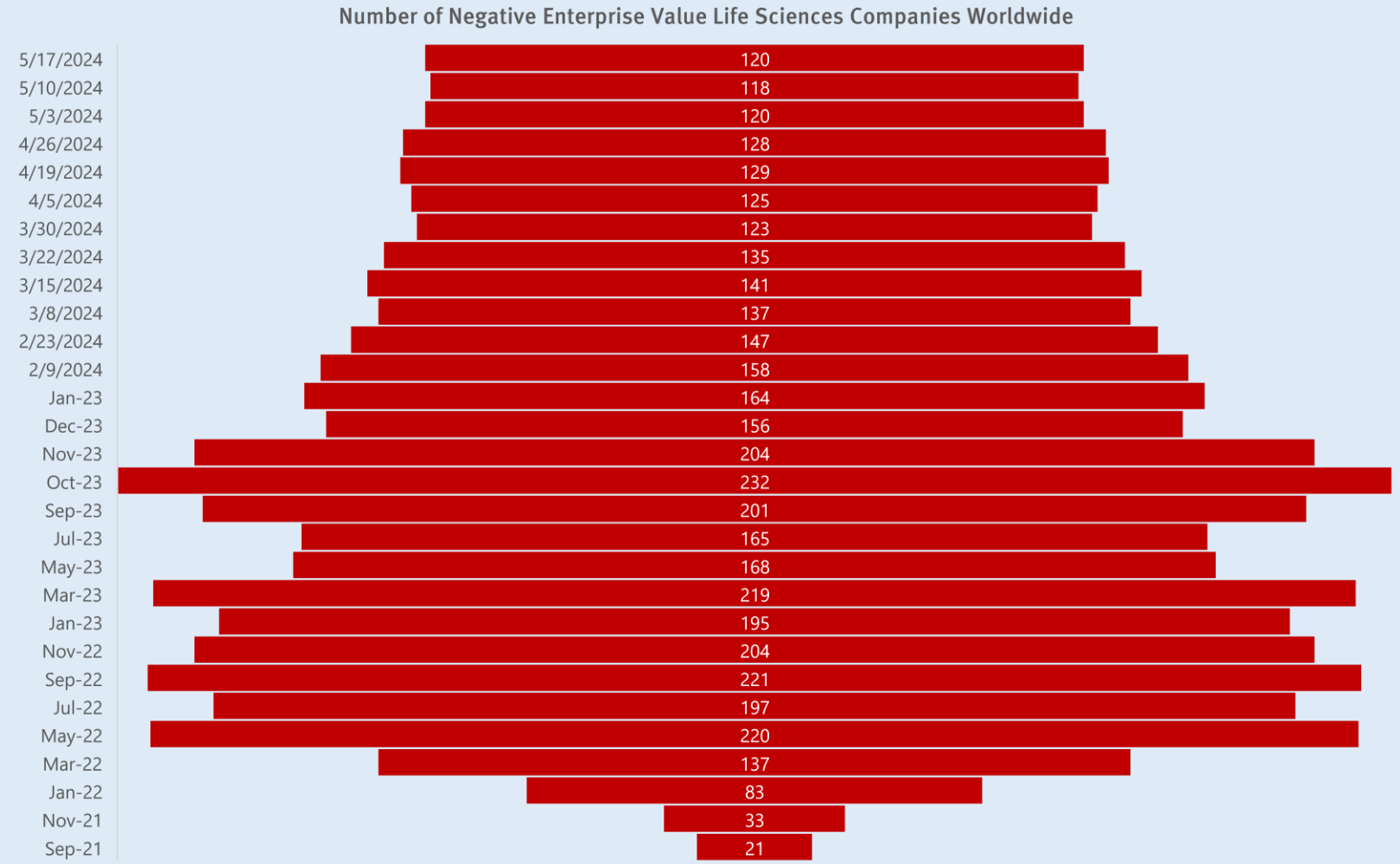
Large caps have performed quite well in recent weeks with particularly strong performance at IDEXX, Alcon, Agilent, Merck KGaA and Vertex. These returns are in dollars and, thus, the three Japanese players on the list have all traded down due to substantial weakness in the Yen. Recent Roche obesity news led that stock up 8.8% but has not had an adverse effect on obesity market leaders Lilly and Novo Nordisk.

Share Price Movement, May 3 to May 17, 2024, Top 40 Life Sciences Companies Sorted by Enterprise Value



Source: CapitalIQ and Stifel analysis

Little Change Last Week in Count of Negative Enterprise Value Life Sciences Companies



Source: CapitalIQ and Stifel analysis

Last Week Sees Short Squeeze in Novavax Amidst Meme Stock Wave

Lecia Bushak, *MM&M*, May 14, 2024 (excerpt)

Don't call it a comeback: Novavax just (briefly) became a meme stock.

The Maryland-based biotech joined the likes of Anglo American, Vodafone and the notorious GameStop in a resurgence of the meme stocks craze from early 2021. Novavax shares jumped nearly 100% on Friday and another 50% on Monday following its announcement last week that it struck a new partnership with Sanofi. Under the licensing agreement, Sanofi will pay Novavax $500 million upfront with up to $700 million in milestone payments, making the deal worth up to $1.2 billion. The agreement also gives Sanofi rights to sell Novavax's COVID-19 vaccine and permits the French pharma giant to work with Novavax in developing new flu-COVID combination vaccines.

News of the deal pacified investor worries as it allowed Novavax to remove its "ongoing concern" warning, which it had originally issued last year after struggling to continue operating amid plummeting COVID-19 sales. Novavax CEO John Jacobs told CNBC that the deal helps the business and "keeps us well capitalized." He noted that the Sanofi partnership also gives Novavax the chance to pivot its strategy more toward "what we're best at" and provide additional value to shareholders.

Meme stocks, which gained notoriety in early 2021 during the GameStop short squeeze, refer to situations where a company's shares skyrocket due to viral social media hype around them. In the last few days, the return of trader Keith Gill — otherwise known as "Roaring Kitty" — to X, the social media platform formerly known as Twitter, spurred the resurgence of so-called meme stocks. Some of those original meme stocks, including GameStop and AMC, jumped more than 70% Monday and continued to rally throughout the trading session Tuesday.

Novavax experienced a short squeeze as a result of Sanofi news as well as the broader market comeback, which involves short sellers quickly buying up shares to close out their positions, which in turn drives stock upwards.

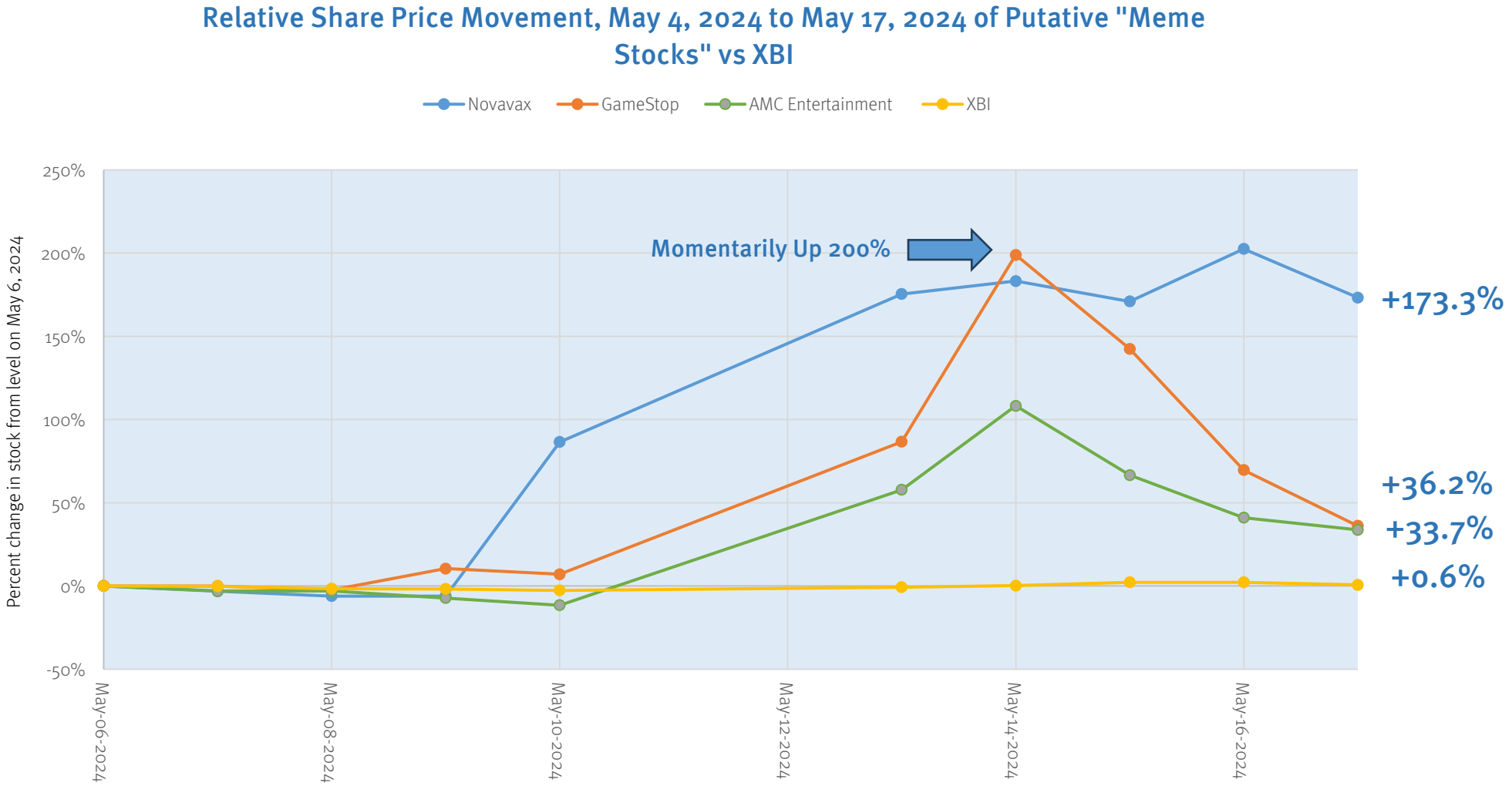
"Roaring Kitty" resurfaced last week, emboldening day traders to create short squeezes in stocks like Game Stop and Novavax.

Source: https://www.mmm-online.com/home/channel/novavax-becomes-meme-stock-sanofi-licensing

Novavax Shares Jump Another 80% on Last Week's "Roaring Kitty Romp"

Image created by Dall-E

Novavax Jumps During Short-Lived Bubble in GameStop and AMC Last Week



Novavax shares kept trading up last week as shorts were squeezed by buying in the stock.

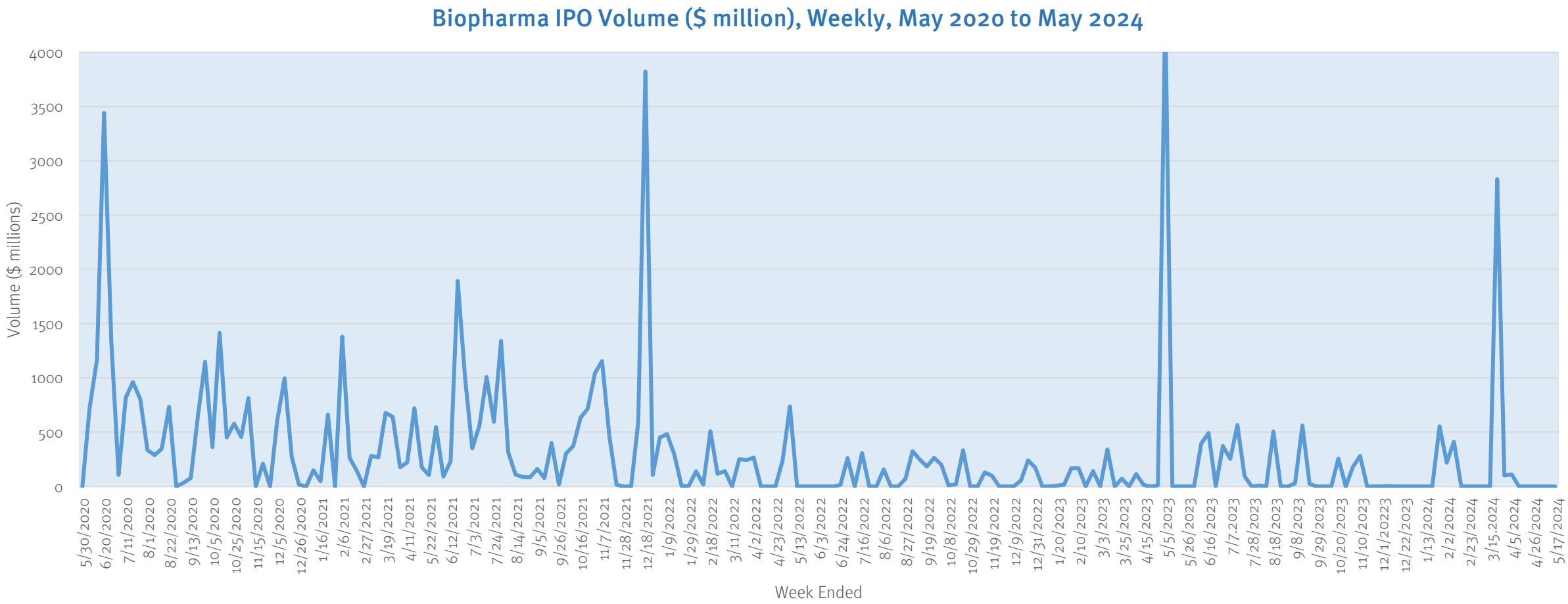
Other heavily shorted biotechs that rose last week were Cassava (up 7.4%) and Anavex (up 18.5%).

Source: S&P CapitalIQ.

Capital Markets Update

No IPO Activity Last Week

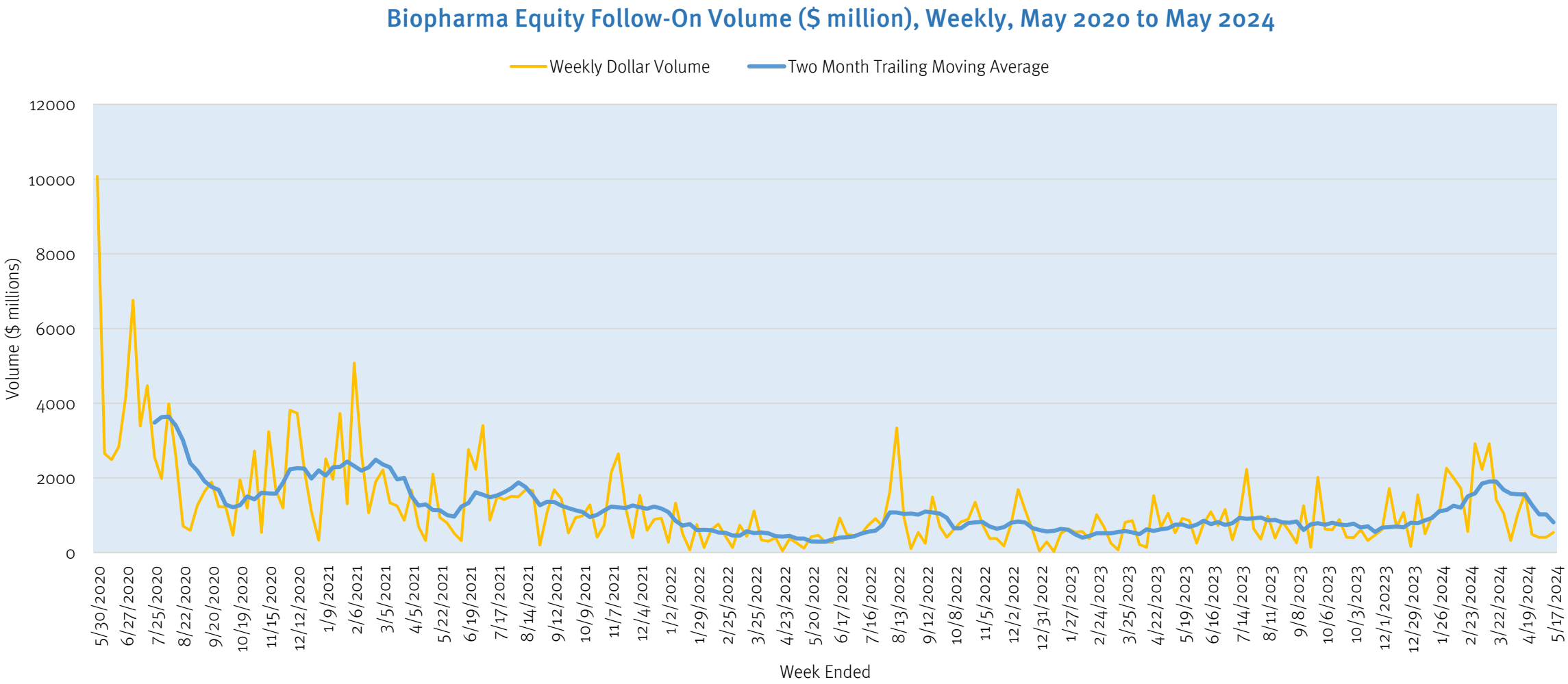
The IPO market remained inactive last week. The last company to go public in the U.S. or Europe debuted six weeks ago. Rapport went public last week with its plans to go public. The pipeline of IPO's on file has continued to swell as issuers anticipate an opening of the window after Memorial Day.



Source: Data from CapitalIQ and Stifel research.

Follow-On Market Quiet Last Week

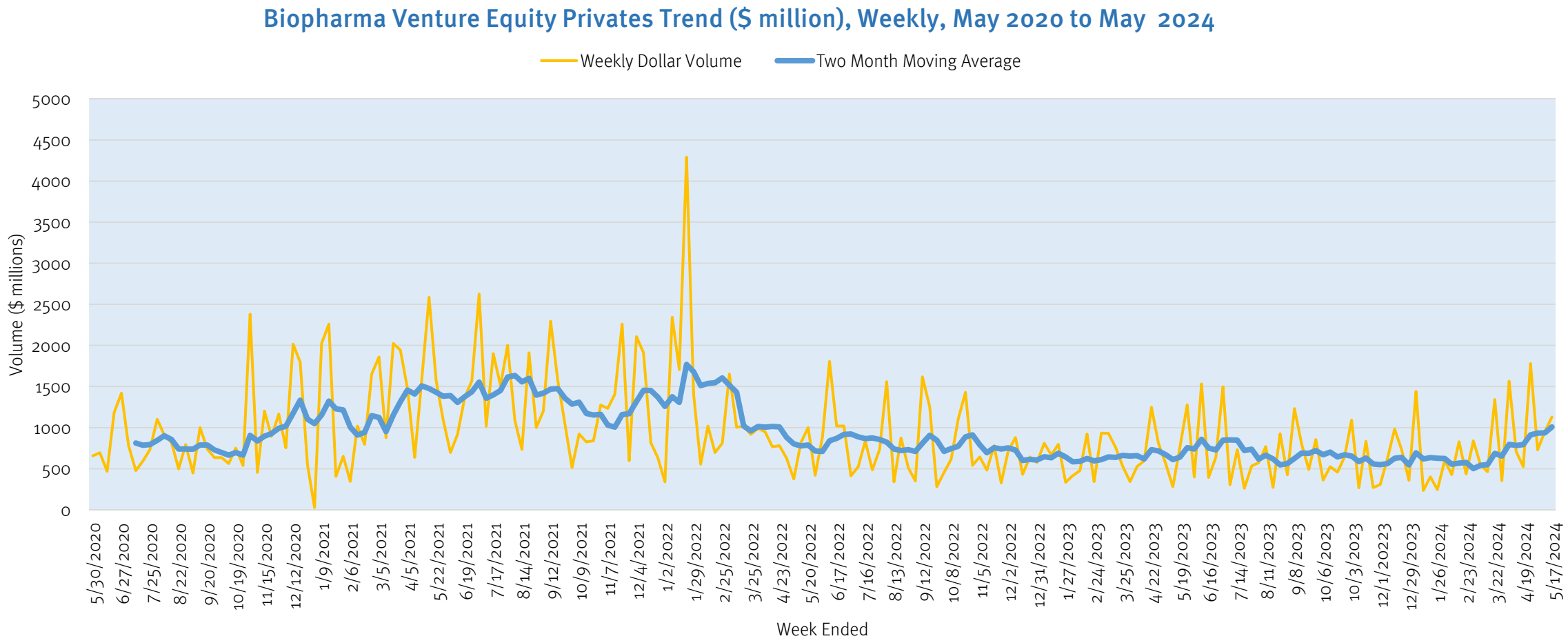
The follow-on market remained quiet last week as the inflation situation sorts itself out. A total of $541 million was raised across 21 issues. The largest issues were by Erasca ($160mm), Allogene ($110mm) and Monte Rosa ($100mm).



Source: Data from CapitalIQ.

Private Venture Equity Market Active Last Week

The venture private market was active last week with $1.1 billion raised by issuers. The largest issues were Hercules ($400mm), Uniquity ($300mm), Lycia ($106mm) and Ajax ($95mm).



Source: Data from CapitalIQ, Crunchbase.

Bain, Atlas, RTW Back New Biotech Developing Obesity Drugs From Hengrui Medicine With $400M

Kyle LaHucik, *Endpoints News*, May 16, 2024 (excerpt)

A new obesity biotech has entered the field — and it has $400 million from well-known life sciences investors to test investigational GLP-1 and GIP candidates licensed from Jiangsu Hengrui Pharmaceuticals.

Bain Capital Life Sciences, Atlas Venture, RTW and Lyra Capital have invested in a new biotech named Hercules CM NewCo, per an announcement this week from China-based Hengrui.

Hercules' pipeline now includes the global, ex-China rights to HRS-7535, HRS9531 and HRS-4729, according to the release.

The deal includes $110 million in upfront payments to Hengrui, according to a source familiar with the deal. Hercules, a placeholder name for the biotech, will be based in the US, the source said. The new company is a partnership between Bain, Atlas and RTW, the source added.

It's a similar approach taken by other blue-chip biotech investors earlier this spring, when ARCH Venture Partners, Population Health Partners, GV, F-Prime Capital and SoftBank Vision Fund 2 backed a new startup called Metsera with $290 million. The financing is being used to advance multiple experimental weight loss drugs licensed from Korean drugmaker D&D Pharmatech as well as an acquisition of London-based Zihipp.

Hengrui Medicine is China's leading pharma company by market cap and has a substantial R&D portfolio.

Source: https://endpts.com/bain-atlas-rtw-back-new-biotech-developing-obesity-drugs-with-400m/

Blackstone Life Sciences Launches Uniquity Bio to Develop Novel Medicines in Immunology & Inflammation

NEW YORK — May 15, 2024: Blackstone (NYSE:BX) today announced the launch of the Blackstone Life Sciences ("Blackstone") portfolio company Uniquity Bio, a clinical-stage drug development company focused on immunology and inflammation. Uniquity Bio is emerging from stealth with an FDA acceptance of its Phase 2 investigational new drug application for solrikitug, a monoclonal antibody targeting TSLP, and up to $300 million in capital from Blackstone to advance the asset in multiple indications.

The company aims to deliver best-in-class efficacy with solrikitug across several critical respiratory and GI indications with significant unmet needs. In the next month, Uniquity Bio will launch Phase 2 clinical trials in chronic obstructive pulmonary disease— the third leading cause of death worldwide, according to the World Health Organization — and asthma, which the WHO estimates affects more than 260 million people across the globe.

"Our investment in Uniquity Bio illustrates Blackstone Life Sciences' commitment to finding, developing and delivering potentially transformative medicines to patients around the world," said Nicholas Galakatos, Ph.D., Global Head of Blackstone Life Sciences. "We are proud to partner with Uniquity's team of veteran industry leaders as they advance solrikitug and expand their immunology and inflammation pipeline with additional programs in the near future."

Solrikitug is a highly potent anti-TSLP monoclonal antibody, which prevents the binding of TSLP to its receptors. Given TSLP's position as the "master switch" cytokine sitting at the top of the inflammatory cascade, solrikitug could have potential utility in a wide array of immunology and inflammation programs. Solrikitug was in-licensed from Merck & Co., Inc.

"We believe solrikitug has the potential to be a life-changing medication for a significant number of patients who currently have very limited treatment options, and we are excited to move into the next phase of development," said Brian Lortie, CEO of Uniquity Bio. "Our approach to development pairs the scientific rigor and quality standards of a global pharma company with the operational agility of a biotech startup, which allows us to move quickly without cutting corners."

Brian Lortie
Chief Executive Officer, Uniquity Bio

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

Lycia Therapeutics Completes $106.6 Million Financing to Advance Pipeline of LYTAC Extracellular Protein Degraders

SOUTH SAN FRANCISCO, Calif., May 13, 2024: Lycia Therapeutics, Inc., a leader in extracellular protein degradation, today announced the completion of an oversubscribed $106.6 million Series C financing. Venrock Healthcare Capital Partners led the round, with participation from new investors Janus Henderson Investors, Marshall Wace and Franklin Templeton, and existing investors Redmile Group, RTW Investments, Blue Owl Healthcare Opportunities (formerly Cowen Healthcare Investments), Invus, Eli Lilly and Company and Alexandria Venture Investments.

Lycia's next-generation degradation approach leveraging lysosomal targeting chimeras, or LYTACs, is designed to target the untapped extracellular proteome, including transmembrane and secreted proteins. Lycia has made notable progress advancing its pipeline of LYTACs and will use the proceeds from the Series C financing to advance its lead programs into the clinic for autoimmune and inflammatory diseases.

Venrock Partner Andrew Gottesdiener, who will join Lycia's Board of Directors in connection with the Series C financing, commented, "Lycia is well aligned with our investment philosophy. They are developing highly innovative medicines that we believe have the potential to deliver meaningful human health advances, and they are backed by a seasoned team who can rapidly execute on the vision and opportunity. I look forward to working with the Lycia team as they advance LYTAC degraders to clinical proof of activity in patients with immune-inflammatory diseases."

"We're thrilled to welcome Venrock and our other new investors as we progress toward becoming a clinical stage company. We've built and continue to enhance the LYTAC platform to access a wide range of extracellular proteins, including high expressing and high turnover targets. This unique flexibility has already yielded a deep, diverse pipeline of LYTAC degraders aimed at depleting difficult-to-drug targets, including many that, to date, have been intractable."

Aetna Wun Trombley
Chief Executive Officer

Source: https://www.globenewswire.com/news-release/2024/05/13/2880276/0/en/Lycia-Therapeutics-Completes-106-6-Million-Series-C-Financing-to-Advance-Pipeline-of-LYTAC-Extracellular-Protein-Degraders-to-the-Clinic.html

Sands Capital's Pulse Fund III Secures $555M Close

May 13, 2024: Sands Capital is pleased to announce the close of our third life sciences fund, Sands Capital Life Sciences Pulse Fund III ("Pulse III"), raising $555 million. Pulse III was met with high demand from both existing and new limited partners. This close increases total Pulse strategy capital commitments to $1.3 billion, including Sands Capital Life Sciences Pulse Fund ("Pulse I") and Sands Capital Life Sciences Pulse Fund II ("Pulse II"). The team will continue investing with the same emphasis on private therapeutics, diagnostics, medical devices, and life sciences tools businesses, in support of the strategy's mission to help transform how diseases are defined, diagnosed, and treated.

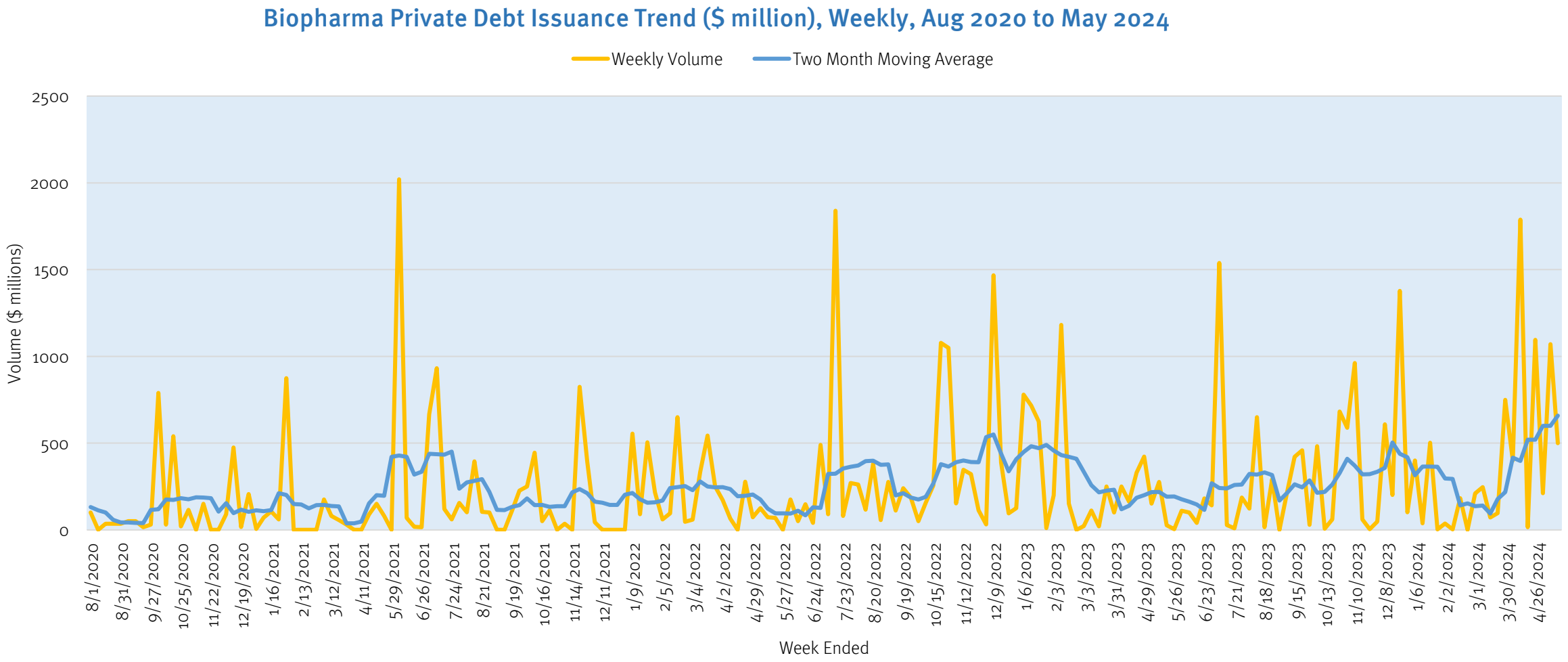
"The life sciences sector continues to innovate at a rapid pace, leading to breakthroughs that benefit both patients and society as a whole," said Stephen Zachary, Managing Partner. "We are grateful to both the investors joining us in Pulse III and the talented management teams we've partnered with since the strategy's inception."

The Pulse investment team comprises senior professionals led by founders, operators, PhDs, and experienced investors with the ability to leverage the resources and capabilities of the entire firm to execute its strategy. The team also draws upon Sands Capital's more than three decades of deep research and experience investing in innovation in public markets.

Source: https://www.sandscapital.com/close-of-life-sciences-pulse-fund/

Biopharma Private Debt Market Remained Active Last Week

The private debt market remained active last week with $500mm raised. The largest deal was a refinancing by Apellis which raised $375 million at close.



Source: Data from CapitalIQ, Crunchbase, Stifel research.

Apellis Pharmaceuticals Refinances Debt with Up to $475 Million Non-Dilutive Credit Facility from Sixth Street

WALTHAM, Mass., May 14, 2024 (GLOBE NEWSWIRE) -- Apellis Pharmaceuticals, Inc. (Nasdaq: APLS), today announced that it has entered into a non-dilutive, senior secured credit facility with Sixth Street, a leading global investment firm, of up to $475 million, with approximately $375 million funded at close. Apellis can draw down an additional $100 million under the facility at the company's option prior to September 2025, subject to satisfaction of certain conditions. Additionally, the Sixth Street agreement also permits Apellis to access $100 million through a separate third-party working capital facility.

Apellis used the majority of the net proceeds to buy out the existing SFJ Pharmaceuticals development liability for approximately $326 million. This buy out eliminates $366 million in payments owed to SFJ through 2027, including approximately $200 million through 2025. Net proceeds to Apellis at closing will be approximately $32 million following the buy out of the SFJ Pharmaceuticals development liability, and fees and expenses associated with the transaction.

"With this transaction, we believe we are uniquely positioned to fund our core operations to positive cash flow without the need to access the capital markets. This marks a pivotal milestone for Apellis," said Tim Sullivan, chief financial officer of Apellis. "Sixth Street is one of the top capital providers within the life sciences sector. Executing this type of deal with market-leading economic terms underscores the quality of our business and the aligned confidence in the opportunities that we have to create meaningful, long-term shareholder value."

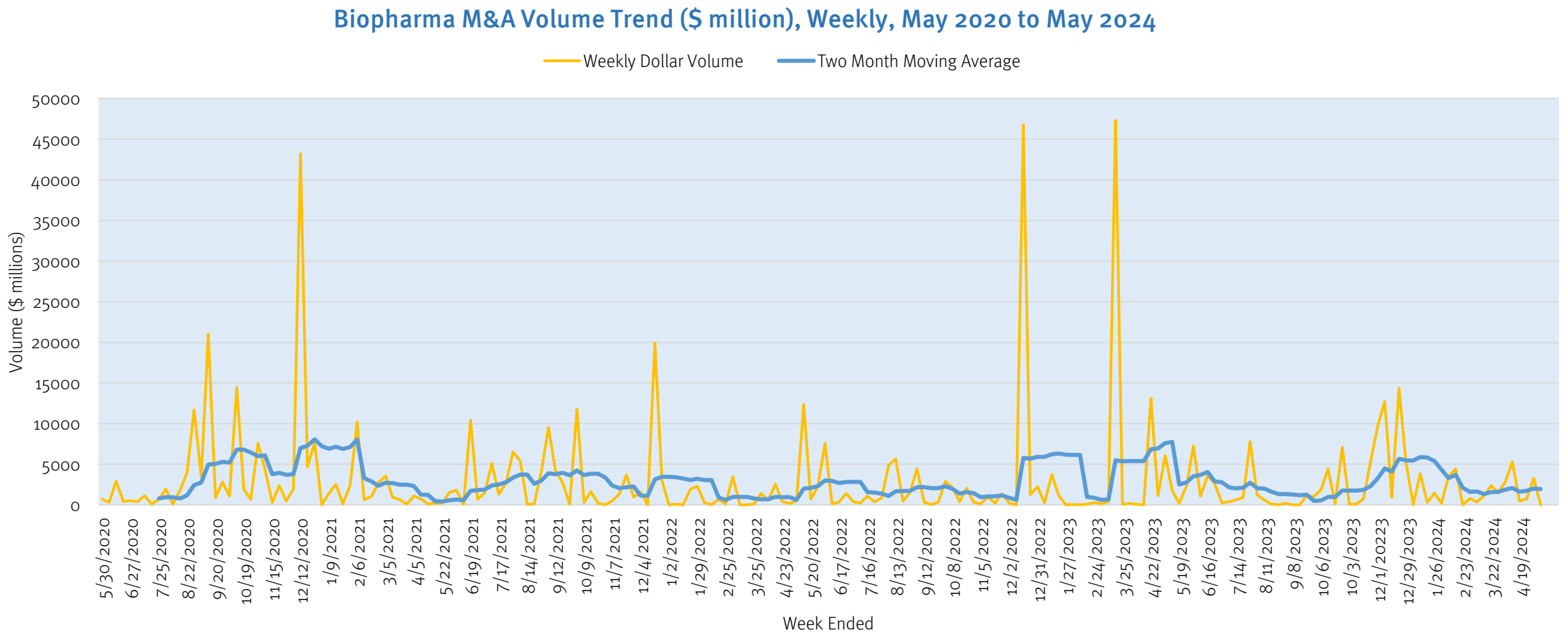
The new senior secured credit facility matures on May 13, 2030, and bears interest at an annual rate equal to the 3-month Secured Overnight Financing Rate (SOFR) + 5.75% (subject to 1.00% floor), with certain additional fees and prepayment terms. There are no scheduled amortization payments during the term of the facility, with all principal due on the maturity date. The credit facility obligations are secured by substantially all assets of Apellis, and the credit facility includes certain affirmative and negative covenants consistent with a facility of this type.

Source: https://investors.apellis.com/news-releases/news-release-details/apellis-pharmaceuticals-refinances-existing-debt-475-million-non

Deal News

Last Week Saw $1.2 Billion in M&A Volume

Last week saw J&J buy Proteologix for $850mm and the Reneo and Onkure merger. Also, Grupo Uriach of Spain acquired Pascoe Pharmazeutische Parate Gesellschaft. Pascoe is a German company with €50mm in revenue.



Source: S&P, CapitalIQ

Reneo Pharmaceuticals And OnKure Announce Merger

IRVINE, Calif., and BOULDER, Colo., May 13, 2024. Reneo Pharmaceuticals, Inc. (Nasdaq: RPHM) and OnKure, Inc., a privately-held, clinical-stage biopharmaceutical company focused on the development of novel precision medicines in oncology, today announced that they have entered into a definitive merger agreement to combine the companies in an all-stock transaction. The combined company will focus on advancing OnKure's pipeline candidates targeting oncogenic mutations in phosphoinositide 3-kinase alpha (PI3Kα), including its lead program OKI-219, which is currently in a Phase 1 clinical trial for the treatment of solid tumors. Upon completion of the transaction, the combined company is expected to operate under the name OnKure Therapeutics, Inc., and trade on the Nasdaq Global Market under the ticker symbol "OKUR".

In connection with the transaction, Reneo Pharmaceuticals has entered into a subscription agreement for a $65 million private investment in public equity (PIPE) financing expected to close concurrently with the closing of the merger, with a group of institutional investors, including Acorn Bioventures, Cormorant Asset Management, Deep Track Capital, Perceptive Advisors, Samsara BioCapital, Surveyor Capital (a Citadel company), and Vestal Point Capital. The transactions are subject to stockholder approval by both companies, the effectiveness of a registration statement to be filed with the U.S. Securities and Exchange Commission, a condition that Reneo Pharmaceuticals have at least $55 million in net cash at the closing (excluding proceeds from the concurrent PIPE financing), the continued listing of the combined company on Nasdaq, and satisfaction of other customary closing conditions.

Including proceeds from the concurrent PIPE financing, the combined company is expected to have approximately $120 million of cash, cash equivalents, and short-term investments at closing. The merger and concurrent PIPE financing are expected to close in 2024.

In February 2024, OnKure initiated a first-in-human clinical trial to evaluate OKI-219, a mutant-selective PI3KαH1047R inhibitor. The PIKture-01 trial is a Phase 1 dose-escalation trial designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of OKI-219 as a monotherapy in patients with advanced solid tumors and in combination with endocrine therapy or HER-2 targeted therapy in patients with advanced breast cancer.

Source: https://reneopharma.com/reneo-pharmaceuticals-and-onkure-announce-proposed-merger/

J&J Acquires Proteologix

NEW BRUNSWICK, NJ (May 16, 2024). Johnson & Johnson (NYSE: JNJ) announced today that it has entered into a definitive agreement to acquire Proteologix, Inc., a privately-held biotechnology company focused on bispecific antibodies for immune-mediated diseases, for $850 million in cash, with potential for an additional milestone payment.

Proteologix's portfolio includes PX128, a bispecific antibody targeting IL-13 plus TSLP, which is ready to enter phase 1 development for moderate to severe atopic dermatitis (AD) and moderate to severe asthma, and PX130, a bispecific antibody targeting IL-13 plus IL-22, which is in preclinical development for moderate to severe AD. Since AD and asthma are both heterogeneous diseases with different disease-driving pathways in distinct patient subpopulations, targeting multiple pathways offers the potential to deliver high-bar efficacy and remission.

PX128 inhibits IL-13-mediated Th2 skin inflammation, an important disease-driving pathway in AD and asthma, as well as TSLP, a mediator of tissue inflammation in AD and asthma. Like PX128, PX130 inhibits IL-13-mediated Th2 skin inflammation. PX130 also inhibits IL-22 to restore the skin barrier and prevent inflammation from environmental triggers, such as allergens. Both assets are designed for infrequent dosing intervals, which offers convenience patients prefer. Together, these pipeline additions demonstrate a strategic approach to build a portfolio of differentiated and complementary bispecifics.

"Atopic dermatitis is the most common inflammatory skin disease, impacting more than 100 million adults worldwide," said David Lee, Global Immunology Therapeutic Area Head, Johnson & Johnson Innovative Medicine. "About 70% of patients using existing standard of care therapies do not reach remission1. Current advanced therapies for AD either target a single pathway and have limited efficacy or are more broadly immunosuppressive, resulting in significant safety concerns. We see an opportunity for best-in-disease efficacy for both PX128 and PX130 as each bispecific antibody targets two different combinations of disease driving pathways that are mediating the skin inflammation in heterogenous subpopulations of AD patients."

Source: https://www.jnj.com/media-center/press-releases/johnson-johnson-to-acquire-proteologix-inc-to-lead-in-atopic-dermatitis-treatment

TSLP Antibodies Have Become Quite the Rage Lately

Several companies and research groups are actively developing antibodies targeting thymic stromal lymphopoietin (TSLP). Notably:

- AstraZeneca and Amgen developed the first-in-class anti-TSLP monoclonal antibody, tezepelumab, which has been approved for the treatment of severe asthma
- J&J has just acquired Proteologix to access its bispecific for TSLP and IL-13.
- Blackstone has just started Uniquity to develop Merck's Phase 2 high potency TSLP antibody.
- Innovent Biologics is conducting a Phase I study on a dual-function antibody, IBI3002, which targets both IL-4Rα and TSLP.
- Sanofi and Regeneron are working on SAR443765, a novel biologic that targets both TSLP and IL-13 for asthma treatment.
- Teva Pharmaceuticals and Biolojic Design have an exclusive license agreement for developing bispecific antibodies targeting TSLP and IL-13.
- GSK acquired Aiolos Bio for $1bn upfront recently to strengthen its respiratory biologics portfolio with the addition of AIO-001, a Phase 2 long-acting anti-thymic stromal lymphopoietin (TSLP) monoclonal antibody. This acquisition aligns with GSK's strategy to expand its offerings for respiratory conditions, particularly asthma.

These efforts indicate a robust interest in leveraging TSLP antibodies for treating various inflammatory and allergic conditions.

Why the Excitement for TSLP as a Target?

TSLP (thymic stromal lymphopoietin) antibodies are gaining popularity due to their potential to effectively treat a range of allergic and inflammatory diseases. Several factors contribute to their increasing attention:

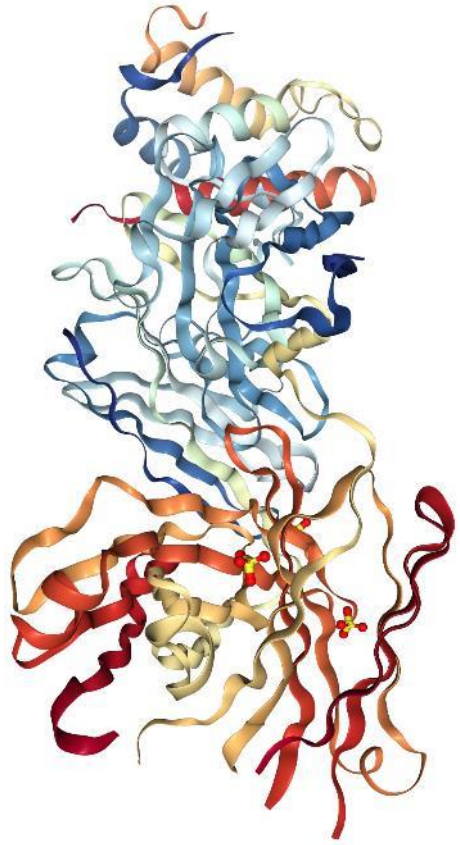
Targeting Key Pathways: TSLP plays a crucial role in initiating and perpetuating allergic inflammation. It is an upstream cytokine involved in the activation and migration of various immune cells, including dendritic cells, T cells, and eosinophils, which are pivotal in the pathogenesis of asthma and other allergic conditions. By blocking TSLP, these antibodies can potentially halt the inflammatory cascade at an early stage.

Broad Therapeutic Applications: TSLP antibodies have shown promise in treating multiple conditions beyond asthma, including atopic dermatitis, chronic rhinosinusitis with nasal polyps, and other eosinophilic disorders. This broad applicability increases their attractiveness in the pharmaceutical market.

Efficacy and Safety: Clinical trials of TSLP antibodies, such as tezepelumab, have demonstrated significant improvements in asthma control and reductions in exacerbations with a favorable safety profile. These results suggest that TSLP antibodies could become a mainstay in the treatment of severe asthma and other related conditions.

Unmet Medical Needs: There is a substantial unmet need for new therapeutic options for patients with severe asthma and other difficult-to-treat allergic diseases. Existing treatments do not adequately control symptoms for all patients, leading to a high burden of disease and healthcare costs. TSLP antibodies offer a novel mechanism of action that addresses this gap.

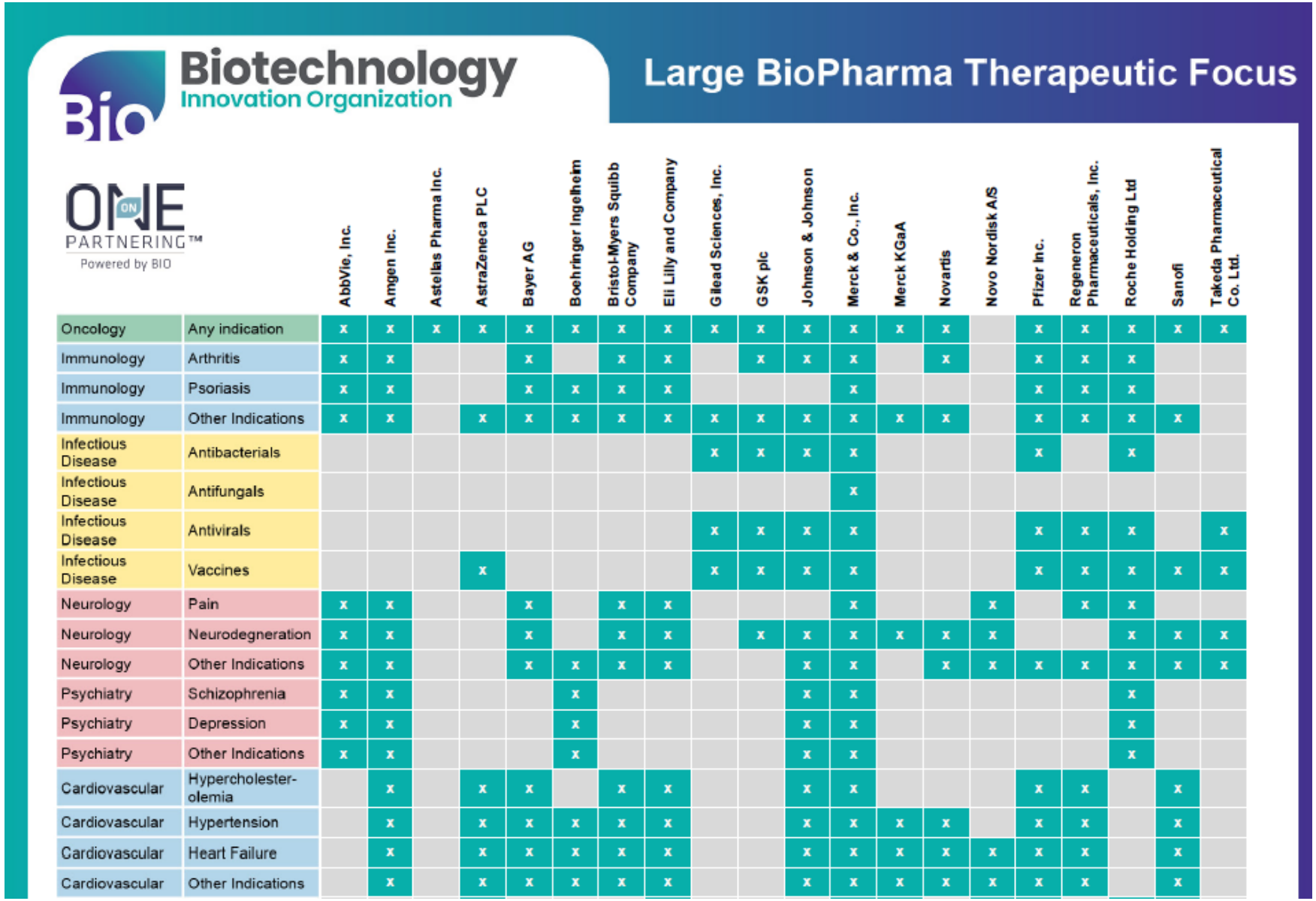
Regulatory Approvals and Market Potential: The approval of TSLP-targeting drugs, such as tezepelumab, by regulatory authorities like the FDA has validated their potential and spurred further interest and investment in this area. The commercial success and ongoing development of new TSLP antibodies indicate strong market confidence.



TSLP Protein

This was written by referencing: https://www.nature.com/articles/d41573-022-00013-5, https://news.europawire.eu/gsk-expands-respiratory-biologics-portfolio-with-aiolos-bio-acquisition/eu-press-release/2024/02/15/12/29/49/129931/, https://www.pharmaceutical-technology.com/news/gsk-aiolos-bio-acquisition/

BIO Publishes a Pharma BD Interest Grid



Biotechnology Innovation Organization

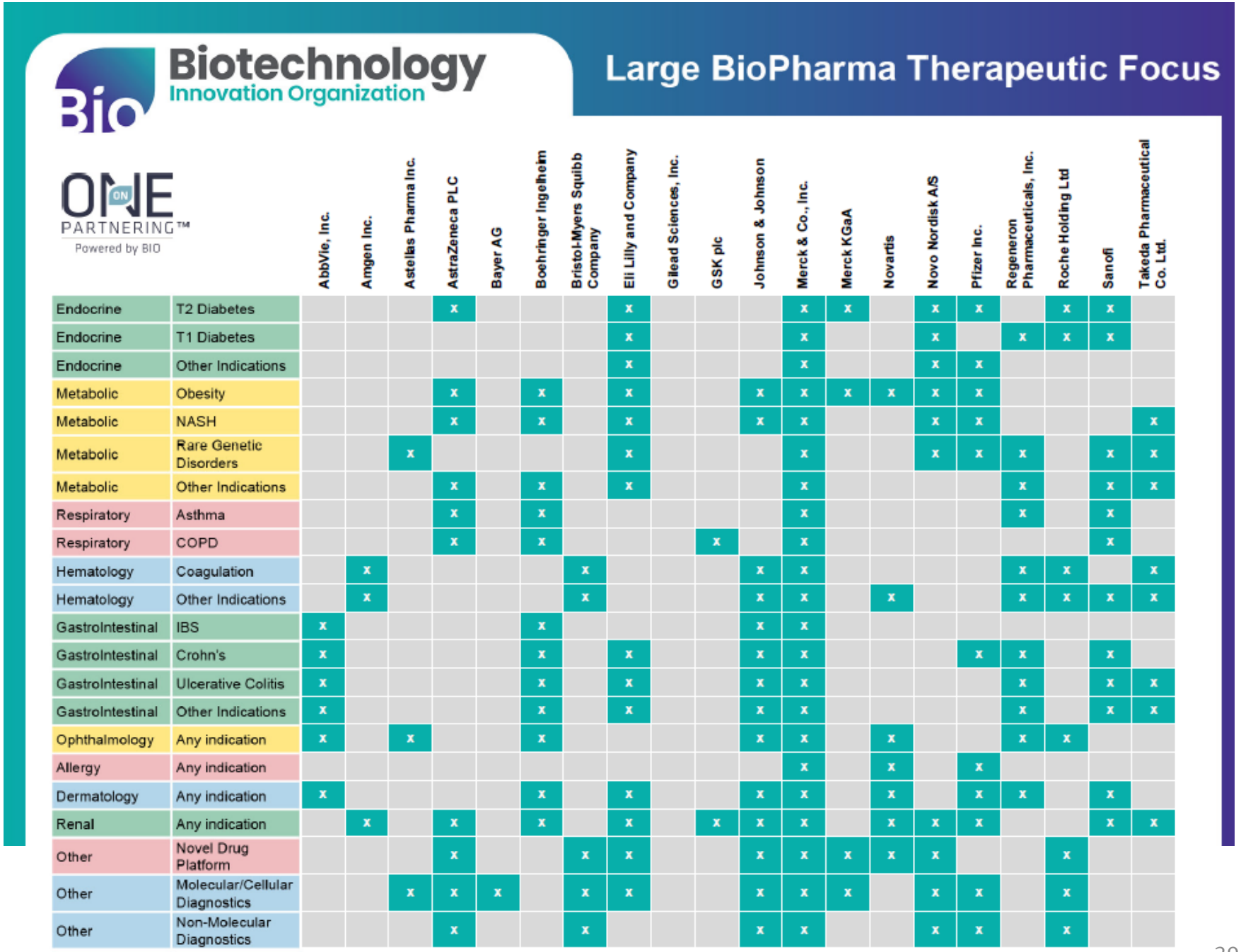
Large BioPharma Therapeutic Focus

ONE ON PARTNERING™ Powered by BIO

		AbbVie, Inc.	Amgen Inc.	Astellas Pharma Inc.	AstraZeneca PLC	Bayer AG	Boehringer Ingelheim	Bristol-Myers Squibb Company	Eli Lilly and Company	Gilead Sciences, Inc.	GSK plc	Johnson & Johnson	Merck & Co., Inc.	Merck KGaA	Novartis	Novo Nordisk A/S	Pfizer Inc.	Regeneron Pharmaceuticals, Inc.	Roche Holding Ltd	Sanofi	Takeda Pharmaceutical Co. Ltd.
Oncology	Any indication	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Immunology	Arthritis	x	x			x		x	x		x	x	x		x		x	x	x		
Immunology	Psoriasis	x	x			x	x	x	x				x				x	x	x		
Immunology	Other Indications	x	x		x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	
Infectious Disease	Antibacterials									x	x	x	x				x		x		
Infectious Disease	Antifungals												x								
Infectious Disease	Antivirals									x	x	x	x				x	x	x		x
Infectious Disease	Vaccines				x					x	x	x	x				x	x	x	x	x
Neurology	Pain	x	x			x		x	x				x			x		x	x		
Neurology	Neurodegeneration	x	x			x		x	x		x	x	x	x	x	x			x	x	x
Neurology	Other Indications	x	x			x	x	x	x			x	x		x	x	x	x	x	x	x
Psychiatry	Schizophrenia	x	x				x					x	x						x		
Psychiatry	Depression	x	x				x					x	x						x		
Psychiatry	Other Indications	x	x				x					x	x						x		
Cardiovascular	Hypercholester-olemia		x		x	x		x	x			x	x				x	x		x	
Cardiovascular	Hypertension		x		x	x	x	x	x			x	x	x	x		x	x		x	
Cardiovascular	Heart Failure		x		x	x	x	x	x			x	x	x	x	x	x	x		x	
Cardiovascular	Other Indications		x		x	x	x	x	x			x	x	x	x	x	x	x		x	

Source: BIO Partnering System, May 2024

BIO Pharma BD Interest Grid (continued)



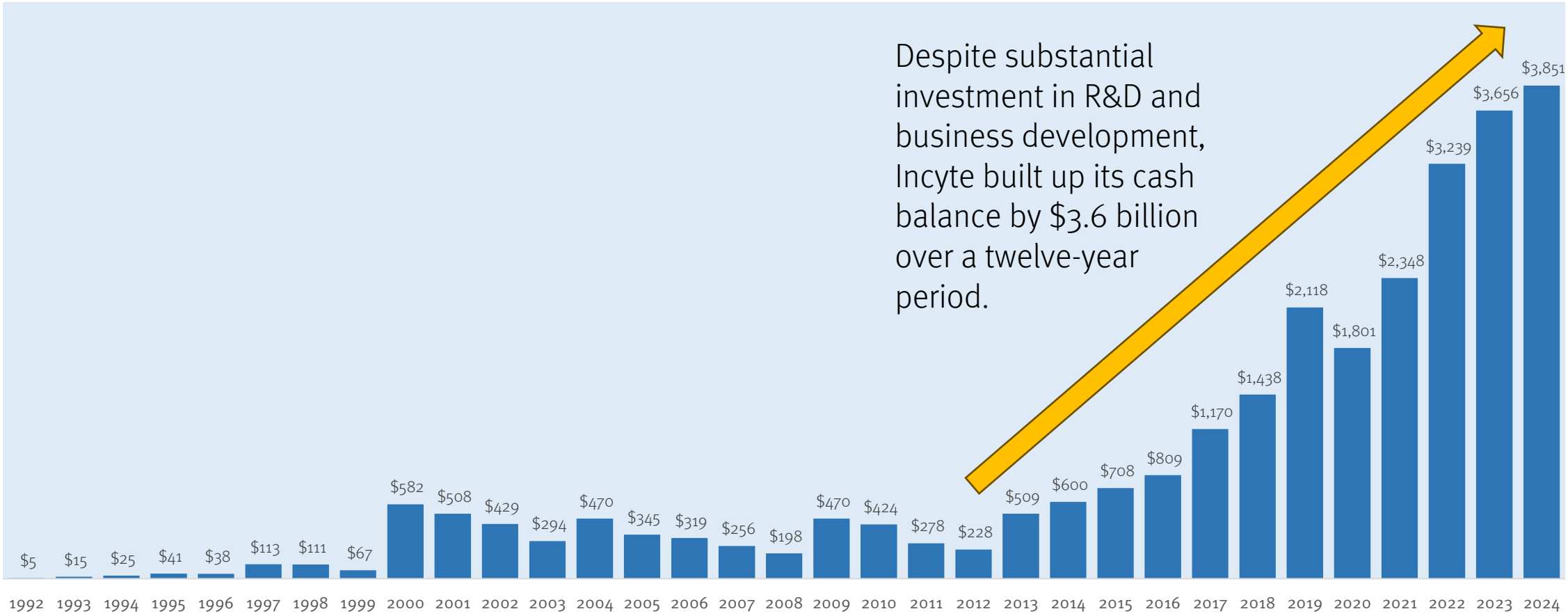
		AbbVie, Inc.	Amgen Inc.	Astellas Pharma Inc.	AstraZeneca PLC	Bayer AG	Boehringer Ingelheim	Bristol-Myers Squibb Company	Eli Lilly and Company	Gilead Sciences, Inc.	GSK plc	Johnson & Johnson	Merck & Co., Inc.	Merck KGaA	Novartis	Novo Nordisk A/S	Pfizer Inc.	Regeneron Pharmaceuticals, Inc.	Roche Holding Ltd	Sanofi	Takeda Pharmaceutical Co. Ltd.
Endocrine	T2 Diabetes				x				x				x	x		x	x		x	x	
Endocrine	T1 Diabetes								x				x			x		x	x	x	
Endocrine	Other Indications								x				x			x	x				
Metabolic	Obesity				x		x		x			x	x	x	x	x	x				
Metabolic	NASH				x		x		x			x	x			x	x				x
Metabolic	Rare Genetic Disorders			x					x				x			x	x	x		x	x
Metabolic	Other Indications				x		x		x				x					x		x	x
Respiratory	Asthma				x		x						x					x		x	
Respiratory	COPD				x		x				x		x							x	
Hematology	Coagulation		x					x				x	x					x	x		x
Hematology	Other Indications		x					x				x	x		x			x	x	x	x
GastroIntestinal	IBS	x					x					x	x								
GastroIntestinal	Crohn's	x					x		x			x	x				x	x		x	
GastroIntestinal	Ulcerative Colitis	x					x		x			x	x					x		x	x
GastroIntestinal	Other Indications	x					x		x			x	x					x		x	x
Ophthalmology	Any indication	x		x			x					x	x		x			x	x		
Allergy	Any indication												x		x		x				
Dermatology	Any indication	x					x		x			x	x		x		x	x		x	
Renal	Any indication		x		x		x		x		x	x	x		x	x	x			x	x
Other	Novel Drug Platform				x			x	x			x	x	x	x	x			x		
Other	Molecular/Cellular Diagnostics			x	x	x		x	x			x	x	x		x	x		x		
Other	Non-Molecular Diagnostics				x			x				x	x			x	x		x		

Source: BIO Partnering System, May 2024

Incyte's Move to Return Capital

Incyte Cash Balance Started to Build up a Dozen Years Ago Due to Success of Jakafi®

Incyte's Cash and Investments Portfolio, 1991 to 2024 ($ millions, fiscal year end)



Source: S&P CapitalIQ

Last Week: Incyte to Buy Back up to $2.0 Billion of its Common Stock

Incyte stock jumped 7.8% on the news of its Dutch Auction self-tender designed to return part of its cash pile.

WILMINGTON, Del.--(BUSINESS WIRE), May 13, 2024. Incyte Corporation (Nasdaq:INCY) (the "Company") today announced that its Board of Directors approved a share repurchase authorization of $2.0 billion. The Company has commenced a modified "Dutch Auction" tender offer to repurchase shares of its common stock for an aggregate purchase price of up to $1.672 billion (the "tender offer").

"This tender offer reflects our confidence in the future outlook of our business, the strength of our commercial product portfolio and our clinical development pipeline and Incyte's long-term value. We believe the current valuation of Incyte stock makes repurchases of our stock an attractive investment and an opportunity to enhance long-term shareholder value," said Hervé Hoppenot, Chief Executive Officer, Incyte. "Our strong balance sheet, cash flow and access to capital enable us to undertake this transaction while also preserving the flexibility to further add to the growth of our business through focused, strategic acquisitions."

In addition, on May 12, 2024, Incyte entered into a separate stock purchase agreement with Julian C. Baker (a member of Incyte's Board of Directors), Felix J. Baker, and entities affiliated with Julian C. and Felix J. Baker, including funds advised by Baker Bros. Advisors LP (collectively, the "Baker Entities"), to repurchase up to $328.0 million of the Company's common stock. This would enable the Baker Entities to maintain their current ownership level of approximately 16.4 percent of Incyte's outstanding common stock. The Baker Entities purchase will be at the same price per share as is determined and paid in the tender offer.

Modified "Dutch Auction" Tender Offer

Incyte is offering to purchase up to $1.672 billion in value of its common stock at a price not greater than $60.00 per share nor less than $52.00 per share, net to the seller in cash, less any applicable withholding taxes and without interest, upon the terms and subject to the conditions set forth in the tender offer documents that are being distributed to stockholders. The Company reserves the right, in its sole discretion, to change the per share purchase price options and to increase or decrease the aggregate value of shares sought in the tender offer, subject to applicable law. In accordance with the rules of the Securities and Exchange Commission ("SEC"), Incyte may purchase in the offer up to an additional 2 percent of its outstanding shares without amending or extending the tender offer. On May 10, 2024, the Nasdaq closing price of the common stock was $53.06 per share. The tender offer will expire at 12:00 midnight, at the end of the day, New York City time, on Monday, June 10, 2024, unless extended.

Source: https://www.businesswire.com/news/home/20240513823141/en/

Why is it So Rare for Companies to Return Cash to Shareholders?

Count us as being among the surprised when Incyte announced last week that it would return up to $1.67 billion in capital through a share repurchase. Share repurchase programs are commonplace in our industry but the scale of the return of capital here is not.

As of March 31, 2024, Incyte was sitting on $3.85 billion in cash with trailing operating cash flow of $820mm. It then announced the acquisition of Escient for $750mm and is offering to spend $1.67bn on share repurchases. That's roughly $2.4 billion out the door or 62% of its cash pile.

It's quite rare to see biopharma's disgorge cash on such a scale.[1] And, given the reality of average returns on R&D investment well below the cost of capital, it's something that should be more common.

Why don't biotech companies disgorge cash more frequently?

The recently deceased Mike Jensen of Harvard Business School penned the "agency theory of free cash flow" in 1986 where he argued that managers waste cash because it benefits them to do so.[2] Later, in his career, he argued that behavioral factors (non-rational) also come into play and that managers have a deep-seeded desire to avoid pain – which can come when resources are tight.[3] We, ourselves, have contributed to this debate noting that corporations should hold cash as a precautionary measure given the possibility of "rainy days".[4]

Peter Kolchinsky of RA Capital in January 2023 argued that biotechs should consider returning cash when their outlook isn't great (particularly when they have negative enterprise value) and that, in the long run, this will be good for them.[5] Conspicuously, there were almost no takers for Kolchinsky's ideas even though the reasoning was sound. Biotech CEO's, almost universally, think that their companies are undervalued and have better prospects than understood.[6]

Having been in the investment banking industry for over thirty years, we have had the opportunity to interact with thousands of management teams and observe their behavior.

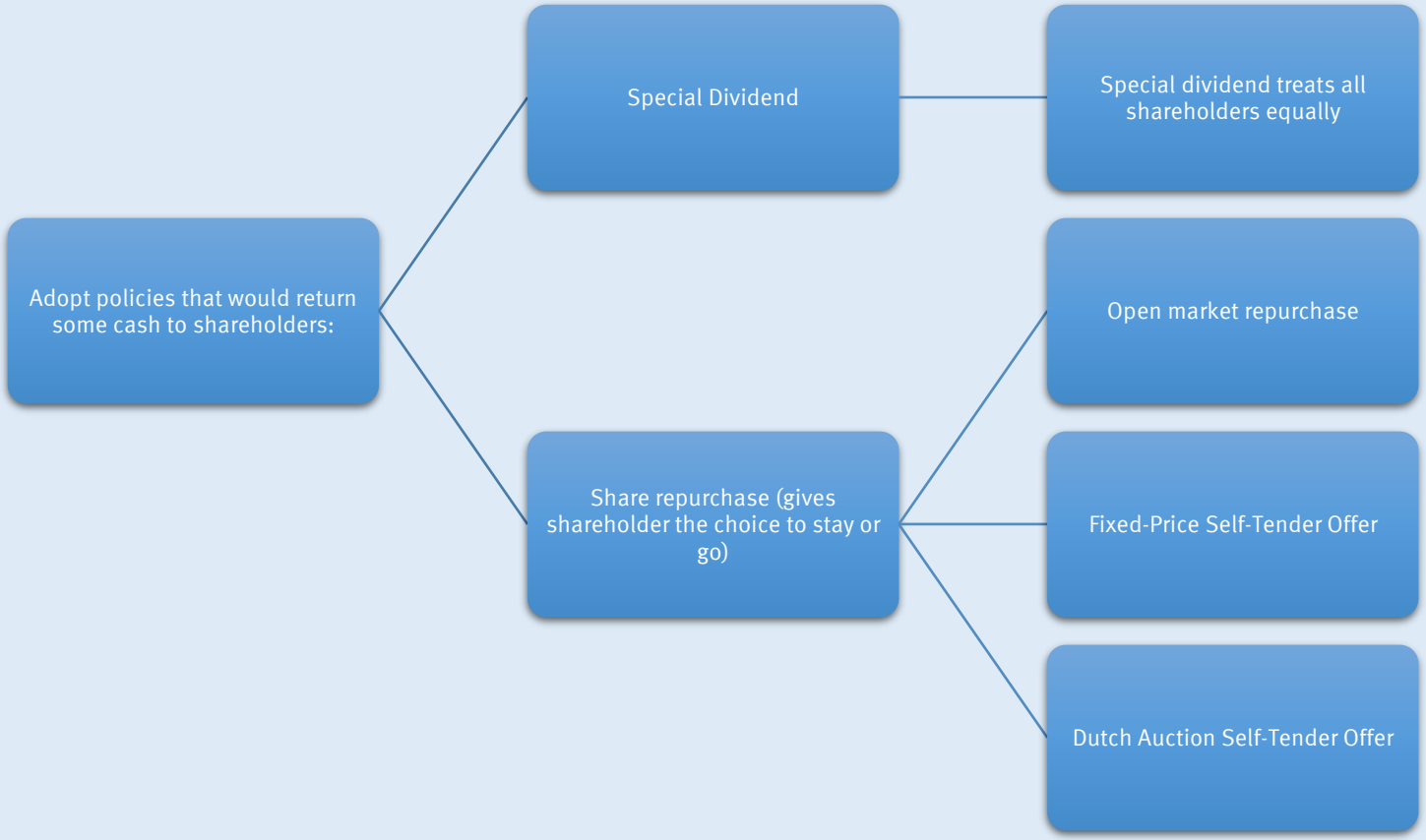
An overwhelming, albeit not universal, motive is to not lose one's job. Corporate managers are optimists by nature and tend to believe that the returns from future investments will be good.[7] Further, they feel quite strongly that they are well-suited to drive their company forward and wish quite strongly not to be replaced. Financial motives are part of it, but pride is also important.

In our experience, managers keep excess cash because it increases their job security and allows them to make more investments. Our experience indicates that Mike Jensen's theory is largely correct.

1 Incyte is offering to repurchase 13% of its market cap. By our calculation, across all life sciences companies, last year only 0.5% of companies repurchase more than 10% of their market cap on net.
2 See https://papers.ssrn.com/sol3/papers.cfm?abstract_id=99580, https://www.sciencedirect.com/science/article/abs/pii/0304405X9090011N
3 https://www.alumni.hbs.edu/stories/Pages/story-bulletin.aspx?num=4928
4 See https://www.sciencedirect.com/science/article/abs/pii/S0304405X99000033 and https://hbr.org/2003/11/how-much-cash-does-your-company-need
5 See https://rapport.bio/all-stories/time-to-reboot-biotech
6 One can liken the biotech ecosystem to Garrison Keillor's Lake Wobegon where all the children are above average.
7 See https://a16z.com/andy/

The Option to Partially Return Capital

- In a partial return of capital, shareholders are offered the chance to cash in their shares at a set value or within a value range.
- The company undertaking the return of capital transaction gives shareholders the option of sticking with a specific business plan or taking their stock back.
- Examples of companies that have effectively used partial return of capital to allow orderly shareholder exit while others stay in include Adimab, Corcept, DaVita, Royalty Pharma and Xbiotech.
- The benefit of a partial recap versus letting shareholders sell on the open market is much less negative pressure on the share price.



Recent Examples of Self-Tender Offers in the Pharma Industry

Self tender offers are rare. Incyte's deal is by far the largest in recent memory. Looking back decades, Incyte's deal is the third largest in the history of the pharma industry. In 2011, Amgen used a Dutch self-tender to repurchase $5 billion in stock and in 2007 Biogen used a self-tender to repurchase $3 billion in stock.

Item	Incyte	Cipher Pharma	Pasithea Tx	Xbiotech	PharmaCyte	Corcept
Date	May 13, 2024	Sep 5, 2023	July 20, 2023	May 17, 2023	May 11, 2023	July 6, 2021
Percent Buyback	12%	5.1%	21.9%	62%	46%	6%
Cash Predeal	$3.9 billion	$40 million	$26.9 million	$205 million	$68 million	$363 million
Dollar Amount	Up to $1.67 billion	$4 million	$4 million	$80 million	$26.3 million	$145 million
Deal Format	Dutch Auction Self Tender	Dutch Auction Self Tender	Fixed Price Self Tender Offer	Dutch Auction Self Tender	Fixed Price Self Tender	Dutch Auction Self Tender

Source: Stifel research and CapitalIQ.

Illustration of a Partial Return of Capital via Self-Tender

XBiotech
Next Generation Antibody Therapy

XBiotech Commences Tender Offer to Purchase up to $420,000,000 of its Shares

January 14, 2020

AUSTIN, Texas, Jan. 14, 2020 (GLOBE NEWSWIRE) -- XBiotech Inc. (NASDAQ: XBIT) ("XBiotech") announced today that it commenced a "modified Dutch auction" tender offer to purchase up to $420,000,000 of its common shares, or such lesser number of common shares as are properly tendered and not properly withdrawn, at a price not less than $30.00 nor greater than $33.00 per common share, to the seller in cash, less any applicable withholding taxes and without interest (the "Offer"). The Offer is made upon the terms and subject to the conditions described in the offer to purchase and in the related letter of transmittal. The closing price of XBiotech's common shares on the NASDAQ Global Select Market on January 13, 2020, the last full trading day before the commencement of the Offer, was $18.62 per share. The Offer is scheduled to expire at 5:00 p.m., New York City time, on February 12, 2020, unless the Offer is extended.

XBiotech believes that the Offer represents an efficient mechanism to provide XBiotech's stockholders with the opportunity to tender all or a portion of their stock and thereby receive a return of some or all of their investment in XBiotech if they so elect. The Offer provides stockholders with an opportunity to obtain liquidity with respect to all or a portion of their stock without the potential disruption to XBiotech's stock price.

The Offer is not contingent upon obtaining any financing. However, the Offer is subject to a number of other terms and conditions, which are described in detail in the offer to purchase. Specific instructions and a complete explanation of the terms and conditions of the Offer will be contained in the offer to purchase, the letter of transmittal and the related materials, which will be mailed to stockholders of record shortly after commencement of the Offer.

None of XBiotech, the members of its Board of Directors (including the Independent Committee who authorized the Offer), the information agent or the depositary makes any recommendation as to whether any stockholder should participate or refrain from participating in the Offer or as to the price or prices at which stockholders may choose to tender their shares in the Offer.

D.F. King & Co., Inc. will serve as information agent for the Offer. Stockholders with questions, or who would like to receive additional copies of the Offer documents may call D.F. King at (212) 269-5550 (banks and brokers) or (866) 856-3065 (all others).

XBiotech
Next Generation Antibody Therapy

XBiotech Announces Final Results of Tender Offer

February 19, 2020

AUSTIN, Texas, Feb. 19, 2020 (GLOBE NEWSWIRE) -- XBiotech Inc. (NASDAQ: XBIT) ("XBiotech") today announced the final results of its "modified Dutch auction" tender offer, which expired at 5:00 p.m., New York City time, on February 12, 2020.

Based on the final count by American Stock Transfer & Trust Co., LLC, the depositary for the tender offer, a total of 40,007,286 common shares, no par value, were properly tendered and not properly withdrawn at or below the maximum purchase price of $33.00 per share. Not all shares tendered through notice of guaranteed delivery were delivered within the required settlement period.

XBiotech has accepted for purchase 14,000,000 common shares at a price of $30.00 per share, for an aggregate cost of approximately $420 million, excluding fees and expenses relating to the tender offer. These shares represent approximately 32.67 percent of the common shares outstanding. The final proration factor for shares that XBiotech has purchased pursuant to the tender offer is approximately 33.25 percent.

To assist shareholders in determining the tax consequences of the tender offer, XBiotech estimates that for purposes of the Income Tax Act (Canada), the paid-up capital per common share was approximately C$8.45 and the "specified amount" (for purposes of subsection 191(4) of the Income Tax Act (Canada)) was C$28.90 as of February 18, 2020. In addition, for purposes of the Income Tax Act (Canada) and any applicable provincial legislation pertaining to eligible dividends, XBiotech designates the entire amount of the deemed dividend arising from its purchase of shares pursuant to the tender offer as an eligible dividend.

Shareholders who have questions or would like additional information about the tender offer may contact the information agent for the tender offer, D.F. King & Co., Inc., at (212) 269-5550 (banks and brokers) or (866) 856-3065 (all others).

XBiotech could have used its excess cash to grow its pipeline or fund some type of acquisition. Instead, it chose to return cash to shareholders. Despite a very challenging biotech environment, XBiotech shareholders have had a very strong performance since the company went public. Most of the return has been realized because of the return of capital in the self-tender transaction.

Mechanics of a Self-Tender Offer

- A self-tender offers several advantages over an open-market repurchase program:
  - Allows a large share repurchase to be accomplished much more quickly
  - Eliminates the price risk of an open-market repurchase program since it is achieved at a single fixed price
  - Has a greater market impact since it is a more visible mechanism
- Self-tender offers can be done on either a fixed-price basis, where the issuer tenders for shares at a fixed price, or a Dutch auction basis
- With a Dutch Auction self-tender, the issuer sets a price range. Then shareholders are invited to tender all or a portion of their shares at any price within the range.

- The Company will repurchase shares at the lowest price in the range that results in the acceptance of the maximum number of shares that the company is seeking to repurchase.
- The mechanics of the two self-tender methods are almost identical. However, a Dutch auction offers the issuer several advantages:
  - Creates flexibility as to the price at which the repurchase is made by offering a price range.
  - Allows the issuer to find shareholders willing to sell at the lowest price.*
  - The price range reduces the risk of overpricing the repurchase while increasing the chance of success.
  - Shareholders often view the Dutch auction as being a fairer process. In effect, the market sets the tender price in a Dutch auction, whereas the issuer sets a single tender price in a fixed price process.

* See Laurie Bagwell, "Dutch Auction Share Repurchases: An Analysis of Shareholder Heterogeneity," *Journal of Finance*, 1992, pp. 71-105.

Signaling Value of Self-Tenders

A significant stock buyback sends a message that management believes their stock to be undervalued.

What gets communicated:

- Exciting growth opportunities
- Future value potential
- Shareowner orientation

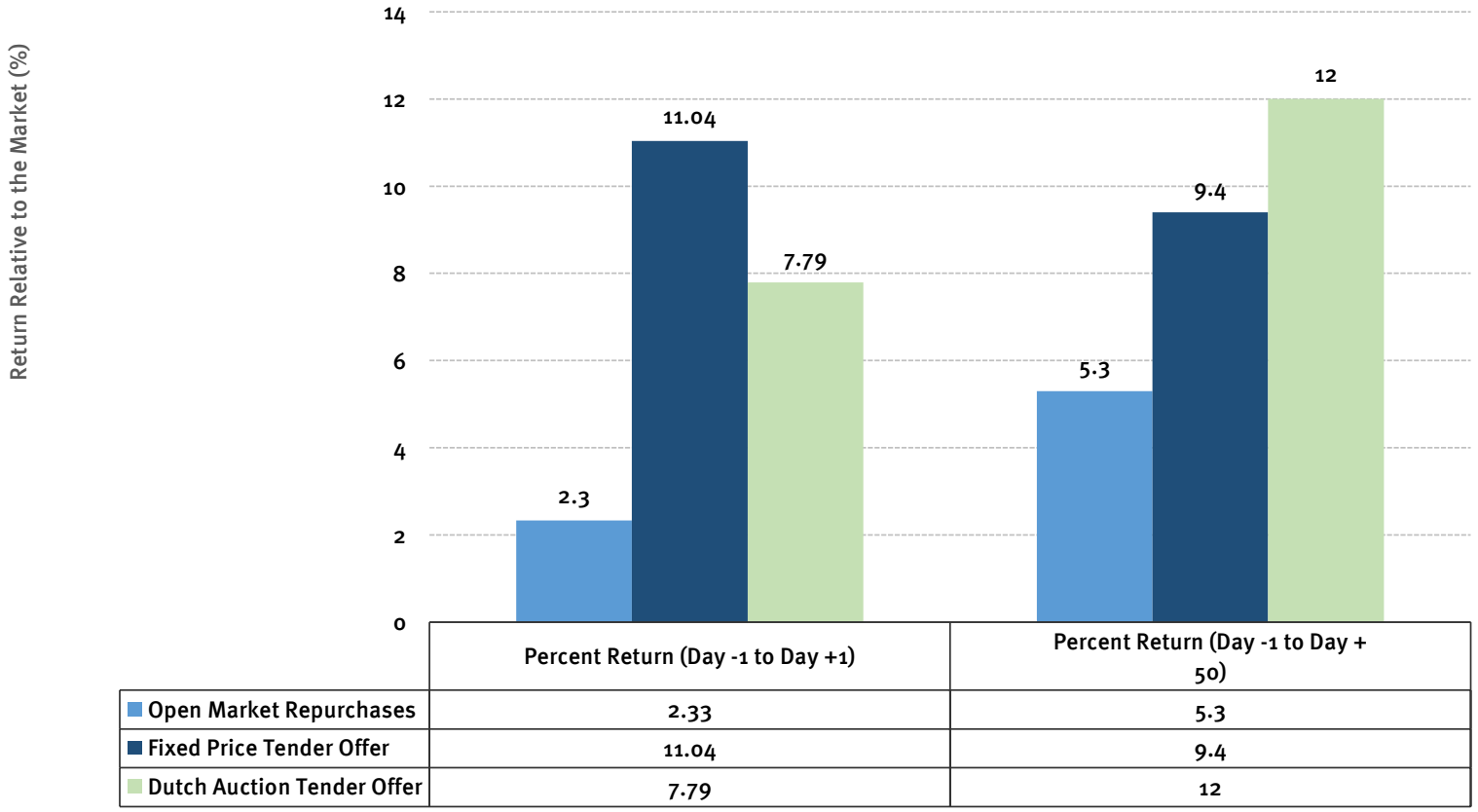
Research strongly supports the idea that buybacks are an effective signaling tool.

- Vermaelen (1981) finds that Dutch Auction tenders results appear to reflect market signals.
- Lie and McConnell (1998) find that earnings improve, on average, after self-tenders (both Dutch Auction and fixed). This is consistent with signaling explanations.
- D'Mello and Shroff (2000) find that undervalued companies are most likely to use Dutch Auction self-tenders.

See Erik Lie and John McConnell, "Earnings signals in fixed-price and Dutch auction self-tender offers," *Journal of Financial Economics* 49, 1998, pp. 161-186; Ranjan D'Mello and Pervin Shroff, "Equity Undervaluation and Decisions Related to Repurchase Tender Offers: An Empirical Investigation," *Journal of Finance* 55, Oct 2000, pp. 2399-2424 and Vermaelen, T. (1981). 'Common Stock Repurchases and Market Signaling: An Empirical Study', *Journal of Financial Economics*, Vol. 9, No. 2, pp. 139-183.

Repurchase Announcement Reaction Stratified by Type of Repurchase: Comment and Jarrell Study

Average Net of Market Return Surrounding Repurchase Announcement (Day o)



	Percent Return (Day -1 to Day +1)	Percent Return (Day -1 to Day + 50)
Open Market Repurchases	2.33	5.3
Fixed Price Tender Offer	11.04	9.4
Dutch Auction Tender Offer	7.79	12

The market reacts positively to all types of repurchases but reacts most positively to self-tender offers.

The market price, on average, rises by 7.79% in the three days surrounding a Dutch Auction tender announcement. While this is somewhat less than that seen for fixed price tenders, Dutch Auctions produce the strongest average result in the long run. By business day 50 after a tender, Dutch Auction companies have a 12% return above the market where fixed price firms have a 9.4% return above the market.

Source: Robert Comment and Gregg Jarrell, 1991, The Relative Signaling Power of Dutch-Auction and Fixed-Price Self-Tender Offers and Open-Market Share Repurchases, *Journal of Finance*, 1991.

Comparison: Special Dividends

An alternative to a self-tender would be to pay a special dividend to all shareholders.

This has the benefit of administrative simplicity but the cost that all shareholders receive a dividend whether they want it or not.

Special dividends are well suited to situations where there is little reason for shareholders to bet on future operations and the company simply wishes to pay out cash.

A relevant case study of how to use special dividends involves the situation of Merrimack Pharmaceuticals. The company experienced a series of clinical failures with its pipeline and decided to liquidate all assets, terminate all employees, pay off all debt and pay out special dividends. While it could have chosen to delist, Merrimack has stayed public on the NASDAQ and still files its reports with the SEC. This allows shareholders to still achieve liquidity should they choose. After selling ONIVYDE® to Ipsen, Merrimack paid a $140mm special dividend in 2017. In 2019, Merrimack paid an additional $20mm special dividend. The company has been successful in achieving quite a few additional small asset sales and deals such that it has an increasing cash balance and no meaningful debt. Following a recent payment from Ipsen, the Board of Directors declared a liquidating cash dividend in the amount of $15.10 per share. The dividend was paid last week (May 17, 2024) and Merrimack will delist next week.

Recent Examples of Biotech Special Dividends

Item	Graphite Bio	LianBio	Sesen Bio	Yumanity	BioNTech	Xbiotech
Date	Mar 8, 2024	Feb 13, 2024	Feb 28, 2023	Dec 5, 2022	Mar 30, 2022	July 6, 2021
Activist Present?	No	Yes	Yes	No	No	No
Amount of Special Dividend ($ millions)	$60	$528	$75	$15	$500	$75
Rationale for one time dividend	Partial return of capital associated with Lenz merger.	This was a liquidating dividend associated with company shut down.	Settlement with activist as part of Carisma reverse merger	Return proceeds of Janssen asset sale concurrently with Kineta reverse merger	Return part of Covid-19 profits. Also announced $1.5bn buyback.	Return part of proceeds of Janssen deal.

Source: Stifel research.

Industry News

Lab-Testing Startups Brace for FDA Rule Change

Brian Gormley, *WSJ Pro*, May 16, 2024 (excerpt)

A move to increase regulation of laboratory tests will raise the cost of developing these diagnostics and narrow the pool of venture capitalists willing to finance them, some investors and entrepreneurs said.

Diagnostics is a difficult market to raise venture capital in because relatively few venture firms have a heavy focus on the sector, said Oriana Papin-Zoghbi, co-founder and chief executive of AOA Dx, a startup developing a test for early ovarian cancer detection that disclosed a $17 million venture financing in October. Most firms that invest in diagnostics are generalists, she said.

Startups tapping advances in genomics and other fields have launched laboratory-developed tests, or LDTs, for cancer and other diseases. For decades, the Food and Drug Administration applied a light touch, saying it had authority to regulate these tests, but usually didn't, a policy it calls enforcement discretion.

Rule changes

That will change under a rule, proposed in late 2023, that became final in April. Citing concerns about LDTs that deliver inaccurate results, or don't perform as well as FDA-authorized tests, the agency plans to require lab-developed tests to be FDA authorized. It plans to phase out its general enforcement-discretion approach to LDTs over four years.

The rule makes exceptions, including for tests that were on the market before the final ruling. In these cases, the agency said it would continue its enforcement-discretion policy.

Lab-developed tests were once considered to be of lower risk and were more narrowly applied. But today they are used widely and for broader populations, the FDA said in April, noting that the agency is aware of examples of LDTs that caused or may have caused patient harm, including tests used to select cancer treatments and aid the management of patients with rare diseases.

Source: https://www.wsj.com/articles/lab-testing-startups-brace-for-fda-rule-change-693a4b38

Bayer Details Layoffs as Company Shake-up Continues

Delilah Alvarado, *Biopharma Dive*, May 14, 2024 (excerpt)

German pharmaceutical company Bayer eliminated 1,500 roles during the first three months of the year as part of a company makeover CEO Bill Anderson promised last year.

Speaking on a first quarter earnings call Tuesday, Anderson said about two-thirds of the 1,500 roles were managerial positions. He did not indicate how many more jobs might be affected in Bayer's ongoing restructuring.

The company listed 98,189 employees at the end of March, down from a count of 99,723 as of December.

Anderson, who joined Bayer as CEO last June, promised a major overhaul of the company after a sluggish year despite prior cost-cutting efforts. Anderson blamed the low performance on the company's levels of bureaucracy and pledged a "radical realignment" of Bayer's internal culture.

Bayer expects to complete the layoffs by the end of 2025 for those in the U.S. Employees in Germany, who have stronger labor protections, will not be officially terminated until the end of 2026.

Source: https://www.biopharmadive.com/news/bayer-layoffs-1500-bureaucracy-restructuring-bill-anderson/716011/

The Medicare Bubble Has Burst

David Wainer, *Wall Street Journal,* May 17, 2024 (excerpt)

For years, the privately run Medicare Advantage business generated outsize profit growth for health-insurance giants.

With hundreds of billions of taxpayer dollars flowing to insurers in a fast-growing market buoyed by aging baby boomers, there was little not to like as far as Wall Street was concerned. Companies like UnitedHealth Group and Humana bet big on the program, and investors generally rewarded them for it. Medicare Advantage, in which the government pays insurers a set amount to manage the care of seniors, recently surpassed traditional Medicare's share of beneficiaries. It was 30% a decade ago.

But the gold rush is over for investors, at least for now. After years of reports, lawsuits and whistleblower accounts accusing big insurers of gaming the system and overcharging the government, the Biden administration has made a series of policy changes that have negatively affected what the plans get paid. Meanwhile, a post-Covid surge in seniors' medical costs caught insurers by surprise.

The high cost of covering seniors is likely a temporary problem for insurers, who get to submit their bids to the Centers for Medicare and Medicaid Services every year. While they are limited in the changes they can make, CVS and others said they are planning to exit some counties and cut back on things such as vision benefits to boost margins.

"The goal for next year is margin over membership," CVS Chief Financial Officer Thomas Cowhey said a a recent conference. "Could we lose up to 10% of our existing Medicare members next year? That's entirely possible." By all indications, other large players such as Humana will also be shifting from growth to profits.

Source: https://www.wsj.com/health/healthcare/the-medicare-bubble-has-burst-141ae3bf

Danish Biotech Says Companies Should Tap into China's 'Impressive Innovation'

Ian Johnston, *Financial Times*, May 16, 2024 (excerpt)

Western pharmaceutical companies need to tap into "mind-bogglingly impressive innovation" in China despite "anti-Chinese sentiment" in US life sciences, the chief executive of Genmab, one of Europe's leading biotech companies, has said.

Jan van de Winkel, head of the DKK132bn ($19bn) Danish biotech that recently announced its first acquisition by buying a US-Chinese drugmaker, said pharma groups could not ignore Chinese biotechs that "are growing very, very rapidly with the government there investing massive amounts of money".

His comments come as US legislation seeking to restrict key Chinese contract manufacturers from working with pharma companies makes its way through Congress, even as their appetite for acquiring biotechs or signing deals to develop Chinese-designed drugs appears undimmed, thanks to high innovation and attractive prices.

AstraZeneca acquired Chinese company Gracell Biotechnologies in December for $1.2bn, and GSK has signed two licensing deals with cancer drugmaker Hansoh Pharma worth about $1.5bn each.

ProfoundBio, the company Genmab acquired for $1.8bn, is based between Suzhou and Washington state, with its research taking place in the Chinese city's BioBay complex, a vast state-backed sciences park. Van de Winkel, who recently visited the site, said: "It's like a new industrial revolution in biotech and life sciences. All the major companies are there and I don't think it's something to be scared of."

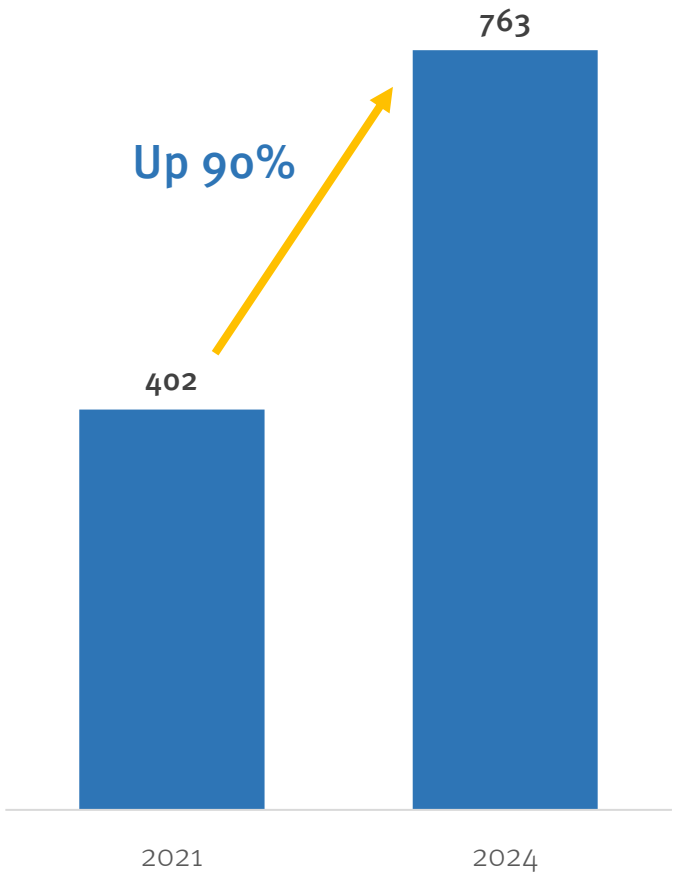
Jan van de Winkel
Chief Executive Officer
Genmab

Source: https://www.ft.com/content/2f3caeee-ff64-47eb-b00e-6568ad1f1858

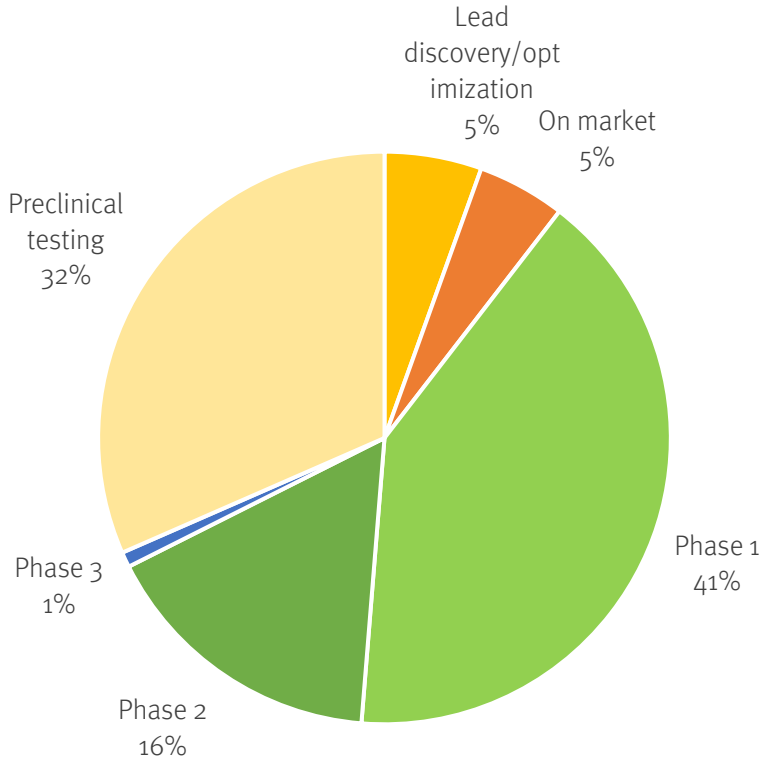
What Direction is China Innovation Headed In?

The number of China-sourced assets available for licensure has grown massively. Assets are largely clinical stage biologics.

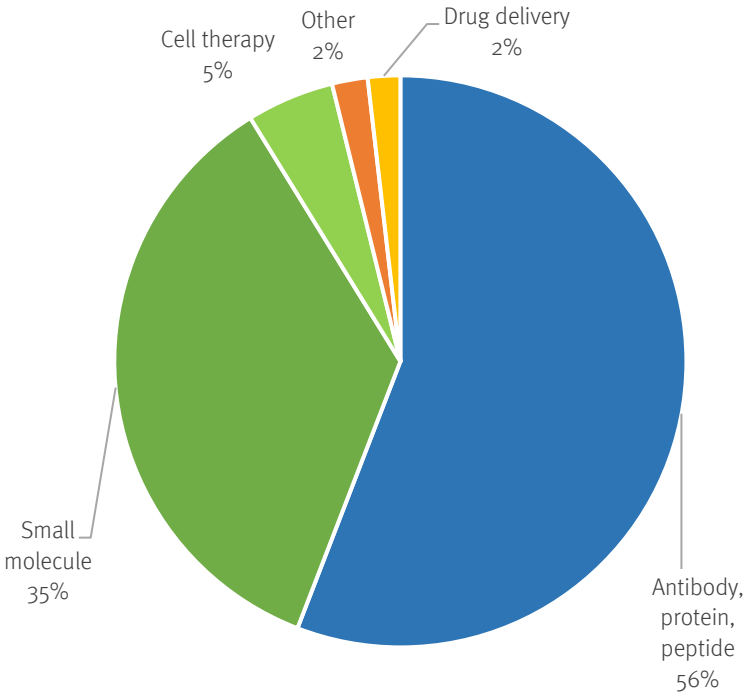
Number of China Sourced Pharmaceutical Assets on BIO Partnering System, 2021 to 2024



Chinese Assets for Licensure at BIO 2024 by Stage of Development (N=763)



Chinese Assets for Licensure at BIO 2024 by Modality(N=546)



Source: BIO Partnering System, 2021 and 2024

CDC Watching Monkeypox Variant

Alice Park, *Time*, May 17, 2024 (excerpt)

Cases of a new group of mpox viruses are rising, potentially posing a risk to people around the world, according to health officials at the U.S. Centers for Disease Control and Prevention (CDC).

So far, the cases have been centered in the Democratic Republic of Congo (DRC) and have not spread beyond Central African countries where the virus remains endemic, the CDC wrote in a report on May 16. But health officials are concerned because this group of viruses—known as clade I mpox viruses—is known to cause more severe illness than the clade II viruses responsible for the previous mpox outbreaks in 2022, which originated in Nigeria. Clade I mpox viruses have a higher fatality rate—killing anywhere from 1.4% to more than 10% of infected people—than clade II, which has a 0.1% to 3.6% mortality rate.

The 2022 outbreaks spread primarily through sexual contact among men who have sex with men. An effective, two-dose vaccine helped to protect these higher risk groups and kept the infections from expanding into an epidemic. (The current vaccine also works against the latest clade I viruses.)

But with a recent increase in global travel, health officials are watching for spread of the latest clade I viruses outside of the regions where it is endemic. According to the CDC report, health officials in DRC reported that clade I infections were reported in 25 of 26 provinces of the country, and that young people were the hardest hit: 67% of cases and 78% of deaths occurred in people 15 years or younger. The virus can cause more severe disease in those with weakened or compromised immune systems."

Source: https://time.com/6979046/mpox-outbreak-africa-vaccine/

Beyond the Pandemic: The Next Chapter of Innovation in Vaccines

Adam Sabow, Jennifer Heller, Michael Conway, and Rosa Poetes, *McKinsey*, May 16, 2024 (excerpt)

Vaccines are vital to global health, saving millions of lives each year. The COVID-19 pandemic underscored their importance, with more than 20 million lives saved in the first year of vaccine deployment alone. This achievement was fueled by an unprecedented acceleration in innovation, with multiple COVID-19 vaccine candidates developed and launched within roughly one year, a process that historically has taken a decade on average.

This level of activity was dramatically different from what we saw in our 2019 analysis, which revealed signs that the vaccine innovation engine had begun to sputter. While the two decades preceding the pandemic saw strong growth in the vaccine industry—with pipelines doubling and annual growth rates of 12 to 15 percent—we identified four indicators of stagnation in 2019: slowing revenue growth (only 5 percent across the industry over the previous five years), a flattening development pipeline, higher attrition rates for vaccines compared with other biologics, and limited progress targeting disease areas of high unmet need, particularly those endemic to low- and middle-income countries (LMICs).

At that time, we highlighted opportunities to reinvigorate vaccine innovation across six major vaccine archetypes (Exhibit 1) by addressing commercial and technical obstacles and advocated for a comprehensive and shared approach among the relevant stakeholders, including manufacturers, governments, academia, research centers, and the private sector.

Innovation is needed across all major vaccine archetypes.

6 archetypes of infectious disease vaccines

	Seasonal limitations[1]	Residual unmet needs[2]	Persisting global threats	Potential outbreaks	Neglected diseases	Nosocomial challenges
Overview	Vaccines targeting pathogens with strains that evolve each season	Improvement to existing vaccines to address unmet needs (including both efficacy limitations and inadequate coverage)	Vaccines targeting high-burden diseases with large potential-patient pools	Vaccines targeting pathogens that have the potential to cause outbreaks	Vaccines targeting historically neglected diseases that disproportionately affect individuals in low- and middle-income countries	Vaccines targeting health-care-acquired infections with larger burden in high-income markets
Profile	◆High commercial potential ◆Moderate technical feasibility	◆Uncertain commercial potential, especially on price ◆Moderate technical feasibility	◆High commercial potential: large burden of disease and potential-patient pools ◆Moderately low technical feasibility	◆Uncertain commercial potential: unclear reliability and scale ◆Moderately low technical feasibility	◆Very low commercial potential ◆Moderately low technical feasibility	◆Moderately high commercial potential but unclear commercial model/indication ◆Moderate technical feasibility
Examples	◆COVID-19 ◆Influenza	◆Malaria ◆Meningitis ◆Pneumococcal ◆Rotavirus ◆Ebola ◆HPV[3] ◆Measles	◆RSV[4] ◆CMV[5] ◆HIV/AIDS ◆Herpes simplex virus ◆Hepatitis C ◆Tuberculosis	◆Chikungunya ◆Marburg virus ◆Middle East respiratory syndrome ◆Hemorrhagic fever	◆Lassa fever ◆Leishmaniasis ◆Schistosomiasis	◆E. coli ◆Norovirus ◆C. difficile ◆Staphylococcus

[1]Strains that evolve each season. [2]Includes both efficacy limitations (level of effectiveness, incomplete strain coverage, limited duration of protection) and inadequate coverage (includes policies or complexities in immunization strategies such as multidose courses). [3]Human papillomavirus. [4]Respiratory syncytial virus. [5]Cytomegalovirus.

Source: https://www.mckinsey.com/industries/life-sciences/our-insights/beyond-the-pandemic-the-next-chapter-of-innovation-in-vaccines

McKinsey & Company

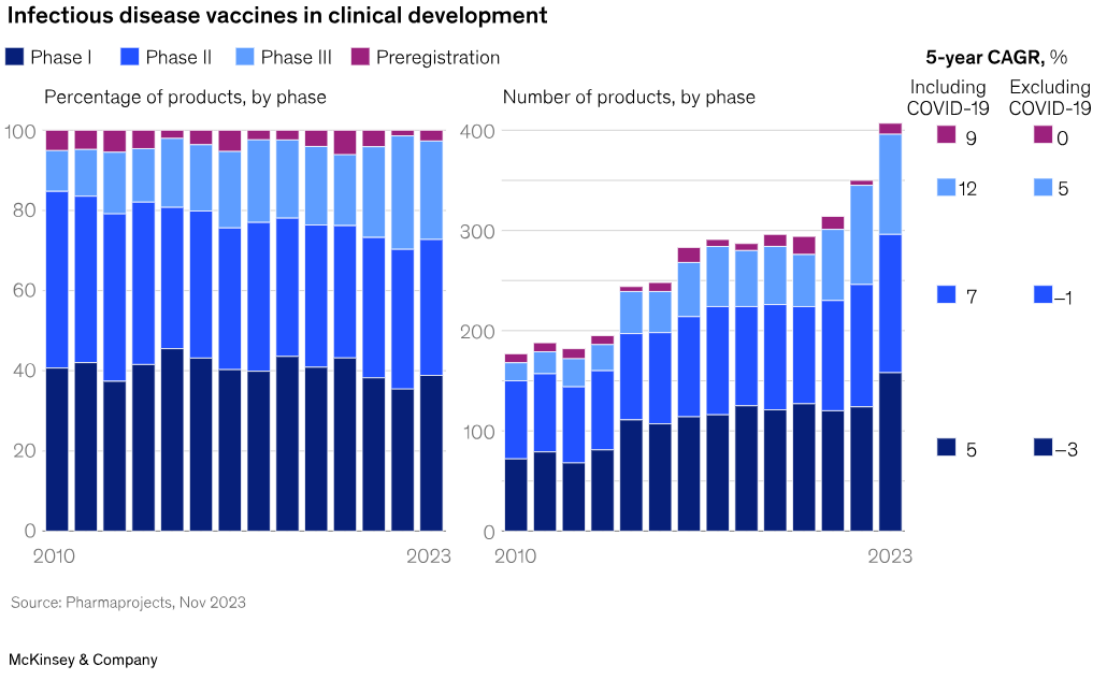
McKinsey on Vaccines (continued)

Now, roughly three years after the surge of innovation spurred by the pandemic, the vaccine industry faces another critical juncture. Despite accelerated vaccine innovation for certain diseases, progress remains uneven, and significant unmet needs persist. This article explores how the pandemic transformed the business case for vaccines. It proposes five actions the vaccine ecosystem can take to harness the pandemic-driven momentum to accelerate vaccine innovation more broadly and to tackle global health challenges more effectively.

The rapid development of COVID-19 vaccines was propelled by multiple factors, including enhanced funding, operational efficiency, technological advancements, and regulatory flexibility. The COVID-19 innovation model has spurred advancements in other areas, particularly in respiratory diseases, which saw ten launches in the United States alone from 2020 to 2023 (up from three between 2016 and 2019). In the past several years, multiple vaccines targeting diseases that primarily affect LMICs, such as dengue and chikungunya, have also been approved by the US Food and Drug Administration (FDA). The vaccine development pipeline has also seen a rise in Phase III candidates (Exhibit 2), which include two meningitis vaccines, a possible human cytomegalovirus (CMV) vaccine, and a promising vaccine against invasive pneumococcal disease in adults.

The overall vaccine development timeline is also compressing (Exhibit 3). Although not as rapid as the unprecedented COVID-19 timeline, which was roughly one year, respiratory syncytial virus (RSV) vaccines have been developed within a three- to five-year time frame (the start of clinical development through regulatory approval), a pace significantly quicker than historical norms. Other vaccine types that are also moving relatively quickly through the clinical phases include Moderna's messenger ribonucleic acid (mRNA) combination vaccine candidate for RSV and seasonal influenza, which is on a three- to four-year projected development timeline.

The pipeline for infectious disease vaccines shows a growing share of late-stage candidates, suggesting an increase in impending launches.



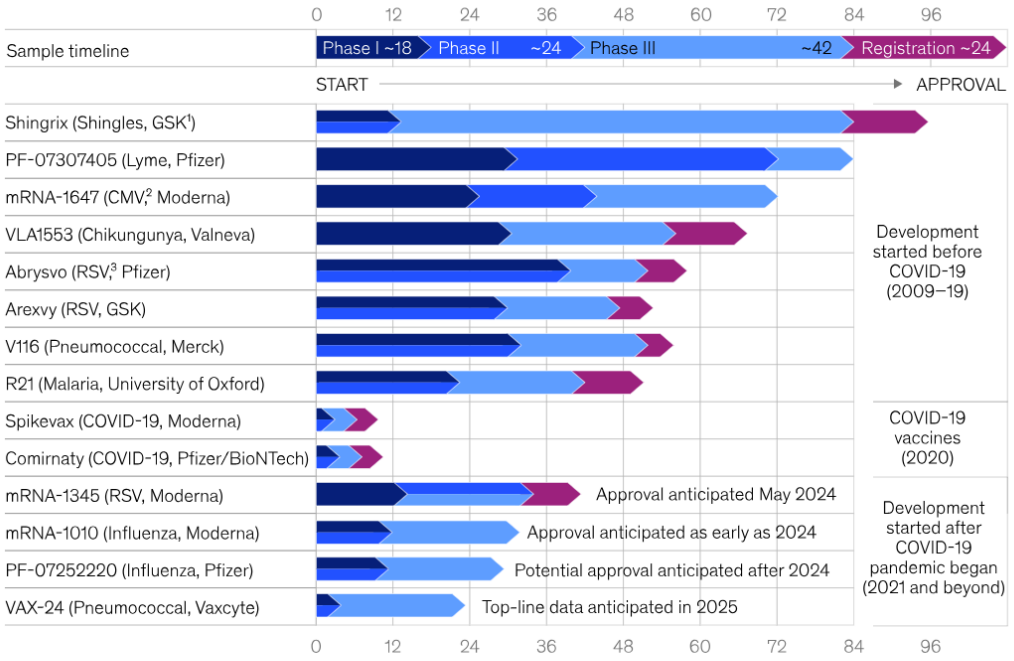
Source: https://www.mckinsey.com/industries/life-sciences/our-insights/beyond-the-pandemic-the-next-chapter-of-innovation-in-vaccines

McKinsey on Vaccines (continued)

Exhibit 3

Vaccine development has accelerated since the innovation surge spurred by the pandemic.

Clinical-development timeline for select infectious disease vaccines, months



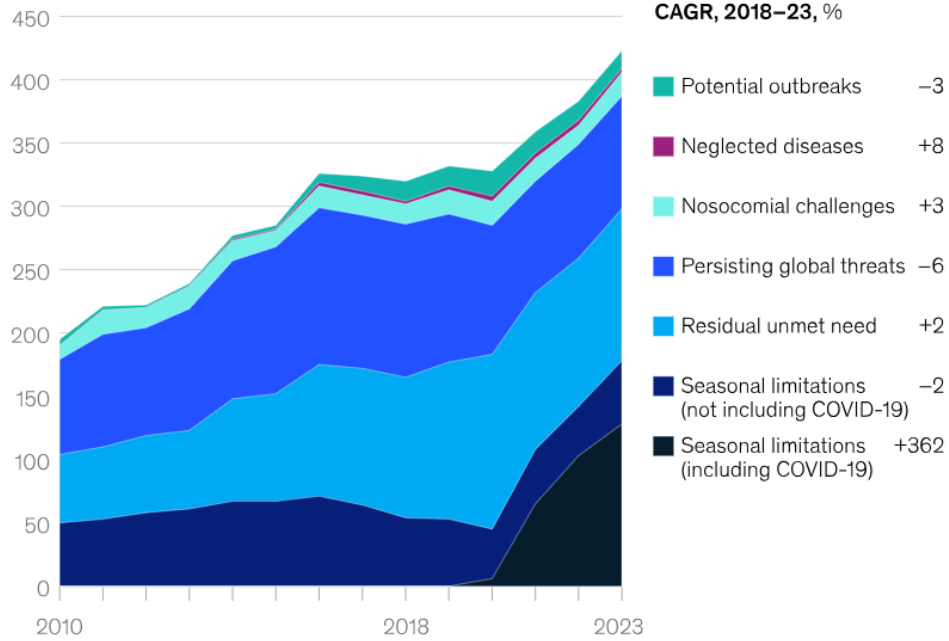
[1]GlaxoSmithKline. [2]Cytomegalovirus. [3]Respiratory syncytial virus.
Source: Company press releases and public announcements

McKinsey & Company

Exhibit 5

With the exception of COVID-19 assets, the number of vaccine programs for infectious diseases has remained largely flat.

Infectious disease vaccines in development globally, by archetype of vaccine innovation, number of products (Phase I to preregistration)



Source: Pharmaprojects, Nov 2023

McKinsey & Company

Source: https://www.mckinsey.com/industries/life-sciences/our-insights/beyond-the-pandemic-the-next-chapter-of-innovation-in-vaccines

Bayer's Elinzanetant Significantly Reduces Hot Flashes Associated with Menopause

Bayer Press Release, Berlin, May 16, 2024

Pivotal OASIS 1 and 2 Phase III studies of investigational compound elinzanetant achieved a statistically significant reduction in frequency and severity of vasomotor symptoms (VMS; also known as hot flashes) over 12 weeks compared to placebo. Consistent benefits were also seen across both studies in all three key secondary endpoints, with significant reduction in frequency of VMS at week 1, improvement in sleep disturbances and menopause-related quality of life. The safety profile in both studies was favorable. These late-breaking data will be presented for the first time during a scientific symposium at the 2024 American College of Obstetricians and Gynecologists (ACOG) annual meeting

Elinzanetant successfully met all four primary endpoints in both studies demonstrating statistically significant reductions in the frequency and severity of moderate to severe VMS from baseline to week 4 and 12 compared to placebo. **Elinzanetant showed in OASIS 1 significant mean reductions versus placebo for frequency at week 4 with -3.29 ($p<0.0001$) and week 12 with -3.22 ($p<0.0001$) and for severity at week 4 with -0.33 ($p<0.0001$) and week 12 with -0.40 ($p<0.0001$).** In OASIS 2, elinzanetant demonstrated significant mean reductions versus placebo for frequency at week 4 with -3.04 ($p<0.0001$) and at week 12 with -3.24 ($p<0.0001$) and for severity at week 4 with -0.22 ($p=0.0003$) and at week 12 with -0.29 ($p<0.0001$). The safety profile of elinzanetant was favorable in both studies with headache and fatigue being the most frequent treatment emergent adverse events (TEAEs) within the elinzanetant groups.

These study results are quite strong and provide both patients and Bayer with good news at a time that it is needed. It will be interesting to see how Bayer's elizanetant compares clinically to Astellas' competing NK3, fezolinetant (VEOZAH®).

Source: https://www.bayer.com/media/en-us/elinzanetant-significantly-reduces-frequency-and-severity-of-moderate-to-severe-hot-flashes-associated-with-menopause/

Halle Berry Gets Behind Legislation on Menopause Research

Amanda Seitz, AP News, May 2, 2024 (excerpt)

WASHINGTON (AP) — Halle Berry is joining a group of bipartisan senators to push for legislation that would put $275 million toward research and education around menopause, the significant hormone shift women go through in middle age.

The legislation calls for the federal government to spend more on clinical trials on menopause as well as the hormone therapy that is used to treat hot flashes and other symptoms.

Berry, 57, shouted about menopause outside the U.S. Capitol on Thursday. She said it's a word her own doctor told her he was scared to say in front of her.

"I'm in menopause, OK?" Berry yelled, eliciting chuckles from the crowd. "The shame has to be taken out of menopause. We have to talk about this very normal part of our life that happens. Our doctors can't even say the word to us, let alone walk us through the journey."

In recent months, the leading Hollywood actor has been candid about the painful symptoms she experienced while going through perimenopause, which occurs before menopause when a woman's estrogen levels start dropping. Her doctor initially misdiagnosed her with herpes, a sexually transmitted disease that both Berry and her partner tested negative for.

Under a proposal by Democratic Sen. Patty Murray of Washington and Republican Sen. Lisa Murkowski of Alaska, $125 million would be set aside for clinical trials, public health and medical research on menopause. The remaining money would help support menopause detection and diagnosis, train doctors on treating menopause and raising public awareness around it.

Actress Halle Berry

Source: https://apnews.com/article/halle-berry-menopause-8fe88d4fd3d4e81a0ddcbedb12a35e08

Marlena Fejzo, author of recent paper on GDF-15 and severe morning sickness, talks about women's health at a *Time* event last week with Dan Skovronsky, CSO, from Eli Lilly, Halle Berry and Alice Park of *Time*.

See: https://time.com/collection/time100-health/

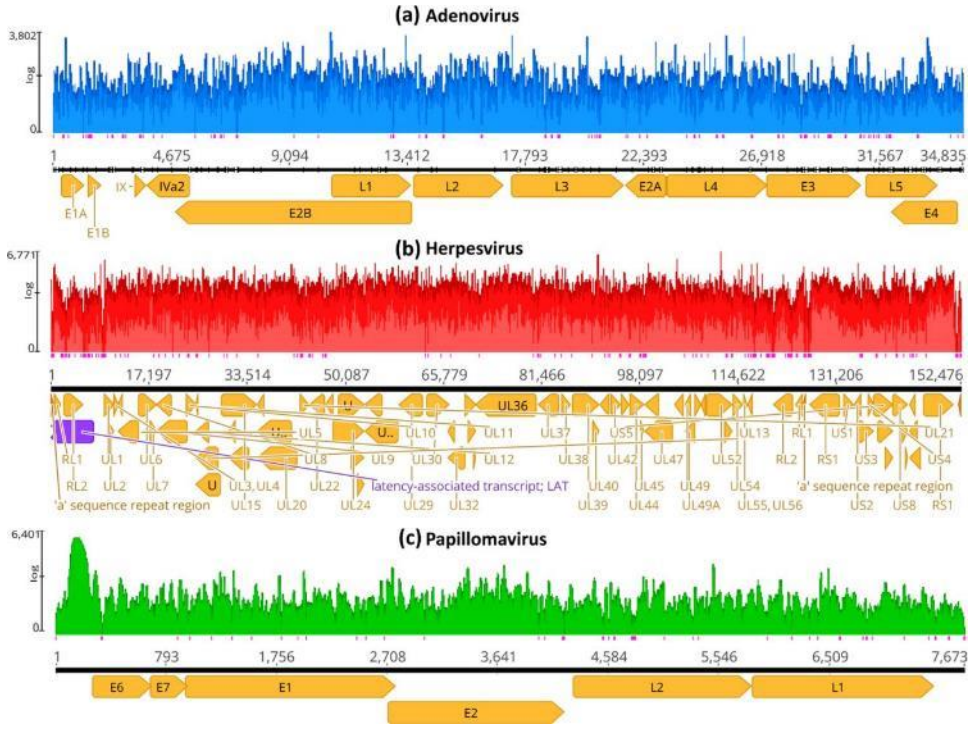
Women's Health, Urology and Nephrology Market Map

Source: PharmaSights. Shows 2023 of products sold by top 40 pharma companies.

The Neanderthals Struggled with Common Cold, HPV and Herpes – Just Like Modern Man

Renata C. Ferreira, Gustavo V. Alves, Marcello Ramon, Fernando Antoneli, Marcelo R. S. Briones, "Reconstructing prehistoric viral genomes from Neanderthal sequencing data," *bioRxiv Preprint*, April 21, 2024

DNA viruses that produce persistent infections have been proposed as potential causes for the extinction of Neanderthals and therefore, the identification of viral genome remnants in Neanderthal sequencing reads is an initial step to address this hypothesis. Here, as proof of concept, we searched for viral remnants in sequencing reads of Neanderthal genome data by mapping to adenovirus, herpesvirus and papillomavirus, which are double stranded DNA viruses that may establish lifelong latency and can, produce persistent infections. The reconstructed ancient viral genomes of adenovirus, herpesvirus and papillomavirus revealed conserved segments, with nucleotide similarity to extant viral genomes, and variable regions in coding regions with substantial divergence to extant close relatives. Sequencing reads mapped to extant viral genomes showed deamination patterns of ancient DNA and that these ancient viral genomes showed divergence consistent with the age of these samples (≈50,000 years) and viral evolutionary rates (10–5 to 10–8 substitutions/site/year). Analysis of random effects shows that the Neanderthal mapping to genomes of extant persistent viruses is above the expected by random similarities of short reads. Also, negative control with a nonpersistent DNA virus does not yield statistically significant assemblies. This work demonstrates the feasibility of identifying viral genome remnants in archaeological samples with signal-to-noise assessment.



Mapping coverage of herpesvirus, papillomavirus and adenovirus using Neanderthal sample derived reads. Reference mapping was done using BBMap [24,25] (https://sourceforge.net/projects/bbmap/). In (a) is the mapping of 180,419 Neanderthal reads (mean coverage 102.2) to adenovirus assembly reference (or template) (KX897164). In (b), the mapping of 1,224,413 reads (mean coverage 171.2) to herpesvirus assembly reference (MN136523). In (c), the mapping of 23,998 Neanderthal reads (mean coverage 115.4) to papillomavirus assembly reference (X74466). Pink vertical bars below the assemblies indicate single strand regions and orange arrows indicate the protein coding genes. The mapping was performed with the same read dataset and these three reference (template) sequences simultaneously, as detailed in Material and Methods, but each depiction shows the corresponding assembly reference sequence of each bam file with the corresponding mapped reads.

Source: https://www.biorxiv.org/content/10.1101/2023.03.16.532919v3.full

Roche CT-388 Obesity Data and Field Update

Roche HQ, Basel Switzerland

Impressive Weight Loss for Roche CT-388

Press Release, Basel, 16 May 2024

Roche announced today positive results from the Phase I clinical trial of CT-388, a dual GLP-1/GIP receptor agonist being developed for the treatment of obesity and type 2 diabetes. The study found that a once-weekly subcutaneous injection of CT-388 over 24 weeks resulted in significant weight loss in healthy adults with obesity compared to placebo. **The weight loss achieved with CT-388 was clinically meaningful, with a mean placebo-adjusted weight loss of 18.8% (p-value < 0.001).** At week 24, 100% of CT-388 treated participants achieved a weight loss of >5%, 85% achieved >10%, 70% achieved >15%, and 45% achieved >20%. The treatment was well tolerated, with mild to moderate gastrointestinal-related adverse events being the most common, consistent with the incretin class of medicines that CT-388 belongs to. All participants with a pre-diabetes status at baseline became normoglycemic after 24 weeks of CT-388 treatment, whereas glycemic status of participants treated with placebo remained largely unchanged during this period.

“We are very pleased to see the significant and clinically meaningful weight loss in people treated with CT-388,” said Levi Garraway, M.D., Ph.D., Roche’s Chief Medical Officer and Head of Global Product Development. “The results are highly encouraging for further development of CT-388 for both obesity and type 2 diabetes and underscore its potential to become a best-in-class therapy with durable weight loss and glucose control.” Obesity is one of the most urgent health challenges in the world with extensive comorbidities, such as type 2 diabetes, cardiovascular diseases, steatohepatitis and chronic kidney disease. Over four billion people - about 50% of the world’s population - are estimated to be impacted by obesity or being overweight by 2035. The growing number puts an incredible strain on societies and healthcare systems around the world.

CT-388 belongs to the class of incretin-based medicines that aim to regulate blood sugar and reduce appetite. It selectively targets and activates two specific receptors in the body, known as GLP-1 and GIP, which integrate nutrient-derived signals to control food intake, energy absorption and assimilation. It is hypothesised that the dual targeting effect of CT-388 could result in a meaningful durable glucose reduction and weight loss, in addition to a favourable safety profile.

Source: https://www.roche.com/media/releases/med-cor-2024-05-16

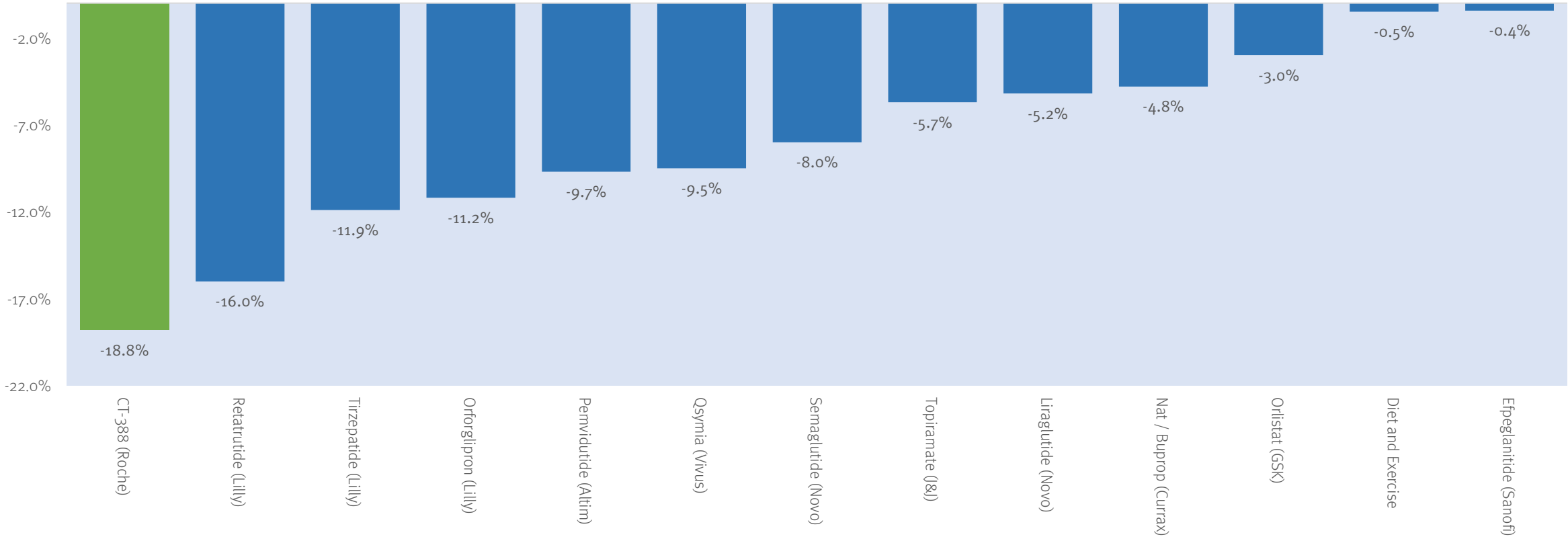

Roche HQ, Basel

Roche Weight Loss Results at 24 Weeks Highly Competitive with Lilly's Retatrutide

To be able to drop 18.8% of body weight with CT-388 in less than a half year is stunning and important therapeutic option for persons who are overweight. Roche is now giving Lilly a run for its money.

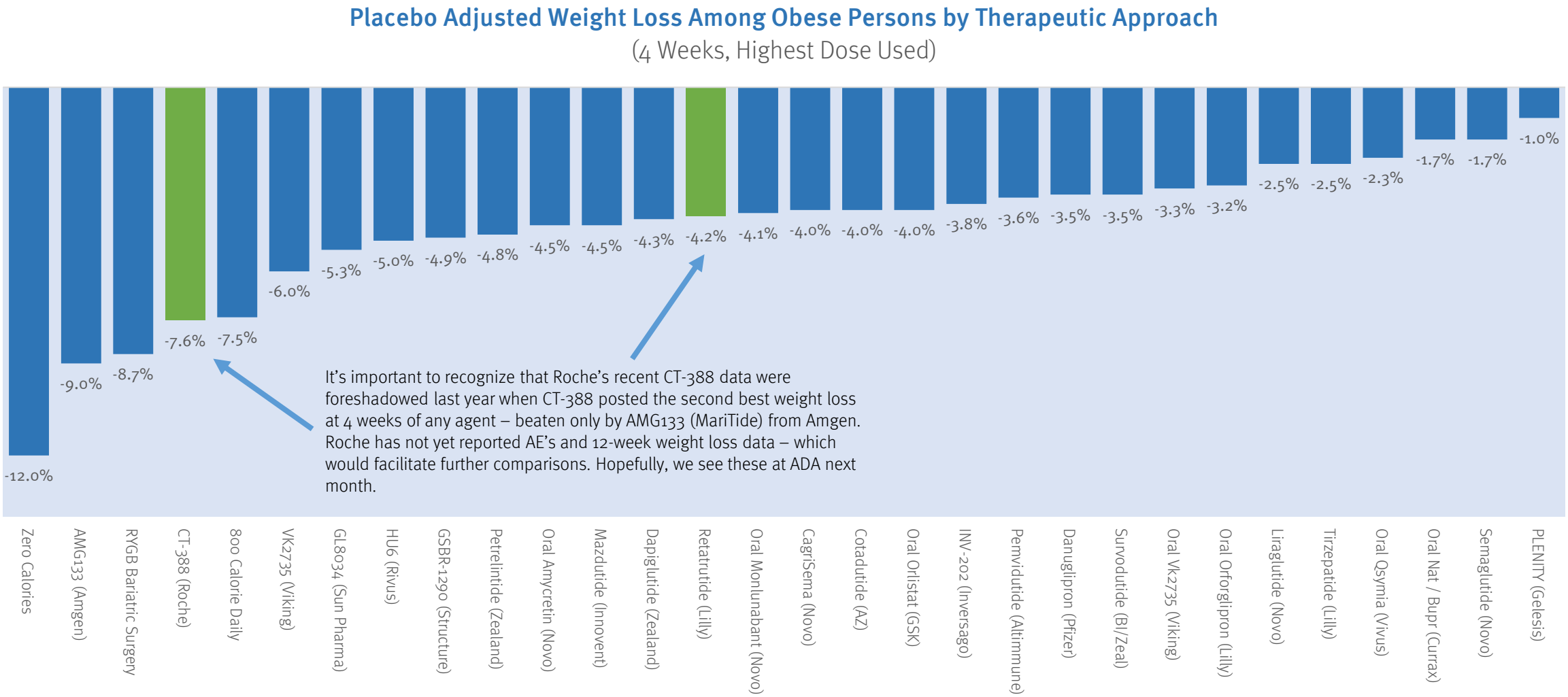
Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach

(24 Weeks, Highest Dose Used)



Source: Stifel analysis of study results for various agents. Note: these results are not from head-to-head studies and patients enrolled could have been different as could have been study protocols, hence comparisons implied here are, at best, indicative of results that could be obtained in actual head-to-head studies. Further, results may be shown from doses that would never be used in the real world.

No Big Surprise in Roche Findings as CT-388 Already Clobbered Retatrutide in 4-Week Study Comparison



Source: Stifel analysis of study results for various agents. Note: these results are not from head-to-head studies and patients enrolled could have been different as could have been study protocols, hence comparisons implied here are, at best, indicative of results that could be obtained in actual head-to-head studies. Further, results may be shown from doses that would never be used in the real world.

Semaglutide Weight Loss Benefit in SELECT Trial Runs for Four+ Years

nature medicine

Article

https://doi.org/10.1038/s41591-024-02996-7

Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial

Received: 1 March 2024

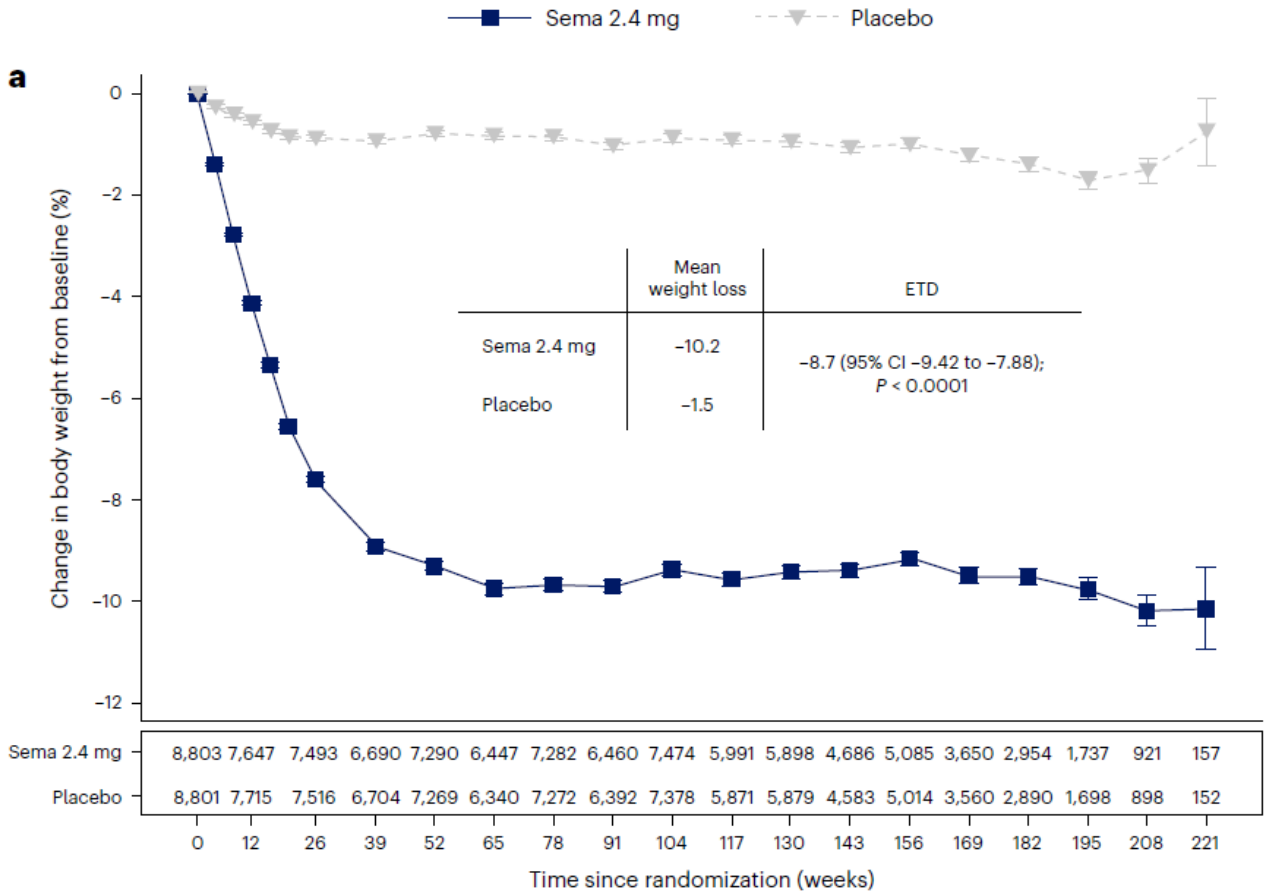
Accepted: 12 April 2024

Published online: 13 May 2024

Check for updates

Donna H. Ryan[1], Ildiko Lingvay[2], John Deanfield[3], Steven E. Kahn[4], Eric Barros[5], Bartolome Burguera[6], Helen M. Colhoun[7], Cintia Cercato[8], Dror Dicker[9], Deborah B. Horn[10], G. Kees Hovingh[5], Ole Kleist Jeppesen[5], Alexander Kokkinos[11], A. Michael Lincoff[12], Sebastian M. Meyhöfer[13], Tugce Kalayci Oral[5], Jorge Plutzky[14], André P. van Beek[15], John P. H. Wilding[16] & Robert F. Kushner[17]

In the SELECT cardiovascular outcomes trial, semaglutide showed a 20% reduction in major adverse cardiovascular events in 17,604 adults with preexisting cardiovascular disease, overweight or obesity, without diabetes. Here in this prespecified analysis, we examined effects of semaglutide on weight and anthropometric outcomes, safety and tolerability by baseline body mass index (BMI). In patients treated with semaglutide, weight loss continued over 65 weeks and was sustained for up to 4 years. At 208 weeks, semaglutide was associated with mean reduction in weight (–10.2%), waist circumference (–7.7 cm) and waist-to-height ratio (–6.9%) versus placebo (–1.5%, –1.3 cm and –1.0%, respectively; P < 0.0001 for all comparisons versus placebo). Clinically meaningful weight loss occurred in both sexes and all races, body sizes and regions.



Source: https://www.nature.com/articles/s41591-024-02996-7

Stunning Paper Last Week Shows that NMDA Antagonists Can Double Effect of GLP-1 on Weight Loss

GLP-1-directed NMDA receptor antagonism for obesity treatment

https://doi.org/10.1038/s41586-024-07419-8

Received: 23 November 2022

Accepted: 12 April 2024

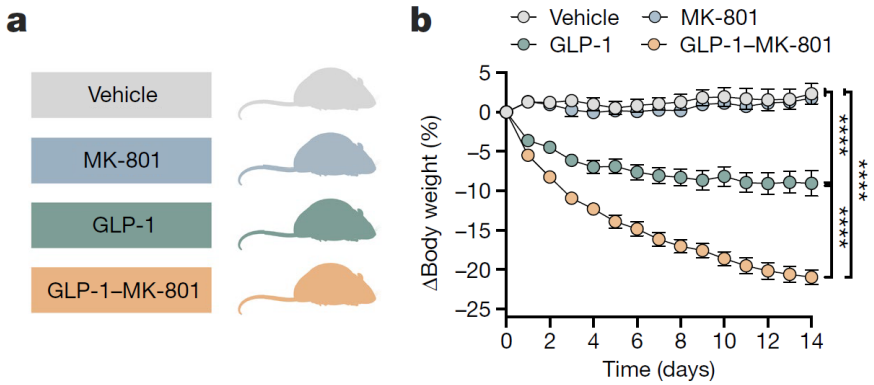
Published online: 15 May 2024

Open access

Check for updates

Jonas Petersen[1,2], Mette Q. Ludwig[1], Vaida Juozaityte[1], Pablo Ranea-Robles[1], Charlotte Svendsen[1], Eunsang Hwang[3], Amalie W. Kristensen[2], Nicole Fadahunsi[1], Jens Lund[1], Alberte W. Breum[1], Cecilie V. Mathiesen[1], Luisa Sachs[1], Roger Moreno-Justicia[1], Rebecca Rohlfs[4], James C. Ford[4], Jonathan D. Douros[4], Brian Finan[4], Bryan Portillo[3], Kyle Grose[3], Jacob E. Petersen[1], Mette Trauelsen[1], Annette Feuchtinger[5], Richard D. DiMarchi[6], Thue W. Schwartz[1], Atul S. Deshmukh[1], Morten B. Thomsen[7], Kristi A. Kohlmeier[2], Kevin W. Williams[3], Tune H. Pers[1], Bente Frølund[2], Kristian Strømgaard[2], Anders B. Klein[1] & Christoffer Clemmensen[1]✉

The *N*-methyl-D-aspartate (NMDA) receptor is a glutamate-activated cation channel that is critical to many processes in the brain. Genome-wide association studies suggest that glutamatergic neurotransmission and NMDA receptor-mediated synaptic plasticity are important for body weight homeostasis[1]. Here we report the engineering and preclinical development of a bimodal molecule that integrates NMDA receptor antagonism with glucagon-like peptide-1 (GLP-1) receptor agonism to effectively reverse obesity, hyperglycaemia and dyslipidaemia in rodent models of metabolic disease. GLP-1-directed delivery of the NMDA receptor antagonist MK-801 affects neuroplasticity in the hypothalamus and brainstem. Importantly, targeting of MK-801 to GLP-1 receptor-expressing brain regions circumvents adverse physiological and behavioural effects associated with MK-801 monotherapy. In summary, our approach demonstrates the feasibility of using peptide-mediated targeting to achieve cell-specific ionotropic receptor modulation and highlights the therapeutic potential of unimolecular mixed GLP-1 receptor agonism and NMDA receptor antagonism for safe and effective obesity treatment.



Mice that were fed at GLP-1 agonist with a NMDA receptor antagonist lost twice as much weight as those fed a GLP-1 agonist alone.

Source: https://www.nature.com/articles/s41586-024-07419-8

GLP-1/NMDA Drug Combo Can Keep Weight Off Even After You Stop Taking It

Emily Price, *Fast Company*, May 17, 2024

A new paper released in *Nature* this week discusses a new therapy for obesity that researchers say leads to more weight loss in mice than existing GLP-1 weight-loss medications, such as Ozempic, Wegovy, and Zepbound, alone.

The medication works a little differently than those injections by specifically smuggling molecules into your brain and changing how it thinks about food. This "Trojan horse" of weight-loss drugs might one day be available for human use.

"I consider the drugs available on the market today as the first generation of weight-loss drugs," says the new study's senior author Christoffer Clemmensen, an associate professor from the Novo Nordisk Foundation Center for Basic Metabolic Research at the University of Copenhagen.

In the group's study, a "Trojan horse" is used to smuggle a molecule into the brain, where it's then able to change the brain's plasticity, ultimately leading to weight loss. The molecule works by blocking a receptor protein called the NMDA receptor.

"The effect of GLP-1 combined with these molecules is very strong," explained Clemmensen. "In some cases, the mice lose twice as much weight as mice treated with GLP-1 only."

Researchers think that by using the drug in the future, patients will potentially be able to get the same effect from GLP-1 medication with a lower dose. They also think that the new drug might work for patients who haven't responded well to drugs like Ozempic, which is name-branded semaglutide; or Monjaro, name-branded tirzepatide.

Researchers say that their drug causes similar side effects to the existing medications; however, since patients will be able to take lower doses to achieve the same results, they may be able to mitigate some of those side effects.

"This family of molecules can have a permanent effect on the brain," said Clemmensen. "Studies have demonstrated that even a relatively infrequent treatment can lead to persistent changes to the brain pathologies. We also see molecular signatures of neuroplasticity in our work, but in this case in the context of weight loss."

Source: https://www.fastcompany.com/91127426/ozempic-wegovy-could-there-be-better-weight-loss-drug

Merck CFO, Caroline Litchfield, Comments on Obesity Drugs Last Week

Caroline Litchfield

We today have a GLP glucagon dual agonist, and we are researching this in NASH. And the data that we have is quite compelling at this stage there was more than 70% liver fat loss for this product, which is superior to what we've seen with other compounds, and there was 10% to 12% weight loss, and that was after, I think, 24 weeks.

So, this is a program we're advancing. And within our company, we have great competency in this area. As we look at the future, our teams are focused in the area of cardiometabolic. We have programs internally beyond MK-624, and we do look externally at the field and the opportunity to see what we can do to bring advancements to patient care.

As we think about obesity, specifically, we do think there's the possibility for second and third waves of innovation, maybe with oral agents, agents that have more tolerability, maybe combination products and maybe products that will have weight loss that is more fat loss, not muscle loss. And it's an area we're focused on. So as a company, we look to build our strength and we will look to invest internally while we'll also evaluate the external landscape.

Caroline Litchfield, ,CFO, Merck

Source: https://seekingalpha.com/article/4693716-merck-and-co-inc-mrk-bofa-securities-2024-health-care-conference-transcript

Bernie Sanders Report Last Week: GLP-1's Could Bankrupt America

United States Senate

HEALTH, EDUCATION, LABOR, AND PENSIONS COMMITTEE

Bernard Sanders, Chair
Majority Staff Report
May 15, 2024

Breaking Point:
How Weight Loss Drugs Could Bankrupt American Health Care

I. Executive Summary

Over the past thirty years, U.S. prescription drug spending has skyrocketed. Spending on prescription drugs jumped from just $47 billion in 1992 to $406 billion in 2022—a 764% increase.[1] Higher prescription drug spending already poses an extraordinary burden on the American people, who are forced to pay higher premiums, taxes, and out-of-pocket costs.

Now, spending on prescription drugs is on the verge of increasing like never before. New drugs for diabetes and weight loss like Novo Nordisk's Ozempic and Wegovy could be potential game changers for the millions of Americans with diabetes and obesity. But these drugs will not do any good for the millions of patients in America who cannot afford them. Further, the outrageously high prices of these drugs have the potential to bankrupt our entire health care system.

Today, Novo Nordisk charges Americans with type 2 diabetes $969 a month for Ozempic, while this same exact drug can be purchased for just $155 in Canada, $122 in Italy, $71 in France, and $59 in Germany. Meanwhile, Novo Nordisk lists Wegovy for $1,349 a month in the U.S. while this same exact product can be purchased for just $186 in Denmark, $137 in Germany and $92 in the United Kingdom.

Novo Nordisk's prices are especially egregious given a recent report from researchers at Yale University that found that these drugs can be profitably manufactured for less than $5 a month.[2]

Nearly half of all American adults are interested in taking weight loss drugs.[3] The U.S. Senate Committee on Health, Education, Labor, and Pensions (HELP Committee) Majority Staff modeled how the emerging class of weight loss drugs—led by Novo Nordisk's Wegovy—could impact prescription drug spending, taking into account estimated manufacturer discounts.

Figure 3: Total retail prescription drug spending from National Health Expenditures data (1992-2022)

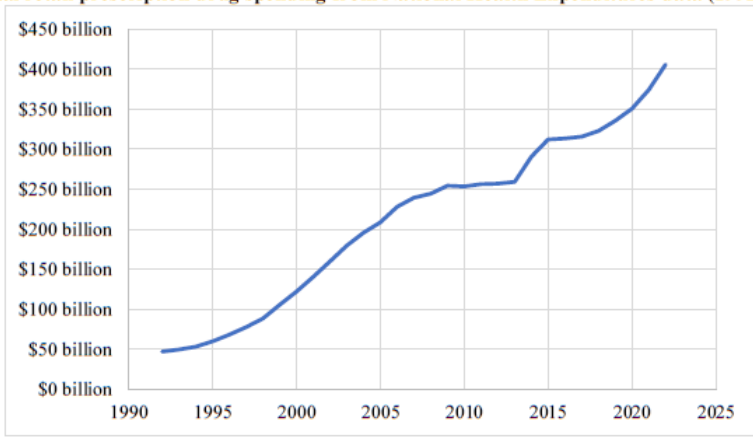
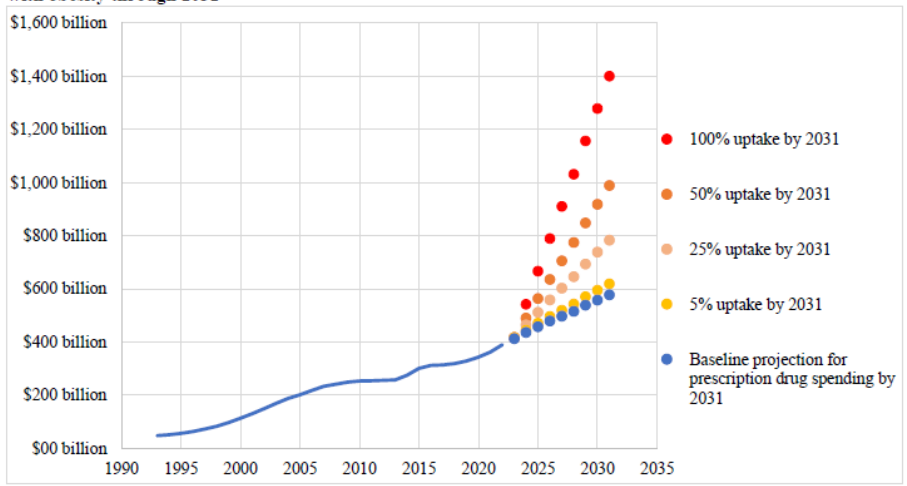


Figure 4: Estimated retail prescription drug spending based on uptake of weight loss drugs among adults with obesity through 2031



Just on new weight loss drugs, the U.S. could cumulatively spend nearly one trillion dollars by 2031 if uptake reached 25 percent, and nearly two trillion dollars if uptake reached 50 percent.[21]

Source: https://www.sanders.senate.gov/press-releases/news-chairman-sanders-releases-report-exposing-how-weight-loss-drugs-could-bankrupt-american-health-care/

Wegovy is Becoming Too Essential for its Elite Price

John Gapper, *Financial Times*, May 17, 2024 (excerpt)

From amphetamines to slimming pills, there is a long history of weight-loss drug crazes that ended in disappointment, or worse. Until anti-obesity medicines such as Wegovy and Zepbound, none of them had started out promisingly and then produced better and broader results.It is surprising, but studies of the health impact of the new generation of weight drugs have steadily brought more encouraging news. One published this week found that patients who took Novo Nordisk's Wegovy sustained weight loss for up to four years. It builds on data from last November showing the drug reduced the risks of heart attacks and death.

Health systems are waking up to the full potential of medicines that were first developed to address diabetes: Eli Lilly's Zepbound anti-obesity injectable was only approved in the US last year. "These drugs are doing more than just one thing and producing benefits across a range of diseases," Naveed Sattar, a Glasgow University professor who chairs the UK government's Obesity Mission, tells me.

But everything comes at a price, and the one attached to the GLP-1 agonist drugs is enormous. Indeed, the more effective they turn out to be in treating a variety of chronic and life-shortening ailments, the higher the looming costs to health insurers and governments. Battles about the prices of innovative drugs are nothing new, but this one is on another financial scale.

The drugs are now testing the rule that no product can be too successful. If they were as cheap and convenient as blood pressure pills and statins, they might soon be routinely prescribed. But they are far from it: Wegovy's list price in the US is $15,600 per year, although insurers obtain discounts. There is a widening gulf between benefit and affordability.

Bernie Sanders, the democratic socialist US senator, this week released a study that claimed these drugs had "the potential to bankrupt Medicare, Medicaid and the entire [US] healthcare system". He wants Novo Nordisk to reduce the US price of Wegovy to the much lower one in Denmark but, even there, the government only provides limited coverage for severe obesity.

Source: https://www.ft.com/content/1d807364-f543-470f-bc5d-7ce0ce4ff38a

Disclosure

STIFEL | Healthcare

Stifel collectively refers to Stifel, Nicolaus & Company, Incorporated and other affiliated broker-dealer subsidiaries of Stifel Financial Corp. The information and statistical data contained herein have been obtained from sources that Stifel believes are reliable, but Stifel makes no representation or warranty as to the accuracy or completeness of any such information or data and expressly disclaims any and all liability relating to or resulting from your use of these materials. The information and data contained herein are current only as of the date(s) indicated, and Stifel has no intention, obligation, or duty to update these materials after such date(s). These materials do not constitute an offer to sell or the solicitation of an offer to buy any securities, and Stifel is not soliciting any action based on this material. Stifel may be a market-maker in certain of these securities, and Stifel may have provided investment banking services to certain of the companies listed herein. Stifel and/or its respective officers, directors, employees, and affiliates may at any time hold a long or short position in any of these securities and may from time-to-time purchase or sell such securities. This material was prepared by Stifel Investment Banking and is not the product of the Stifel Research Department. It is not a research report and should not be construed as such. This material may not be distributed without Stifel's prior written consent.

Stifel, Nicolaus & Company, Incorporated | Member SIPC & NYSE | www.stifel.com