Biopharmaceutical Sector

Weekly Update – April 22, 2024

© 2024. All rights 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:

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)

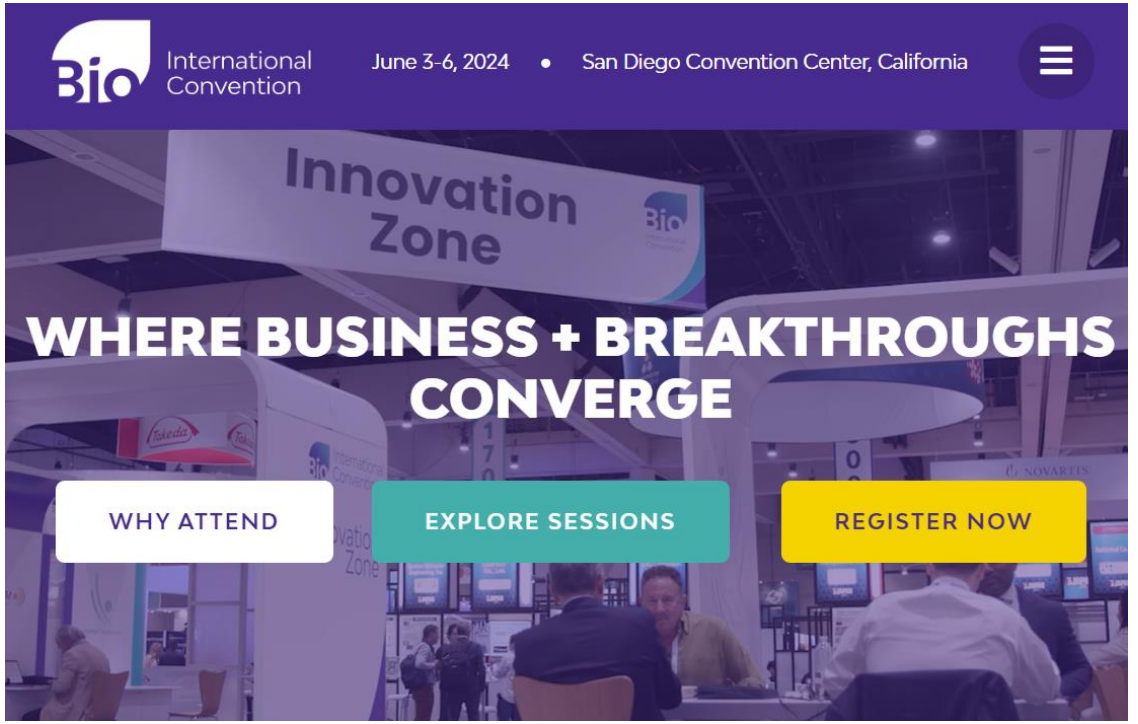
Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on April 19, 2024.

The next event will be on April 26, 2024.

Please join us.

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



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

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

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

Macroeconomics Update

Are Rates High Enough? Fed Resets Clock on Interest-Rate Cuts

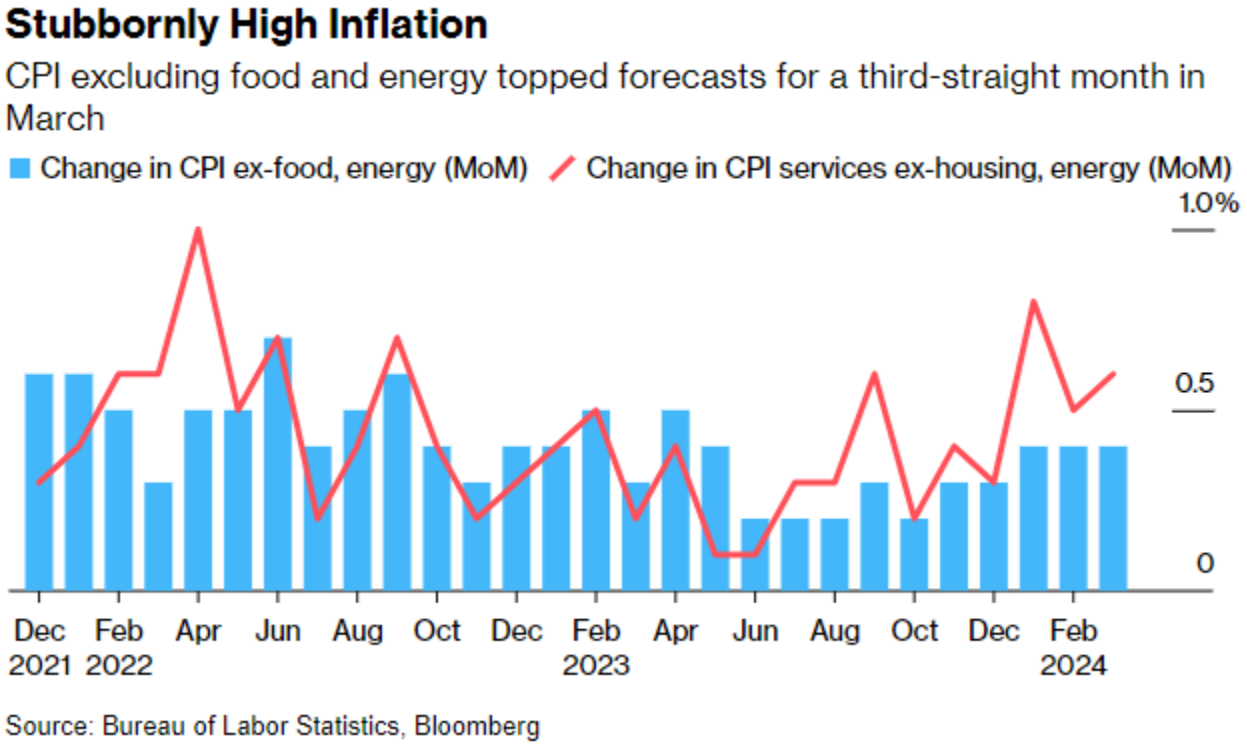
Catarina Saraiva, *Bloomberg*, April 19, 2024 (excerpt)

A string of disappointing inflation data has forced the Federal Reserve to reset the clock on its first interest-rate cut and re-evaluate the trajectory of price growth.

Chair Jerome Powell cemented that message this week when he said it's likely going to take "longer than expected" to gain the confidence needed to lower rates, dashing hopes for more than two cuts in 2024. Some worry there may be none at all.

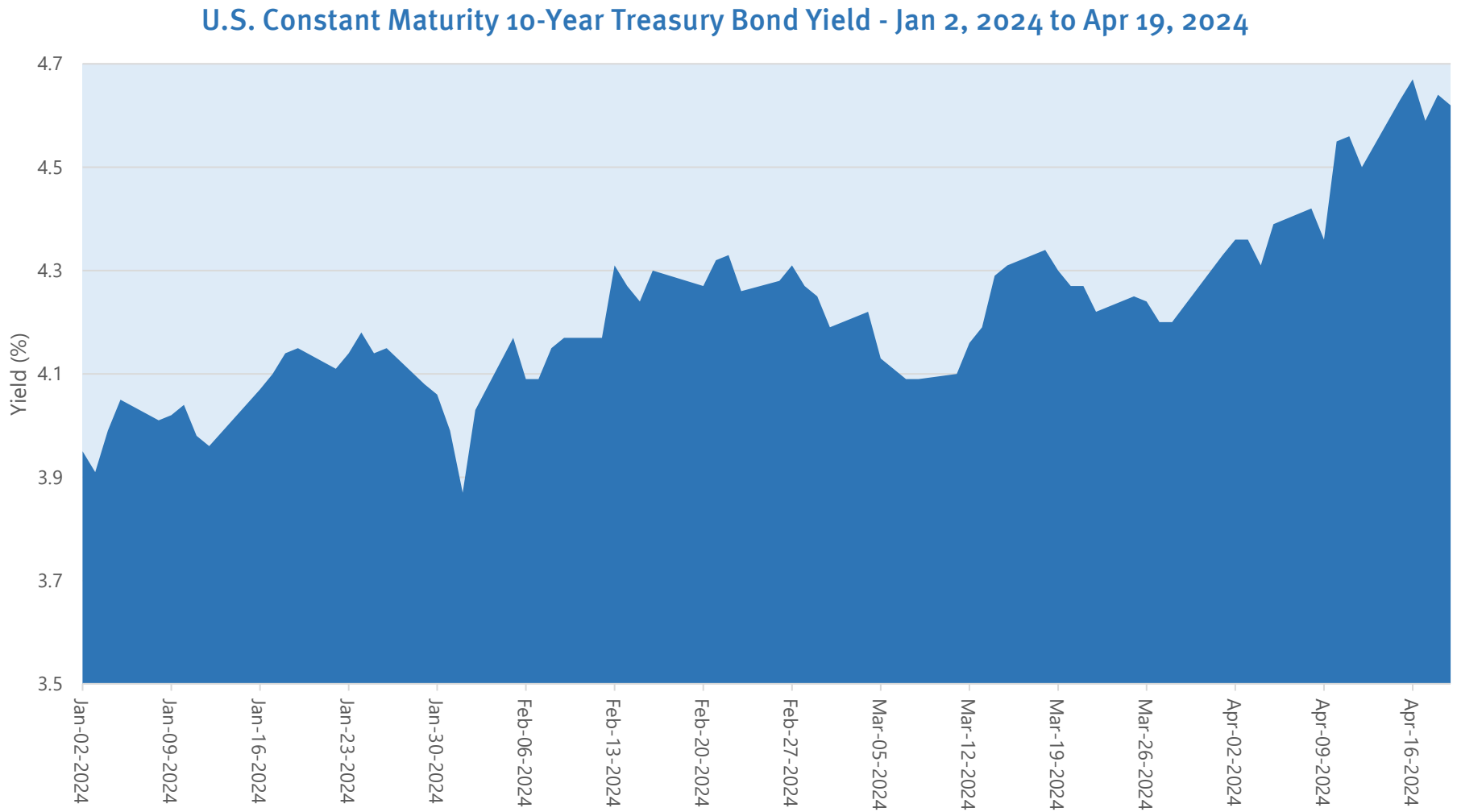
"This is confirmation that the Fed's willing to wait it out," said Diane Swonk, chief economist at KPMG LLP. "There's concern of how little it took to stimulate the economy, that there's still a lot of demand."

Powell's lack of urgency to adjust rates echoes that of his colleagues. But the enduring strength of the economy and labor market, alongside a market rally at the start of the year, has also reignited a debate about just how restrictive monetary policy is.



Source: https://www.bloomberg.com/news/articles/2024-04-19/fed-s-powell-rethinks-interest-rate-cuts-for-2024-to-combat-inflation

10-Year Treasury Yield Up 32 Basis Points in Last Month

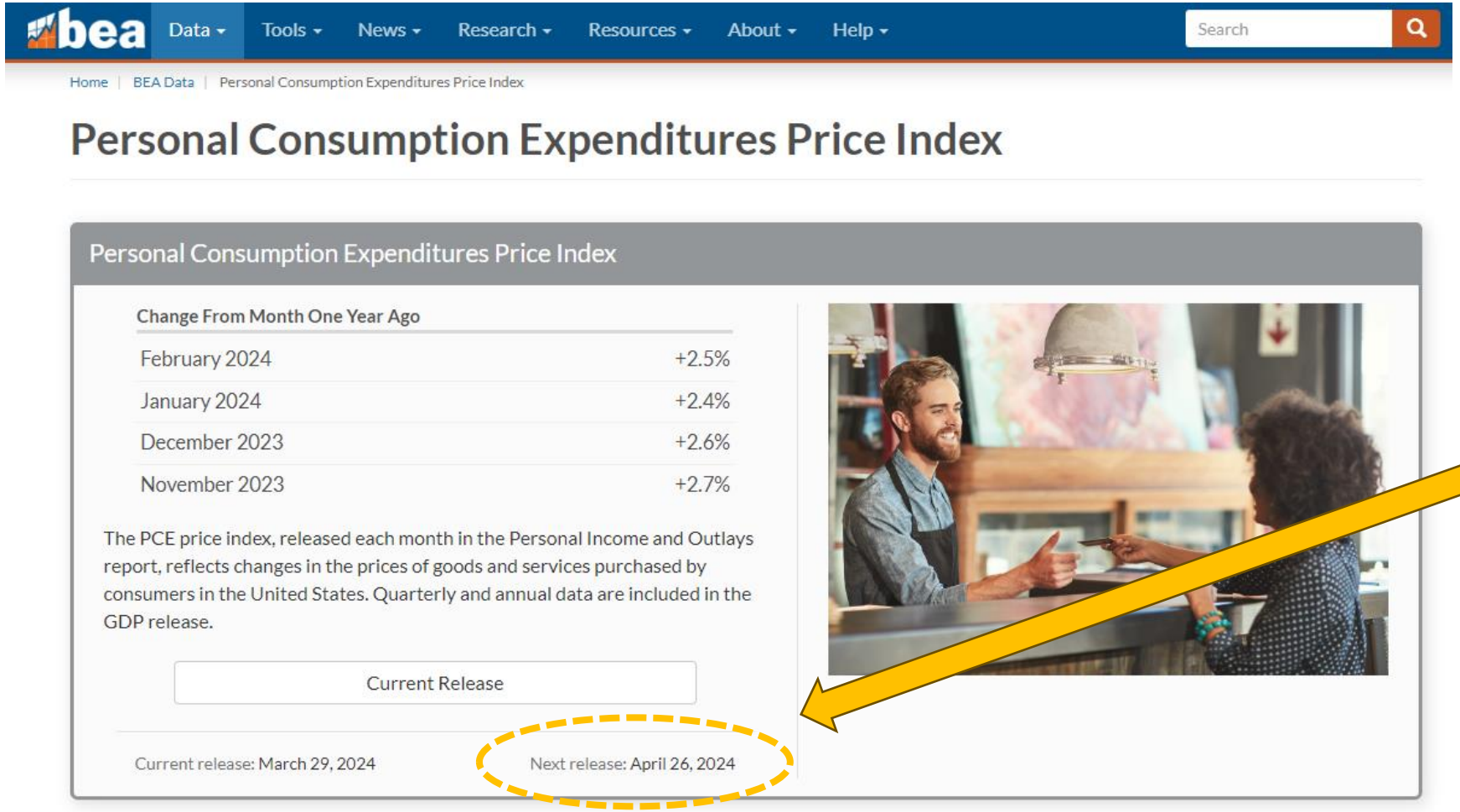


Last month's 32 basis point jump in the 10-year yield has hit biotech quite hard.

The rally of late last year was linked to improving macro conditions and the recent market drop has been linked to rising rates caused by persistent inflation.

Source: S&P CapitalIQ

More Inflation Data Next Week



We are going to see PCE inflation data released next Thursday (April 26th). Given the importance of this number for the Fed's stance, investors chose to lighten up on stocks last week.

No one wants to be going super long the market in front of that number.

Source: https://www.bea.gov/data/personal-consumption-expenditures-price-index

Biopharma Market Update

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

The XBI Closed at 82.93 Last Friday (April 19), Down 6% for the Week

The XBI is down 7% since the year began. Quite the change from a week ago where we were flat for the year. Rising Treasury yields explain the drop. The rise in the VIX indicates that we have entered a more uncertain environment than what prevailed a few weeks ago.

Biotech Stocks Down Last Week

Return: April 12 to Apr 19, 2024

Nasdaq Biotech Index: -3.1%
Arca XBI ETF: -6.0%
Stifel Global Biotech EV (adjusted): -9.3%*
S&P 500: -3.1%

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

Nasdaq Biotech Index: -7.0%
Arca XBI ETF: -7.2%
Stifel Global Biotech EV (adjusted): +11%*
S&P 500: +4.1%

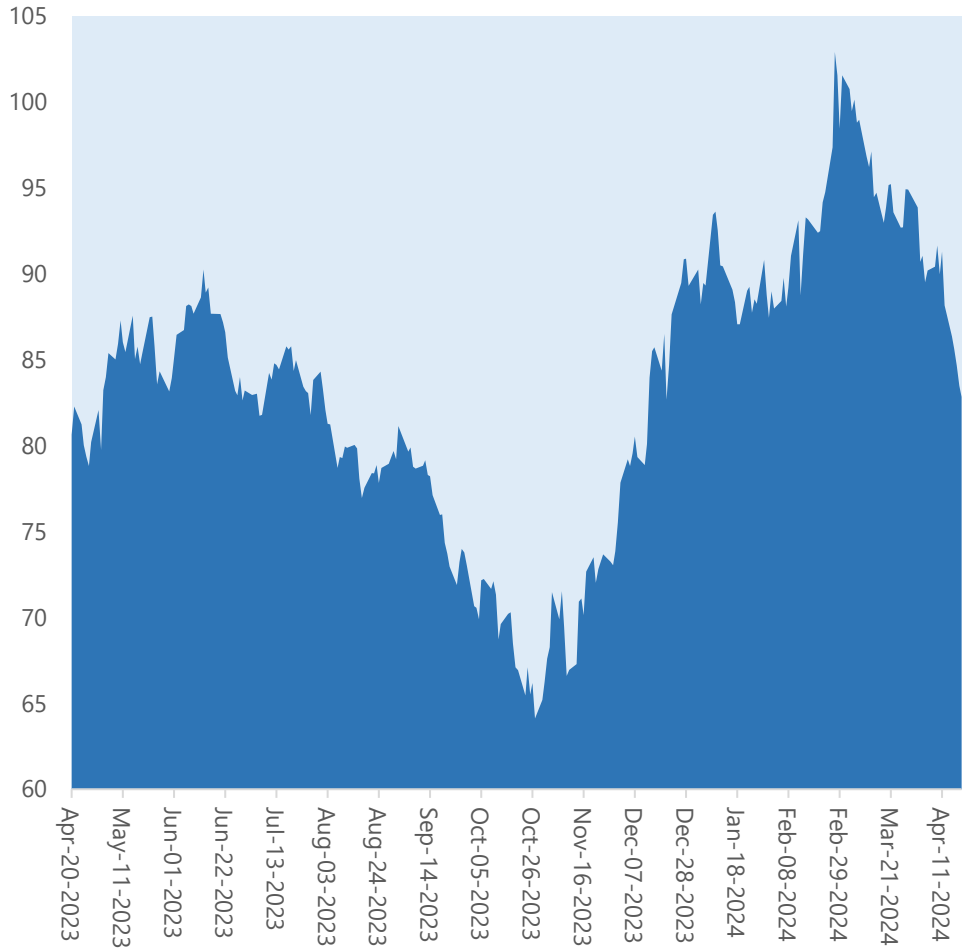
VIX Up Big

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

10-Year Treasury Yield Up

Jan 20, 2023: 3.48%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Feb 23, 2024: 4.26%
Mar 29, 2024: 4.20%
Apr 5, 2024: 4.39%
Apr 19, 2024: 4.62%

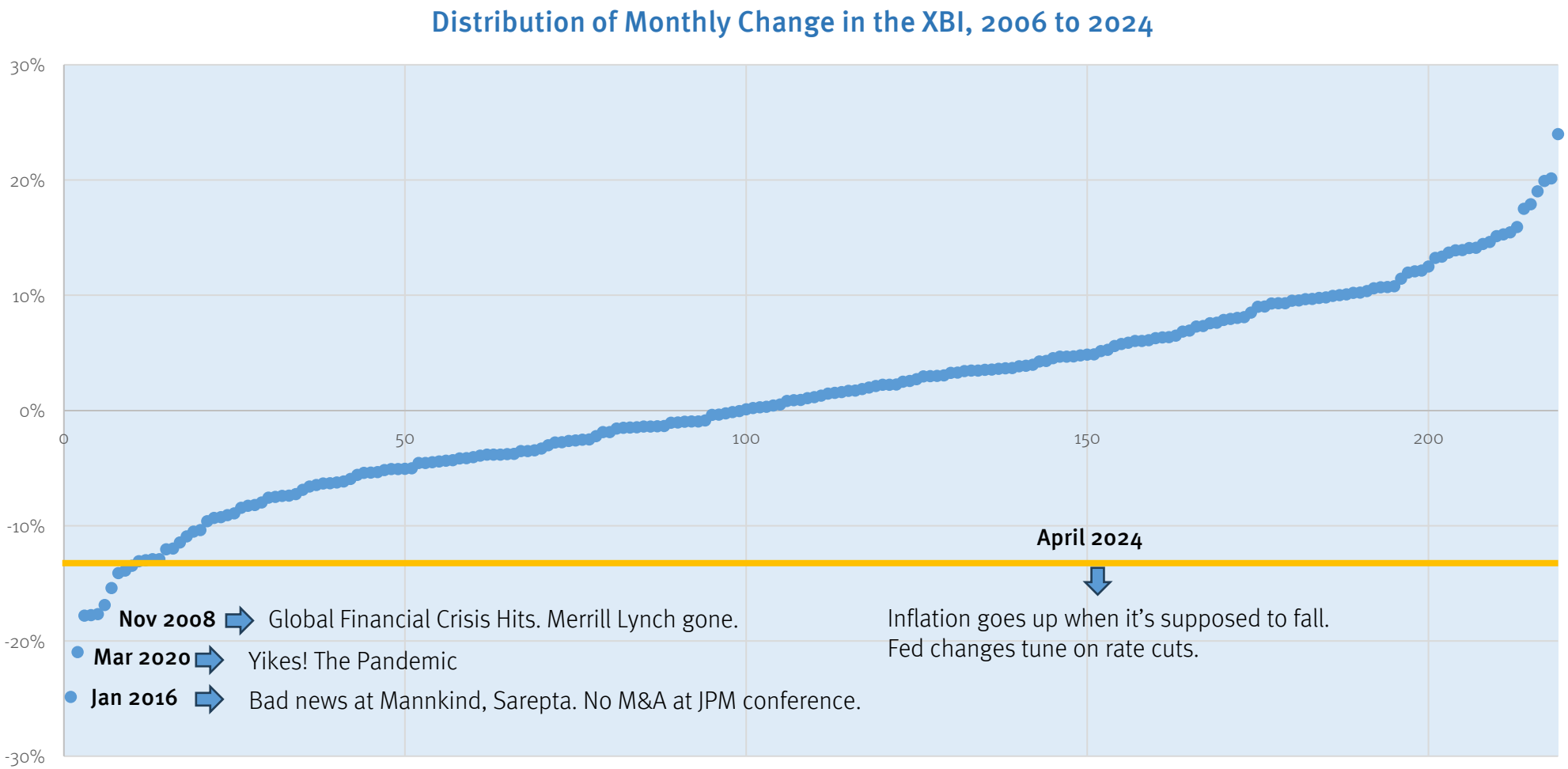
XBI, April 20, 2023 to Apr 19, 2024



Source: S&P Capital IQ and Stifel analysis

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

13% Drop in XBI in Last Month at the Wrong Tail End of Distribution of Monthly Changes

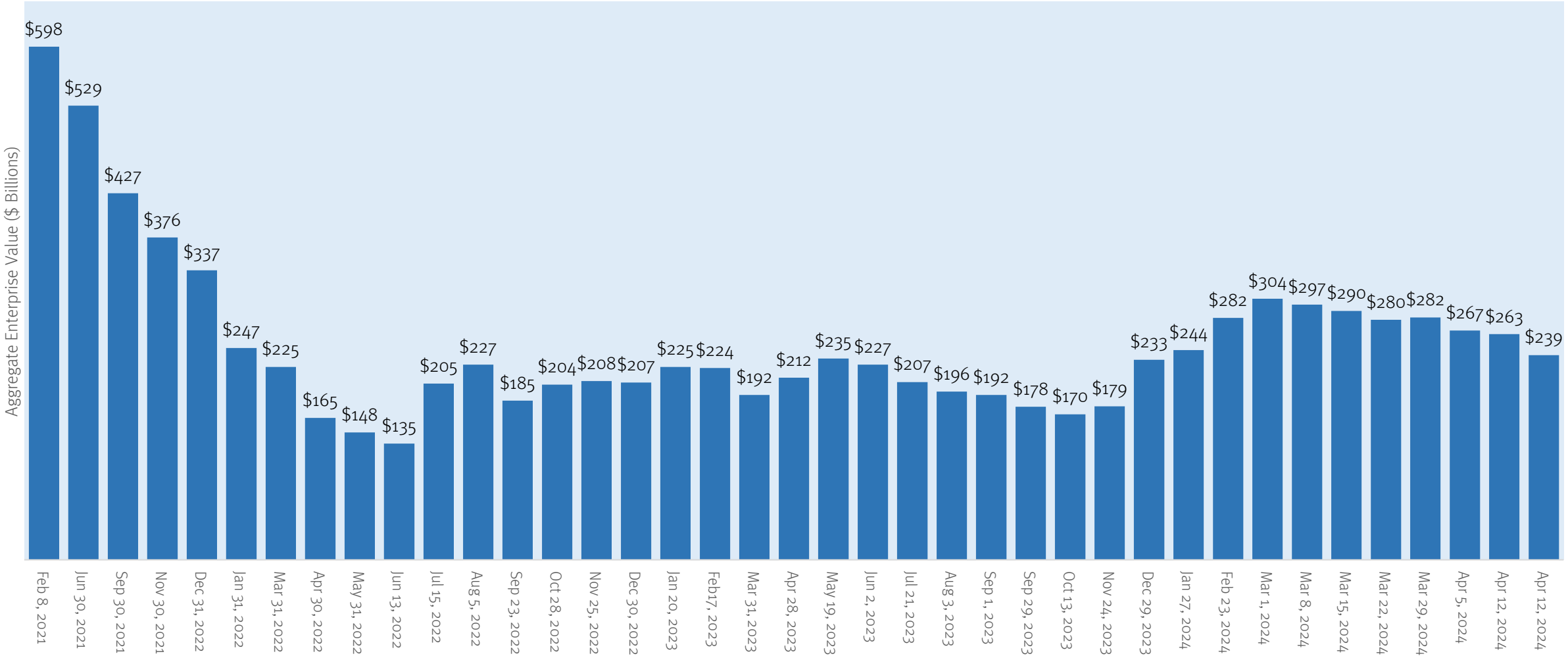


The 13% drop in the XBI over the last 30 days was the 12th worst one month performance in the eighteen years that the XBI has been tracked.

Total Global Biotech Sector Value Down 9.3% Last Week

This was the biggest percentage drop in biotech values in over six months. The total enterprise value of the global biotech sector is up 11% year-to-date on an addition/exit corrected basis.

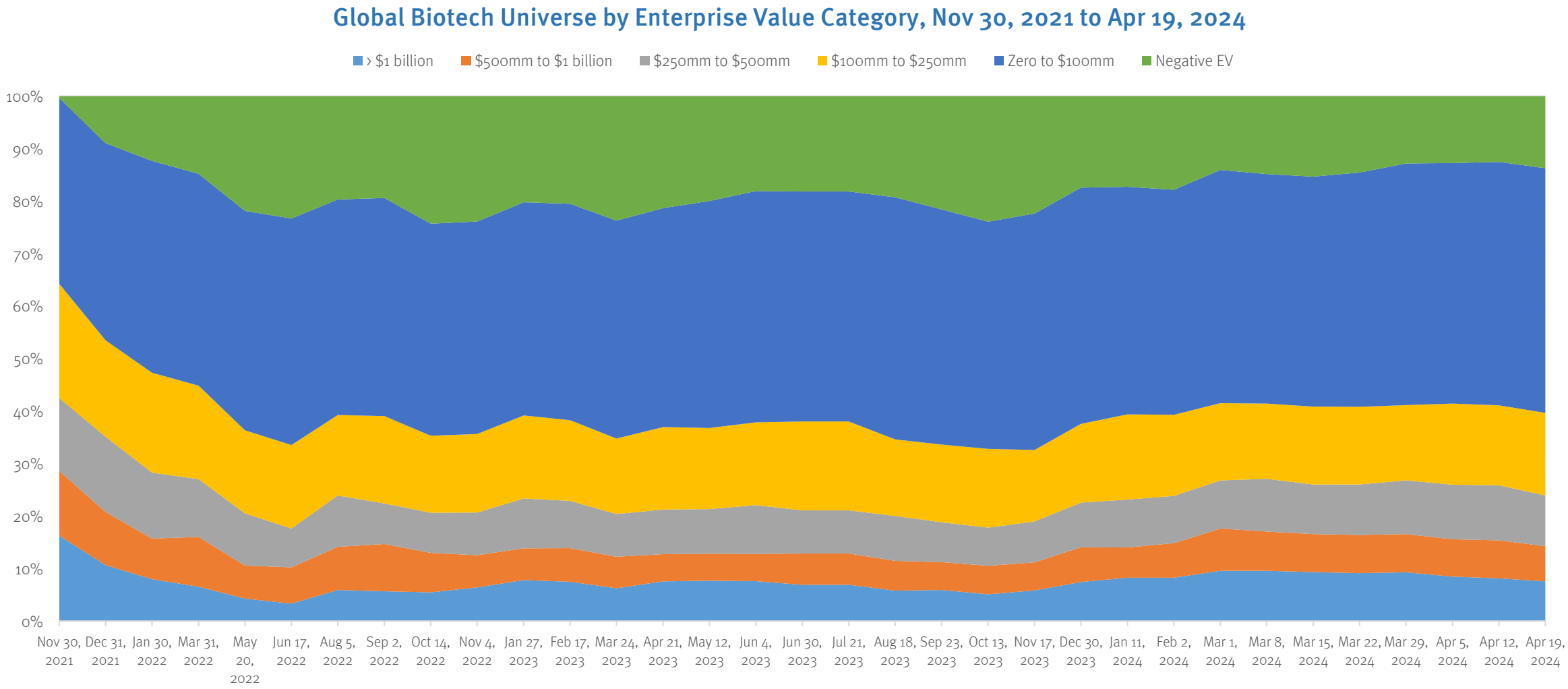
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Apr 19, 2024 ($ Billions)



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

Global Biotech Neighborhood Analysis

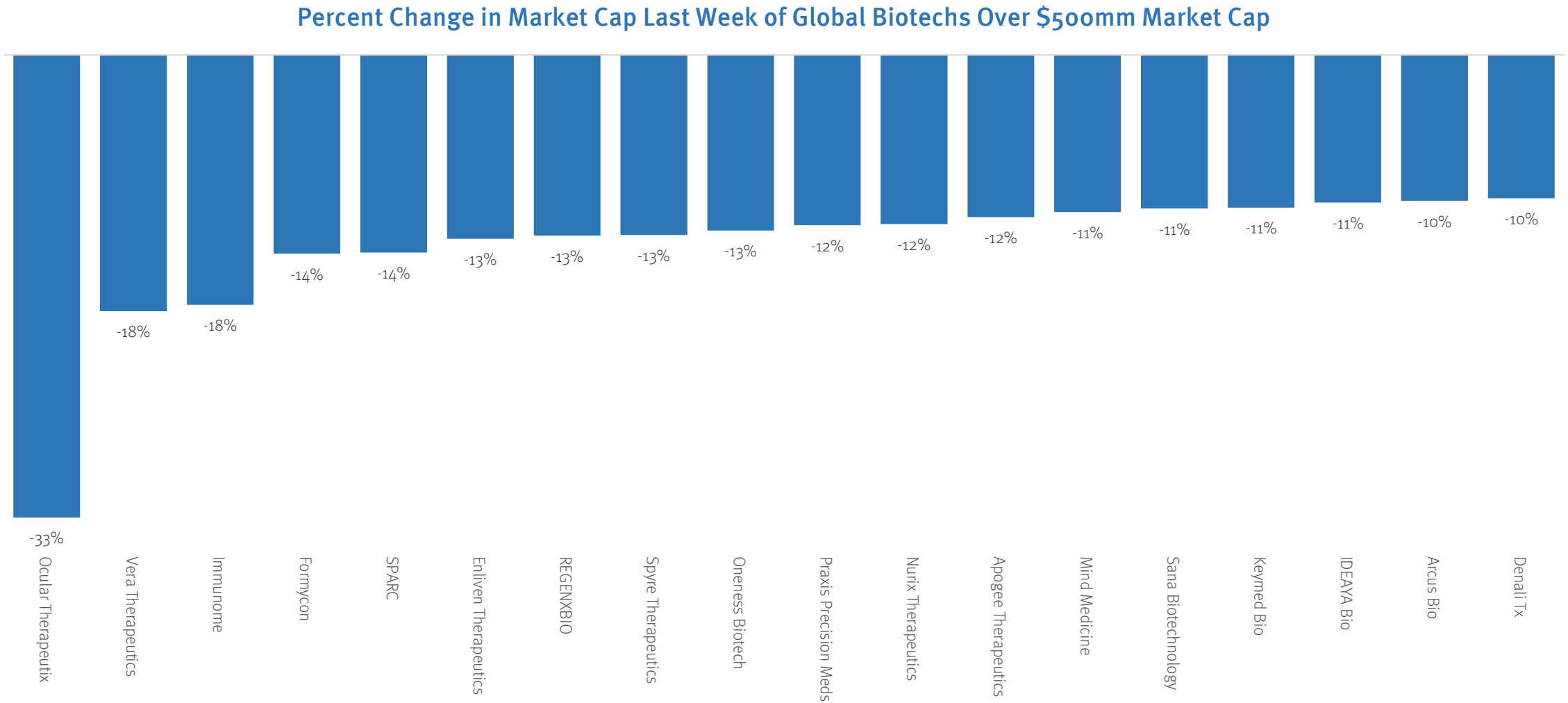
In sympathy with a very weak tape, last week saw the ranks of $250mm+ biotechs drop by 8% while the population of negative EV biotechs grew by 10%.



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

A Tough Week for Biotech

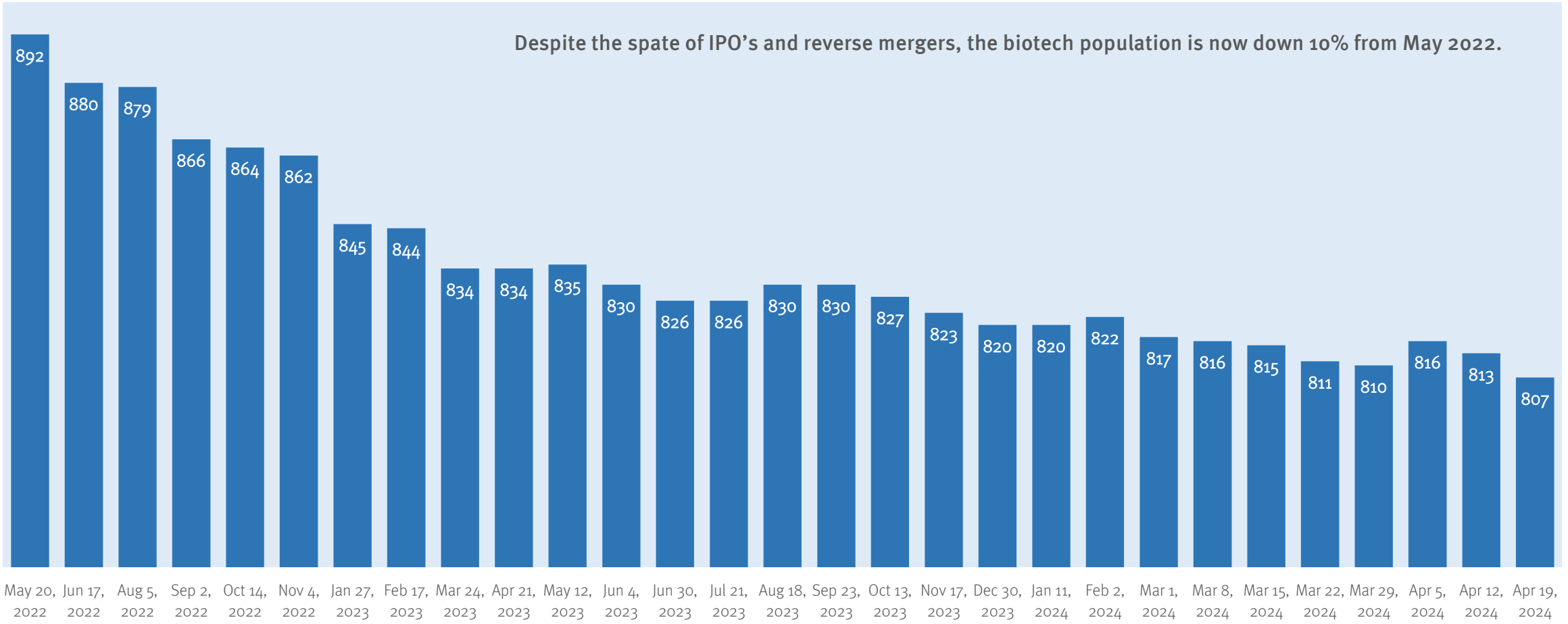
73% of all biotechs were down for the week. Of the top 150 biotechs by market cap, over 80% were down last week. This chart lists 18 of the top 150 that were down 10% or more last week.



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

Biotech Population Continuing to Shrink

Number of Publicly Traded Biotech Companies Worldwide, May 2022 to Mar 2024



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

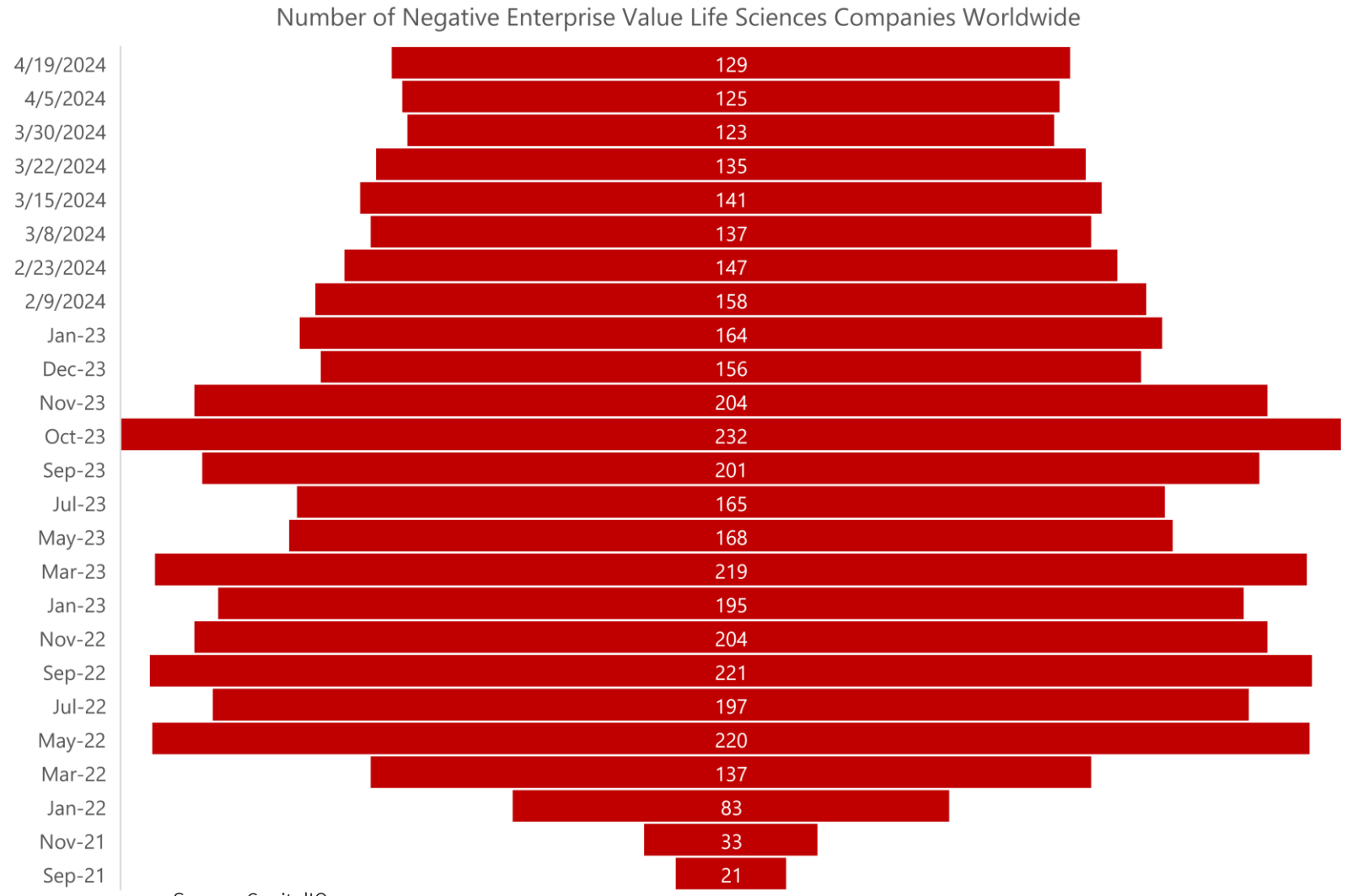
Life Sciences Sector Total Value Dropped 2.2% Last Week

It was not a pleasant week for the life sciences. As a whole, the sector dropped in value by 2.2% ($205 billion). Biotech, diagnostics, HCIT and life science tools were hardest hit subsectors. No subsector was up for the week.

Sector	Firm Count	Enterprise Value (Apr 19, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$76,812	-2.4%	-3.5%	-4.5%
Biotech	795	$238,462	-9.3%	-14.8%	-5.1%
CDMO	39	$141,021	-3.0%	-9.1%	-23.8%
Diagnostics	81	$254,559	-5.5%	-8.0%	-8.5%
OTC	30	$26,427	-1.1%	-7.2%	-9.9%
Pharma	716	$5,949,822	-1.2%	-4.7%	0.9%
Services	38	$183,031	-3.2%	-9.3%	-10.6%
Tools	51	$666,006	-4.6%	-9.5%	-10.7%
Devices	181	$1,617,070	-2.6%	-5.8%	-5.7%
HCIT	10	$17,012	-4.9%	-17.4%	-36.3%
Total	**2022**	**$9,162,223**	**-2.2%**	**-5.8%**	**-2.0%**

Source: CapitalIQ

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



Source: CapitalIQ

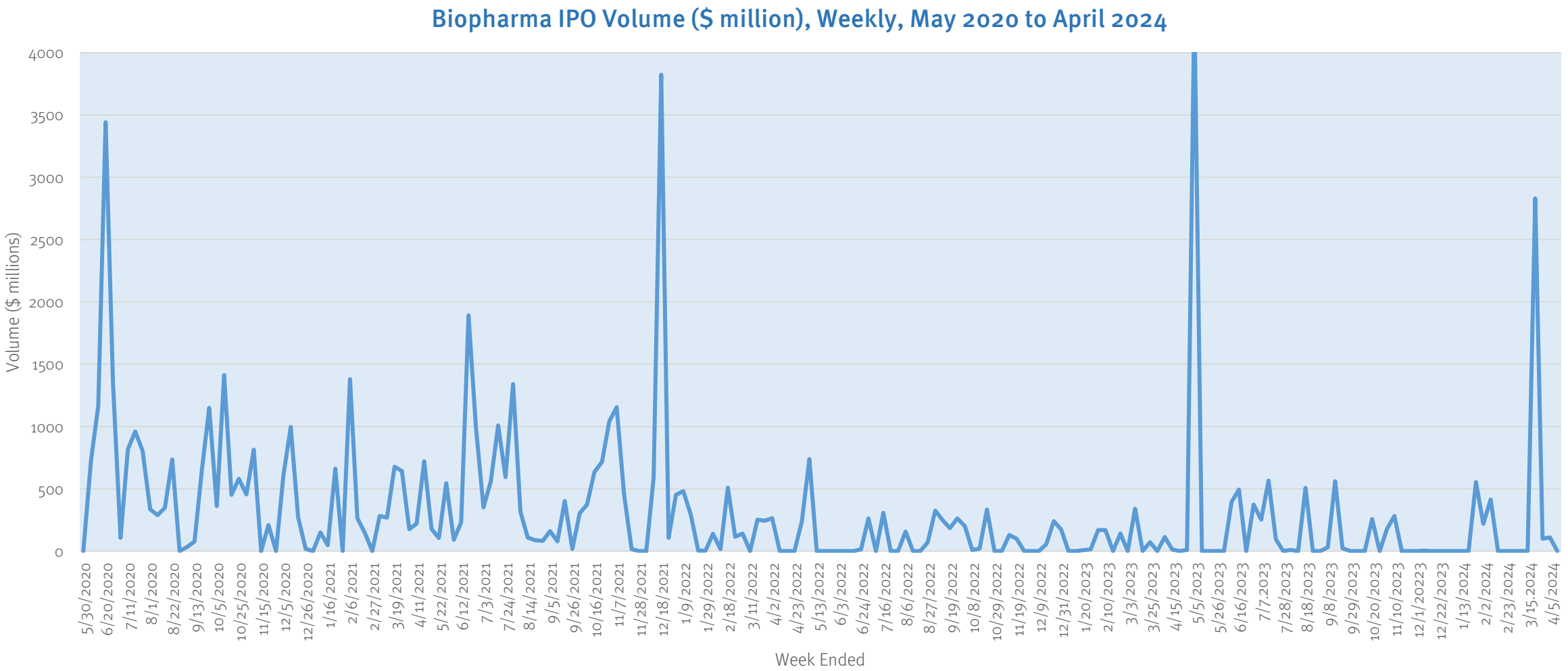
The count of negative EV life sciences companies worldwide rose to 129 from 125 two weeks ago.

Investors are not driving nearly as many companies to negative EV as they had in the past.

Capital Markets Update

No IPO Activity Last Week

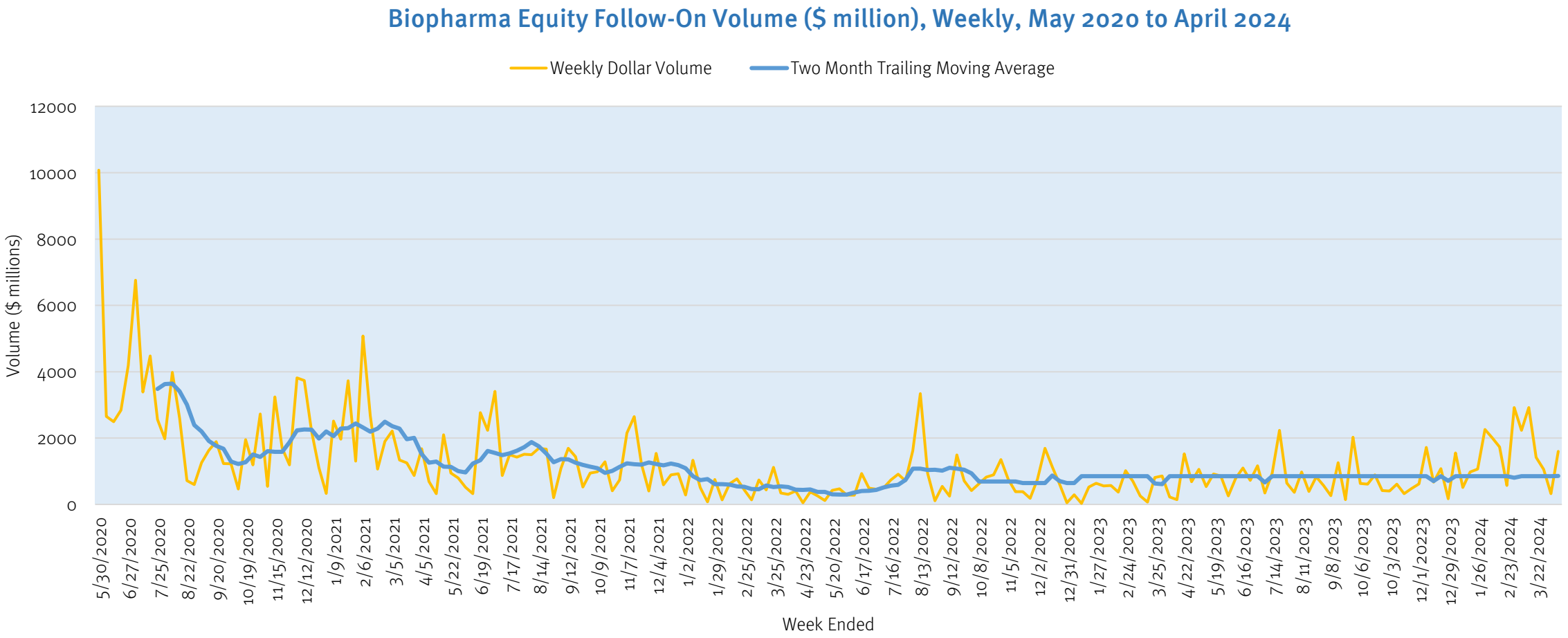
The IPO market was quiet last week.



Source: Data from CapitalIQ and Stifel research.

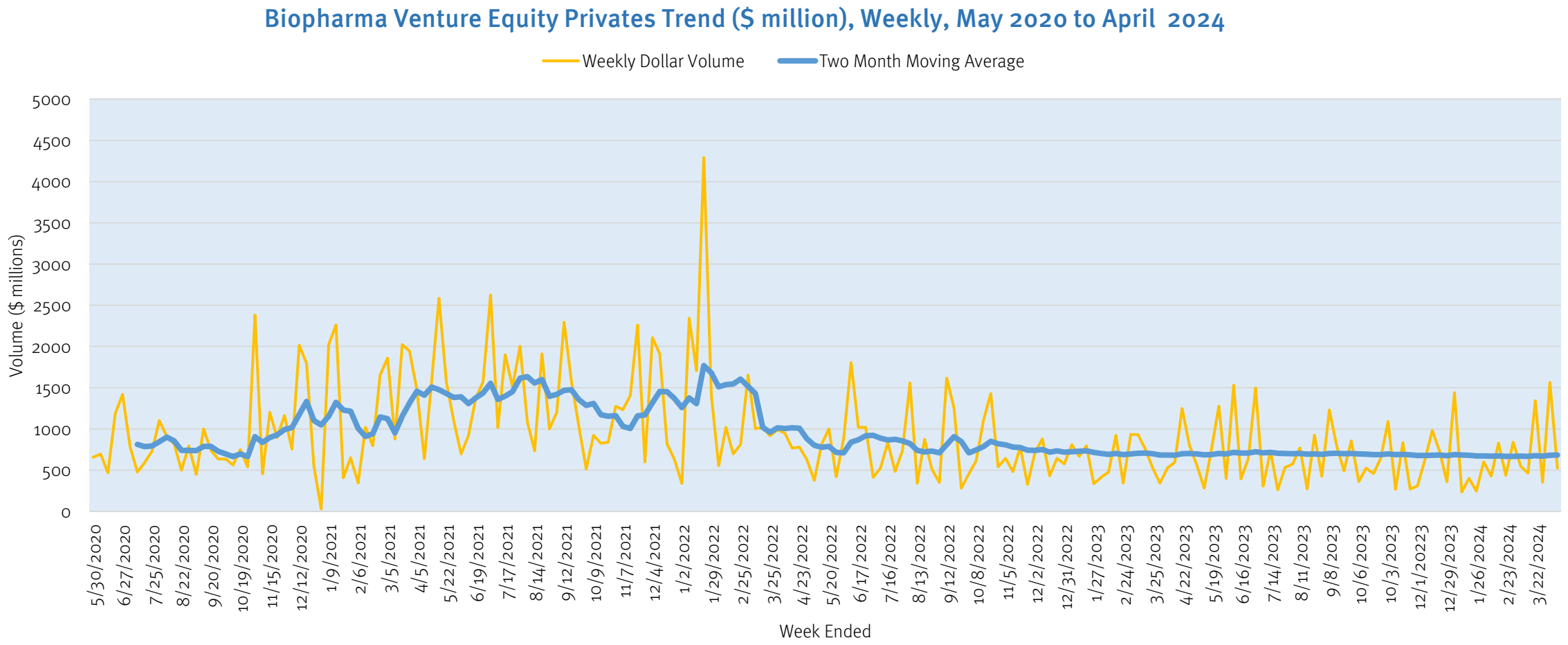
Follow-On Market Active Last Week

Despite a challenging market, the follow-on market remained strong last week with $1.6 billion in offerings. Intra-Cellular led the pack with a $500 million offering following excellent MDD data.



Private Venture Equity Investment Activity Slow Last Week

The venture private market was slow last week with $525 million raised by issuers across the globe in this market. The largest offering was a $290 million raise by Metsera.



Source: Data from CapitalIQ, Crunchbase.

Asher Bio Closes $55 Million Series C Financing to Advance Lead Program into Phase 1b Clinical Trials

SOUTH SAN FRANCISCO, Calif. April 16, 2024 - Asher Biotherapeutics, a biotechnology company developing precisely-targeted immunotherapies for cancer, autoimmune, and infectious diseases, today announced the closing of a Series C financing, which raised $55 million. The financing was led by RA Capital Management, and included new investors AstraZeneca (LSE/STO/Nasdaq: AZN) and Bristol Myers Squibb, along with existing investors Janus Henderson Investors, Third Rock Ventures, Wellington Management and Boxer Capital and other undisclosed institutional investors.

Asher Bio plans to use the proceeds from this financing to advance the clinical development of its lead program, AB248, a novel CD8+ T cell selective IL-2, generated by fusing a reduced potency IL-2 mutein to an anti-CD8β antibody. AB248 is currently being investigated in a Phase 1a/1b study, which is evaluating AB248 as a monotherapy and in combination with KEYTRUDA® (pembrolizumab), in patients with recurrent locally advanced or metastatic solid tumors, including melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head and neck (SCCHN), previously treated with a PD1 or PD-L1 checkpoint inhibitor.

AB248 was specifically engineered to selectively and potently activate CD8+ T-cells, while avoiding natural killer (NK) cells, which can act as a pharmacological sink and contribute to toxicity, and regulatory T (Treg) cells, which are immunosuppressive. Initial pharmacokinetic and pharmacodynamic data from the ongoing Phase 1a/1b clinical trial support AB248's proof of mechanism and activity with a highly differentiated clinical profile. Early data shows potent and selective CD8+ T cell activation without substantial changes to Treg and NK cell numbers and initial evidence of anti-tumor activity, with a generally well-tolerated safety profile.

"Asher's groundbreaking cis-targeting platform offers a highly differentiated approach to immunotherapy, with the potential to overcome the limitations of other immune-based treatments by maximizing efficacy and limiting off-target toxicities," said Jake Simson, RA Capital Management. "The company has produced promising preclinical and early clinical data to date and we are excited to continue to support Asher as they further advance their lead program in the clinic."

Source: https://www.businesswire.com/news/home/20240416383585/en/

"We are delighted to have the continued support of RA Capital, and excited to add two top biopharmaceutical companies and experts in oncology to our investor syndicate. We are committed to delivering a new class of highly selective cis-targeted immunotherapies for cancer, which are designed to activate only the desired immune cell type to potentially maximize efficacy and limit off-target toxicities. "

Craig Gibbs
Chief Executive Officer
Asher Biotherapeutics

Biotech Private Fundraising in 2024: A Story of Haves and Have-nots

Fewer firms are raising money. But those that can are getting record-breaking investment

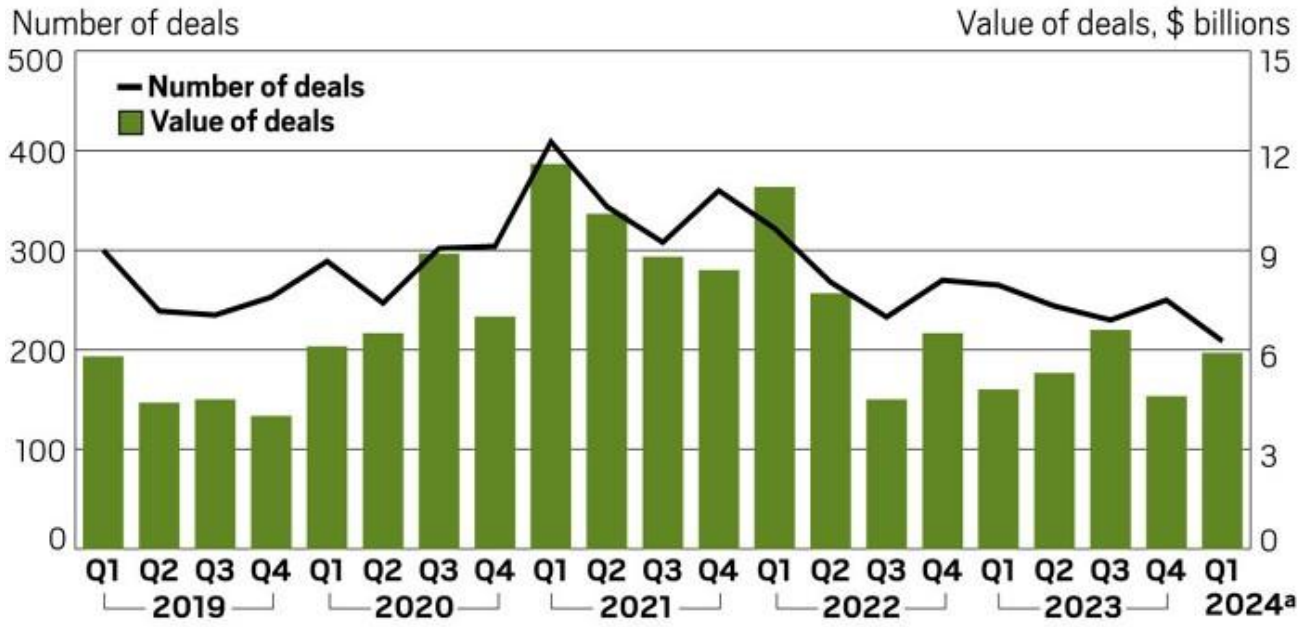
Rowan Walrath, C&EN, April 17, 2024

If you're a biotech start-up looking for funds in 2024, either you're lucky enough to raise a nine-figure venture round, or you're scrounging for what's left over.

In the first quarter of this year, biotechnology and pharmaceutical companies collectively raised $5.9 billion across 209 rounds, according to the latest Venture Monitor report from PitchBook and the National Venture Capital Association (NVCA). The dollar amount is an increase from the 2023 quarterly average, but it's spread across fewer deals. The total deal count is the lowest since the third quarter of 2018, during which PitchBook recorded 202 venture rounds. Before that, only 2016 saw so few deals.

The dip is especially low among early-stage deals. Industry watchers say investors are still risk averse and, consequently, prioritizing investment in companies whose drug candidates are farther along in development.

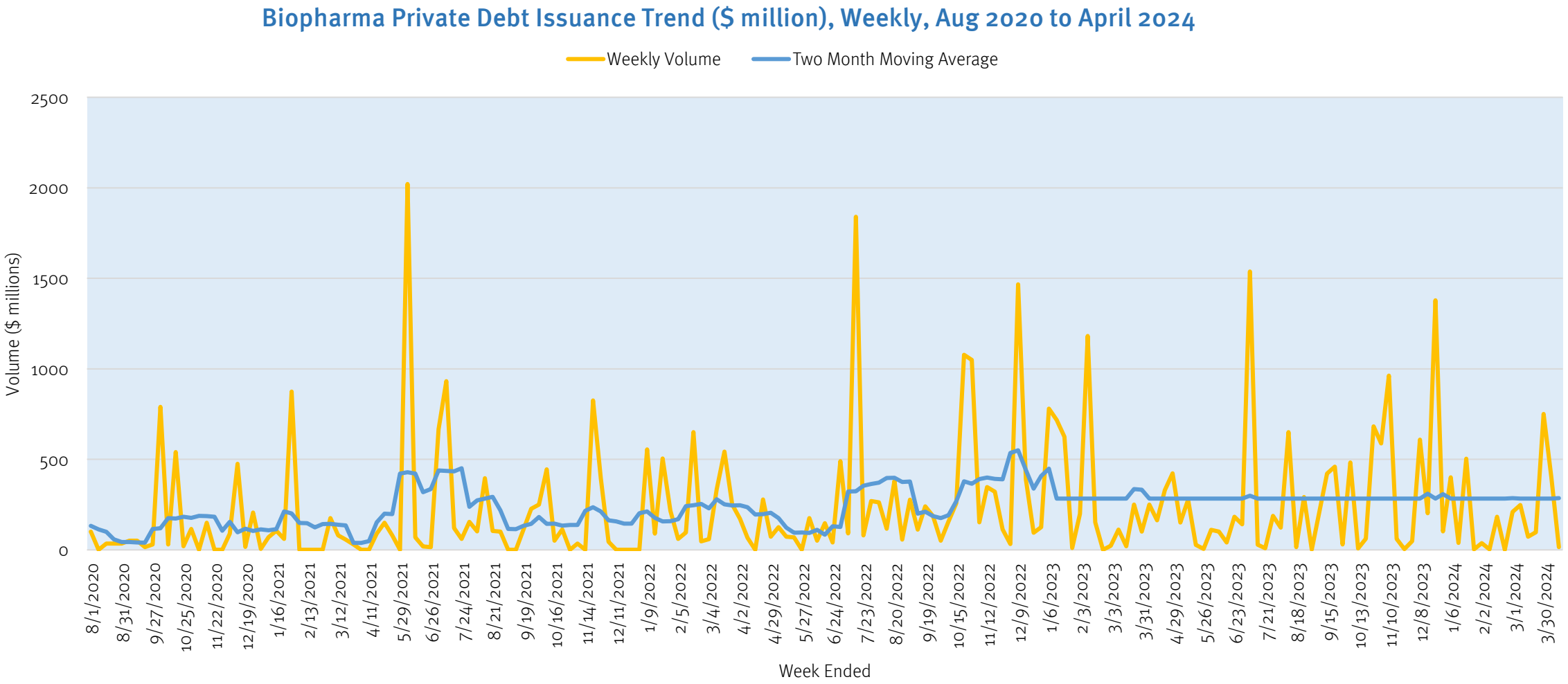
"I think the bar is still high," says Katie McCarthy, chief innovation officer at the Halloran Consulting Group. "Investors have really reestablished their expectations. They do want to ensure there's a reasonable amount of risk."



Source: https://cen.acs.org/business/finance/Biotech-fundraising-2024-story-havesnots/102/i12

Biopharma Private Debt Market Quiet Last Week

Last week saw very little capital raised for biopharmas in the private debt market.



Source: Data from CapitalIQ, Crunchbase, Stifel research.

Regeneron Ventures Launches with $500 Million Commitment to Fuel Promising Biotechnology Innovation

GREENWICH, Conn., April 15, 2024 (GLOBE NEWSWIRE) -- Regeneron Ventures announces its formation as a venture capital fund focused on promising biopharmaceutical, health care and health technology companies. The fund's general partner will be independently managed by former Regeneron executives Jay S. Markowitz, M.D., and Michael Aberman, M.D., who together will lead investment strategy of the fund. Regeneron Pharmaceuticals, Inc. is the fund's exclusive limited partner and has committed $100 million annually for five years.1

"Understanding that the most groundbreaking, transformative approaches to preventing and treating disease may yet to be discovered, the fund will invest for the long-term, agnostic to therapeutic area, technology and stage of development," said Markowitz.

Drs. Markowitz and Aberman both started their professional careers in medicine before transitioning into investing and operational roles in biotech. They share Regeneron's patient-centric mission and commitment to doing well by doing good.

"Our goal is to cultivate an ecosystem where the next generation of biotech companies can thrive, drawing on the lessons learned and successes achieved at Regeneron and throughout our careers," said Aberman. "Together, we will strive to identify and support groundbreaking advancements that push the boundaries of what's possible in science and medicine."

About Regeneron Ventures
Regeneron Ventures is a health care venture capital fund launched in April of 2024. Our purpose is to invest wisely to help build and grow companies that become great by improving health. Although we operate independently from our single and exclusive limited partner, Regeneron Pharmaceuticals, Inc., we share the same patient-centric, science-based mission, principles, and values. Our investment mandate includes health care broadly, but our interest is skewed towards biotechnology, devices, tools, and enabling technologies. We base our investment decisions on the quality of the people, science, and data.

Source: https://www.globenewswire.com/news-release/2024/04/15/2862541/0/en/Regeneron-Ventures-Launches-with-500-Million-Commitment-to-Fuel-Promising-Biotechnology-Innovation.html

VC Firm Canaan Adds $100M-Plus for Biotech Bets and Tacks on a Pfizer Vet to Gauge Early Science

May Bayer, FierceBiotech, April 17, 2024

What's another $100 million tacked onto a previously raised $850 million? Evidently, for venture firm Canaan Partners, tons.

The private financing outfit has added a fresh nine-digit sum a year after closing its thirteenth fund. General Partner Julie Grant told Fierce Biotech that the money will act as a designated pool for biotech investments.

"The additional capital that's been raised will be invested alongside the main fund," she said. "It will allow us to do more deals in biopharma with the exact same strategy of going for early company formation, syndicated series A and syndicated series Bs and Cs."

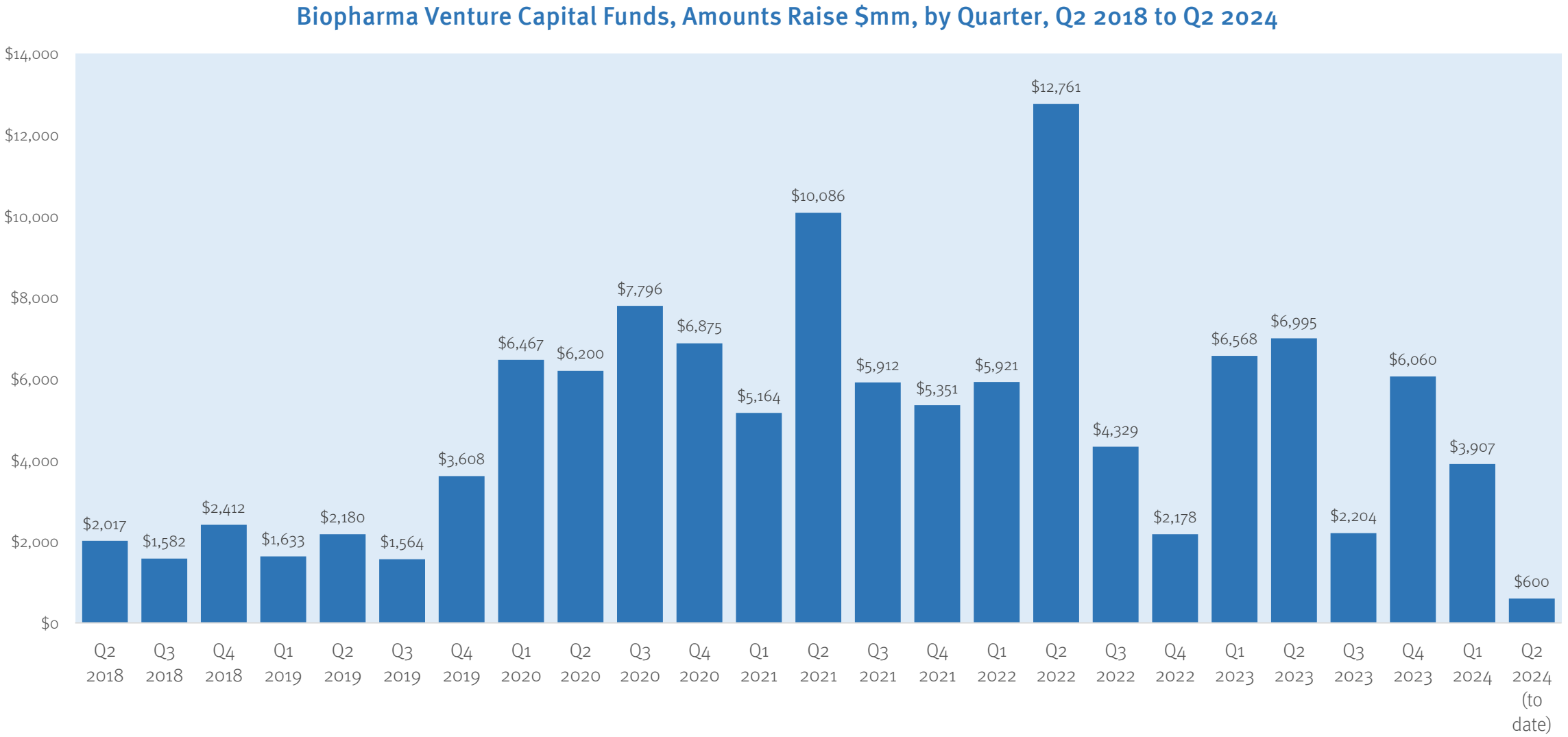
The cash extends the total amount raised since early 2023 past $1 billion, with nearly half of the capital designated for the firm's healthcare team. Think of the extra $100 million as a cherry on top for the biopharma investors. The other half of the roughly $1 billion will be for Canaan's technology investors, with previous bets being placed on startups like Instacart and Turo, among others. Grant says the company plans to invest in 15 to 16 companies over the next three years using the money raised over the last year-plus.

The firm has jumped aboard at least two biotech raises so far this year, including Nocion Therapeutics' $62 million raise, money that's expected to be used to advance an inhaled chronic cough med. Canaan also contributed to Alterome Therapeutics' $132 million series B led by Goldman Sachs. Alterome is working on developing small-molecule, precision cancer treatments.

It's not just capital that Canaan is adding. Joining the team as a venture partner is Uwe Schoenbeck, Ph.D., who is coming across from Pfizer. Schoenbeck previously served as senior vice president and chief scientific officer of the Big Pharma's emerging science and innovation unit under the larger R&D umbrella. That team worked to bridge early science and young biotechs with Pfizer's R&D ecosystem, an effort that included Pfizer's Center for Therapeutic Innovation.

Source: https://www.fiercebiotech.com/biotech/canaan-adds-another-100m-biotech-bets-and-tacks-pfizer-vet-gauge-early-science

Pace of Venture Fund New Capital Formation Down in 2024

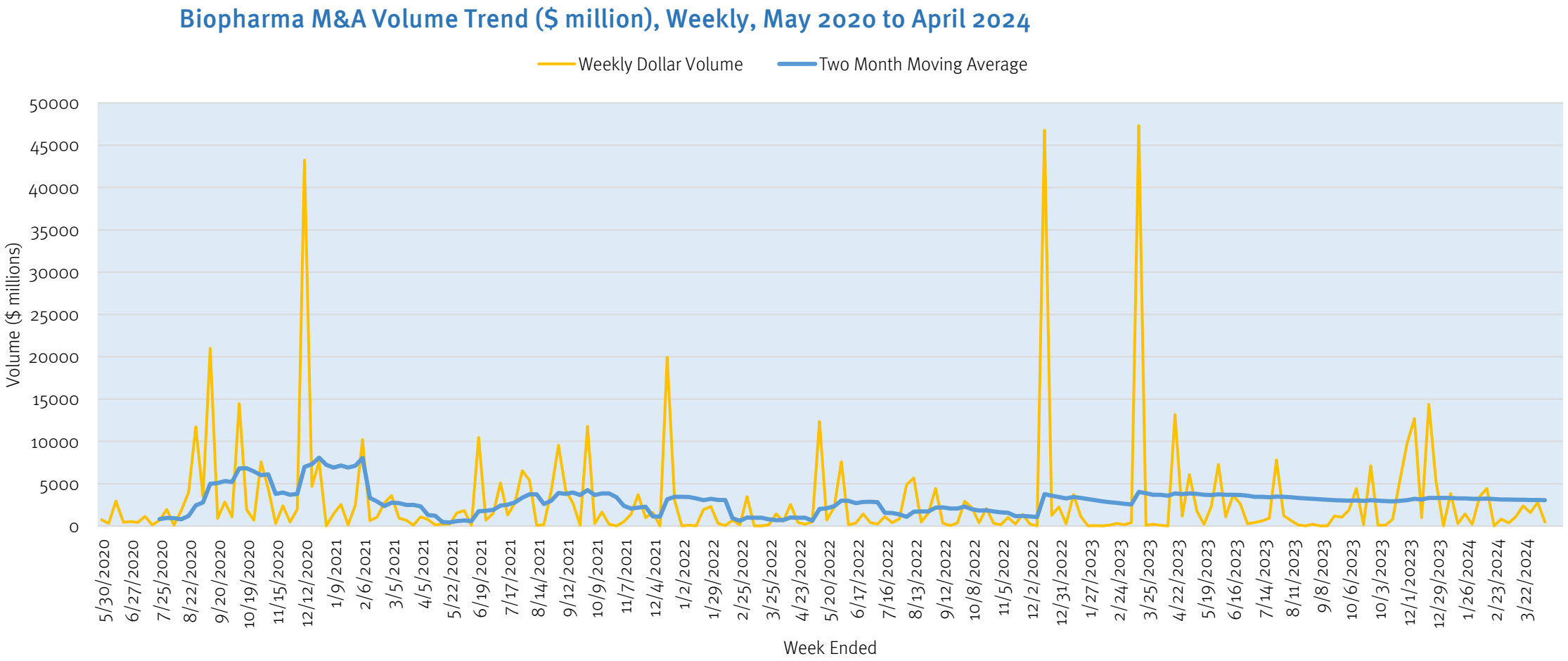


Source: Stifel Venture Funding Database

Deals Update

Last Week Saw $455 Million in Announced M&A Volume

The largest announcement last week was an offer to acquire Vanda Pharma.



Source: S&P, CapitalIQ

Vanda Pharmaceuticals Receives Unsolicited Takeover Proposal from Future Pak

WASHINGTON, April 17, 2024 /PRNewswire/

Vanda Pharmaceuticals Inc. ("Vanda" or the "Company") (Nasdaq: VNDA) today confirmed that, since March 2024, it received several unsolicited proposals from Future Pak, LLC ("Future Pak"), to acquire all of the outstanding shares of Vanda (the "Conditional Proposals"). The most recent proposal from April 1 offered $7.25 - $7.75 per share, subject to certain terms and conditions.

The Vanda Board of Directors (the "Board"), in consultation with its independent financial and legal advisors, consistent with its fiduciary duties, carefully reviewed the Conditional Proposals and unanimously concluded that they are not in the best interests of the Company and its shareholders, as they significantly undervalue the Company.

In reaching its conclusions about each of the Conditional Proposals, the Board considered, among other things, Vanda's robust clinical development pipeline, expanding commercial presence, significant cash balance and long-term future growth prospects. Vanda has established a resilient business with a diverse product set, a history of top-line growth and durable cash flow.

The Board believes the Conditional Proposals are opportunistic attempts to purchase the Company's shares at a discount to Vanda's intrinsic value and would transfer significant value to Future Pak at the expense of Vanda shareholders, including approximately $6.751 per share in cash and marketable securities. Future Pak's latest unsolicited proposal provides a mere 7 – 15% premium to such cash balance, ascribing therefore very little value to the Company's significant revenue stream and pipeline.

Source: https://www.prnewswire.com/news-releases/vanda-pharmaceuticals-confirms-rejection-of-unsolicited-takeover-proposals-from-future-pak-302119534.html

Industry News

Boehringer Ingelheim Reports Strong Growth in 2023 and Accelerates Late-stage Pipeline

Ingelheim, Germany, April 16, 2024

Boehringer Ingelheim today announced a strong acceleration of its pipeline in 2023, as pivotal trials in key research areas progressed as planned. Research & Development (R&D) investments increased by 14.2% to EUR 5.8 billion. R&D investments were substantial, at 22.5% of net sales. Group net sales rose by 9.7%* to EUR 25.6 billion in 2023, driven by 10.3%* growth in Human Pharma and 6.9%* growth in Animal Health. Both businesses outperformed their markets.

In 2023, regulators awarded five additional FDA fast-track designations and one FDA breakthrough therapy designation in the US, as well as one EMA PRIME scheme acceptance in Europe. With a focus on therapeutic research areas in cardiovascular, renal and metabolic diseases (CRM), oncology, respiratory diseases, immunology, mental health, and retinal health, the company is a pioneer in breakthrough treatments in areas of high unmet patient needs.

“I am excited to see how balanced and healthy our pipeline looks today,” said Hubertus von Baumbach, Chairman of the Board of Managing Directors.

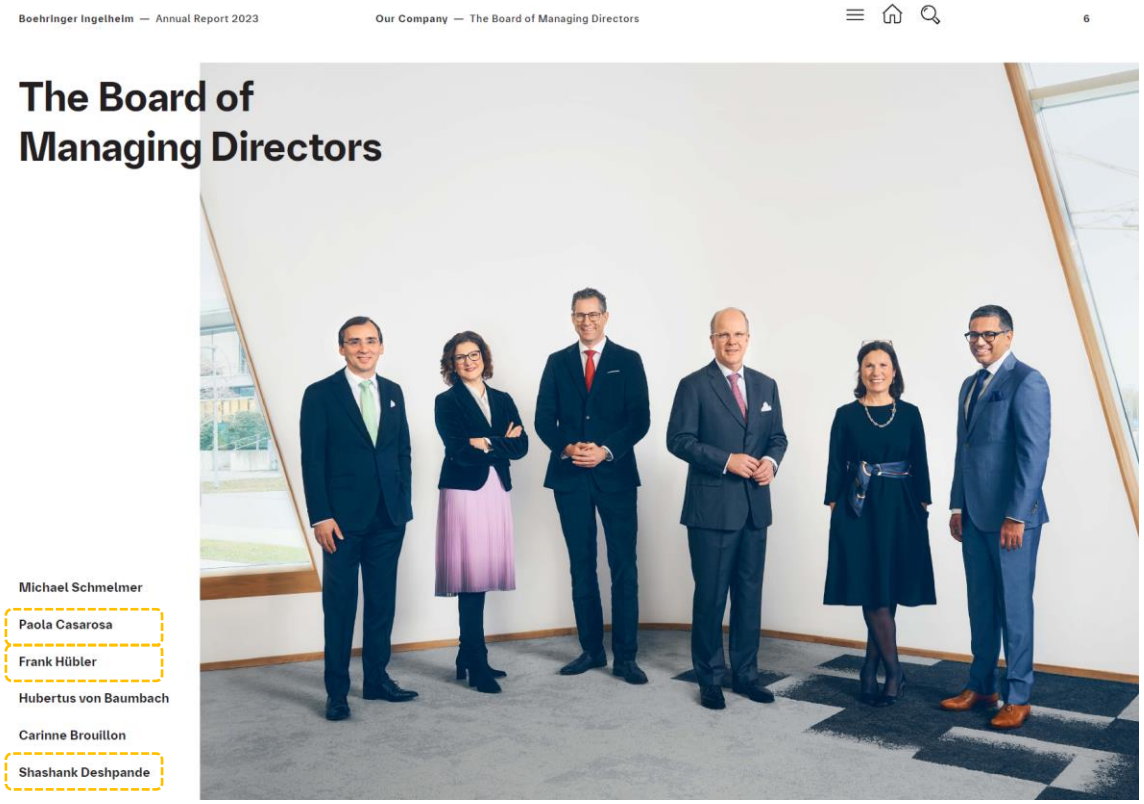
The company plans to start ten new phase II and III trials in the next 12-18 months, aiming for 25 new treatment launches in Human Pharma until 2030. In Animal Health, 20 additional launches are expected across markets until 2026, including product updates, indication expansion and new products. For 2024, Boehringer Ingelheim expects a slight year-on-year increase in revenues on a comparable basis, adjusted for currency and extraordinary effects.

Source: https://www.boehringer-ingelheim.com/about-us/corporate-profile/boehringer-ingelheim-strong-growth-pipeline-acceleration-2023

Major Management Refresh at BI in 2024

Paola Casarosa has taken over R&D. Frank Hubler has taken over finance and Shashank Deshpande has taken over animal health.

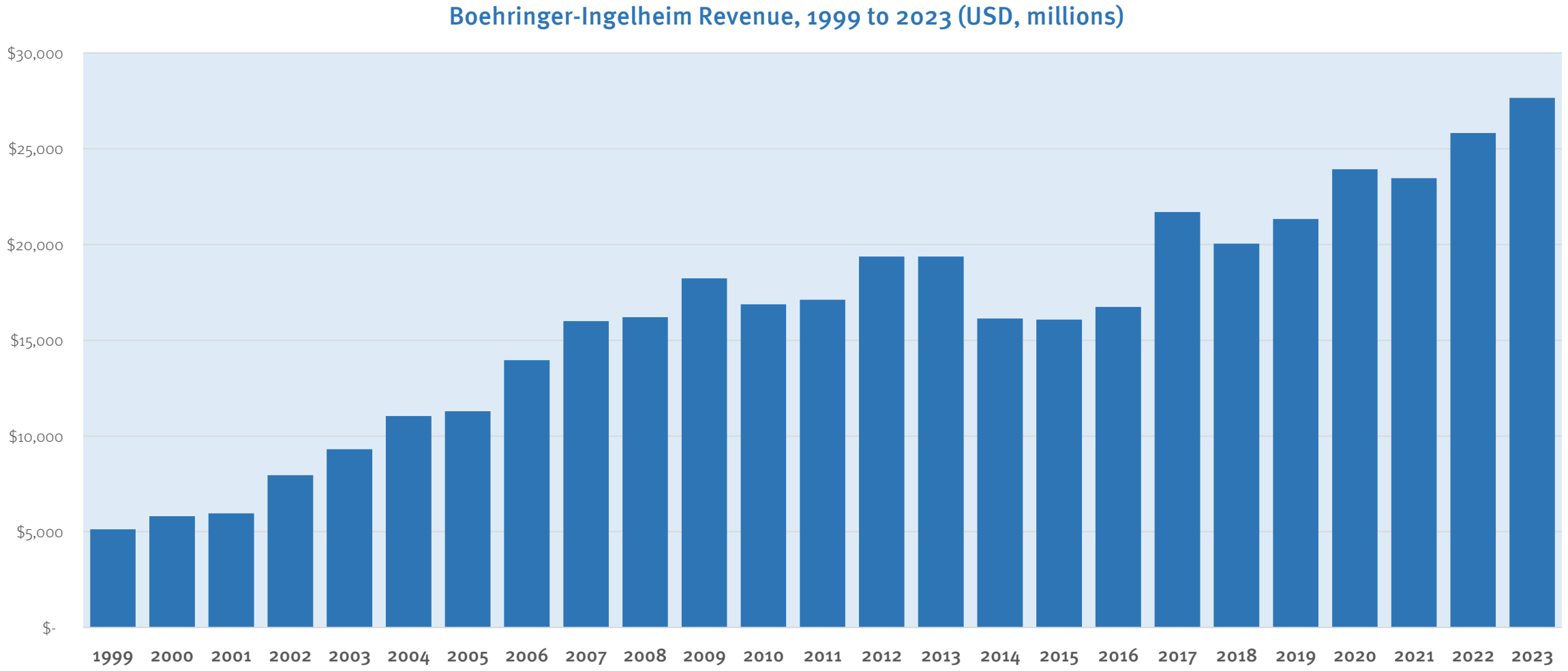
2023 Annual Report



2022 Annual Report

BI Growth of 7% CAGR Over 24 Years

Last Year, BI delivered $27.7 billion in revenue up by 7.1% from the year before. BI has been a relatively steady grower over a long period of time. With a substantial revenue stream from AbbVie's Skyrizi and a strong pipeline, BI is expected to deliver excellent growth into the foreseeable future.



Source: S&P CapitalIQ and Stifel research

Boehringer Ingelheim Has a Deep Pipeline

Some of the more important bets in the pipeline include the KRAS multi-inhibitor, the obesity programs, the P53 antagonist and a full suite of T-cell engagers. BI's PDE4B inhibitor for IPF/PPF has also gained a breakthrough designation from FDA and has large potential.

Development pipeline end of 2023

Cardiovascular, renal and metabolic diseases	Phase
GLP-1/F GF 21 agonist *	Phase I
NPY2r agonist * †	Phase I
> Anti-fibrotic agent	Phase I
Heart disease modulator *	Phase II
BI 764198 * TRPC6 Inhibitor | FSGS	Phase II
Survodutide (BI 456906) * GLP1/GCGR agonist | NASH/MASH Fast Track Designation granted by the US Food and Drug Administration Breakthrough Therapy Designation ↗	Phase II
BI 685509 sGC activator | CSPH	Phase II
BI 690517 + Empagliflozin Aldosterone synthase inhibitor + SGLT 2 inhibitor | CKD Fast Track Designation granted by the US Food and Drug Administration	Phase II
> Survodutide (BI 456906) * GLP1/GCGR agonist | Obesity	Phase III
Empagliflozin/New indication SGLT2 inhibitor | Prevention of HF post MI Fast Track Designation granted by the US Food and Drug Administration	Phase III
> Empagliflozin/New indication SGLT2 inhibitor | CKD	Registration[1]
Oncology	**Phase**
B7-H6/CD3 T-cell engager *	Phase I
DLL 3/CD3 T-cell engager *	Phase I
CD137/FAP agonist *	Phase I
Ezabenlimab (PD-1 antibody)†	Phase I
Zongertinib (HER2 TKI) Fast Track Designation granted by the US Food and Drug Administration	Phase I
> KRAS Multi-Inhibitor	Phase I
> KISIMA® cancer vaccine *†	Phase I
Brigimadlin * MDM2-p53-antagonist	Phase I
SIRPα-antagonist *	Phase I
> STING agonist (2nd generation)	Phase I
> VSV - GP *†	Phase I
> BI 764532* DLL 3/CD3 T-cell engager | 2L SCLC	Phase II
> BI 764532* DLL 3/CD3 T-cell engager | 3L ES-SCLC Fast Track designation granted by the US Food and Drug Administration	Phase II
> BI 764532 * DLL 3/CD3 T-cell engager | 2L epNEC Fast Track designation granted by the US Food and Drug Administration	Phase II
> BI 764532 * DLL 3/CD3 T-cell engager | LC-NEC Fast Track designation granted by the US Food and Drug Administration	Phase II
> Brigimadlin (BI 907828) * MDM2-p53 antagonist | 2L + BTC	Phase II
> Brigimadlin (BI 907828) * MDM2-p53 antagonist | 2L NSCLC	Phase II
> Brigimadlin (BI 907828) * MDM2-p53 antagonist | DDLPS Fast Track designation granted by the US Food and Drug Administration	Phase III
Respiratory diseases	**Phase**
Ion channel inhibitor	Phase I
Lysophospholipase inhibitor	Phase I
> IL11 antibody *	Phase I
BI 1291583 * CatC inhibitor | nCFB	Phase II
Nerandomilast (BI 1015550) PDE4B inhibitor | PPF	Phase III
Nerandomilast (BI 1015550) PDE4B inhibitor | IPF Breakthrough Therapy Designation ↗	Phase III
Immunology	**Phase**
PD-1 antibody	Phase I
> Immunomodulator	Phase I
TREM-1 antibody	Phase I
BI 706321 Kinase inhibitor | CD	Phase II
> BI 685509 sGC activator | SSc	Phase II
Spesolimab IL36R antibody | HS	Phase II
> Spesolimab IL36R antibody | NS	Phase II
> Spesolimab IL36R antibody | PG	Phase II
> Spesolimab IL36R antibody | GPP flare prevention Breakthrough Therapy Designation ↗	Registration
Chronic and complex mental health conditions	**Phase**
NMDA regulator	Phase I
> Digital therapeutic *	Phase I
BI 1358894 * TRPC 4/5 | MDD	Phase II
BI 1358894 * TRPC 4/5 | PTSD Fast Track designation granted by the US Food and Drug Administration	Phase II
Iclepertin GlyT1 inhibitor | CIAS Breakthrough Therapy Designation ↗	Phase III
> CT-155 * Prescription digital therapeutic | schizophrenia	Phase III
Retinal Health	**Phase**
Phospholipid modulator	Phase I
Vascular modulator	Phase I
C3-binding polypeptide	Phase I
BI 765128 Ischemia modulator | DR	Phase II
BI 764524 Sema3A antibody | DR	Phase II

Development pipeline end of 2023 (continued)

[1] Approved in the EU and US for the treatment in adults of chronic kidney disease, other submissions ongoing
† Being investigated only in combination with other therapies
> Key Pipeline Advances in 2023
* Partnered projects or acquired assets
↗ Breakthrough Therapy Designation or equivalent granted by the US, EU, China, or Japan

Indication abbreviations:

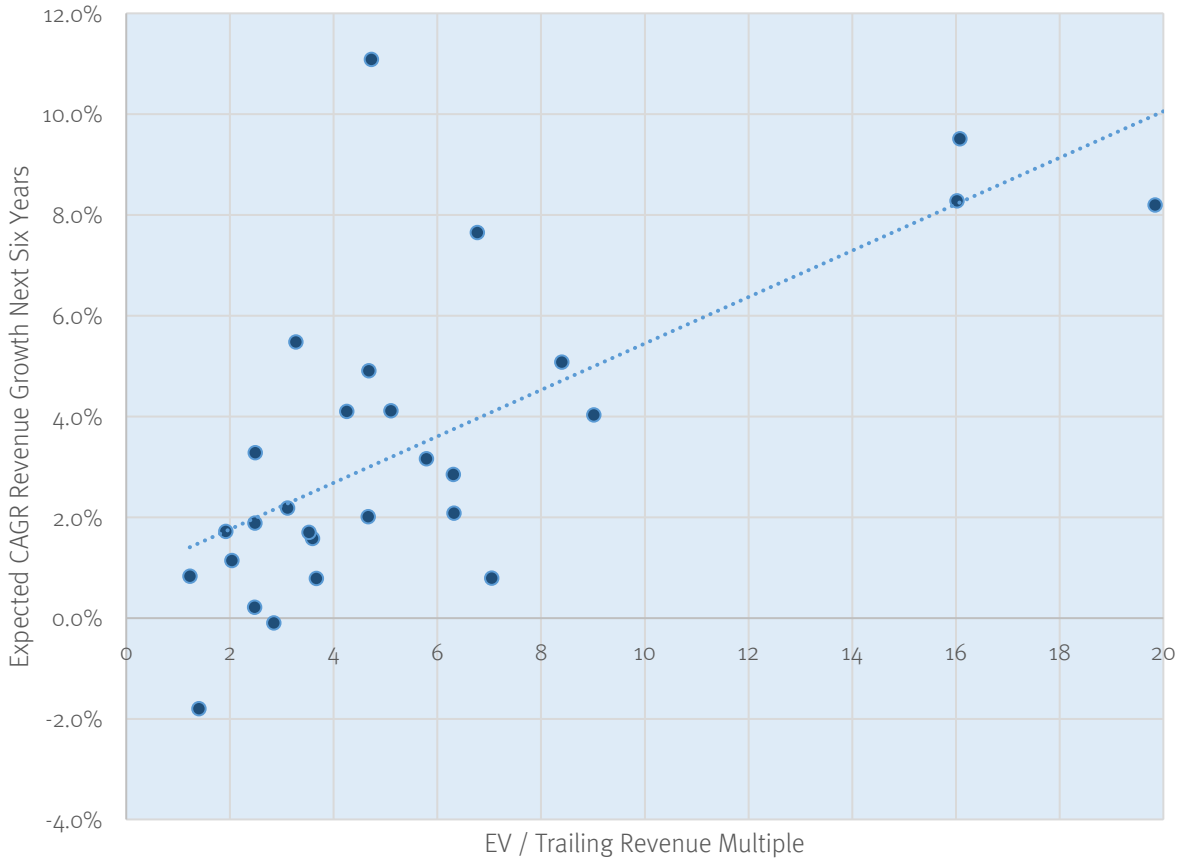
2L+BTC	2nd line treatment, advanced biliary tract cancer	HF	Heart failure
2L epNEC	2nd line treatment of extra-pulmonary neuroendocrine carcinoma	HS	Hidradenitis suppurativa
		IPF	Idiopathic pulmonary fibrosis
2L NSCLC	2nd line treatment of non-small cell lung cancer	LC-NEC	Large cell neuroendocrine carcinoma
2L SCLC	2nd line treatment of small cell lung cancer	MASH	Metabolic dysfunction-associated steatohepatitis
3L ES-SCLC	3rd line treatment of extensive stage small cell lung cancer	MDD	Major depressive disorder
		MI	Myocardial infarction
CD	Crohn's disease	NASH	Non-alcoholic steatohepatitis
CIAS	Cognitive impairment associated with schizophrenia	nCFB	non-cystic fibrosis bronchiectasis
CKD	Chronic kidney disease	NS	Netherton syndrome
CSPH	Clinically significant portal hypertension	PG	Pyoderma gangrenosum
DDLPS	Dedifferentiated liposarcoma	PPF	Progressive pulmonary fibrosis
DR	Diabetic Retinopathy	PTSD	Post-traumatic stress disorder
FSGS	Focal segmental glomerulosclerosis	SSc	Systemic sclerosis
GPP	Generalized pustular psoriasis		

Source: https://annualreport.boehringer-ingelheim.com/2023/download/index.html

Boehringer Ingelheim: The Quiet Giant

Our calculations would suggest that a publicly-traded Boehringer-Ingelheim would be the world's fourth most valuable pharmaceutical company.

Growth Expectations to 2028 vs EV to Revenue Multiple Today (Top 28 Global Pharmas by EV, April 19, 2024)



The Pearson correlation between expected revenue growth and the ratio of EV to revenue today is 0.7 among top pharma companies.

This is quite a strong relationship and indicates that investors are primarily focused on future growth prospects.

Boehringer-Ingelheim will see its top product, Jardiance®, go off patent in 2025. However, it has a very strong pipeline and barnburner revenue stream from OFEV® and Skyrizi® which take it to end of decade. We would expect historical 7% growth to hold up over time.

A 7% expected revenue growth rate (extrapolating the historical growth rate) would suggest a trading multiple of 13 times trailing revenue. This would put Boehringer's value at $360 billion. The #4 pharma in the world. More valuable the Merck but less valuable than J&J, Lilly and Novo Nordisk.

Source: S&P CapitalIQ and Stifel research

America's Moves Against Chinese Biotech Will Hurt Patients at Home

The Economist, April 18, 2024

America's crackdown on Chinese trade is broadening. On the campaign trail on April 17th President Joe Biden proposed tripling tariffs on steel imports, citing China's unfair trade practices. Having choked off China's access to advanced semiconductors and moved to ban TikTok, a Chinese-owned social-media app, lawmakers are eyeing a new target: biotechnology. The biosecure act, which has bipartisan support in Congress, proposes to end government contracts for firms that count Chinese biotech companies as clients or suppliers. American officials have previously said they want to guard a "small yard" of sensitive technologies with a "high fence". This bill illustrates that the yard is getting bigger, with sorry consequences for American consumers.

It uses the threat of ending lucrative federal contracts to sever American firms' ties with Chinese genomic sequencers, makers of sequencing machines and makers of large-molecule drugs such as weight-loss injectables. It extends the ban to any biotech firm with its headquarters in an adversary country, and mentions four Chinese companies by name.

The lawmakers claim that Chinese biotech firms have stolen intellectual property (IP) and collaborated with the People's Liberation Army (pla) and the Chinese government's repression of Uyghurs. (WuXi AppTec says it is not aware of unauthorised transfers of ip.) Yet here too the biosecure act is an overreaction. Western biopharma firms are notoriously protective of their ip and are surely best placed to decide whom to trust with their drug recipes. Chinese firms that are militarily or morally compromised should be targeted on an individual basis, not by dint of their nationality or industry.

The muddier the motivation behind the legislation seems, the harder it is to escape the conclusion that old-fashioned protectionism is at play. And that is a problem, because it means the bill would unduly hurt American consumers, without delivering any of the supposed security benefits.

If the legislation passes, as seems likely, drug shortages and delayed clinical trials for medicines would probably follow. Every large Western pharma firm and many small ones would have to abandon supply chains and find new partners for trials. Biotech startups in particular rely on cheap Chinese manufacturers to bring their products to market. And that would go against another stated intention of the Biden administration: to lower drug prices.

We continue to be befuddled by the U.S. government campaign to limit Wuxi Apptec.

The latest allegation that Wuxi is handing customer patent information over to the Chinese government (no evidence of this) ignores the reality that all ICT patents get filed well before issuance with the Chinese government anyway.

This reminds us very much of Congressional allegations that the film industry was infiltrated by communists in the 1950s. These were very damaging and turned out to be largely unfounded.

The downsides of limiting interaction with Wuxi are considerable as emphasized in this article and the *Forbes* article on the next page.

Source: https://www.economist.com/leaders/2024/04/18/americas-moves-against-chinese-biotech-will-hurt-patients-at-home

BIOSECURE ACT Not Good News for Drug Shortages

Forbes, April 17, 2024

According to the American Society of Health System Pharmacists, 323 drugs are currently experiencing shortages in the United States, the highest number the organization has seen since it began recording drug shortages in 2001. These include chemotherapies, ADHD medications, oxytocin and more. And the threat of shortages has a chance to be exacerbated further, at least in the short term, due to pending bipartisan legislation in both houses called the BIOSECURE Act,. If enacted, it might prevent American companies from working with key Chinese biotech contractors like WuXi AppTec, WuXi Biologics and MGI Tech. Stock prices have fallen significantly for these companies since the bill was introduced, and drug companies have warned investors that passage of the bill could have manufacturing impacts as well as cause delay in clinical trials.

Defenders of the bill say that this will ultimately improve competition – and decrease reliance on China. “We have seen this play before with Huawei and America’s telecoms sector. This bipartisan and bicameral bill will ensure U.S. taxpayer funds do not advance efforts by BGI and other [Chinese Communist Party]-backed companies to put Americans at long-term risk,” bill cosponsor Senator Bill Hagerty (R-TN) said in a press release when the bill was introduced.

So far it’s not clear whether the bill will pass this year, and what the ultimate legislation will look like. But given that pharmaceutical supply chains are complicated and involve years-long contracts (not to mention regulatory approvals), attorneys in the healthcare sector have been advising clients to start preparing to make changes. Industry trade group Biotechnology Innovation Organization announced it would support the legislation last month after initially opposing it, as the group walks the tightrope between trying to allay shortages but also support American manufacturing. The group expressed its desire to “work with Congress and the White House to develop policies and legislation that align with and advance a vibrant biotechnology industry for the United States and its allies.”

Source: https://www.forbes.com/sites/katiejennings/2024/04/17/innovationrx-legislation-could-prevent-pharma-companies-from-working-with-chinese-contractors

Interview with David Altshuler of Vertex on Pain Meds

Matthew Perrone, *AP News*, April 15, 2024 (excerpt)

Q: Why is Vertex interested in new drugs for treating pain?
David Altshuler: There is a great need for additional medicines to help people manage pain. There are medicines like Tylenol that are modestly effective but they're very well tolerated. And there's medicines such as opioids that are very effective but unfortunately have side effects, as well as addictive potential.

Q: How did you develop these drugs?
Vertex has been working on this for 20 years, and the insight that led to the medicines actually came from studies of people who had a rare condition where they are insensitive to pain. They can feel things, sense temperature, but do not feel pain. This was actually identified in a family of fire walkers who could walk on hot coals. So scientists figured out that that condition was due to inherited differences in a particular protein that has a role in pain signaling— so if you lack this function you don't feel pain. So we and many others have worked for decades to make a medicine that could recapitulate that naturally-occurring phenomenon.

Q: Are you testing this approach in patients with long-term pain?
We also did a study of diabetic peripheral neuropathy, which is long-term pain caused when people with diabetes have damaged nerves. That was also a positive study that showed clinically meaningful reduction in pain. So based on that study, a phase 2 study, we're now planning for a phase 3 study.

Q: What comes next?
For acute pain we're preparing to file for FDA approval based on our data. For the longer-term pain, what's called neuropathic pain, it's earlier in the development stage but the data is encouraging so far. So we're continuing studies to determine if it's possible to apply for approval there.

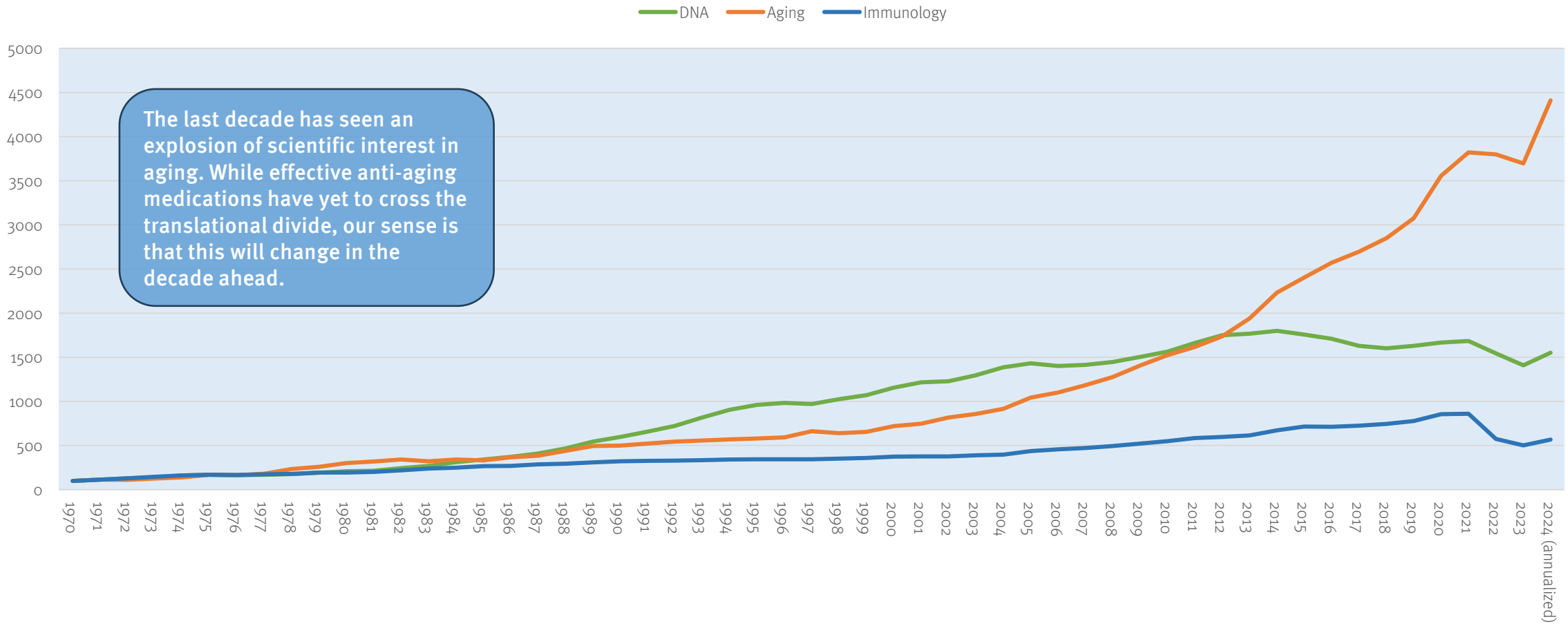
David Altshuler
Chief Scientific Officer
Vertex Pharma

Source: https://apnews.com/article/vertex-pharmaceuticals-pain-drug-opioid-medication-study-5ec38713f486ccbab827b7dd04aa8484

Hot Topics: Growth of Scientific Interest in Aging Outpacing Growth of Interest in Immunology and Genetics

Number of Publications in Pubmed with the Word "Aging", "DNA" or Immunology, 1970 to 2024 Relative to 1970

(Indexed to 1970, 2024 figure annualized as of April 20, 2024)



Cerevel Parkinson's Data Adds Lustre to AbbVie Acquisition

Phil Taylor, *Pharmaphorum*, April 19, 2024 (excerpt)

Cerevel Therapeutics' Parkinson's disease therapy tavapadon has shown efficacy in a phase 3 trial, reinforcing its blockbuster potential and no doubt delighting AbbVie, which has agreed to buy the company in an $8.7 billion deal.

Tavapadon is just one part of a pipeline that AbbVie chief executive Rick Gonzalez said had "multibillion-dollar sales potential" when the deal was announced last year, alongside other late-stage programmes like schizophrenia therapy emraclidine.

That confidence now seems to have been well placed. The dopamine D1/D5 partial agonist has met its main objective in the pivotal TEMPO-3 trial as an add-on to mainstay Parkinson's treatment levodopa, achieving a statistically significant reduction in 'on' time – when symptoms are under control – compared to placebo without troublesome dyskinesia side effects.

While patients with Parkinson's initially start taking drugs like levodopa to manage symptoms, these often fail to control symptoms throughout a 24-hour period and tend to lose their efficacy as the disease progresses, leading to periods of 'off' time when symptoms like tremor, stiffness, and slowness of movement occur.

In TEMPO-3, adding tavapadon to levodopa resulted in an increase of 1.1 hours in 'on' time – 1.7 hours versus 0.6 hours with placebo – after 27 weeks, accompanied by a significant reduction in 'off' time and a favourable side-effect profile, according to Cerevel. The primary endpoint in the 507-subject study was measured using patient-completed diary data.

The company says the drug is the first and only D1/D5 receptor partial agonist being studied as a once-daily treatment for Parkinson's, and some analysts have suggested that if it gets approved, it could make sales of $500 million to $1 billion a year.

How cool is this?

Cerevel hits it big on tapadon in a notoriously difficult disease to treat.

In retrospect, Cerevel might have benefitted from not selling so soon.

AbbVie shares were up last week on the news in a week when nearly 90% of all large caps traded down.

Source: https://pharmaphorum.com/news/cerevel-parkinsons-data-adds-lustre-abbvie-acquisition

Branded Parkinson's Disease Market Today Only $2 Billion

Source: PharmaSights (https://www.pharmasights.com/market-scanner/central-nervous-system)

Why Queasiness Kills Hunger: Brain Circuit Identified

Gillian Dohrn, *Nature*, April 18, 2024 (excerpt)

No one wants to eat when they have an upset stomach. To pinpoint exactly where in the brain this distaste for eating originates, scientists studied nauseated mice.

The work, published in Cell Reports on 27 March1, describes a previously uncharacterized cluster of brain cells that fire when a mouse is made to feel nauseous, but don't fire when the mouse is simply full. This suggests that responses to satiety and nausea are governed by separate brain circuits.

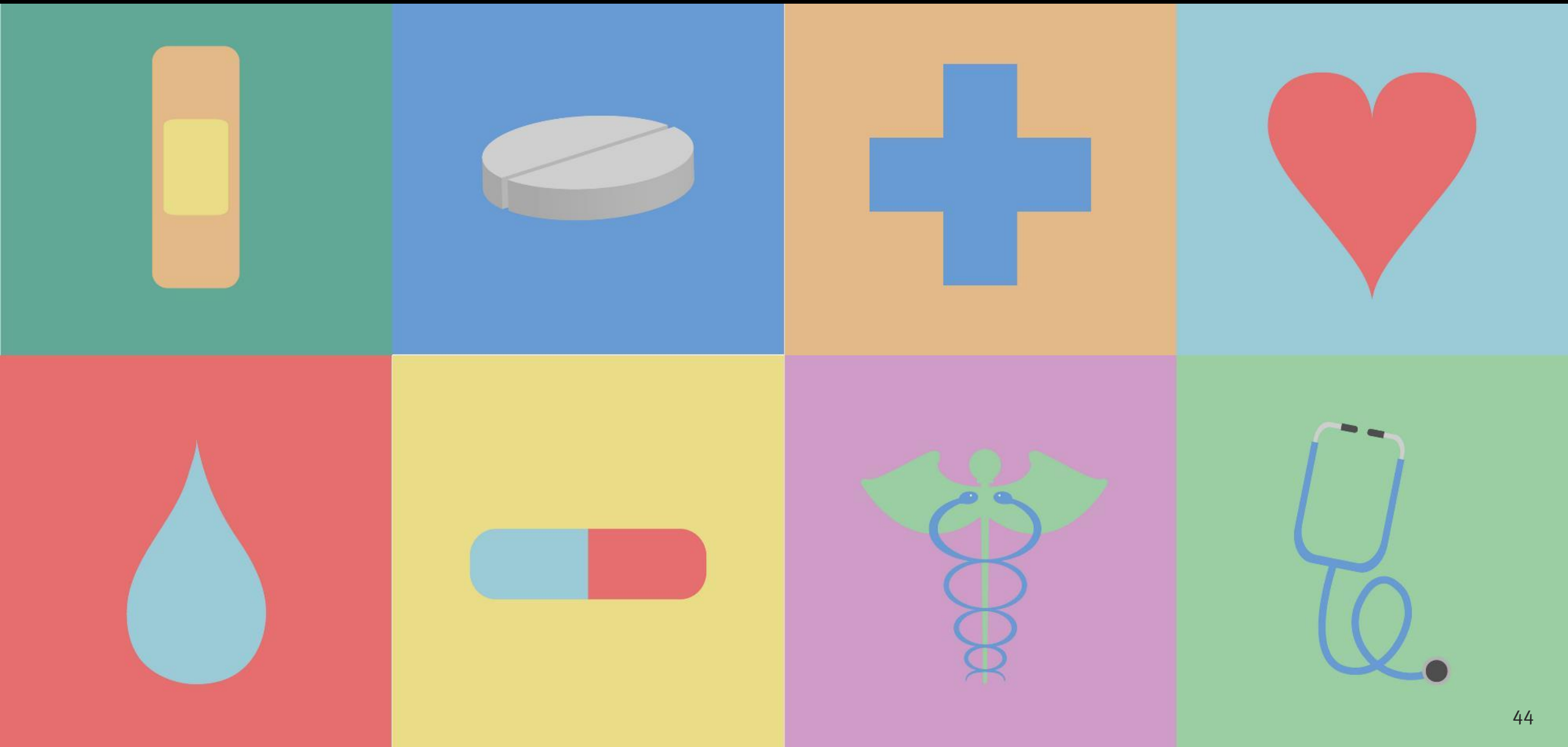
"With artificial activation of this neuron, the mouse just doesn't eat, even if it is super hungry," says Wenyu Ding at the Max Planck Institute for Biological Intelligence in Martinsried, Germany, who led the study.

Ding and colleagues suspected that this group of neurons was involved in processing negative experiences, such as feeling queasy, so they injected the mice with a chemical that induces nausea and then scanned the animals' brains. This confirmed that the neurons are active when mice feel nauseous.

Using a light-based technique called optogenetics, the team artificially activated the neurons of mice that had been deprived of food in the hours before the experiment. When the neurons were 'off', the mice ate. When the researchers turned them on, the mice walked away mid-chow.

Source: https://www.nature.com/articles/d41586-024-01037-0

Advisory Board Talk on High-Cost Drug Landscape



Stream of Spending on High-Cost Drugs Continues

The Advisory Board is a consultancy firm that provides content on leading edge topics to groups of clients including payors and hospitals.

Spending to grow in key therapeutic areas

Projected U.S. sales in 2024

- **Oncology: $116.6B**
  Largest growth in breast cancer treatment
- **Neurology: $38.8B**
  Largest growth in headache and migraine treatment
- **Diabetes: $37.6B**
  Growth driven by GLP-1 demand

23% Projected sales growth for GLP-1s in 2024

Two blockbusters expected to launch

Projected U.S. impact

Resmetirom

Nonalcoholic steatohepatitis (NASH)

- **5M-22M** eligible patients
- **$39.4K/year** list price[1]
- Projected annual sales:
  - **$155M** in 2024
  - **$1.8B** in 2028

Donanemab

Alzheimer's disease

- **1.4M** eligible patients
- **$20K/year** list price[1]
- Projected annual sales:
  - **$489M** in 2024
  - **$1.7B** in 2028

Projection based on ICER cost effectiveness analyses.

Source: Evaluate Pharma; Institute for Clinical and Economic Review, Resmetirom and obeticholic acid for non-alcoholic steatohepatitis (NASH), Draft Evidence Report, February 2023; Ross et al., Cost-effectiveness of Adacunamab and Donanemab for Early Alzheimer's Disease in the US, JAMA Neurology, 79(5), March 2022.

Source: https://www.advisory.com/topics/market-trends/2024/03/navigate-evolving-high-cost-drug-landscape

Spending on Cell and Gene Therapies to Hit a New High

Anticipated FDA cell and gene therapy approvals in 2024

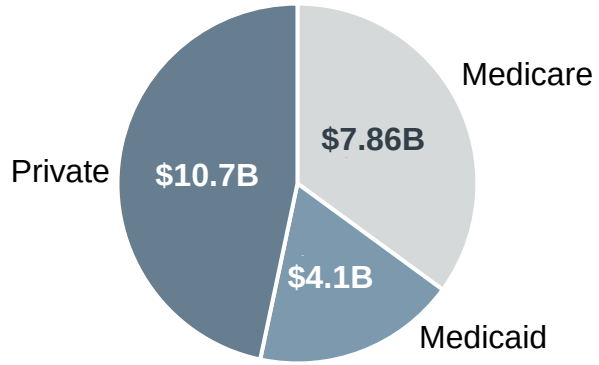
Therapy	*Estimated U.S. disease prevalence (patients)*	*Projected U.S. 2024 sales*
Afami-cell *Cell therapy for rare cancer*	7,300	$7M
Tab-cel *Cell therapy for rare cancer*	0.1-0.6 cases per 100K (estimated incidence rate)	$25M
Zevor-cel *CAR-T for rare cancer*	49,000	$2M
Fidanacogene elaparvovec *Gene therapy for hemophilia B*	4,000	$6M
Upstaza *Gene therapy for rare genetic disorder*	<100	$51M
Libmeldy *Gene therapy for rare genetic disorder*	9,300	$11M

2024 by the numbers

$22.4B
Estimated spend on gene therapies

93,000
Estimated patients treated by gene therapies

Breakdown of projected spend by payer type



Sources: "Estimating the Financial Impact of Gene Therapy in the U.S.," NBER Working Paper No. 28628, April 2021; Evaluate Pharma database; Alliance for Regenerative Medicine, Sector Snapshot, August 2022; "Aromatic L-amino acid decarboxylase deficiency," MedlinePlus; Petara, MR, et. al., Post-transplant lymphoproliferative disorders… , Cancer Letters, 369(1), December 2015.

Patient demand for GLP-1s to persist amid shortages

High projected spend in 2024

$25B In projected sales for GLP-1s

72% Of projected GLP-1 sales are for **diabetes**

Rising patient demand

44% Of surveyed people with obesity would **change jobs to gain coverage** for obesity treatment

1.7% Of U.S. population received a semaglutide prescription in 2023, a **40-fold increase** from 2018

Growing indications

Positive results from new clinical trials (**cardiovascular**, **heart failure**, **kidney disease**) may lead to new indications and better outcomes data

Shortages will continue

Mounjaro, Zepbound, Ozempic, and Wegovy are projected to have intermittent shortages across 2024

Source: Evaluate Pharma database: "FDA Drug Shortages, Food and Drug Administration"; Burger L., & Mathews E., "Novo rations Ozempic starter kits amid surge in use for weight loss," Reuters, November 2023; "Survey: Living with obesity in the time of GLP-1s," Ro and Obesity Action Coalition, April 2023; McPhillips D., "CNN Exclusive: Prescriptions…," CNN, September 2023.

Alzheimer's drugs stay covered, but restrictions apply

Concerns over serious side effects, short-term clinical benefits, and high costs lead to stringent coverage

Aduhelm (aducanumab)		Leqembi (lecanemab)
Accelerated FDA approval, June 2021	**Approval details**	Traditional FDA approval, June 2023
40% of patients on a high dose developed brain swelling or bleeding	**Safety concerns**	**17%** of patients experienced brain bleeds; **13%** experienced mild to moderate brain swelling
• **15%** jump in the Part B premium between 2021 and 2022 • Utilization management and restrictive coverage of Aduhelm contributed to **3%** decline in the Part B premium for 2023	**Financial impact to Medicare**	• **$26,500** for one year of treatment, excluding genetic tests, frequent brain scans, and safety monitoring • **22%** of total projected Part B spend attributed to Leqembi based on 5% utilization and 2021 data
• Requires participation in clinical trial • Studies must include diverse populations • Participation in registry and follow-up care	**Medicare coverage requirements**	• Diagnosis of mild cognitive impairment • Documented beta-amyloid plaque • Participation in registry and follow-up care

Sources: "New Alzheimer's Drugs Spark Hope for Patients and Cost Concerns for Medicare," Kaiser Family Foundation, July 2023; "Medicare Coverage Policy…" CMS, April 2022; Belluck P & Robbins R., F.D.A. Approves Alzheimer's Drug Despite Fierce Debate Over Whether It Works, New York Times, June 2021; Burke FJ, et al., "Lecanemab: Looking Before We Leap," *Neurology*, July 2023; Belluck P., "What to know if you're considering the Alzheimer's Drug Leqembi," New York Times, July 2023; CMS, Statement: Broader Medicare Coverage of Leqembi Available Following FDA Traditional Approval, July 2023.

Source: https://www.advisory.com/topics/market-trends/2024/03/navigate-evolving-high-cost-drug-landscape

Policy ramps up to target increasing drug costs

In 2024, policymakers are likely to tackle drug costs and access at the state and federal levels, using levers including:

- Medicare drug price negotiation
- Proposed federal policy to regulate pharmacy benefit managers (PBMs)
- State pharmaceutical regulation
- Direct and indirect remuneration fees (DIR)
- Proposed Center for Medicare and Medicaid Innovation (CMMI) payment models

Source: https://www.advisory.com/topics/market-trends/2024/03/navigate-evolving-high-cost-drug-landscape

Impact of the Inflation Reduction Act still Unknown

Medicare drug price negotiation will continue to roll out…

February 2024

Centers for Medicare and Medicaid Services (CMS) sent an initial offer to drug companies with proposal for maximum for price

September 2024

CMS to publish the Medicare maximum fair price for selected negotiated drugs

February 2025

CMS will release the next 10 Part D drugs up for negotiation

Ozempic is likely to be among those selected, with gross Part D spend in 2021 totaling $2.6B

Source: https://www.advisory.com/topics/market-trends/2024/03/navigate-evolving-high-cost-drug-landscape

…but pending lawsuits may cause disruption

Lawsuits currently pending to block government from enforcing results of Medicare drug price negotiation

Potential impact of successful challenges:

- Limit or negate potential savings to Medicare program and beneficiaries from drug negotiation
- Greater restrictions on federal regulatory authority in healthcare

What to watch for across 2024:

- Rolling District Court decisions
- Ongoing appeals
- Potential for cases to rise to Supreme Court

Sources: CMS, Medicare Drug Price Negotiation Program: Selected Drugs for Initial Price Applicability Year 2026; Cubanski J and Neuman T., A Small Number of Drugs Account for a Large Share of Medicare Part D Spending, Kaiser Family Foundation, July 2023; O'Neill Institute, Health Care Litigation Tracker: Inflation Reduction Act, Georgetown University Law Center.

This Election Year, Federal Policymakers Take on PBMs

Current proposed legislation regarding pharmacy benefit managers (PBMs)

Pharmacy benefit manager reform act

S. 1339

- Regulates commercial market
- Policies target:
  - Spread pricing
  - Rebate pass-through
  - Transparency
  - Step therapy

Status: **Passed committee**

Modernizing and ensuring PBM accountability act

S. 2973

- Regulates Medicare and Medicaid
- Policies target:
  - Delinking
  - Vertical integration
  - Spread pricing
  - Transparency
  - P&T committees

Status: **Introduced to Senate**

Lower cost, more transparency act

H.R. 5378

- Regulates commercial market
- Policies target:
  - Spread pricing
  - Rebate pass-through
  - Transparency
  - Step therapy

Status: **Passed House**

ONGOING

FTC investigation of PBMs

Requested information:

- Payments to other companies
- Pharmacy network participation
- Formularies, prescription drug lists, and tiering
- Pharmacy reimbursement data and rebate contracts

Source: Bath NW & Itzkowitz M, Understanding PBM Reform..., Manatt, October 2023; Minemyer P, "FTC launches investigation…" Fierce Healthcare, June 2022.

1. .

Source: https://www.advisory.com/topics/market-trends/2024/03/navigate-evolving-high-cost-drug-landscape

Initial PBM Regulations May Be Narrow

If Congress moves forward with a PBM regulation, the final bill is likely to:

Have a narrower reach

Example: Focus on government programs such as Medicare and Medicaid

Require transparency and federal reporting

Example: Send data on drug prices to the Department of Health and Human Services

Target spread pricing

Example: Ban PBMs from charging Medicaid programs more than the price the PBM paid to the pharmacy ("spread pricing")

Regulate preferred pricing for vertically integrated organizations

Example: Ban steering patients to PBM-owned pharmacies

Source: https://www.advisory.com/topics/market-trends/2024/03/navigate-evolving-high-cost-drug-landscape

Healthcare Leaders Must Adjust to New State Drug Policies

A wave of new policies focused on drug pricing in 2023

831 bills proposed in 50 states (plus DC and Puerto Rico)

Main targets

PBMs and health plans

- Examples: PBM transparency and reporting, affordability boards, spread pricing, pharmacy/patient steerage, consumer cost-sharing (including copay adjustment programs)

Life sciences manufacturers

- Examples: Patient out-of-pocket caps on insulin and epinephrine, drug importation programs, reporting drug prices and increases

Health systems

- Examples: 340B reporting and transparency

States to watch in 2024

150 bills **enacted** in 44 states in 2023

Texas established the Texas Pharmaceutical Initiative to launch a statewide transparent PBM

What to watch: Reaction of PBMs competing in Texas' commercial market

Florida passed a drug importation law in 2023, allocating $15M to purchase drugs from Canada

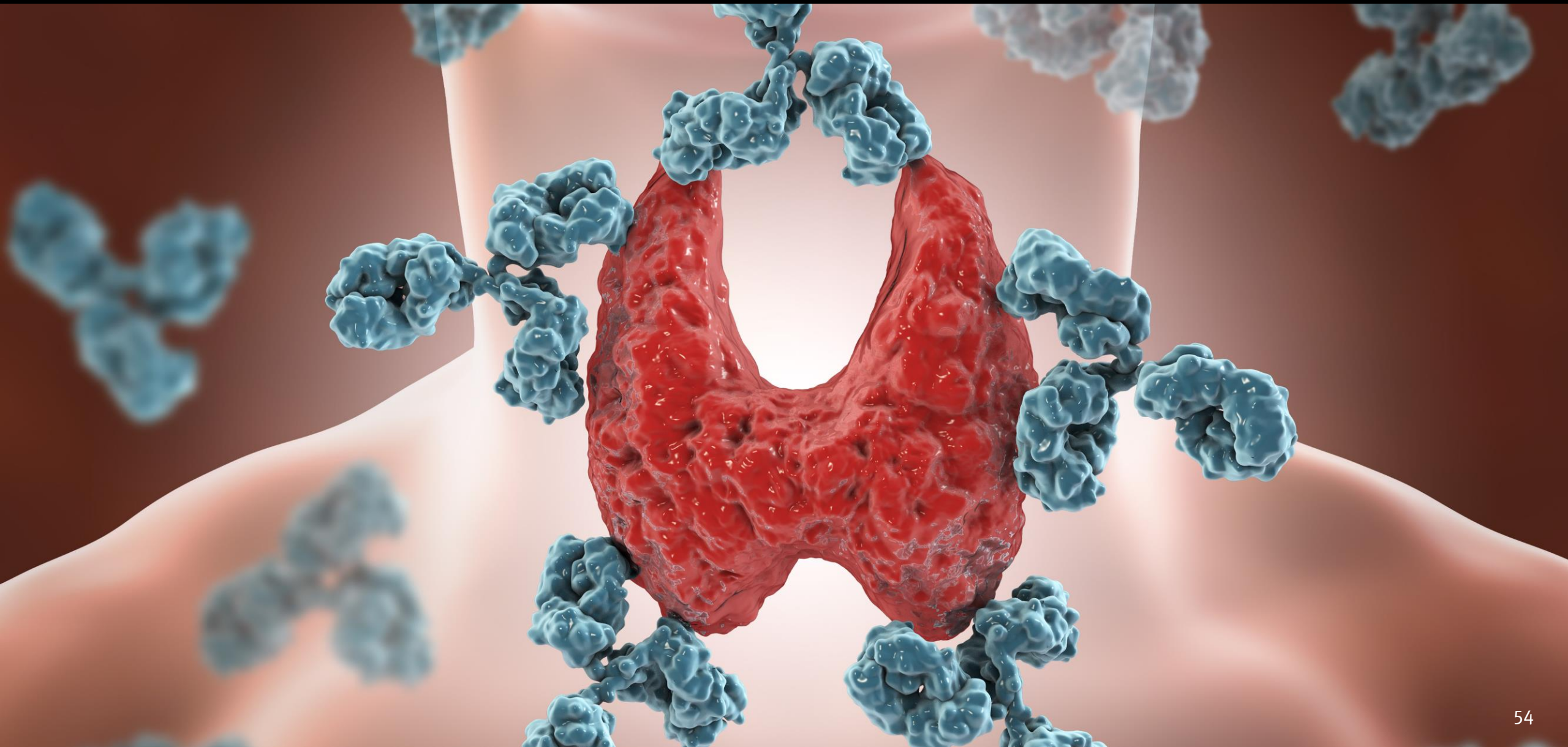
What to watch: Program success and popularity

Minnesota and New Jersey passed bills in 2023 creating prescription drug affordability boards

What to watch: Impact on state drug spend

Sources: Becker C, "Prescription Drug Bills in 2023: 5 Emerging Policy Trends." *National Conference of State Legislatures*. March 2023; "2023 State Legislative Action to Lower Pharmaceutical Costs." *National Academy for State Health Policy*. November 2023.

Autoimmune Thyroiditis: An Unmet Need



Autoimmune Thyroiditis / Hashimoto's Disease

2% of women

experience Hashimoto's disease in any given year.

Over 14 million women a year in US and Europe.

Caused by immune system attack on thyroid.

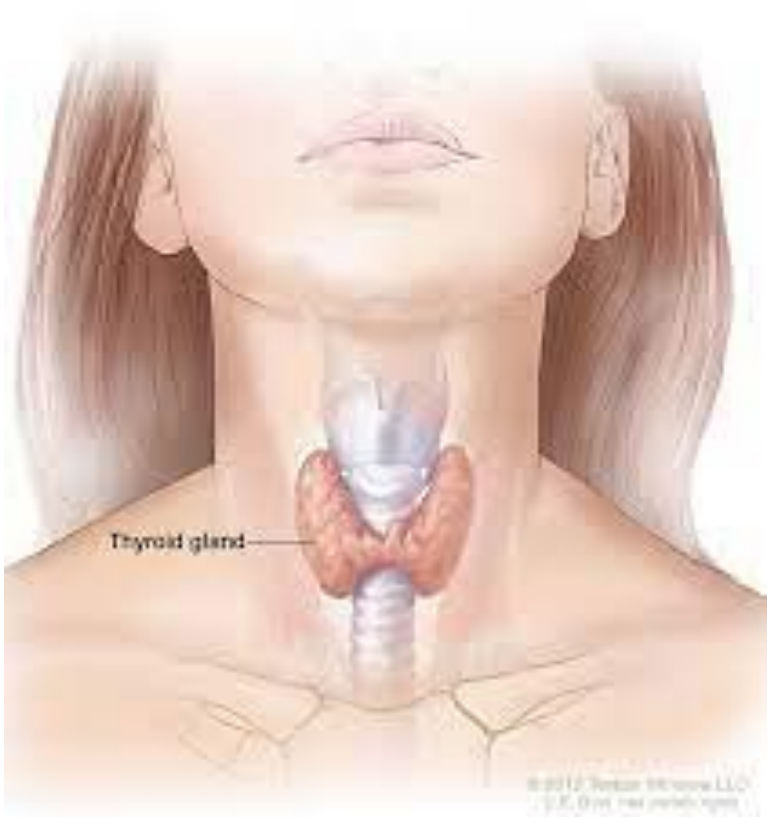
One of the most common autoimmune diseases.

Mainstay treatment is levothyroxine.

Ratio of women to male sufferers is 10 to 1.

We refer to the disease as hypothyroidism (HT).

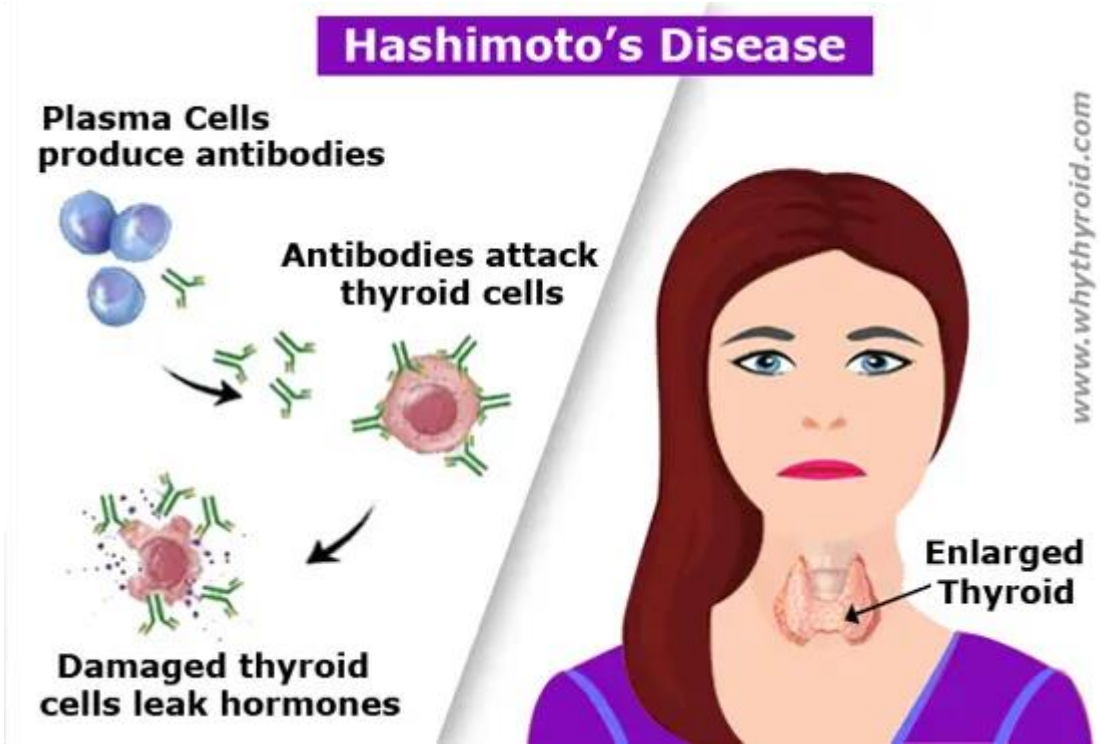
Biotech today very active on Grave's Disease but, to our knowledge, there is no known pipeline on HT.



Source: https://www.ncbi.nlm.nih.gov/books/NBK285557/

Initial Effect is Leak of Hormones

- The symptoms of thyroiditis depend on the type of thyroiditis and its phase. Most types of thyroiditis cause thyrotoxicosis symptoms followed by hypothyroid symptoms.
- Subacute thyroiditis and acute infectious thyroiditis usually also cause pain in your thyroid area. Some people with thyroiditis have an enlarged thyroid gland (goiter).
- The thyrotoxic phase of thyroiditis is usually short, lasting one to three months. If your thyroid cells are damaged quickly and there's a leak of excess thyroid hormone, you might experience symptoms of hyperthyroidism (overactive thyroid), which include:
  - Fast heart rate.
  - Increased appetite.
  - Unexplained weight loss.
  - Anxiety and nervousness.
  - Irritability.
  - Trouble sleeping
  - Increased sweating and sensitivity to heat.
  - Tremors.



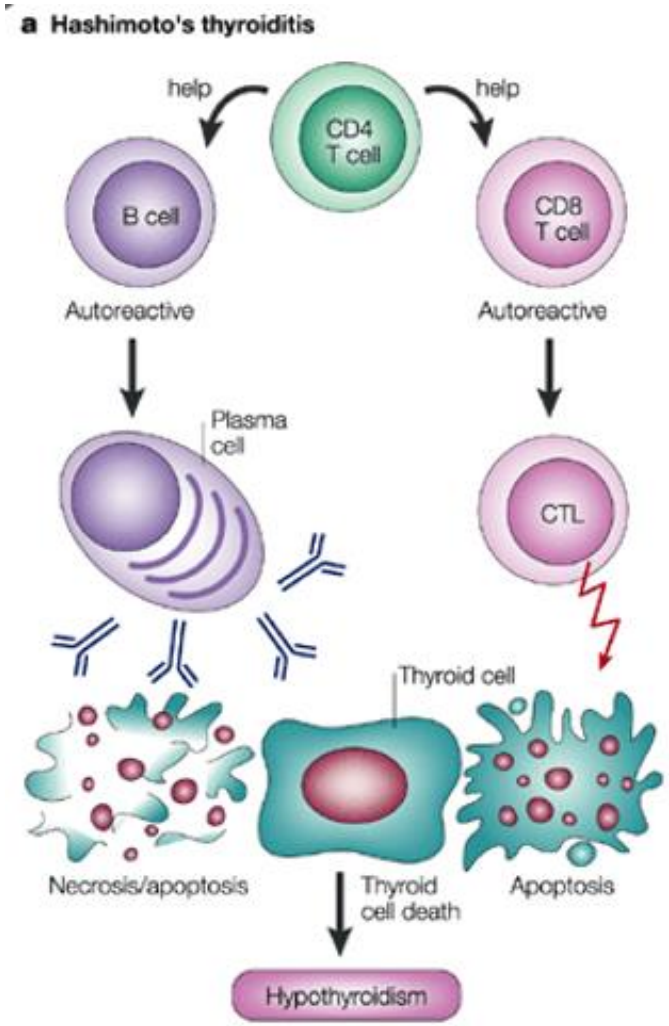
Source: https://my.clevelandclinic.org/health/diseases/15455-thyroiditis

HT Caused by an Autoimmune Reaction

The currently accepted mechanism of pathogenesis of HT involves three stages. In the early phase, antigen presenting cells (APC), mainly dendritic cells and macrophages, infiltrate the thyroid gland (for details see Figure 1). The infiltration may be induced by an environmental factor (iodine, toxins, infectious agent), which causes cell damage and the exposure of thyrocyte specific proteins. These proteins serve as their own source of antigenic peptides that are presented on the cell surface of APC after processing. Thyroid APC migrate to the lymph node where interactions occur between the APC cells, activated T cells, and B cells, leading to the induction of a variety of autoantibodies against thyroid-specific antigens.

In the next step, B lymphocytes, cytotoxic T cells, and macrophages infiltrate the thyroid. In this phase there is a clonal expansion of lymphocytes and propagation of lymphoid tissue in the thyroid gland.

In the final stage, “autoreactive” T cells, B cells, and antibodies cause a massive destruction of the thyrocytes. In addition to cell-mediated immune mechanisms, HT is characterized by the production of antibodies against a variety of thyroid-specific antigens, such as thyroglobulin (TG) and peroxidase (TPO), but also the TSH receptor, sodium/iodine (NIS) symporter, and pendrin has been recently reported.



Source: https://www.touchendocrinology.com/thyroid/journal-articles/hashimotos-thyroiditis-in-adolescents/

HT has Broad and Negative Impacts on the Quality of Life

Mikulska AA, Karaźniewicz-Łada M, Filipowicz D, Ruchała M, Główka FK. Metabolic Characteristics of Hashimoto's Thyroiditis Patients and the Role of Microelements and Diet in the Disease Management-An Overview. Int J Mol Sci. 2022 Jun 13;23(12):6580.

HT negatively affects wellbeing and quality of life, because thyroid hormones are responsible for the rate of basal metabolism, metabolism of carbohydrates, proteins, and fats, in addition to thermogenesis. Clinical symptoms usually occur as a result of hypothyroidism and are characterized by local and systemic manifestations. HT affects various systems, including the cardiovascular, gastrointestinal, pulmonary, hematopoietic, reproductive, neuropsychiatric, as well as the skin. The symptoms of HT are non-specific (concentration problems, chronic fatigue, weakness, dry skin, changes in body weight and constipation) and they depend on the severity of HT.

Source: https://pubmed.ncbi.nlm.nih.gov/35743024/

HT Leads to Weight Gain and Decreased Metabolic Rate

Sanyal D, Raychaudhuri M. Hypothyroidism and obesity: An intriguing link. Indian J Endocrinol Metab. 2016 Jul-Aug;20(4):554-7.

Body composition and thyroid hormones appear to be closely related. Thyroid hormones regulate basal metabolism, thermogenesis and play an important role in lipid and glucose metabolism, food intake and fat oxidation. Thyroid dysfunction is associated with changes in body weight and composition, body temperature and total and resting energy expenditure (REE) independent of physical activity.

Hypothyroidism is associated with decreased thermogenesis, decreased metabolic rate, and has also been shown to correlate with a higher body mass index (BMI) and a higher prevalence of obesity.[2] There is clinical evidence suggesting that even mild thyroid dysfunction in the form of subclinical hypothyroidism is linked to significant changes in body weight and represents a risk factor for overweight and obesity; however, this remains a gray area.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4911848/

HT is Often Associated with PCOS

Batóg G, Dołoto A, Bąk E, Piątkowska-Chmiel I, Krawiec P, Pac-Kożuchowska E, Herbet M. The interplay of oxidative stress and immune dysfunction in Hashimoto's thyroiditis and polycystic ovary syndrome: a comprehensive review. Front Immunol. 2023 Jul 31;14:1211231.

In recent years, there has been a significant increase in the concomitant incidence of Hashimoto's thyroiditis (HT) and polycystic ovary syndrome (PCOS), both in terms of incidence, etiology, and clinical consequences. PCOS patients suffering from autoimmune thyroid diseases show insulin resistance, impaired glucose tolerance, weight gain, and metabolic and reproductive complications. Studies have shown that chronic stress and its consequence, i.e. oxidative stress, play an important role in the pathomechanism of both disorders. It has also been shown that long-term exposure to stress triggers biological mechanisms, in particular related to the regulation of the inflammatory cascade, which plays a key role in autoimmune diseases.

Source: https://pubmed.ncbi.nlm.nih.gov/37588599/

Leading Therapy is Levothyroxine for Life

Mikulska AA, Karaźniewicz-Łada M, Filipowicz D, Ruchała M, Główka FK. Metabolic Characteristics of Hashimoto's Thyroiditis Patients and the Role of Microelements and Diet in the Disease Management-An Overview. Int J Mol Sci. 2022 Jun 13;23(12):6580.

The therapy of hypothyroidism as a result of HT is a daily, oral administration of synthetic thyroid hormone-levothyroxine, at a dosage of 1.6–1.8 micrograms per kilogram of body weight. The substitution therapy must be taken for life in order to maintain normal TSH levels. In addition to the use of LT_4, an appropriate diet and supplementation may be an important aspect of the treatment process.

Source: https://pubmed.ncbi.nlm.nih.gov/36332368/

Levothyroxine is the Third Most Prescribed Drug in the US

Source: https://clincalc.com/DrugStats/Default.aspx

ClinCalc DrugStats Database

Free U.S. Outpatient Drug Usage Statistics

ClinCalc.com » Pharmacy » DrugStats Database

Drug Search:

Enter a generic or brand medication name

Enter a generic or brand medication name

The Top 200 Drugs of 2021

Search:

Rank	Drug Name	Total Prescriptions (2021)	Total Patients (2021)	Annual Change
1	Atorvastatin	116,702,335	28,111,470	0
2	Metformin	91,151,043	19,883,763	↑ 1
3	Levothyroxine	89,309,050	19,064,382	↓ 1
4	Lisinopril	88,272,557	20,475,892	0
5	Amlodipine	73,569,606	17,734,288	0
6	Metoprolol	65,529,551	15,535,072	0
7	Albuterol	61,469,064	18,070,429	0
8	Losartan	55,245,074	13,363,279	↑ 1
9	Omeprazole	54,561,969	13,900,115	↓ 1
10	Gabapentin	47,125,973	10,697,239	0
11	Sertraline	39,206,397	8,478,900	↑ 1
12	Hydrochlorothiazide	39,038,822	9,665,980	↓ 1
13	Rosuvastatin	32,632,145	8,006,428	↑ 4
14	Montelukast	30,996,712	7,119,519	0
15	Escitalopram	30,505,719	6,499,379	0
16	Simvastatin	30,492,289	7,839,909	↓ 3
17	Dextroamphetamine; Dextroamphetamine Saccharate; Amphetamine; Amphetamine	30,371,088	3,990,803	↑ 5

Some HT Harms Remain After Levothyroxine Therapy

Mikulska AA, Karaźniewicz-Łada M, Filipowicz D, Ruchała M, Główka FK. Metabolic Characteristics of Hashimoto's Thyroiditis Patients and the Role of Microelements and Diet in the Disease Management-An Overview. Int J Mol Sci. 2022 Jun 13;23(12):6580.

The cross-sectional study conducted by Yalcin et al. indicates that autoimmunity of the thyroid gland may have an impact on impaired health-related quality of life, depression and anxiety in euthyroid patients with HT independent of levothyroxine (LT_4) substitution. Some studies reported that even euthyroid HT patients have an increased predisposition to depression and anxiety disorders.

Source: https://pubmed.ncbi.nlm.nih.gov/36332368/

Not All Cases of Hypothyroidism Well Controlled with Levothryoxine

Kahaly GJ, Gottwald-Hostalek U. Use of levothyroxine in the management of hypothyroidism: A historical perspective. Front Endocrinol (Lausanne). 2022 Nov 2;13:1054983

Most cases of hypothyroidism can be controlled adequately using LT_4 monotherapy, as described above. However, a minority of LT_4-treated patients continue to report symptoms reminiscent of hypothyroidism despite having TSH controlled to within the reference range. Careful examination may reveal a hitherto undiscovered explanation for these symptoms in most, but not all, patients. Variations in the activity of deiodinases, in part due to LT_4 treatment, may alter the relative availability of T_4 and T_3 in peripheral target tissues, which may underlie the persistence of hypothyroid symptoms in some patients.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9666762

Levothyroxine Associated with Heightened Cancer Risk

Wändell P, Carlsson AC, Li X, Sundquist J, Sundquist K. Levothyroxine treatment is associated with an increased relative risk of overall and organ specific incident cancers - a cohort study of the Swedish population. Cancer Epidemiol. 2020 Jun;66:101707. doi: 10.1016/j.canep.2020.101707. Epub 2020 Mar 26.

High thyroid hormone values have been associated with an increased risk of incident cancers, especially breast cancer but also lung cancer and any solid cancers. We explored whether there is an increased risk of overall and cause-specific cancers in those receiving levothyroxine treatment. We included all individuals ≥ 18 years in Sweden (N = 8,573,313) on January 1 2009, and identified patients with two or more dispensed prescriptions of levothyroxine 2005-2006 (n = 253,193, 3.0 %). A cancer diagnosis in the Swedish Cancer Register 2009-2015 was used as outcome. We excluded patients with a cancer diagnosis before 2005. Cox regression was used (hazard ratios, HRs, and 95 % confidence intervals, CI) with adjustments for age, socioeconomic/neighborhood factors and co-morbidities. Totally 399,751 cases of incident cancer were identified, with a slight increased overall risk associated with levothyroxine treatment for both men, adjusted HR 1.06 (95 % CI 1.03-1.10), and women, adjusted HR 1.08 (95 % CI 1.07-1.10). For men, increased risks were found for cancers of the thyroid gland and other endocrine glands. For women, increased risks were found for cancers of the breast, endometrium, other female genitals (ovaries not included), stomach, colon, liver, pancreas, urinary bladder, skin, leukemia, and unspecified primary tumor. Unlike men, for women, no increased risk was found for cancer of the thyroid gland. In conclusions, levothyroxine treatment was associated with an excess cancer risk, including many different types of cancer, especially among women. Our results need confirmation by other studies, but levothyroxine is recommended to be prescribed only on approved indications.

Source: https://pubmed.ncbi.nlm.nih.gov/32222650/

Levothyroxine Can Be Associated with Higher Cardiovascular Disease Risk

Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. J Clin Endocrinol Metab. 2010 Jan;95(1):186-93.

Context: For patients on T(4) replacement, the dose is guided by serum TSH concentrations, but some patients request higher doses due to adverse symptoms.

Setting: A population-based study of all patients in Tayside, Scotland, was performed. All patients taking T(4) replacement therapy (n = 17,684) were included.

Main outcome measures: Fatal and nonfatal endpoints were considered for cardiovascular disease, dysrhythmias, and fractures. Patients were categorized as having a suppressed TSH (‹or=0.03 mU/liter), low TSH (0.04-0.4 mU/liter), normal TSH (0.4-4.0 mU/liter), or raised TSH (›4.0 mU/liter).

Results: Cardiovascular disease, dysrhythmias, and fractures were increased in patients with a high TSH: adjusted hazards ratio, 1.95 (1.73-2.21), 1.80 (1.33-2.44), and 1.83 (1.41-2.37), respectively; and patients with a suppressed TSH: 1.37 (1.17-1.60), 1.6 (1.10-2.33), and 2.02 (1.55-2.62), respectively, when compared to patients with a TSH in the laboratory reference range. Patients with a low TSH did not have an increased risk of any of these outcomes [hazards ratio: 1.1 (0.99-1.123), 1.13 (0.88-1.47), and 1.13 (0.92-1.39), respectively].

Conclusions: Patients with a high or suppressed TSH had an increased risk of cardiovascular disease, dysrhythmias, and fractures, but patients with a low but unsuppressed TSH did not. It may be safe for patients treated with T(4) to have a low but not suppressed serum TSH concentration.

Source: https://pubmed.ncbi.nlm.nih.gov/32222650/

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