Biopharmaceutical Sector

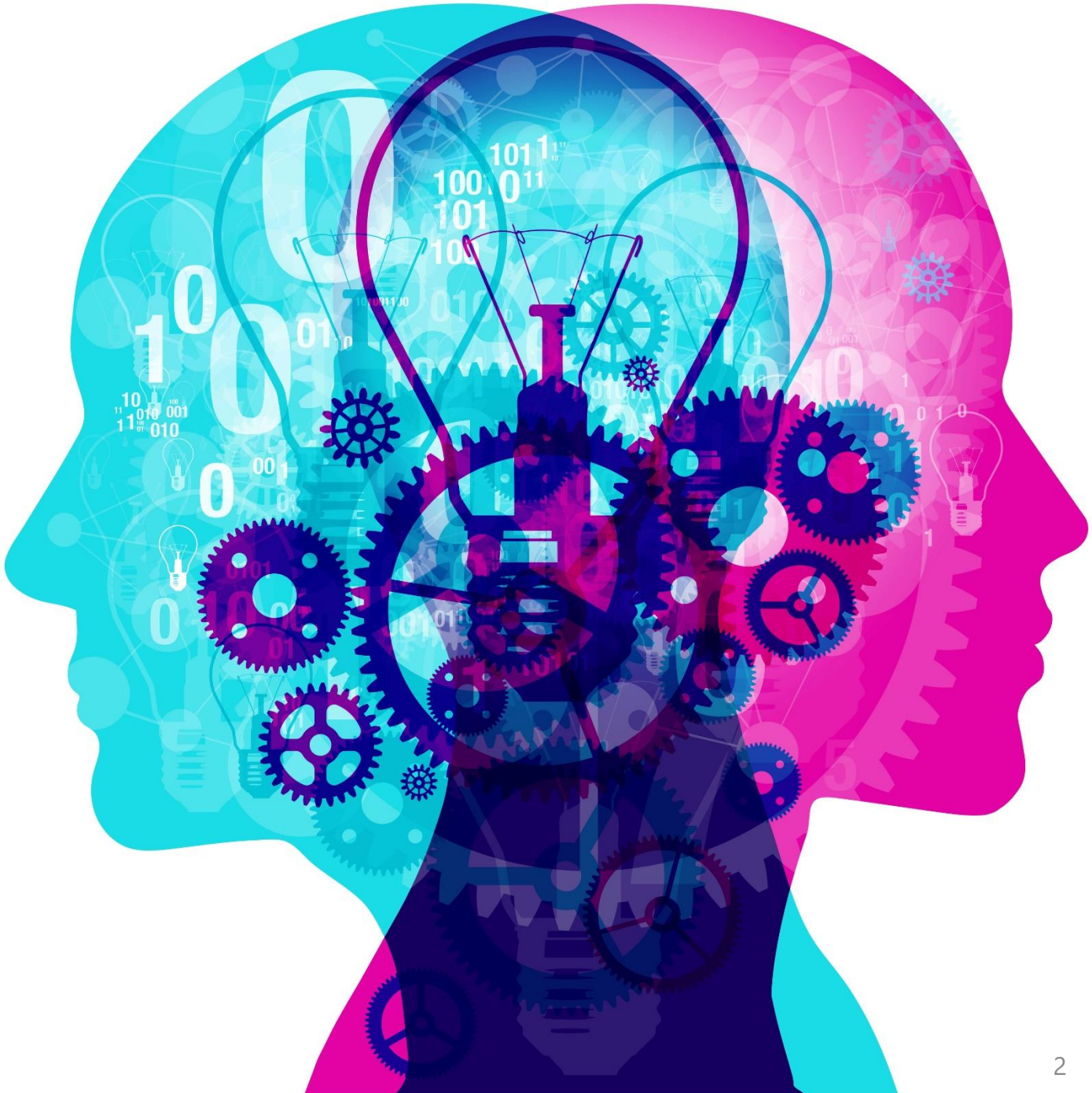
Weekly Update – August 7, 2023

STIFEL | Healthcare

Table of Contents

STIFEL | Healthcare

555 Madison Ave, Suite 1201, New York NY 10022, +1-(212) 257-5801
Web: www.stifel.com



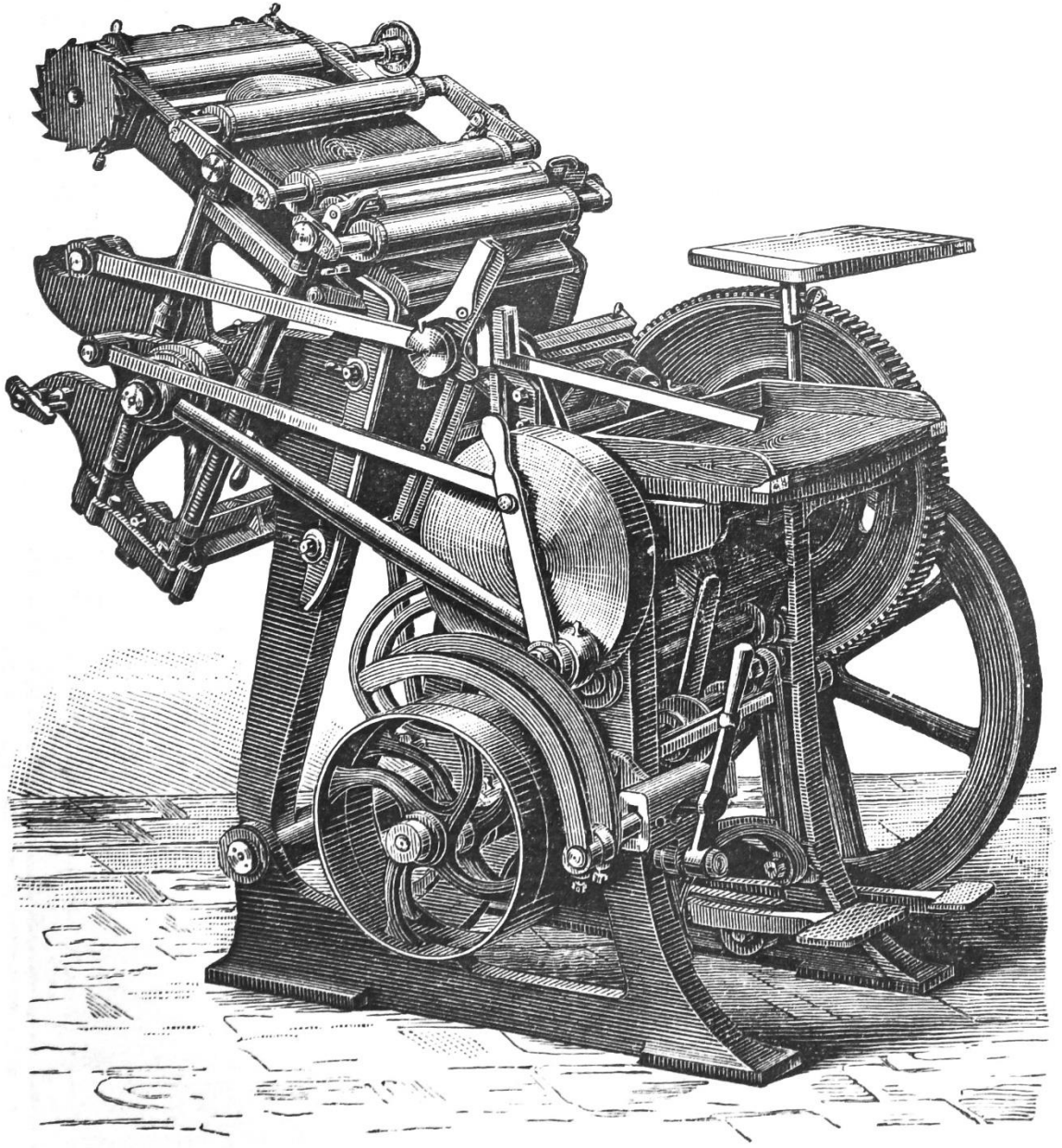
Mental processes. Source: Getty Images

Publication Note

Our publishing schedule has shifted for the Summer to once every two weeks.

We will be publishing our next update on August 21 and then on September 5th.

If you are not on the mailing list for this publication and wish to be added, please notify Natasha Yeung (yeungn@stifel.com).



Old and creaky printing press. Source: Getty Images

Join Us at These Upcoming Events

1

Biotech Hangout held its latest event on August 4th.

The next event will be on August 14th

Note that the time for the event has changed to noon EDT.

Please join us.

August 4th Replay
https://twitter.com/i/spaces/1RDGlalkYOdJL

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

2

biofuture™

New York City | October 4-6, 2023

Innovators & Investors Come Together to Shape the Future of Healthcare

At this year's summit, BioFuture attendees will be exploring the exciting mashup between rapidly evolving fields including biopharma, digital medicine, big data, AI, healthcare systems, payors, and more. The coming decade will dramatically accelerate the transformation of the healthcare ecosystem. Be part of the discussions that will shape and transform the future of healthcare.

To Learn More
https://biofuture.com/

Venture Capitalists Have the Best Quotes

"This is an industry of exceptions. Exceptional companies and exceptional people."

Otello Stampacchia, Omega Fund, Aug 2023

"Biology always wins."

David Sable, Special Situations Fund, Aug 2023

"You say crossover. Oh you mean, a Series B."

Prominent VC, April 2022

"Two companies fighting over a niche market are like two bald men fighting over a comb."

Eugene Kleiner

"You can only set yourself on fire once."

Oleg Nodelman, EcoR1 (on cutting R&D to save money)

"I have only two enemies: the disease and the clock."

Tal Zaks, Orbimed, 2021 (on Covid vaccines at Moderna)

Macro Update

Back of Fifty Dollar Bill, Getty Images

Fed Governor Michelle Bowman Comments on Inflation on August 5, 2023

As you likely know, at our most recent meeting in July, the Federal Open Market Committee (FOMC) raised the target range for the federal funds rate by 25 basis points—to a range of 5-1/4 to 5-1/2 percent—and we continue to reduce the Fed's securities holdings. Since March 2022, the FOMC has been tightening monetary policy as part of our ongoing effort to lower unacceptably high inflation. Since then, we have seen some progress, and inflation has declined from last year's very high level. Most recently, after more than six months of stubbornly high readings, the June consumer price index showed lower core inflation, a measure that excludes food and energy prices. While this development is a positive sign that monetary policy is contributing to lower inflation, both total and core inflation remain well above our 2 percent target.

Michelle Bowman

At the same time, the economy and the labor market have remained strong as the FOMC has tightened monetary policy. Real gross domestic product grew slightly more than 2 percent at an annual rate in the first half of the year, well above many forecasters' expectations. Consumer spending has been robust, and the housing sector appears to be rebounding with accelerating growth in house prices and a pickup in new housing starts. The most recent employment report showed a strong labor market with low unemployment and solid job gains. The pace of job gains has slowed, which is a sign that labor market demand and supply are coming into better balance. But the demand for workers continues to exceed the supply of available job seekers, adding upward pressure on prices.

The banking system continues to be strong and resilient. While banks have tightened lending standards in response to higher interest rates and funding costs, there have not been signs of a further sharp contraction in credit from the stress earlier this year that would slow economic activity. Though loan balance growth has slowed, banks have continued to increase lending to households and businesses.

Given the strong economic data and still elevated inflation, I supported the FOMC's decision in July to further increase the target range for the federal funds rate. **I also expect that additional rate increases will likely be needed to get inflation on a path down to the FOMC's 2 percent target.**

The recent lower inflation reading was positive, but I will be looking for consistent evidence that inflation is on a meaningful path down toward our 2 percent goal as I consider further rate increases and how long the federal funds rate will need to remain at a restrictive level. I will also be watching for signs of slowing in consumer spending and signs that labor market conditions are loosening.

Source: https://www.federalreserve.gov/newsevents/speech/bowman20230805a.htm

The Case for a Soft Landing in the Economy Just Got Another Boost

NPR, All Things Considered, August 4, 2023

Odds of a soft landing may have just gotten a little better.

The latest employment report from the Labor Department shows job growth held steady last month, boosting hopes that the Federal Reserve may be able to curb inflation without triggering a sharp jump in unemployment.

U.S. employers added 187,000 jobs in July. While job growth has moderated, it hasn't come close to stalling, even after the Fed raised interest rates to the highest level in 22 years.

Source: https://www.npr.org/2023/08/04/1192120360/jobs-employers-economy-soft-landing-recession-inflation. Photo from Getty Images.

Fitch Downgrades the United States' Long-Term Ratings to 'AA+' from 'AAA'; Outlook Stable

Fitch Ratings, August 1, 2023

Fitch Ratings - London - 01 Aug 2023: Fitch Ratings has downgraded the United States of America's Long-Term Foreign-Currency Issuer Default Rating (IDR) to 'AA+' from 'AAA'. The Rating Watch Negative was removed and a Stable Outlook assigned. The Country Ceiling has been affirmed at 'AAA'.

Ratings Downgrade: The rating downgrade of the United States reflects the expected fiscal deterioration over the next three years, a high and growing general government debt burden, and the erosion of governance relative to 'AA' and 'AAA' rated peers over the last two decades that has manifested in repeated debt limit standoffs and last-minute resolutions.

Erosion of Governance: In Fitch's view, there has been a steady deterioration in standards of governance over the last 20 years, including on fiscal and debt matters, notwithstanding the June bipartisan agreement to suspend the debt limit until January 2025. The repeated debt-limit political standoffs and last-minute resolutions have eroded confidence in fiscal management. In addition, the government lacks a medium-term fiscal framework, unlike most peers, and has a complex budgeting process. These factors, along with several economic shocks as well as tax cuts and new spending initiatives, have contributed to successive debt increases over the last decade. Additionally, there has been only limited progress in tackling medium-term challenges related to rising social security and Medicare costs due to an aging population.

Rising General Government Deficits: We expect the general government (GG) deficit to rise to 6.3% of GDP in 2023, from 3.7% in 2022, reflecting cyclically weaker federal revenues, new spending initiatives and a higher interest burden. Additionally, state and local governments are expected to run an overall deficit of 0.6% of GDP this year after running a small surplus of 0.2% of GDP in 2022. Cuts to non-defense discretionary spending (15% of total federal spending) as agreed in the Fiscal Responsibility Act offer only a modest improvement to the medium-term fiscal outlook, with cumulative savings of USD1.5 trillion (3.9% of GDP) by 2033 according to the Congressional Budget Office. The near-term impact of the Act is estimated at USD70 billion (0.3% of GDP) in 2024 and USD112 billion (0.4% of GDP) in 2025. Fitch does not expect any further substantive fiscal consolidation measures ahead of the November 2024 elections.

Source: https://www.fitchratings.com/research/sovereigns/fitch-downgrades-united-states-long-term-ratings-to-aa-from-aaa-outlook-stable-01-08-2023

Fitch Downgrades America

The rating agency may be too optimistic about the U.S. fiscal future.

Excerpt, Editorial Board, *Wall Street Journal,* August 2, 2023

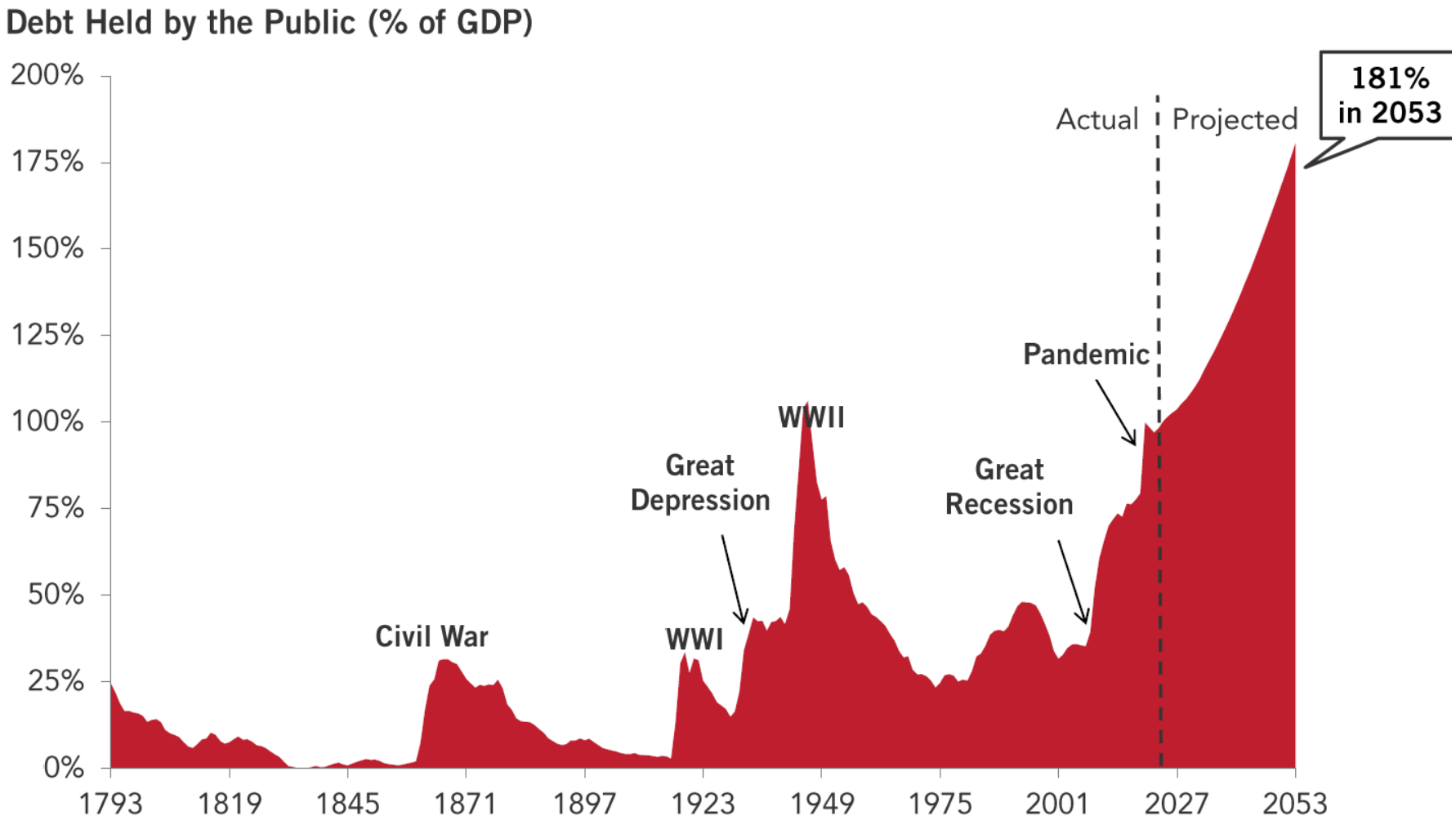
The ratio of U.S. debt held by the public to GDP in 2011 was only 65.5%, while the Congressional Budget Office expects it to be 98.2% this year. That's up from 79.4% before the pandemic, and it is expected to rise to 115% of GDP by 2033 on present budget trend. As Fitch notes, U.S. "general government debt," including state and local government, is more than two-and-a-half times greater than the median 39.6% of GDP for a AAA rating.

The future looks worse. The deficit in the first nine months of this fiscal year hit $1.39 trillion, up 169% from the same period the year before. The deficit is supposed to shrink when the economy grows, but revenue isn't keeping pace with runaway spending. The debt-ceiling deal this year did little to curtail the spending bulge still in the pipeline from the first two Biden years. Interest on the debt this year is expected to be $663 billion, which is $188 billion more than all corporate tax revenue.

Democrats are attacking Fitch, and Treasury Secretary Janet Yellen criticized the decision as "arbitrary and based on outdated data." Outdated? Her own department on Monday increased the government's expected borrowing from July to September to $1 trillion from $733 billion. That's for three months.

Source: https://www.wsj.com/articles/fitch-downgrades-u-s-debt-credit-rating-3b8e71d3. Photo from Getty Images.

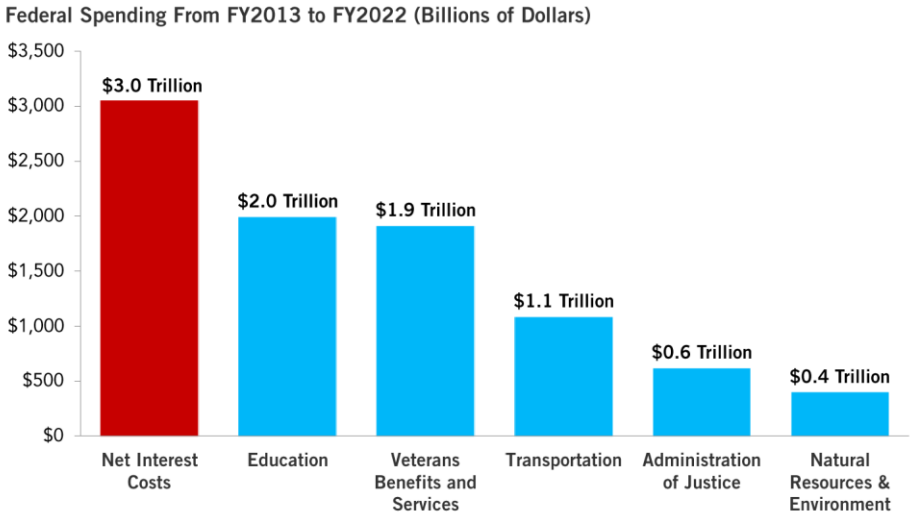
U.S. Debt / GDP Ratio Increasing



SOURCES: Congressional Budget Office, *The 2023 Long-Term Budget Outlook*, June 2023, *The Budget and Economic Outlook: 2023 to 2033*, February 2023, and *The Budget and Economic Outlook: 2020 to 2030*, January 2020.

Source: https://www.pgpf.org/chart-archive/pgpf-chart-pack

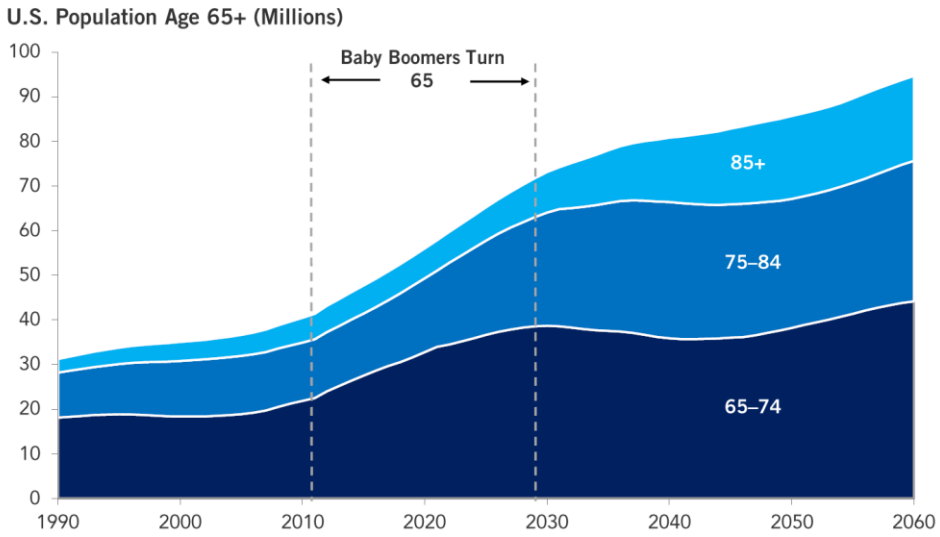
Over the past decade, the U.S. spent more on interest on the national debt than it did on other national priorities



SOURCES: Office of Management and Budget, *Historical Tables, Budget of the United States Government: Fiscal Year 2024*, March 2023.
NOTE: Education includes education, training, employment, and social services.

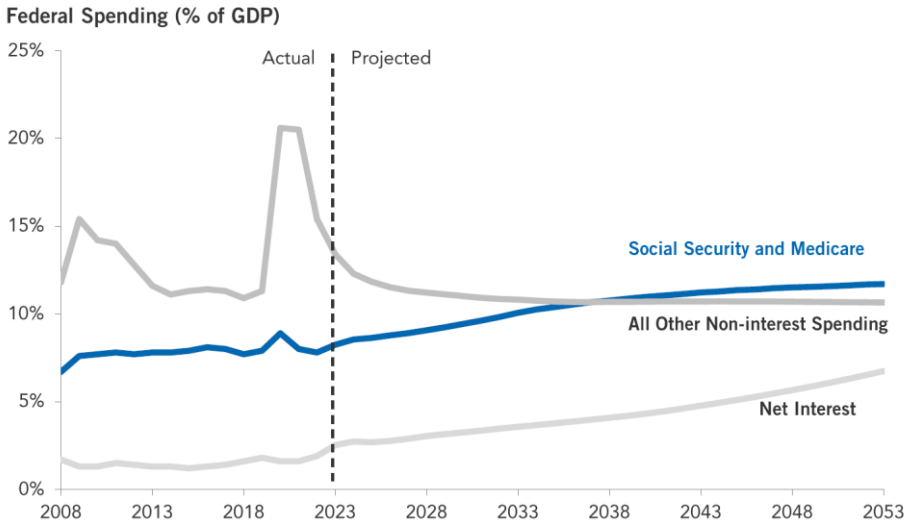
PGPF.ORG

The elderly population is growing rapidly and living longer



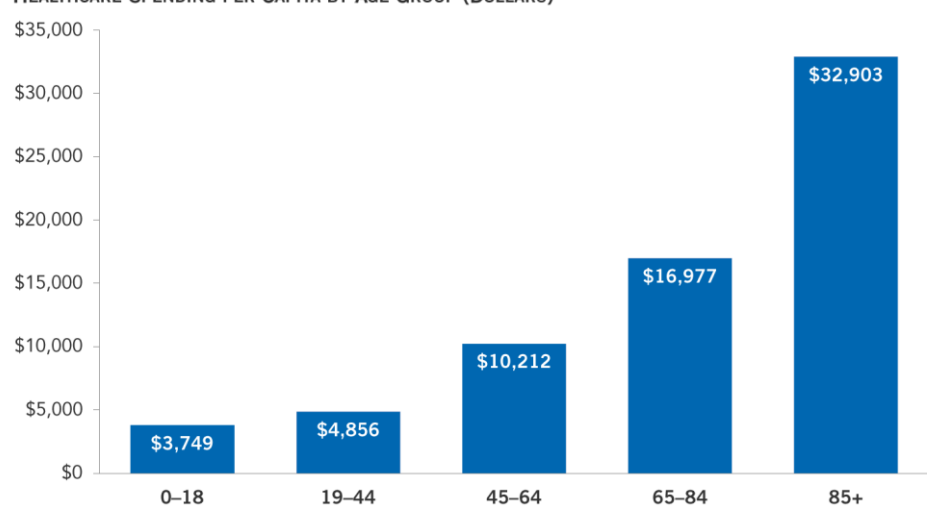
SOURCES: U.S. Census Bureau, *National Intercensal Estimates; 2016 Population Estimates*, June 2017; and *2017 National Population Projections*, September 2018.

Spending for Social Security and Medicare will continue to climb



SOURCES: Congressional Budget Office, *The 2023 Long-Term Budget Outlook*, June 2023, and Office of Management and Budget, *Historical Tables, Budget of the United States Government: Fiscal Year 2024*, March 2023.

Medical spending increases rapidly with age



SOURCE: Centers for Medicare and Medicaid Services, *National Health Expenditures by Age and Gender*, April 2019.
NOTE: Data are for 2014.

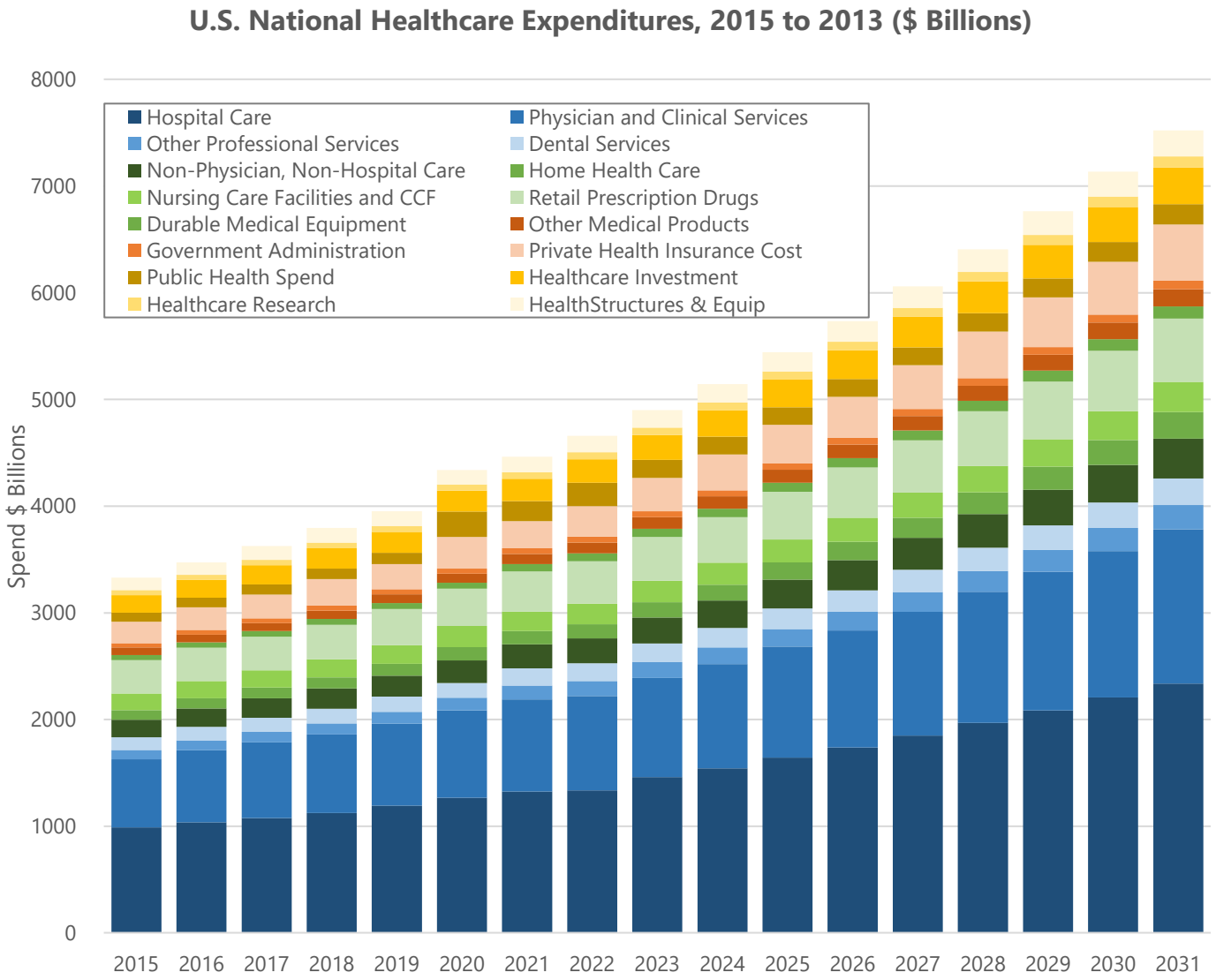
The U.S. debt downgrade last week and these charts tell an important story – which is that U.S. deficit spending is increasingly unsustainable.

As we witness an ongoing fight over the IRA, there is an important backdrop – which is the $1.85 trillion U.S. spend on Medicare and Medicaid could be, ultimately, threatened by the overall fiscal situation in the United States.

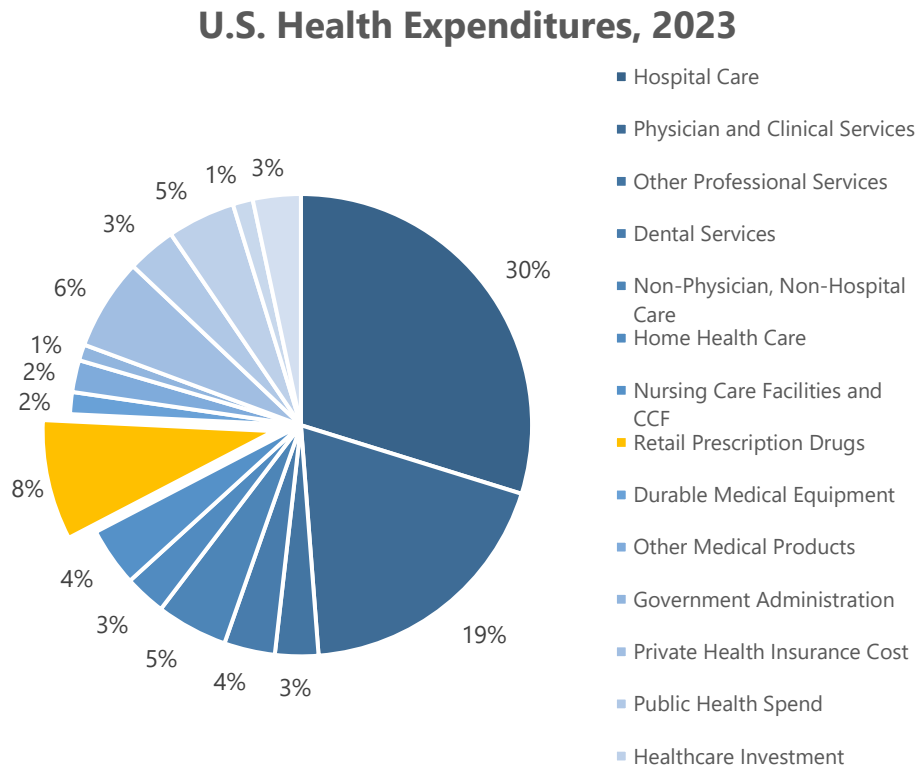
U.S. demographics are increasingly important. An aging population will put increasing pressure on medical spend – which accentuates fiscal pressure.

Source: https://www.pgpf.org/chart-archive/pgpf-chart-pack

U.S. Healthcare Spend to Exceed $7 Trillion by 2030

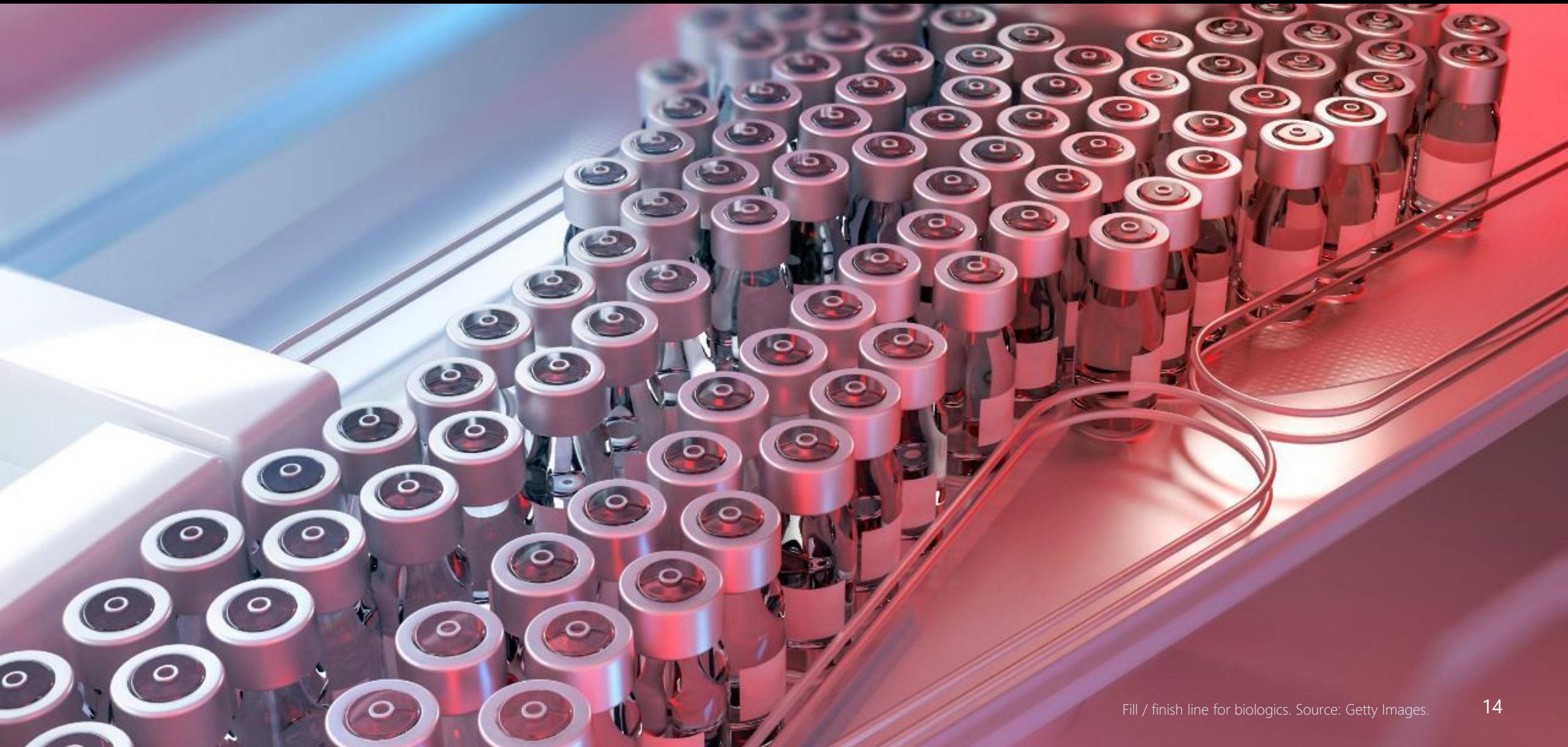


Spend on prescription drugs outside of hospitals / nursing homes is 8% of total.



Source data: https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet

Biopharma Market Update



Fill / finish line for biologics. Source: Getty Images.

Biotech Stocks Down Again Last Week

The XBI was down last week by 3.1% and is now down 2% for the year. The overall market, measured by the S&P 500, was soft last week in the wake of Fitch's credit downgrade of the United States. The VIX and Treasury yields popped up on the news.

Biotech Stocks Down Last Week

Return: July 30 to August 3, 2023

Nasdaq Biotech Index: -1.5%
Arca XBI ETF: -3.1%
Stifel Global Biotech (EV): -4.4%*
S&P 500: -2.2%

Return: Jan 1 to August 3, 2023

Nasdaq Biotech Index: -3.4%
Arca XBI ETF: -2.1%
Stifel Global Biotech: -5.1%*
Stifel Global Biotech (adjusted): +6.1%*
S&P 500: +16.6%

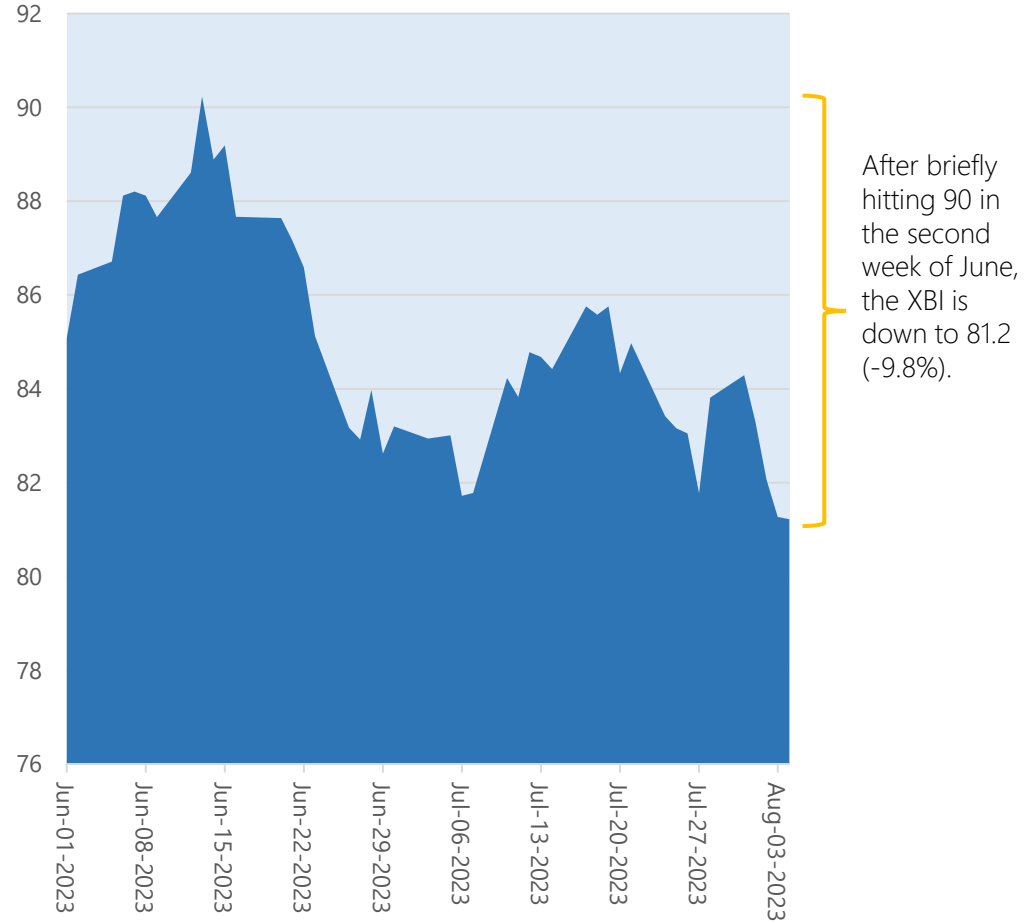
VIX Up

Oct 21: 29.7%
Jan 20: 19.9%
Mar 17: 24.6%
Apr 28: 15.8%
May 26: 18.0%
June 23: 13.4%
July 21: 13.6%
Aug 3: 17.1%

10-Year Treasury Yield Up

Oct 21: 4.2%
Jan 20: 3.48%
Mar 17: 3.39%
Apr 28: 3.44%
May 26: 3.8%
June 23: 3.74%
July 21: 3.84%
Aug 3: 4.05%

XBI, June 1, 2023 to August 3, 2023

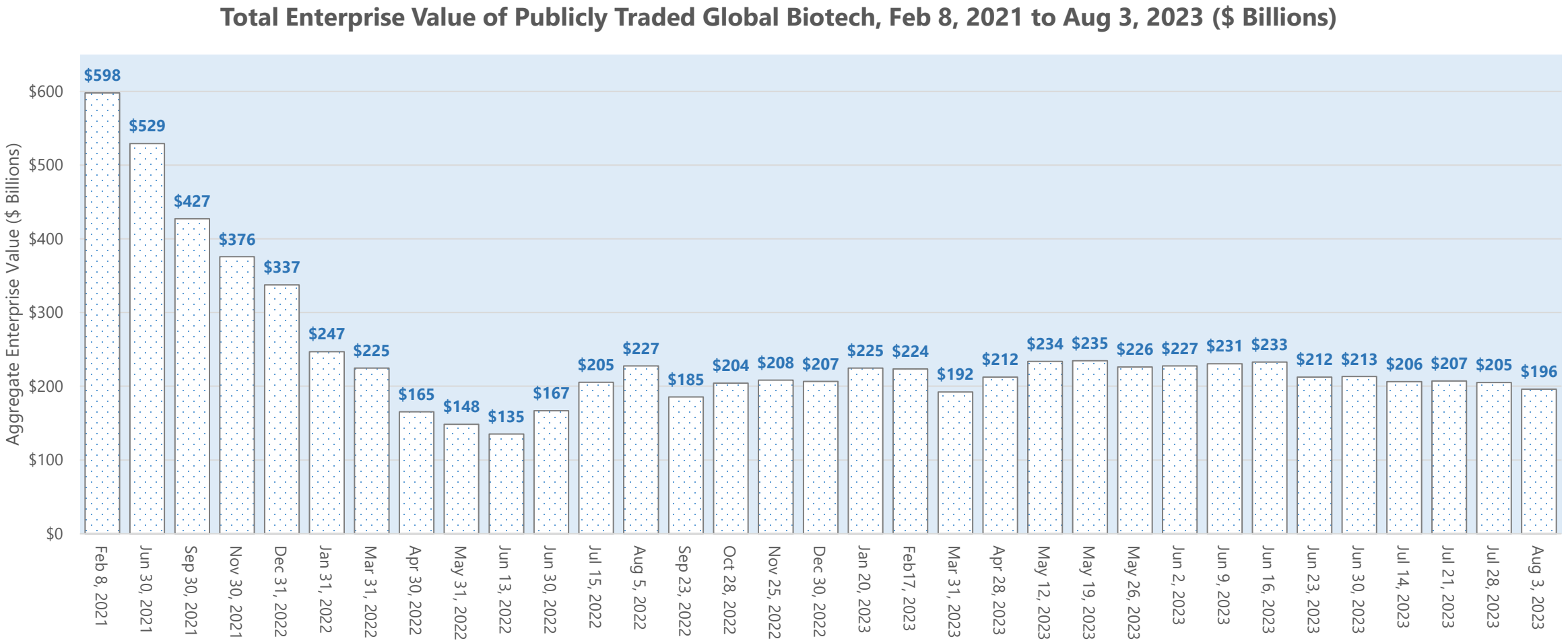


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Down 4.4% Last Week

The total value of the global biotech sector dropped 4.4% (or $9bn last week) and is down 5.4% (-$11.2bn) in the last two weeks. This was not caused by exits but value declines of incumbents. On an exit-adjusted basis, biotech valuations are up 6.1% for the year to date.



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

How Did Biotech Drop $11.2 Billion in Value in Two Weeks?

Top 20 Value Decliners, Global Public Biotech Population, Jul 20 to Aug 3, 2023

Company	HQ Country	Market Cap ($mm, Aug 3, 2023)	Percent Drop in Market Cap	Dollar Drop in Market Cap ($mm)
Cerevel Therapeutics	United States	$3,539	-23.5%	-$1,086
Karuna Therapeutics	United States	$6,983	-9.5%	-$735
Recursion Pharma	United States	$2,481	-19.8%	-$614
Mesoblast	Australia	$252	-66.3%	-$495
Bavarian Nordic	Denmark	$1,717	-22.3%	-$493
CRISPR Therapeutics	Switzerland	$4,248	-10.2%	-$481
Arrowhead Pharma	United States	$3,383	-12.3%	-$474
Madrigal Pharma	United States	$3,557	-9.9%	-$389
Beam Therapeutics	United States	$2,006	-15.4%	-$366
ImmunityBio, Inc.	United States	$906	-26.1%	-$320
Intellia Therapeutics	United States	$3,505	-8.3%	-$318
Mersana Therapeutics	United States	$142	-66.9%	-$287
SpringWorks	United States	$1,586	-14.3%	-$264
Stoke Therapeutics	United States	$270	-49.0%	-$259
Zai Lab	China	$2,680	-8.0%	-$234
RemeGen	China	$3,934	-5.5%	-$229
Viking Therapeutics	United States	$1,310	-14.6%	-$223
Kodiak Sciences	United States	$170	-55.3%	-$210
Oneness Biotech	Taiwan	$2,703	-7.2%	-$209
Denali Therapeutics	United States	$3,784	-5.1%	-$205
			Sum	-$7.892

It was quite a rough two weeks for the sector. We don't see any specific triggers other than some incremental macro uncertainty caused by the Fitch credit downgrade of the United States.

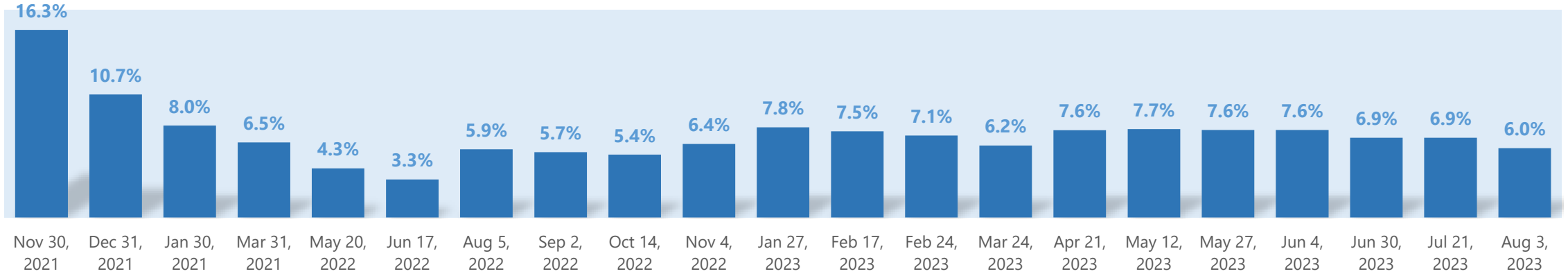
The chart at left shows that the top 20 decliners dropped $7.9bn, led by a 23.5% drop in Cerevel on clinical delay, a 9.5% drop in Karuna also on a clinical delay and a 19.8% drop in Recursion as a bit of AI froth wore off.

There were only three companies that gained $200mm or more in market cap in the same time period. These were Revolution Medicines (up $561mm), Morphic (up $277mm) and EqRx (up 237mm).

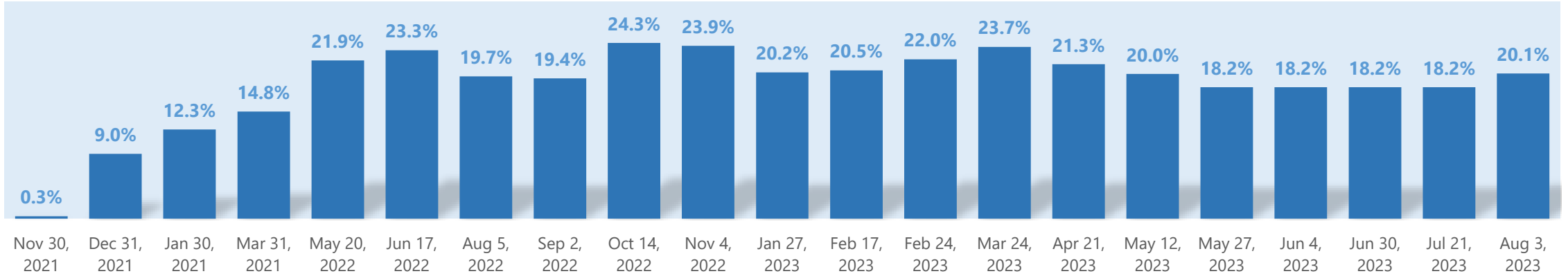
Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Biotech Neighborhood Analysis: The Good Neighborhood is Depopulating

Percent of Biotechs with an Enterprise Value of $1bn or More

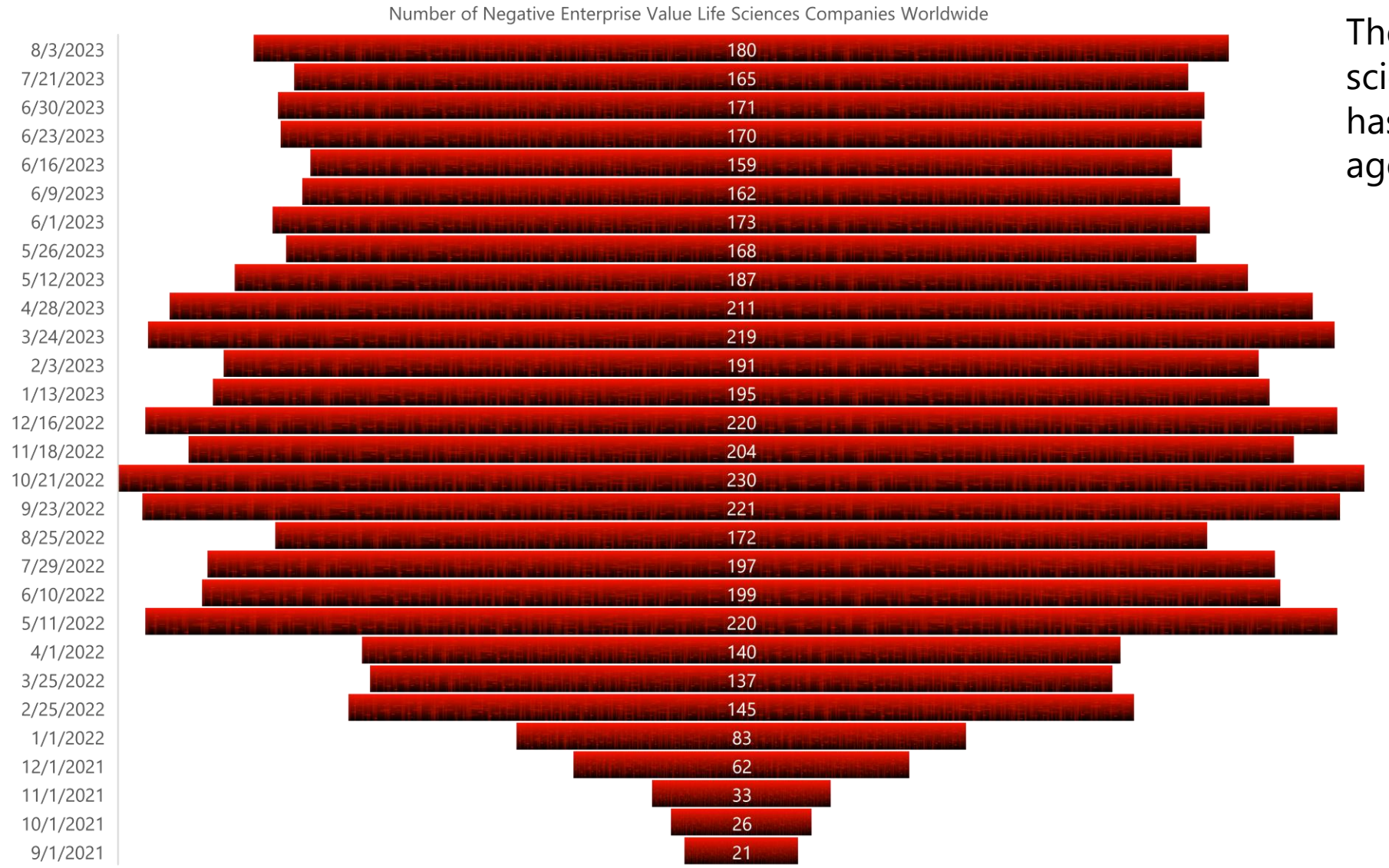


Percent of Biotechs with Negative Enterprise Value



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

Number of Negative Enterprise Value Life Sciences Companies Rose Sharply in Last Two Weeks



Source: CapitalIQ

The count of negative EV life sciences companies worldwide has risen from 165 three weeks ago to 180 last Friday.

Bear Market Aphorisms

"Bear markets don't act like a medicine ball rolling down a smooth hill. Instead, they behave like a basketball bouncing down a rock-strewn mountainside; there's lots of movement up and sideways before the bottom is reached."

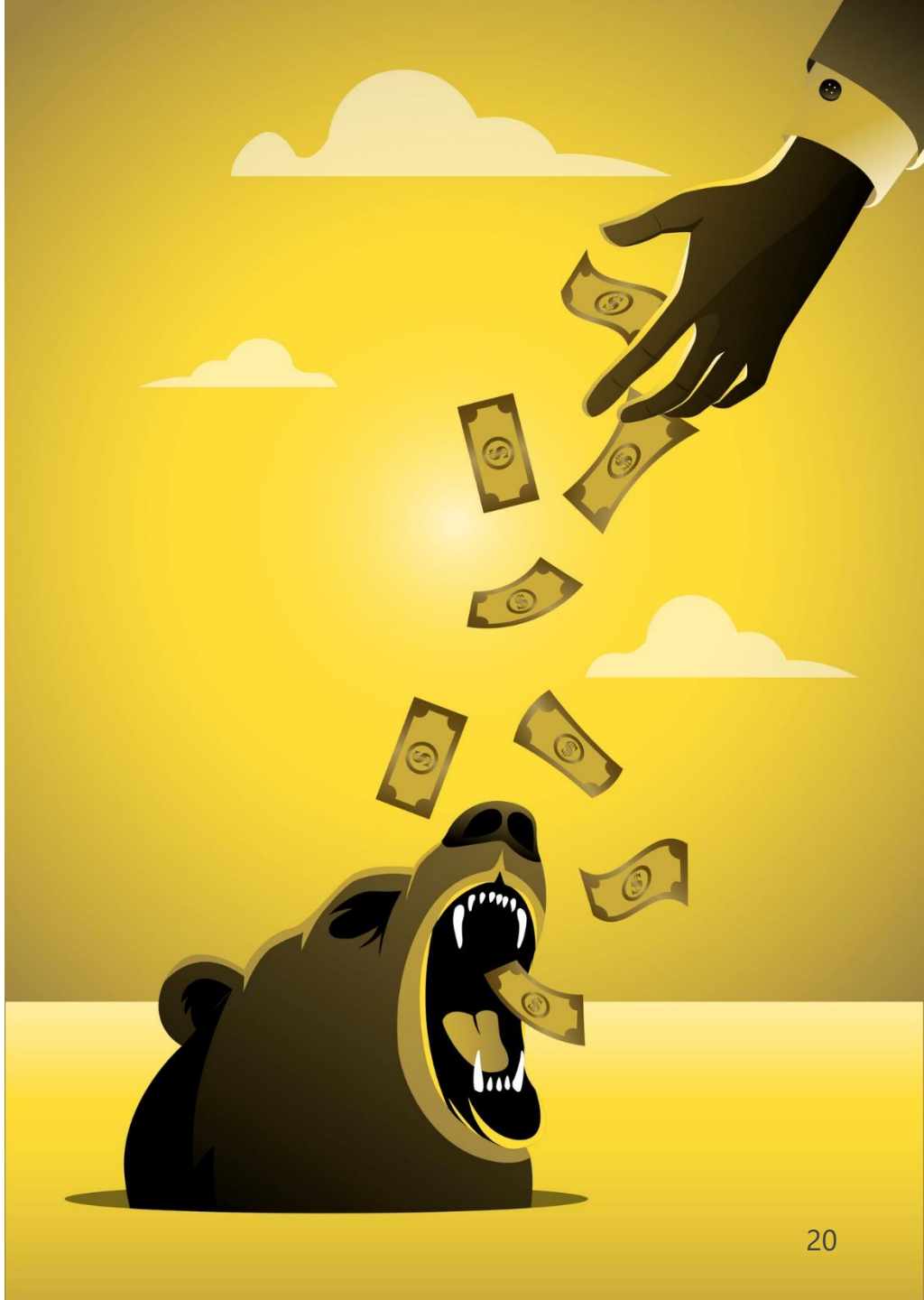
Thomas Turov

"If only the human body could handle trauma as well as biotechnology stocks do."

Alex Berenson

"Missing the bottom on the way up won't cost you anything. It's missing the top on the way down that's always expensive."

Peter Lynch



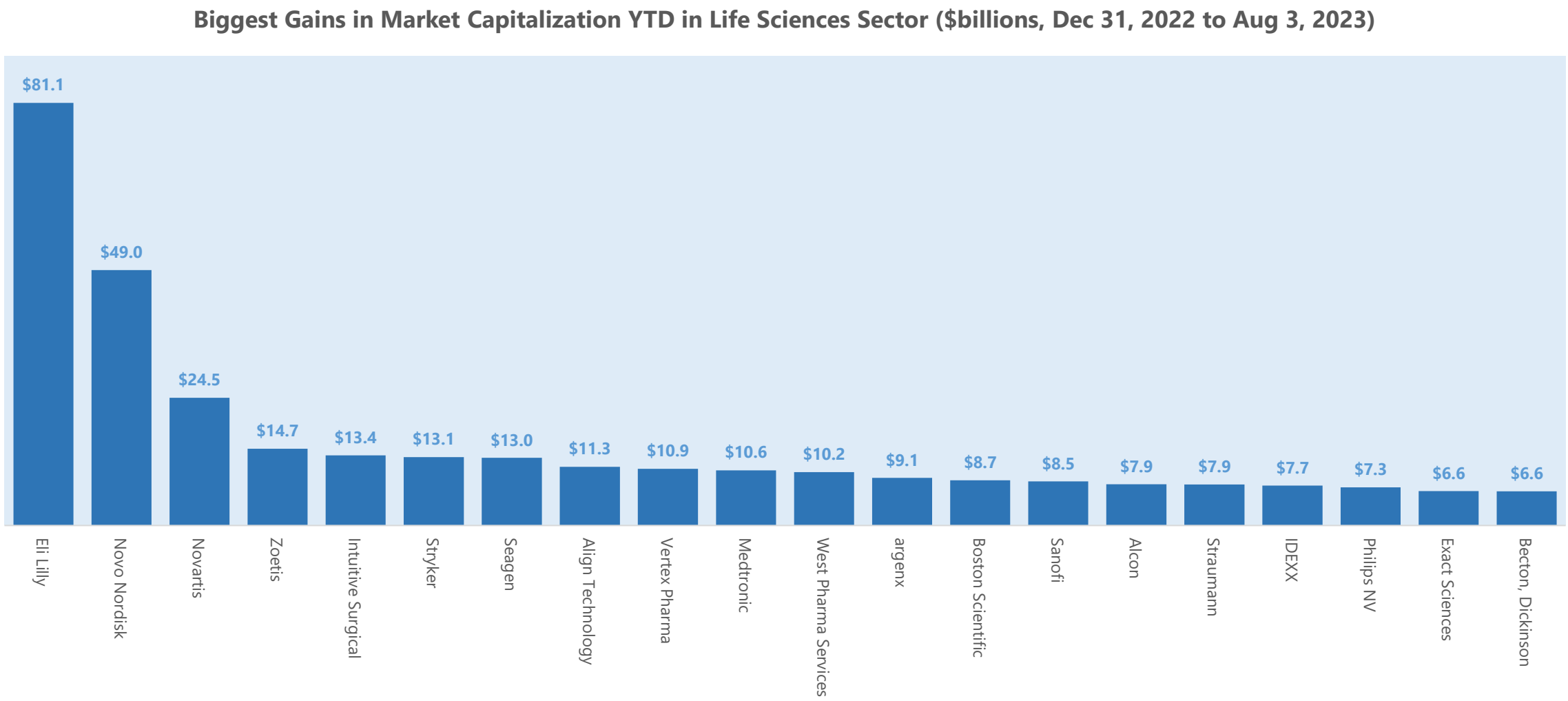
Public Life Sciences Sector Value Dropped Last Week

The total enterprise value of the publicly traded life sciences sector dropped by 2.5% last week ($234 billion). The sectors that declined the most were diagnostics, biotech and devices. In contrast, HCIT and pharma services had positive returns.

Sector	Firm Count	Enterprise Value (August 3, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$80,663	-0.2%	4.2%	-9.3%
Biotech	820	$195,997	-5.4%	-1.7%	-5.1%
CDMO	40	$174,945	-0.8%	5.1%	-19.2%
Diagnostics	83	$270,462	-6.6%	0.4%	4.8%
OTC	32	$30,817	-0.8%	1.7%	13.3%
Commercial Pharma	726	$5,755,521	-2.1%	1.2%	3.8%
Pharma Services	41	$213,141	0.8%	5.0%	-12.8%
Life Science Tools	54	$722,091	-1.8%	5.5%	-11.3%
Devices	183	$1,658,879	-3.7%	-1.6%	-0.1%
HCIT	11	$29,373	0.9%	17.8%	-4.8%
Total	**2071**	**$9,136,814**	**-2.5%**	**1.1%**	**0.5%**

Source: CapitalIQ

Three Pharmas (Lilly, Novo and Novartis) Have Outpaced the Sector by Value Gains Thus Far in 2023



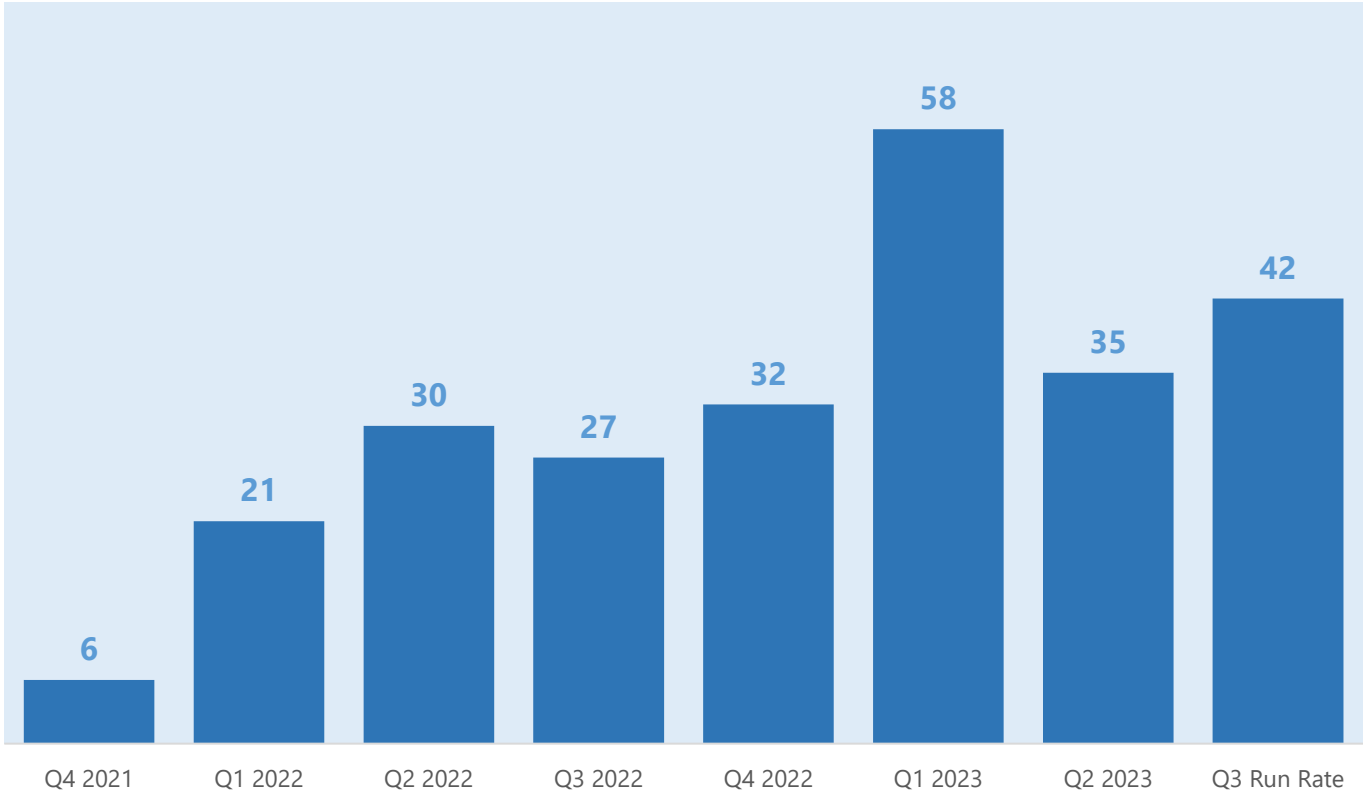
Source: CapitalIQ

Employment Conditions in Biopharma Sector

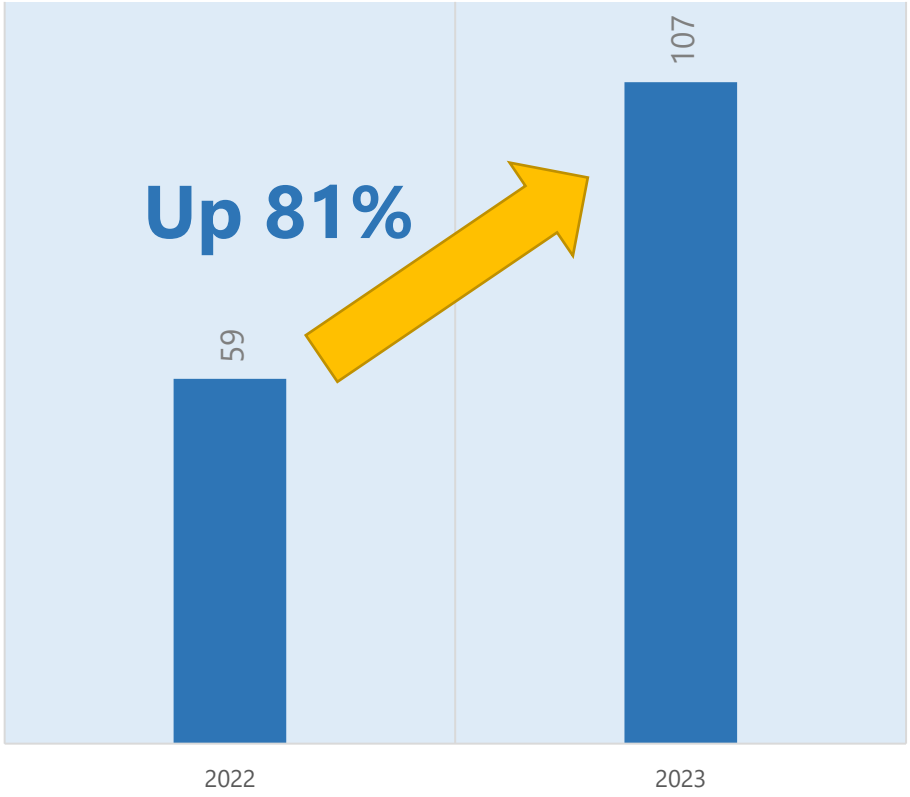
Image of employment market. Source: Getty Images.

Layoff Announcements 81% More Common in First Seven Months of 2023 vs. Same Period in 2022

Quarterly Count of Biopharma Industry Layoff Announcements, Q4 2021 to Present



Layoff announcements in first seven months of year



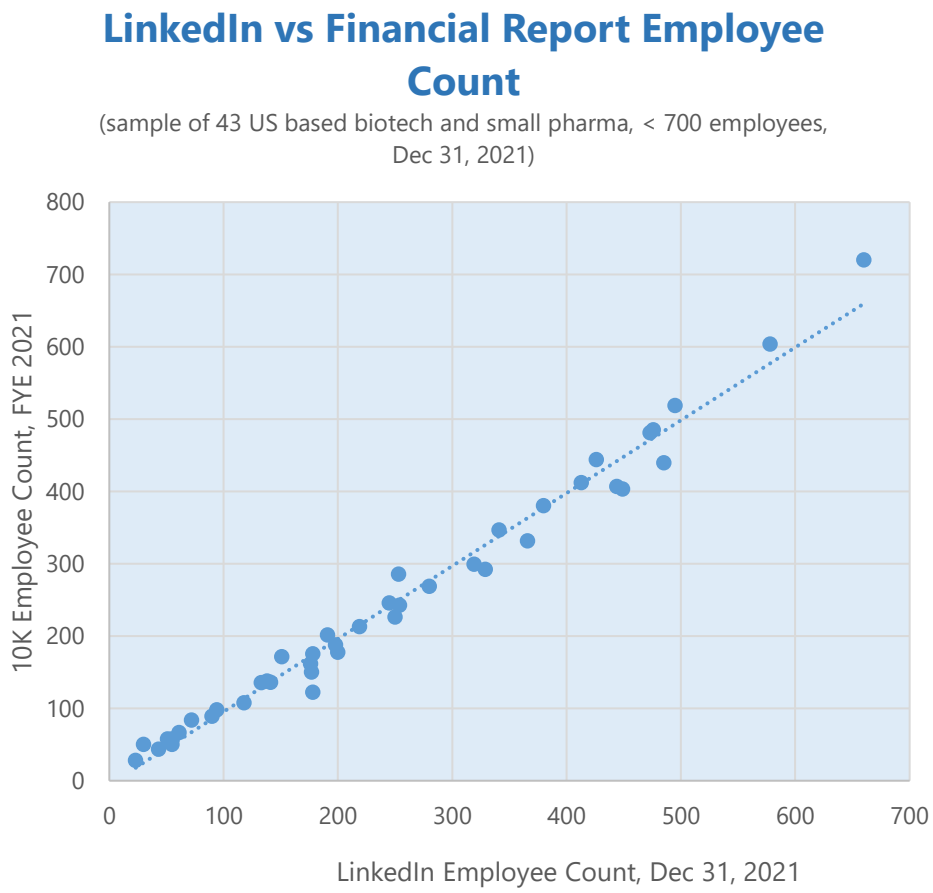
Data Source: Fierce Biotech

Measuring Actual Employment Levels Using LinkedIn

We have opted to track contemporaneous employment changes in biotech (and pharma) using LinkedIn. This business social networking site is heavily used in the U.S. as it's a good place for employees to share information and be seen by recruiters. For U.S. domiciled companies with largely domestic operations LinkedIn gives a very good sense of employee count.

This is shown in the chart at right which compares Dec 31, 2022 employee count from LinkedIn by biotech and specialty pharma to the count provided in each company's 10K report. The correlation between the two was 0.996 and the counts were not biased.

LinkedIn is used less by employees outside the U.S. and Europe. It is also used less by blue collar employees who traditionally avoid inter-company networking and job seeking facilitated by the site. Because there is no automated method to collect LinkedIn data, we have opted to hand collect a sample of employment data on 78 biopharma companies rather than to collect data on every company. We have attempted to oversample companies that are in the news with layoffs. This data will give a good picture of what is going on.



Source: CapitalIQ and LinkedIn.

Listing of 78 Companies Included in Employment Study

Big Pharma	Large Pharma	Smaller Pharma	MidCap Biotech	Small Cap Biotech
AbbVie	Biogen	Akebia Therapeutics	AkesoBio	Agios Pharma
Amgen	BioNtech	Athenex[b]	Apellis Pharma	Annexon
AstraZeneca	Gilead	Blueprint	Arcus Biosciences	Atara Biopharma
Bristol-Myers Squibb	Incyte	Chemocentryx[a]	Arrowhead	Avalo Therapeutics
Eli Lilly	Moderna	Neurocrine	Arvinas	Bluebird Bio
GSK	Regeneron	Optinose	Beam Therapeutics	Bone Therapeutics [c]
J&J	Seagen	Otonomy[b]	BridgeBio	Chinook
Merck	Takeda	Puma Biotechnology	Cerevel Therapeutics	Cortexyme[c]
Novartis	Vertex	Zai Lab	CRISPR Therapeutics	Elevation Oncology
Novo Nordisk			Cytokinetics	Galapagos
Pfizer			Denali Therapeutics	I-Mab Biopharma
Roche			Fate Therapeutics	Immunic Tx
Sanofi			ImmunityBio	Lyell Immunopharma
			Innovent	Nektar
			Intellia	Passage Bio
			Ionis Pharma	Precision Biosciences
			Iovance	Silverback[c]
			IVERIC Bio[a]	Taysha Gene
			Karuna Therapeutics	Turning Point Therapeutics[a]
			Kymera Therapeutics	
			Mirati Therapeutics	
			Prometheus Biosciences	
			Relay Therapeutics	
			Springworks Therapeutics	
			Vir Biotech	
			Xencor	
			Xenon Pharma	
			Zentalis Pharma	

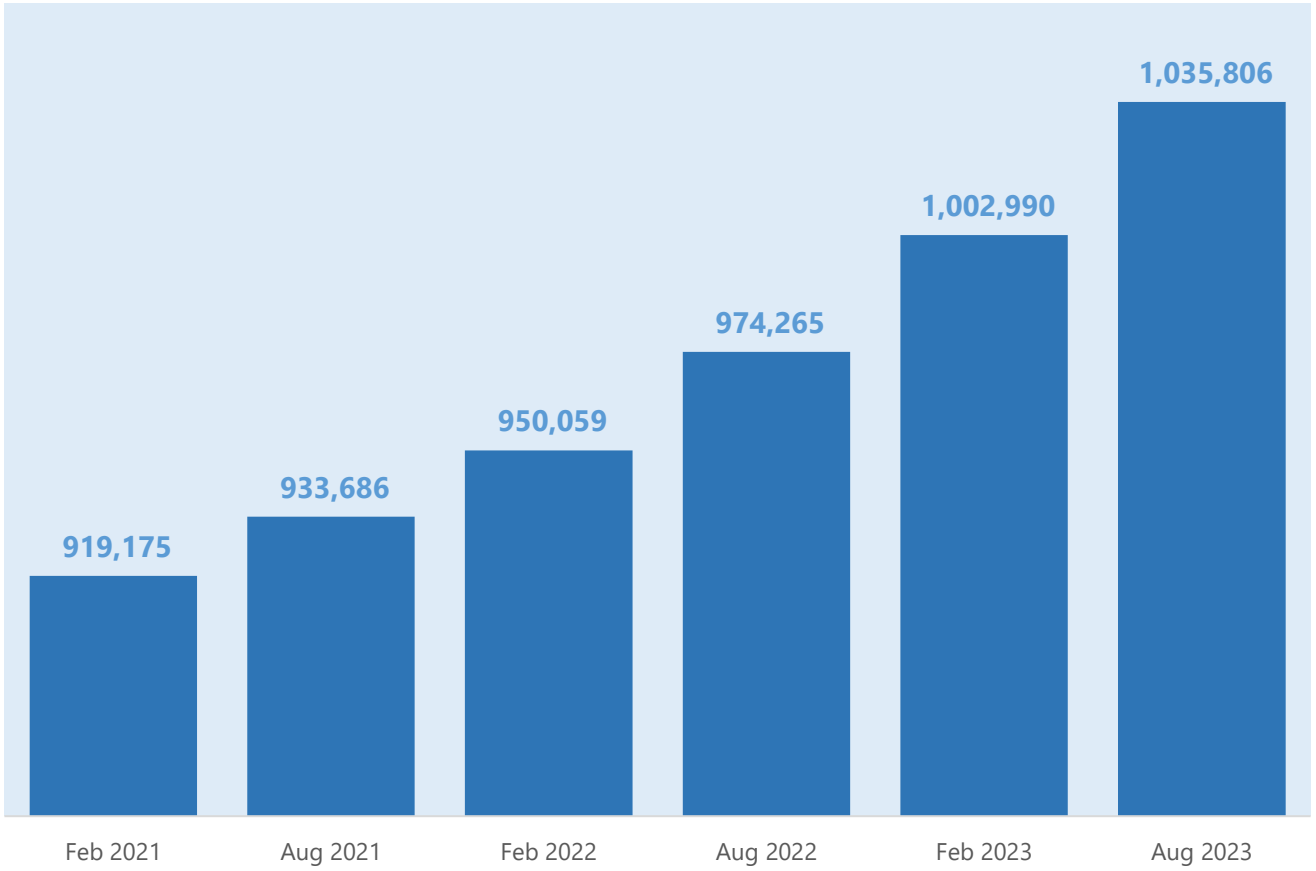
Study approach: We selected all U.S. and EU publicly listed companies in the big and large cap pharma categories. We randomly chose nine names from the small pharma list; 29 names from the midcap biotech list and 15 names from the small cap list.

This panel was selected in Feb 2021 and is carried forward even though some companies (e.g., Turning Point) have been bought and others barely remain in existence.

[a]This company was acquired after we put together our panel
[b]This company went bankrupt or chose to liquidate
[c]This company merged and was kept in our sample.

As a Whole the Biopharma Sector is *Adding* Employees

Total Employee Count in Sample of 78 Public Biopharmas
Feb 2021 to Feb 2023



Despite the impression one might get from media stories, the biopharma sector is not shedding employees, on balance. In the six-month period from Feb 2023 to Aug 2023 the sector added more employees than in any half-year period since started tracking the statistics in 2021.

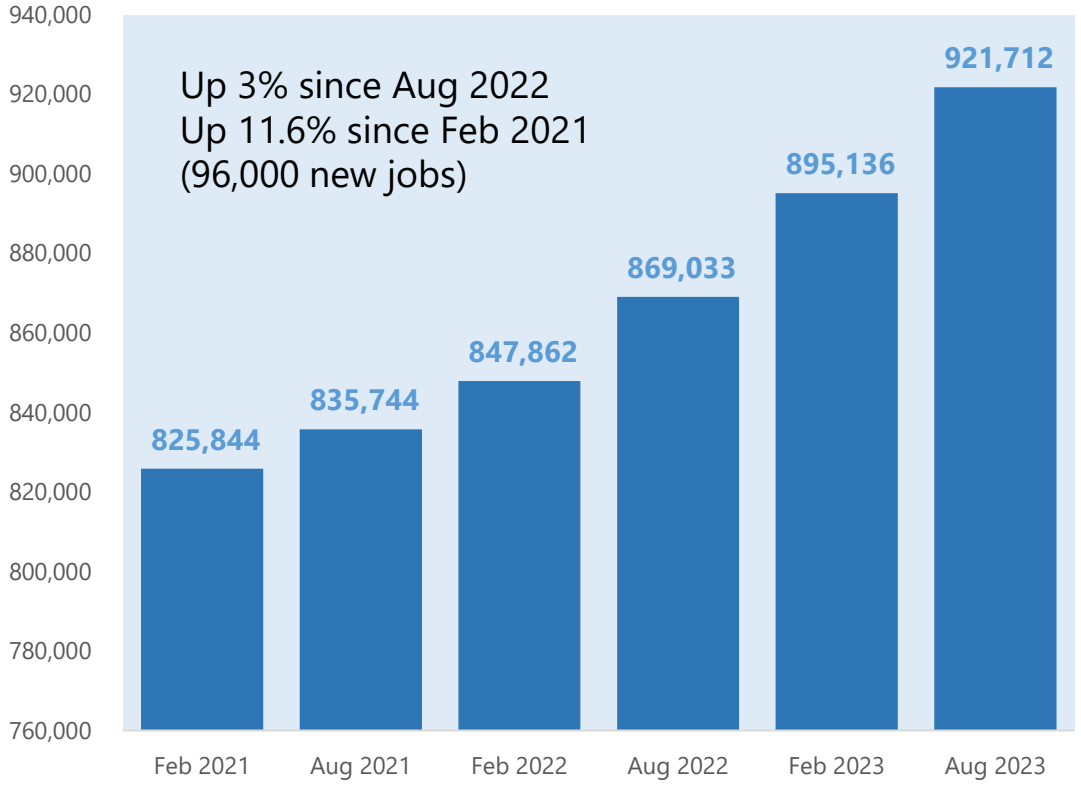
Source: Stifel Analysis of LinkedIn Employee Insight Data, Aug 1, 2023.

Big Pharma and Large Pharma Employment is Up

Big Pharma employment is up 3% in the August '22 to August '23 period versus 4% the year before. Large biopharma pharma (e.g., Vertex, Regeneron, Incyte) employment is up 3.3% in the same period versus 7.2% in the year before.

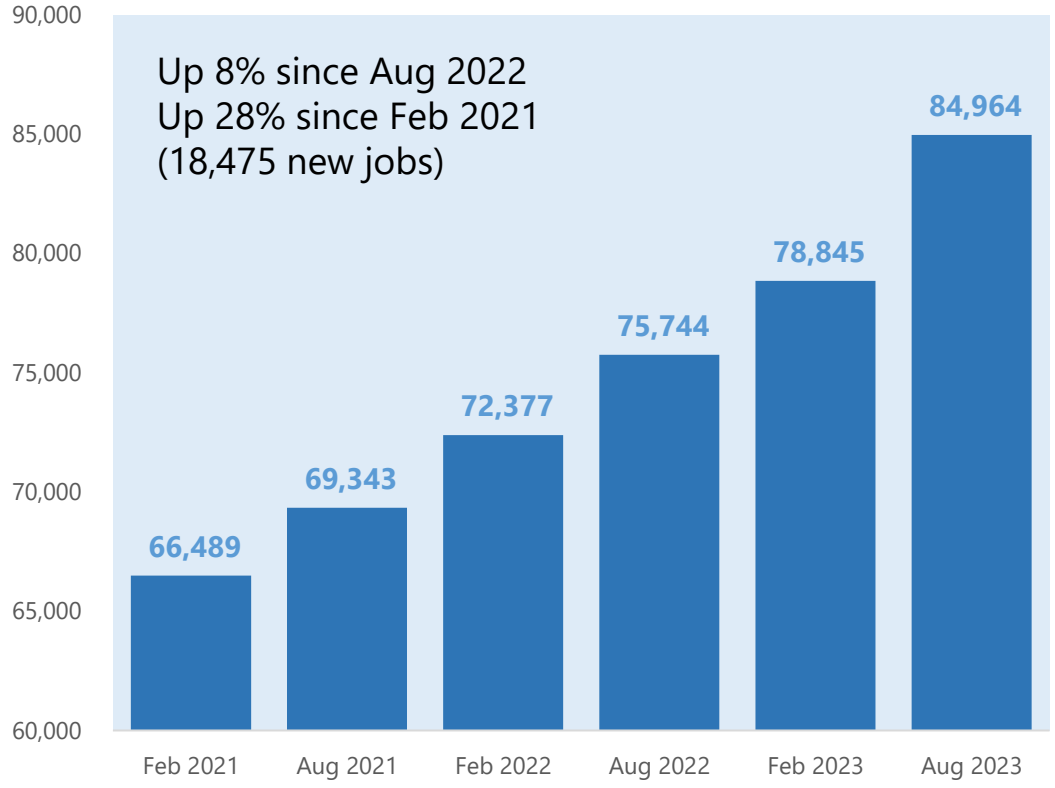
Employee Count in Sample of 13 Big Pharmas

Companies, Feb 2021 to Aug 2023



Employee Count in Sample of 8 Large Pharmas

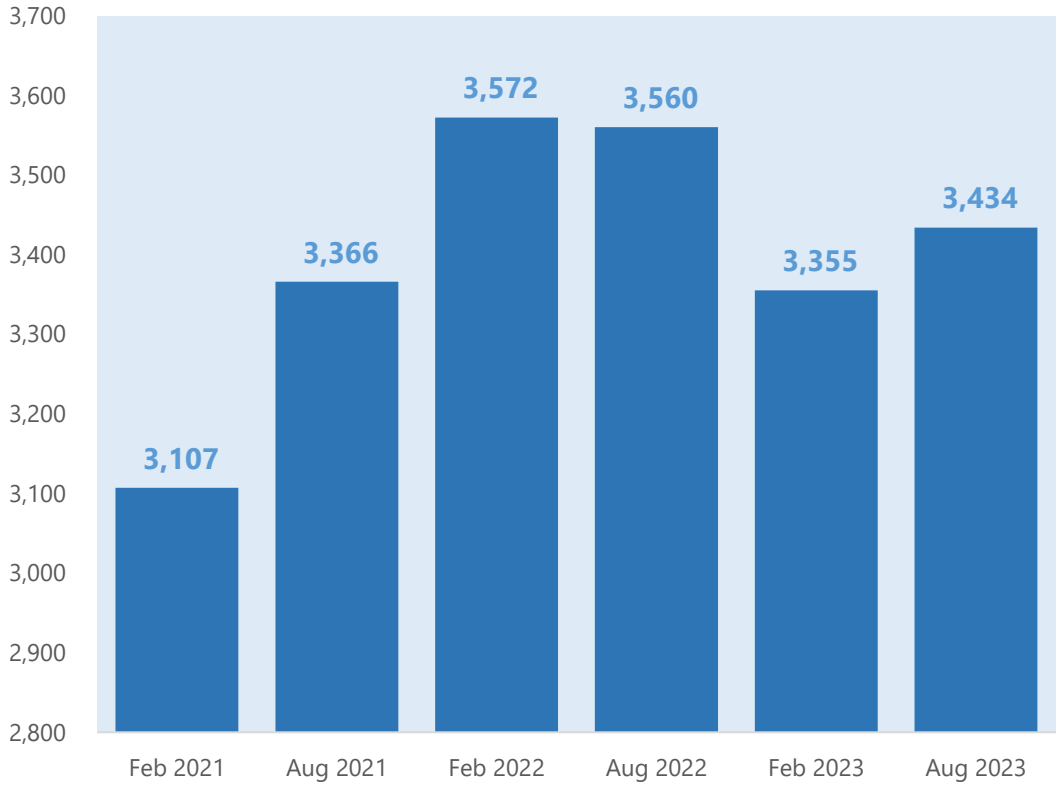
Companies, Feb 2021 to Aug 2023



Source: Stifel Analysis of LinkedIn Employee Insight Data, Aug 1, 2023. The "Large Pharma" group includes Takeda, Gilead, Regeneron, Biogen, Vertex, Seagen, BioNTech and Incyte.

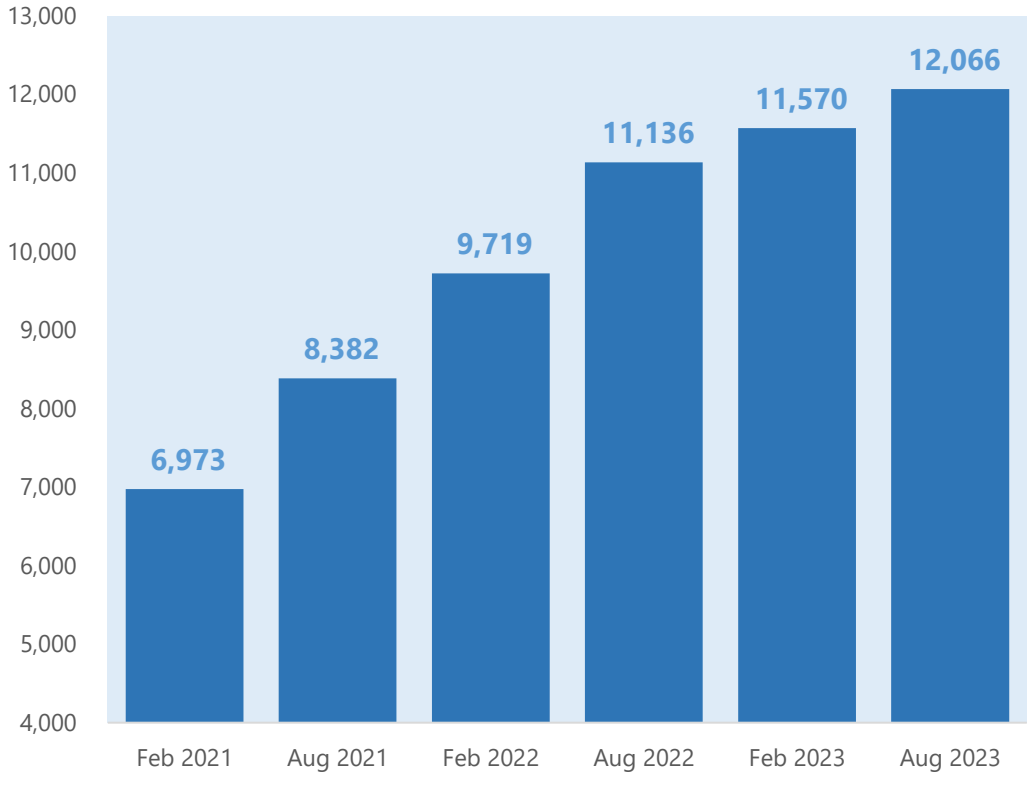
Mid-Cap Employment is Growing Fastest and Spec Pharma Employment Recovering

Employee Count in 10 Specialty Pharmas
Feb 2021 to Aug 2023



Up 2.4% in the last 12 months. Up 10.5% since Feb 2021.

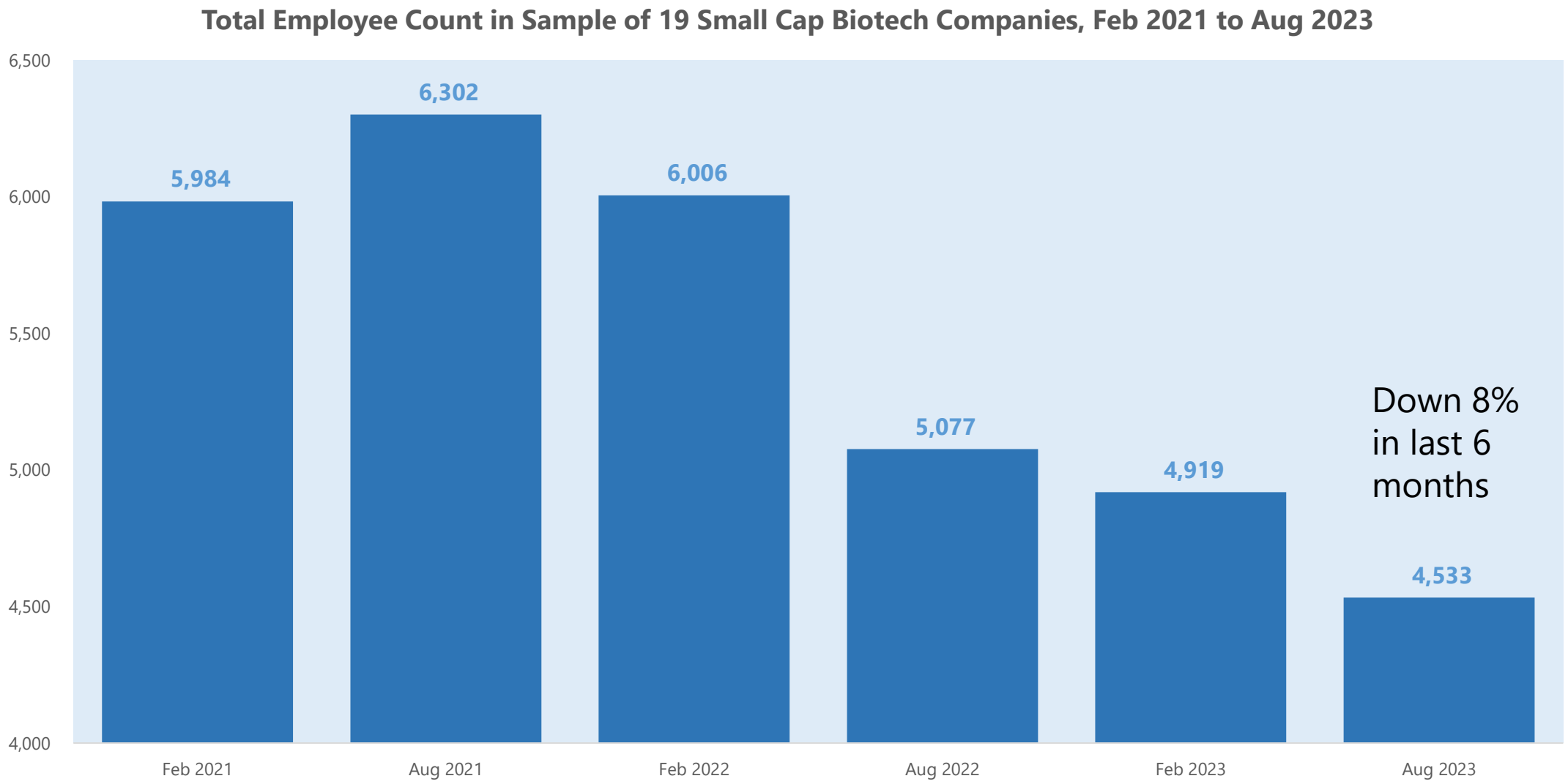
Employee Count in 28 MidCap Biotechs
Feb 2021 to Aug 2023



Up 4.3% in the last 12 months. Up 73% since Feb 2021.

Source: Stifel Analysis of LinkedIn Employee Insight Data, Aug 1, 2023.

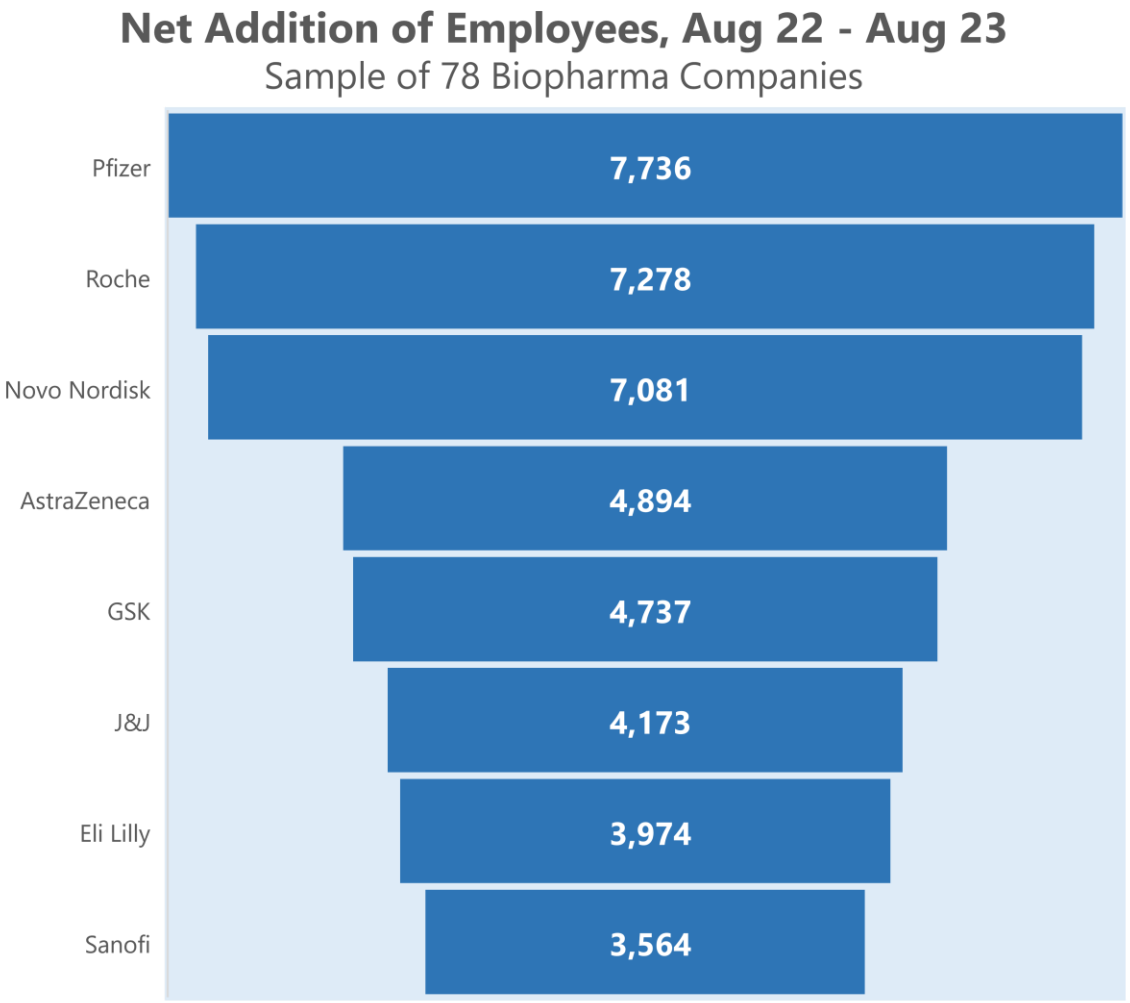
Small Cap Biotech Employment Down 24% from Feb '21

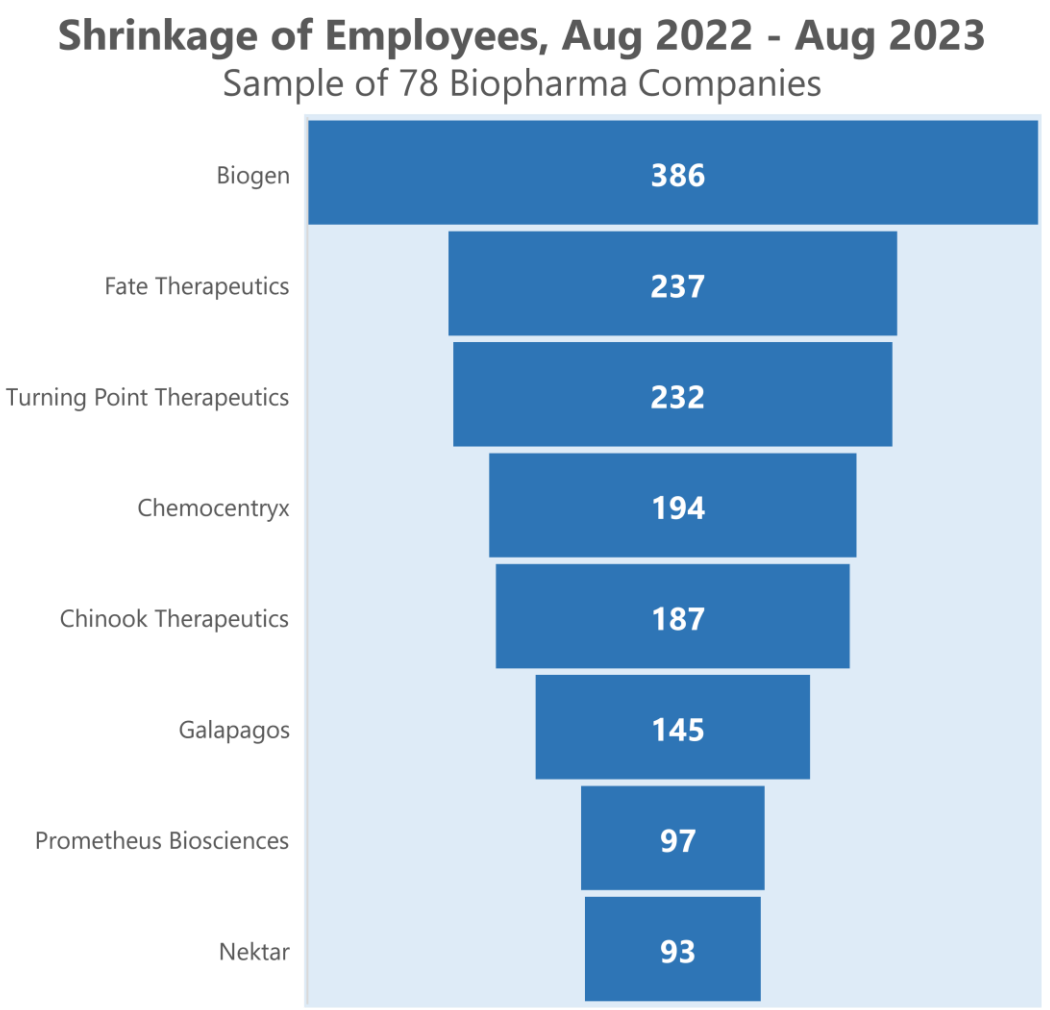


Source: Stifel Analysis of LinkedIn Employee Insight Data, Aug 1, 2023.

Change in Head Count in Last Year by Company

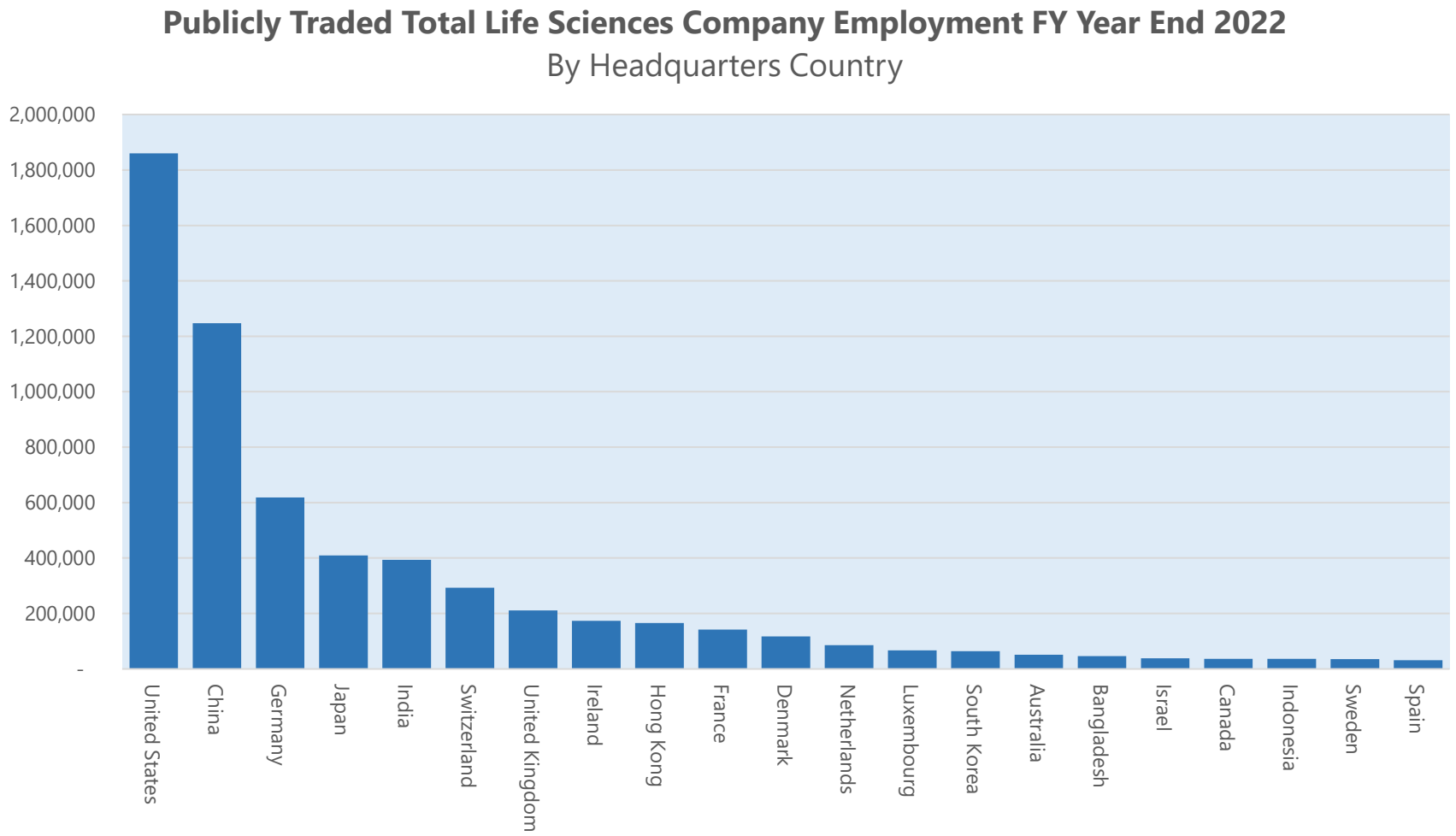
Big pharma has been growing quite aggressively during the biotech downturn.





Source: Stifel Analysis of LinkedIn Employee Insight Data, Aug 1, 2023. Note: when a company like Chemocentryx is bought, the employees are shifted to the acquirer's headcount.

Total Public Company Sector Life Sciences Employment FY End 2022 by Country



These data are from year-end financial statements reported by CapIQ rather than LinkedIn and encompass all publicly reporting companies in the life sciences sector.

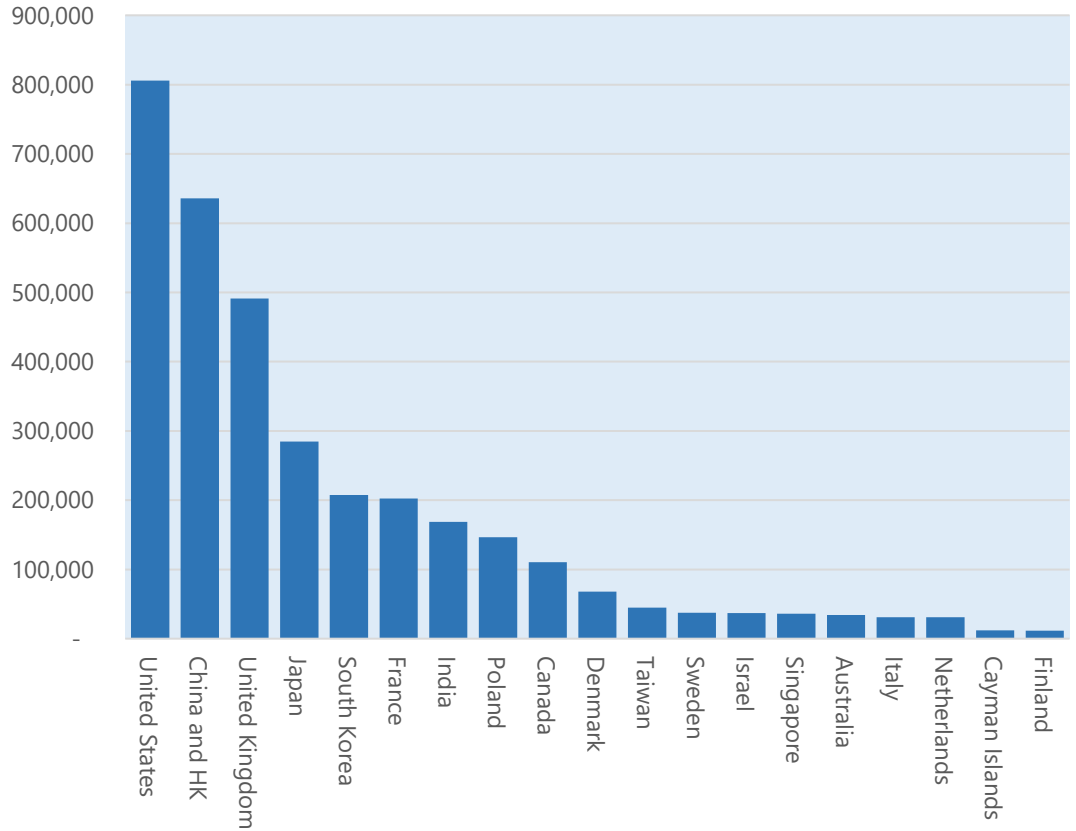
U.S. headquartered companies are the largest employers in the industry by far, followed by China, Germany, Japan and India.

Source: CapitalIQ

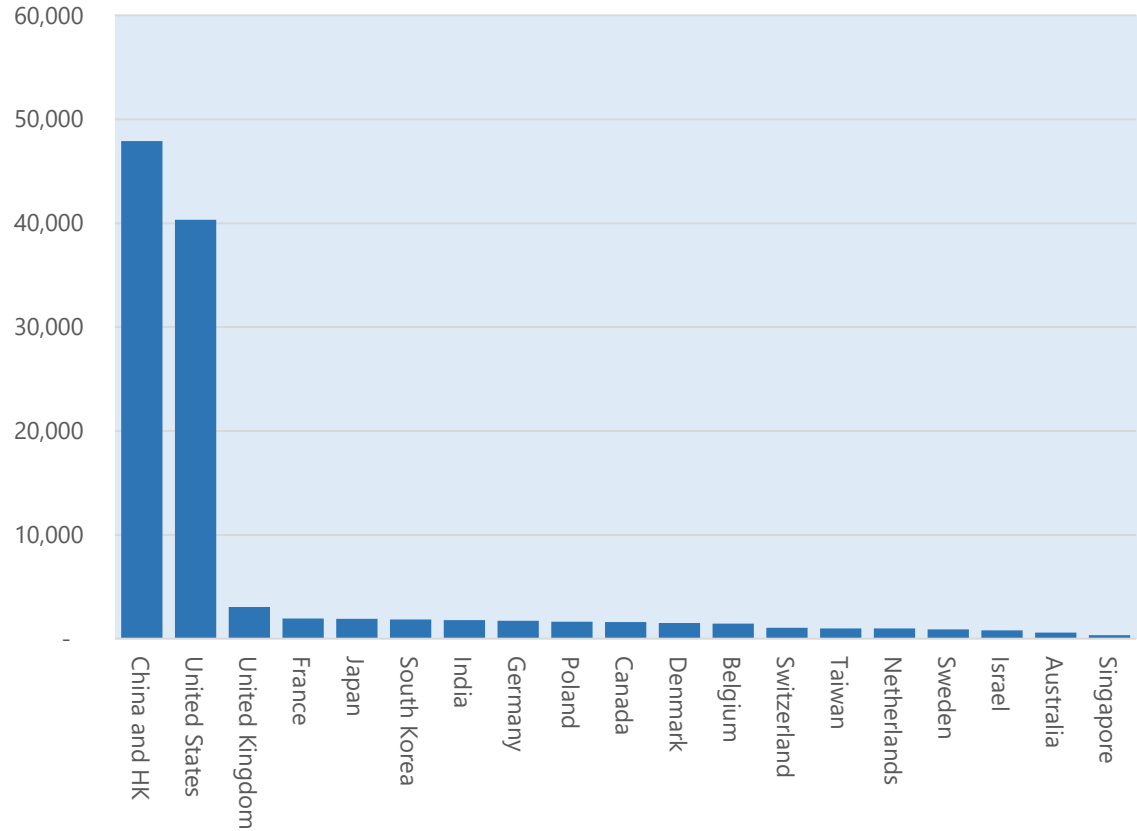
Total Public Company Employment FY End 2022 in Biotech and Commercial Pharma by Country

U.S., Chinese and UK companies are the leading pharma employers by country. China leads biotech employment and all other countries other than China and the US are quite small employers (at least as measured by domiciled publicly traded companies).

Publicly Traded Commercial Stage Pharma Employment by Headquarters Country, FY End 2022



Publicly Traded Biotech Employment by Headquarters Country, FY End 2022



Source: CapitalIQ

BIO: Bioscience Industry a Job Creation Machine

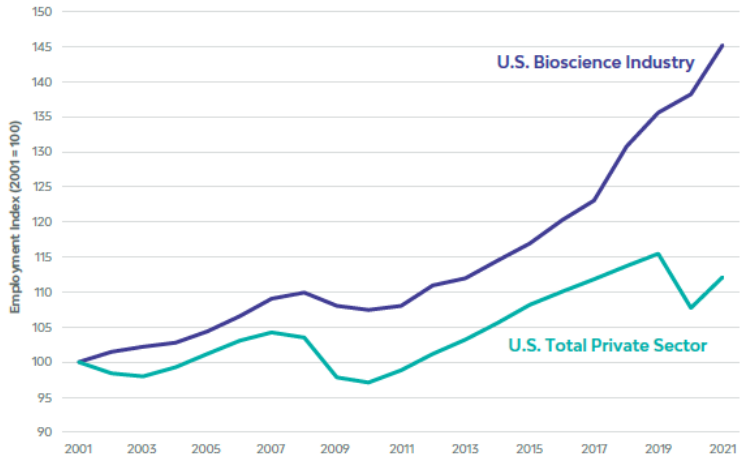
TEConomy/BIO

The U.S. Bioscience Industry:

Fostering Innovation and Driving America's Economy Forward

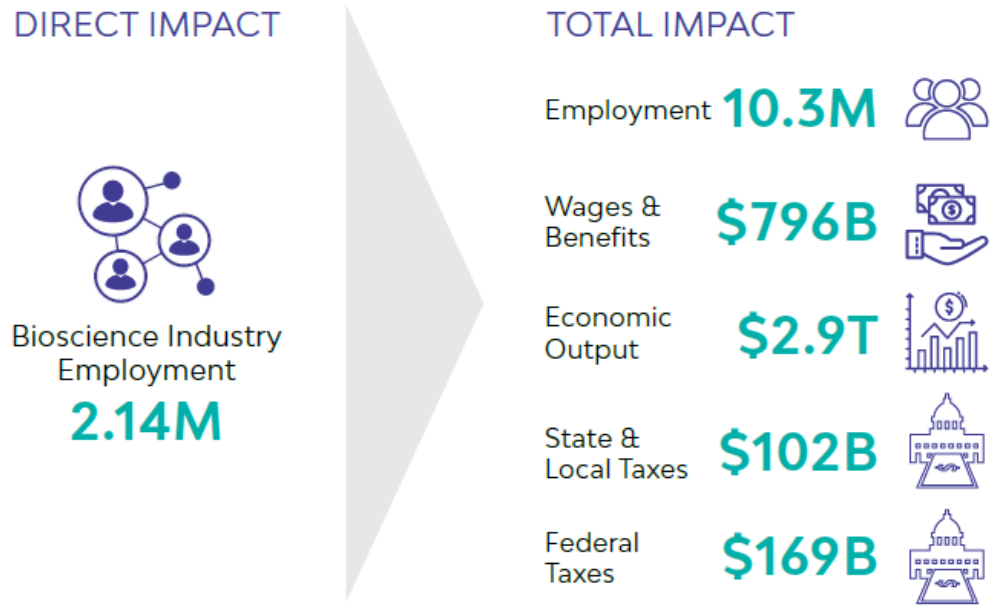
2022

Figure 4: Employment Growth Trends for the U.S. Bioscience Industry and Private Sector, 2001-21



Source: TEConomy Partners analysis of U.S. Bureau of Labor Statistics, QCEW data; enhanced by Lightcast (Datarun 2022.3).

Figure 1: Economic Impacts of the U.S. Bioscience Industry, 2021



Source: TEConomy Partners data and analysis using U.S. IMPLAN Input-Output Model.

Source: https://www.bio.org/value-bioscience-innovation-growing-jobs-and-improving-quality-life

Illustrative Impact of Life Sciences Employment: California

Figure 1: Number of Payroll Jobs and YOY Growth in California Life Science Sectors in 2022

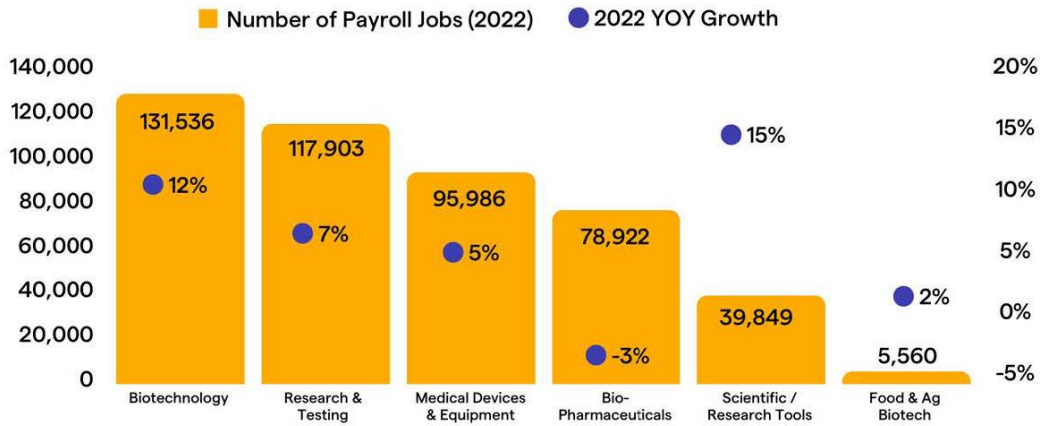


Figure 2: Overall Impact of Life Science: Employment, Labor Income, and Output

Impact Type	Direct Impact	Indirect Impact	Induced Impact	Total	Multiplier
Employment	469,756	319,460	402,132	1,191,349	2.5X
Labor Income	$66.9B	$33.1B	$29.6B	$129.6B	1.9X
Output	$242.6B	$87.2B	$83.9B	$413.7B	1.7X

Source: https://www.biocom.org/news/eir/

Industry News

Lab workers looking at experiment: Getty Images.

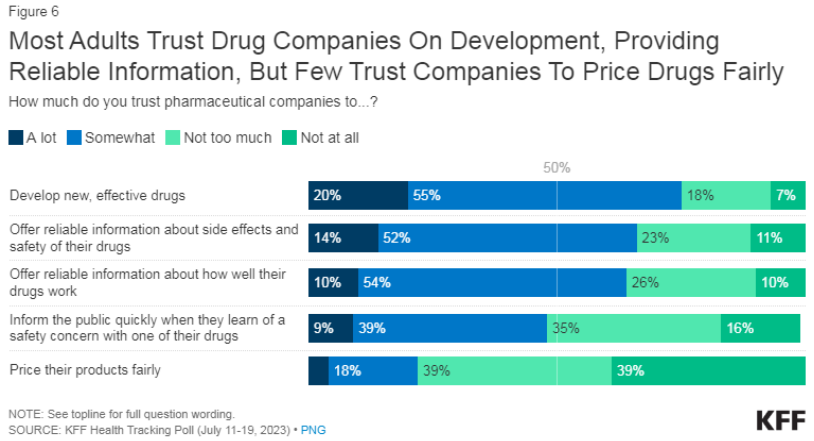
Kaiser Family Foundation Poll: Americans Trust Pharma Companies To Develop Drugs But Do Not Think That They Price Them Fairly

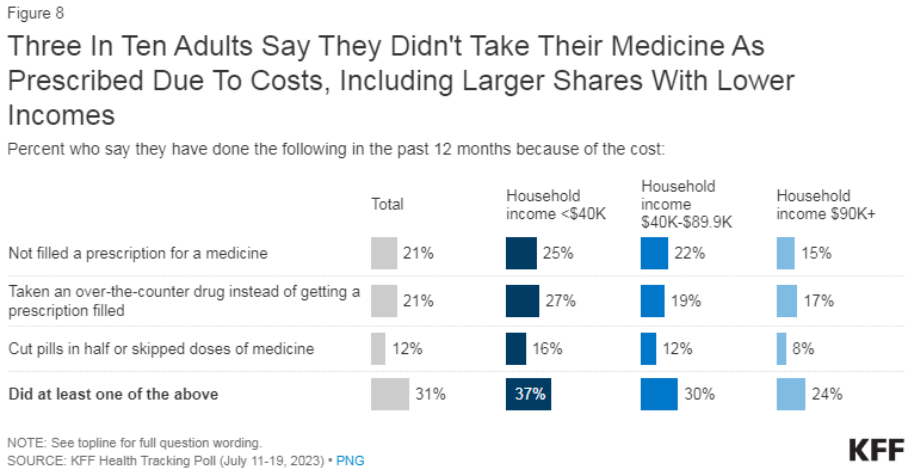
KFF Health Tracking Poll August 4, 2023

A majority of the public say they trust pharmaceutical companies to develop new drugs (75%) and provide reliable information about safety and side effects (66%) as well as drug effectiveness (64%) – but far fewer adults (22%) say they trust these pharmaceutical companies to price their products fairly. A large majority of adults (83%), including majorities across parties, see pharmaceutical profits as a major factor contributing to the cost of prescription drugs.

Notable shares of adults (28%) report difficulty affording prescription drugs, with another three in ten adults (31%) reporting not taking their medicine as prescribed in the past year due to the cost. Lower income adults are more likely than those with higher household incomes to report experiencing these cost-related prescription drug issues.

Majorities across partisans say there is not enough regulation over drug pricing, however, just under a year after the passage of the Inflation Reduction Act, few adults in the U.S. are aware of the law's provisions aimed at reducing the cost of prescription drugs in Medicare.





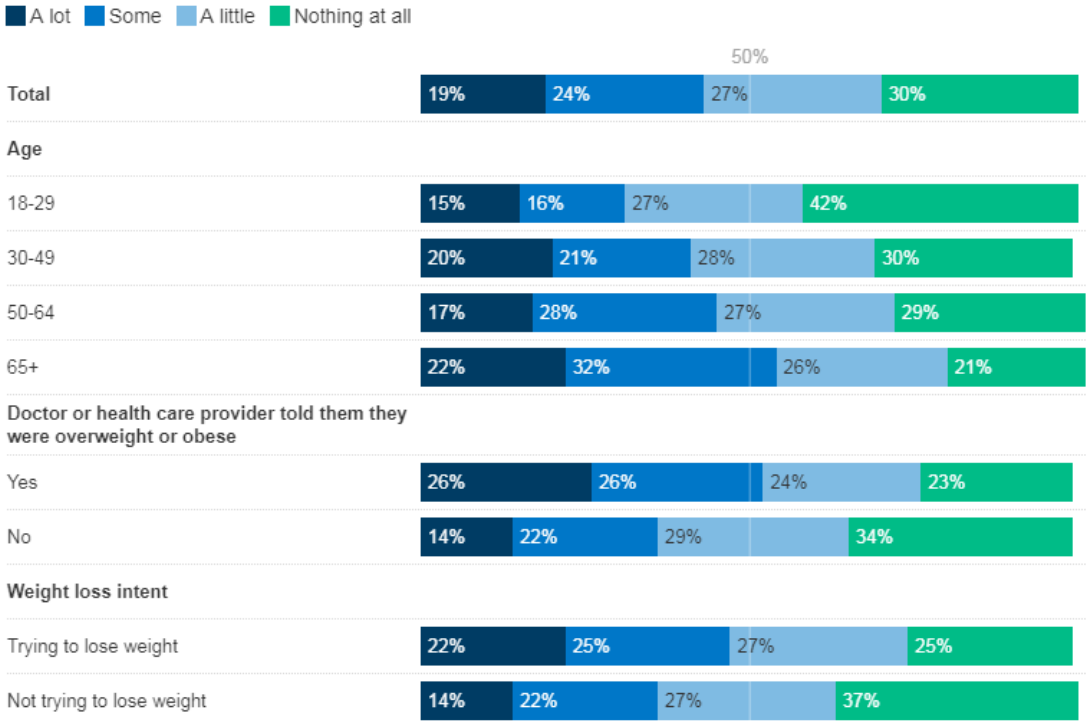
Source: https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-july-2023-the-publics-views-of-new-prescription-weight-loss-drugs-and-prescription-drug-costs/

KFF Poll Asked About Obesity Drugs

Figure 1

Most Adults Have Heard About New Weight Loss Drugs, Including Larger Shares Older Adults And Those Trying To Lose Weight

How much have you heard, if anything, about a new class of drugs being used for weight loss, such as Ozempic, Wegovy, and Mounjaro?



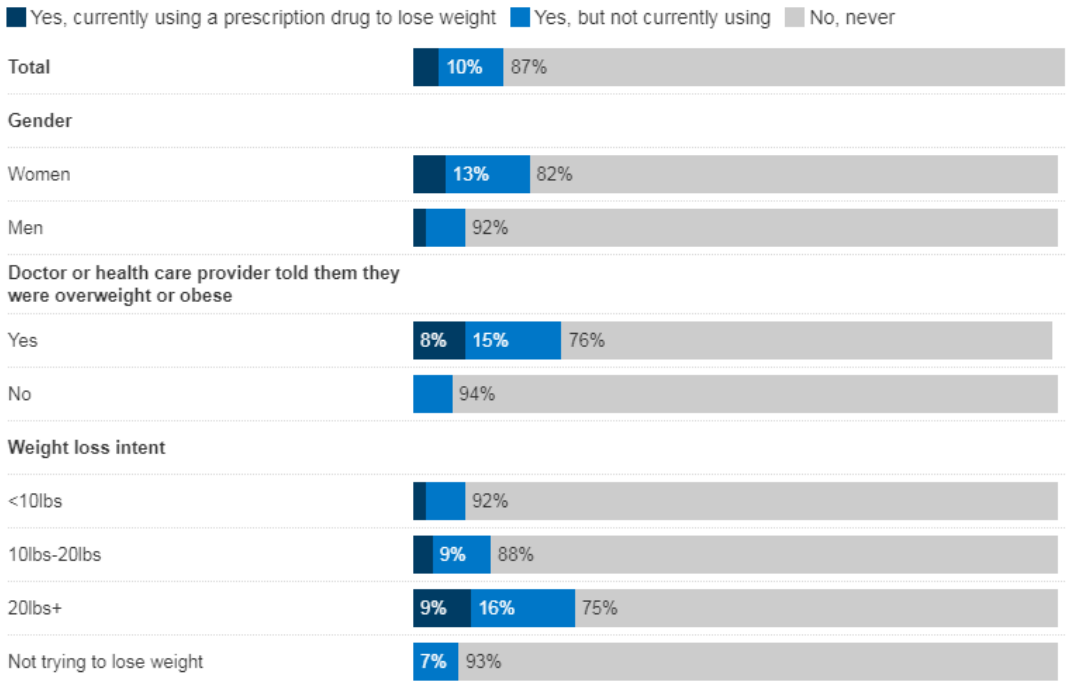
NOTE: See topline for full question wording.
SOURCE: KFF Health Tracking Poll (July 11-19, 2023) • PNG

KFF

Figure 2

Few Adults Are Currently Using Or Have Ever Used Any Prescription Drugs To Lose Weight

Are you currently or have you ever used a prescription drug to lose weight? This does not include any over-the-counter medications or supplements.



NOTE: See topline for full question wording.
SOURCE: KFF Health Tracking Poll (July 11-19, 2023) • PNG

KFF

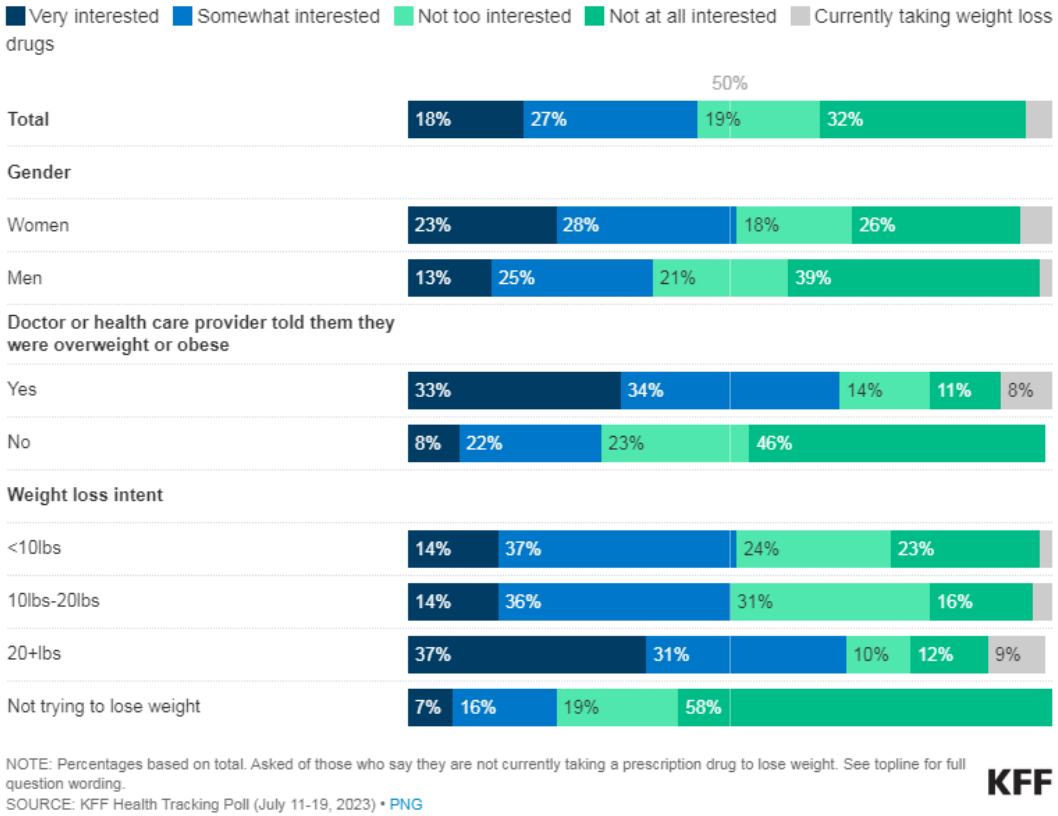
Source: https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-july-2023-the-publics-views-of-new-prescription-weight-loss-drugs-and-prescription-drug-costs/

KFF Poll: About Half of U.S. Adults Would Take an Obesity Drug

Figure 3

About Half Of Adults Say They Would Be Interested In Taking A Safe, Effective Weight-Loss Drug

If you heard that a prescription weight loss drug was safe and effective, how interested would you be in using that prescription drug to lose weight?

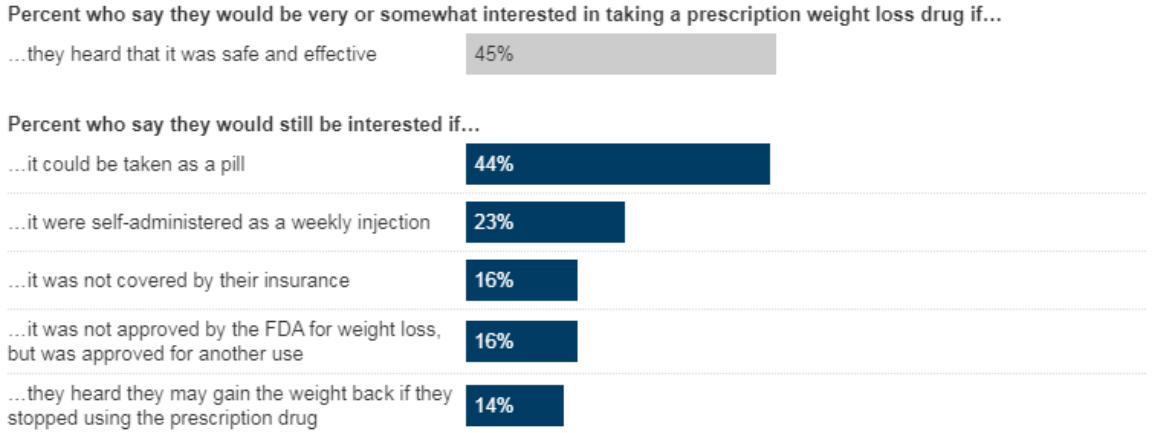


NOTE: Percentages based on total. Asked of those who say they are not currently taking a prescription drug to lose weight. See topline for full question wording.
SOURCE: KFF Health Tracking Poll (July 11-19, 2023) • PNG

KFF

Figure 4

About Half Of Adults Are Interested In Taking Weight Loss Drugs As A Pill, Fewer Are Interested If They May Gain Weight Back After Stopping



Some of the more interesting findings from this survey include (1) how few people have tried prescription weight loss drugs, (2) how well recognized they are, (3) how many more would prefer an oral over an injectable and (4) how important long-term weight loss is to consumers.

Source: https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-july-2023-the-publics-views-of-new-prescription-weight-loss-drugs-and-prescription-drug-costs/

National Institutes of Health
Turning Discovery Into Health

Wednesday, August 2, 2023

NIH selects Dr. Jeanne Marrazzo as director of the National Institute of Allergy and Infectious Diseases

Lawrence A. Tabak, D.D.S., Ph.D., acting director for the National Institutes of Health, has named Jeanne M. Marrazzo, M.D., as director of NIH's National Institute of Allergy and Infectious Diseases (NIAID). Dr. Marrazzo is currently the director of the Division of Infectious Diseases at the University of Alabama at Birmingham. She is expected to begin her role as NIAID Director in the fall. NIAID conducts and supports basic and applied research to better understand, treat and ultimately prevent infectious, immunologic and allergic diseases.

"Dr. Marrazzo brings a wealth of leadership experience from leading international clinical trials and translational research, managing a complex organizational budget that includes research funding and mentoring trainees in all stages of professional development," said Dr. Tabak. "I look forward to welcoming Dr. Marrazzo to the NIH leadership team. I also want to extend my gratitude to Hugh Auchincloss, Jr., M.D., for serving as acting director of NIAID after long-time director Anthony S. Fauci, M.D., stepped down in December 2022."

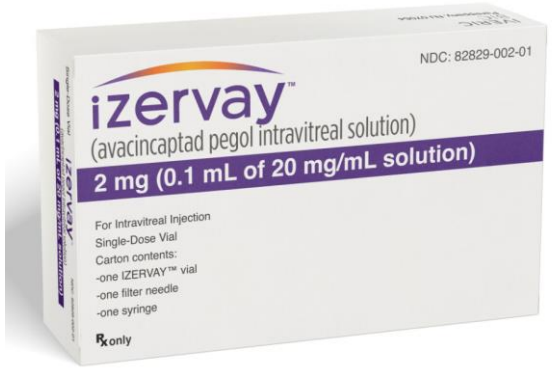
Jeanne M. Marrazzo, M.D. *UAB/Lexi Coon.*

Source: https://www.nih.gov/news-events/news-releases/nih-selects-dr-jeanne-marrazzo-director-national-institute-allergy-infectious-diseases

Dr. Marrazzo's research in discovery and implementation science has focused on the human microbiome, specifically as it relates to female reproductive tract infections and hormonal contraception; prevention of HIV infection using biomedical interventions, including PrEP and microbicides; and the pathogenesis and management of bacterial vaginosis, sexually transmitted diseases in HIV-infected persons and management of antibiotic resistance in gonorrhea. She has been a principal investigator on NIH grants continuously since 1997 and has served frequently as a peer reviewer and advisory committee member. Dr. Marrazzo also has served as a mentor to trainees at all stages of professional development, including on NIH-funded training grants, and was the recipient of the American Sexually Transmitted Diseases Association's Distinguished Career Award, the highest recognition of contributions to research and mentoring in the field.

FDA Approves Astellas' IZERVAY® for Geographic Atrophy

Tokyo--/PR NEWSWIRE/--Aug. 5, 2023-- stellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas"), today announced the U.S. Food and Drug Administration (FDA) approved IZERVAY™ (avacincaptad pegol intravitreal solution) for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) on August 4, 2023. IZERVAY, a new complement C5 inhibitor, is the only approved GA treatment with a statistically significant reduction ($p<0.01$) in the rate of GA progression at the 12-month primary endpoint across two Phase 3 clinical trials.



Pravin U. Dugel, MD, President, Iveric Bio, An Astellas Company
"We are thrilled to receive FDA approval of IZERVAY and to offer a new therapy to physicians and appropriate patients in the U.S. Time matters, vision matters, and safety matters in this devastating progressive disease. We would like to thank everyone involved in reaching this milestone and helping us deliver on our commitment to pioneer transformational therapies for retinal diseases."

The FDA approval was based on the GATHER1 and GATHER2 Phase 3 clinical trials, which evaluated the safety and efficacy of monthly 2 mg intravitreal administration of IZERVAY in patients with GA secondary to AMD. The rate of GA growth was evaluated at baseline, 6 months, and 12 months. In each registrational trial, over a 12-month period, the primary analysis showed a statistically significant reduction in the rate of GA growth in patients treated with IZERVAY compared to sham. Slowing of disease progression was observed as early as 6 months with up to a 35% reduction in the first year of treatment.

Source: https://www.prnewswire.com/news-releases/iveric-bio-receives-us-fda-approval-for-izervay-avacincaptad-pegol-intravitreal-solution-a-new-treatment-for-geographic-atrophy-301894042.html

FDA Approves Biogen / Sage Oral Treatment for Postpartum Depression

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Aug. 4, 2023-- Sage Therapeutics, Inc. (Nasdaq: SAGE) and Biogen Inc. (Nasdaq: BIIB) announced the U.S. Food and Drug Administration (FDA) approved ZURZUVAETM (zuranolone) 50 mg for adults with postpartum depression (PPD). ZURZUVAE is the first and only oral, once-daily, 14-day treatment that can provide rapid improvements in depressive symptoms for women with PPD. ZURZUVAE is expected to launch and be commercially available in the fourth quarter of 2023 shortly following scheduling as a controlled substance by the U.S. Drug Enforcement Administration, which is anticipated to occur within 90 days.

Additionally, the FDA issued a Complete Response Letter (CRL) for the New Drug Application (NDA) for zuranolone in the treatment of adults with major depressive disorder (MDD). The CRL stated that the application did not provide substantial evidence of effectiveness to support the approval of zuranolone for the treatment of MDD and that an additional study or studies will be needed. Sage and Biogen are reviewing the feedback and evaluating next steps.

"Maternal mental health has been sidelined for far too long, but today's approval of ZURZUVAE helps to change that. Women have been waiting for an oral medicine that can specifically and rapidly improve the symptoms of PPD and we are proud to be able to deliver that," said Barry Greene, Chief Executive Officer at Sage Therapeutics.

Sage announced approval of zuranalone for postpartum depression after the market close on Friday.

However, Biogen / Sage received a CRL for the same drug in MDD.

The CRL indicated that at least one additional study would be required of the drug prior to approval.

The requirement for an additional study is not good news.

Source: https://investor.sagerx.com/news-releases/news-release-details/fda-approves-zurzuvaetm-zuranolone-first-and-only-oral-treatment

nature immunology

Article

https://doi.org/10.1038/s41590-023-01578-y

Hallmarks of CD8$^+$ T cell dysfunction are established within hours of tumor antigen encounter before cell division

Received: 16 August 2022

Accepted: 7 July 2023

Published online: 03 August 2023

Michael W. Rudloff[1], Paul Zumbo[2,3], Natalie R. Favret[1], Jessica J. Roetman[1], Carlos R. Detrés Román[1], Megan M. Erwin[1], Kristen A. Murray[1], Sriya T. Jonnakuti[1], Friederike Dündar[2,3], Doron Betel[3,4,5] & Mary Philip[1,6,7]

Tumor-specific CD8+ T cells (TST) in patients with cancer are dysfunctional and unable to halt cancer progression. TST dysfunction, also known as exhaustion, is thought to be driven by chronic T cell antigen receptor (TCR) stimulation over days to weeks. However, we know little about the interplay between CD8$^+$ T cell function, cell division and epigenetic remodeling within hours of activation. Here, we assessed early CD8$^+$ T cell differentiation, cell division, chromatin accessibility and transcription in tumor-bearing mice and acutely infected mice. Surprisingly, despite robust activation and proliferation, TST had near complete effector function impairment even before undergoing cell division and had acquired hallmark chromatin accessibility features previously associated with later dysfunction / exhaustion. Moreover, continued tumor/antigen exposure drove progressive epigenetic remodeling, 'imprinting' the dysfunctional state. Our study reveals the rapid divergence of T cell fate choice before cell division in the context of tumors versus infection.

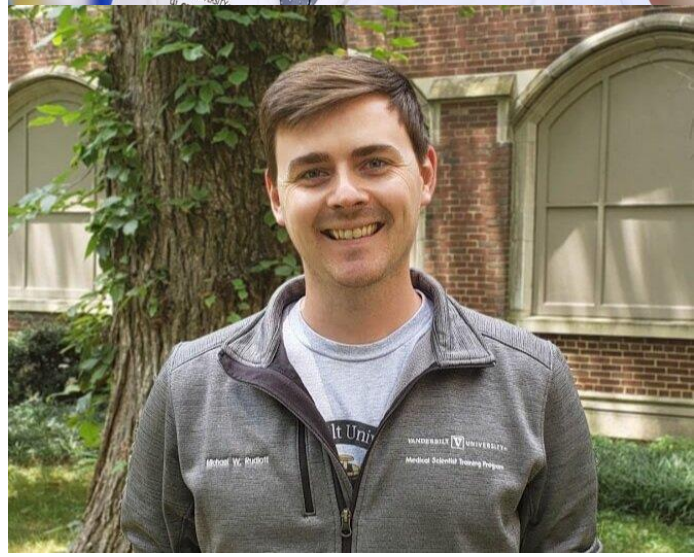
This group of Vanderbilt researchers look at the well-known phenomenon of T-cell anergy in the face of cancer – sometimes called T-cell exhaustion.

While they can't explain the specific cause of anergy they add something previously unknown. It happens right away, and T-cells continue expanding rapidly but without effector function.

Near complete impairment of T-cell effector function occurs within hours of encountering a tumor.

Source: https://www.nature.com/articles/s41590-023-01578-y

Mary Phillip and Michael Rudloff of Vanderbilt Comment on Their Paper on T-Cell Dysfunction and Cancer



The Conversation, Aug 3, 2023

"By the time most patients are diagnosed with cancer, their immune system has been interacting with developing cancer cells for months to years. We wanted to go back earlier in time to figure out what happens when T cells first encounter tumor cells.

To do this, we used mice genetically engineered to develop liver cancers as they age, similarly to how liver cancers develop in people. We introduced trackable cytotoxic T cells that specifically recognize liver cancer cells to analyze the T cells' function and monitor which of the genes are activated or turned off over time.

We also used these same trackable T cells to study their response in mice infected with the bacteria Listeria. In these mice, we found that the T cells were highly functional and eliminated infected cells. By comparing the differences between dysfunctional T cells from tumors and highly functional T cells from infected mice, we can home in on the genes that code for critical proteins that T cells use to regulate their function.

In our previous work, we found that T cells become dysfunctional with dramatically altered genetic structure within five days of encountering cancer cells in mice. We had originally decided to focus on the very earliest time points after T cells encounter cancer cells in mice with liver cancer or metastatic melanoma because we thought there would be fewer genetic changes. That would have allowed us to identify the earliest and most critical regulators of T cell dysfunction.

Instead, we found multiple surprising hallmarks of T cell dysfunction within six to 12 hours after they encountered cancer cells, including thousands of changes in genetic structure and gene expression."

Source: https://theconversation.com/immune-cells-that-fight-cancer-become-exhausted-within-hours-of-first-encountering-tumors-new-research-210947

CD8$^+$ T cells maintain killing of MHC-I-negative tumor cells through the NKG2D–NKG2DL axis

nature cancer

Received: 8 December 2022

Accepted: 20 June 2023

Published online: 03 August 2023

Check for updates

Emily C. Lerner[1,2,9], Karolina I. Woroniecka[3,9], Vincent M. D'Anniballe[1], Daniel S. Wilkinson[4,5], Aditya A. Mohan[5], Selena J. Lorrey[6], Jessica Waibl-Polania[3], Lucas P. Wachsmuth[1,3], Alexandra M. Miggelbrink[3], Joshua D. Jackson[5], Xiuyu Cui[5], Jude A. Raj[1], William H. Tomaszewski[6], Sarah L. Cook[4,5], John H. Sampson[4,5], Anoop P. Patel[4,5,7], Mustafa Khasraw[4], Michael D. Gunn[6,8] & Peter E. Fecci[4,5]

The accepted paradigm for both cellular and anti-tumor immunity relies upon tumor cell killing by CD8$^+$ T cells recognizing cognate antigens presented in the context of target cell major histocompatibility complex (MHC) class I (MHC-I) molecules. Likewise, a classically described mechanism of tumor immune escape is tumor MHC-I downregulation. Here, we report that CD8$^+$ T cells maintain the capacity to kill tumor cells that are entirely devoid of MHC-I expression. This capacity proves to be dependent instead on interactions between T cell natural killer group 2D (NKG2D) and tumor NKG2D ligands (NKG2DLs), the latter of which are highly expressed on MHC-loss variants. Necessarily, tumor cell killing in these instances is antigen independent, although prior T cell antigen-specific activation is required and can be furnished by myeloid cells or even neighboring MHC-replete tumor cells. In this manner, adaptive priming can beget innate killing. These mechanisms are active in vivo in mice as well as in vitro in human tumor systems and are obviated by NKG2D knockout or blockade. These studies challenge the long-advanced notion that downregulation of MHC-I is a viable means of tumor immune escape and instead identify the NKG2D–NKG2DL axis as a therapeutic target for enhancing T cell-dependent anti-tumor immunity against MHC-loss variants.

A strategy that tumor cells use to survive is to shed MHC Class I molecules – which classically T-cells require.

However, most tumor cells express NKG2D as well. This paper shows that T-cells can kill tumor cells expressing this antigen. However, such killing requires T-cell interaction with a relevant APC.

Source: https://www.nature.com/articles/s43018-023-00600-4

Pharma Earnings News

Vertex Raises 2023 Guidance

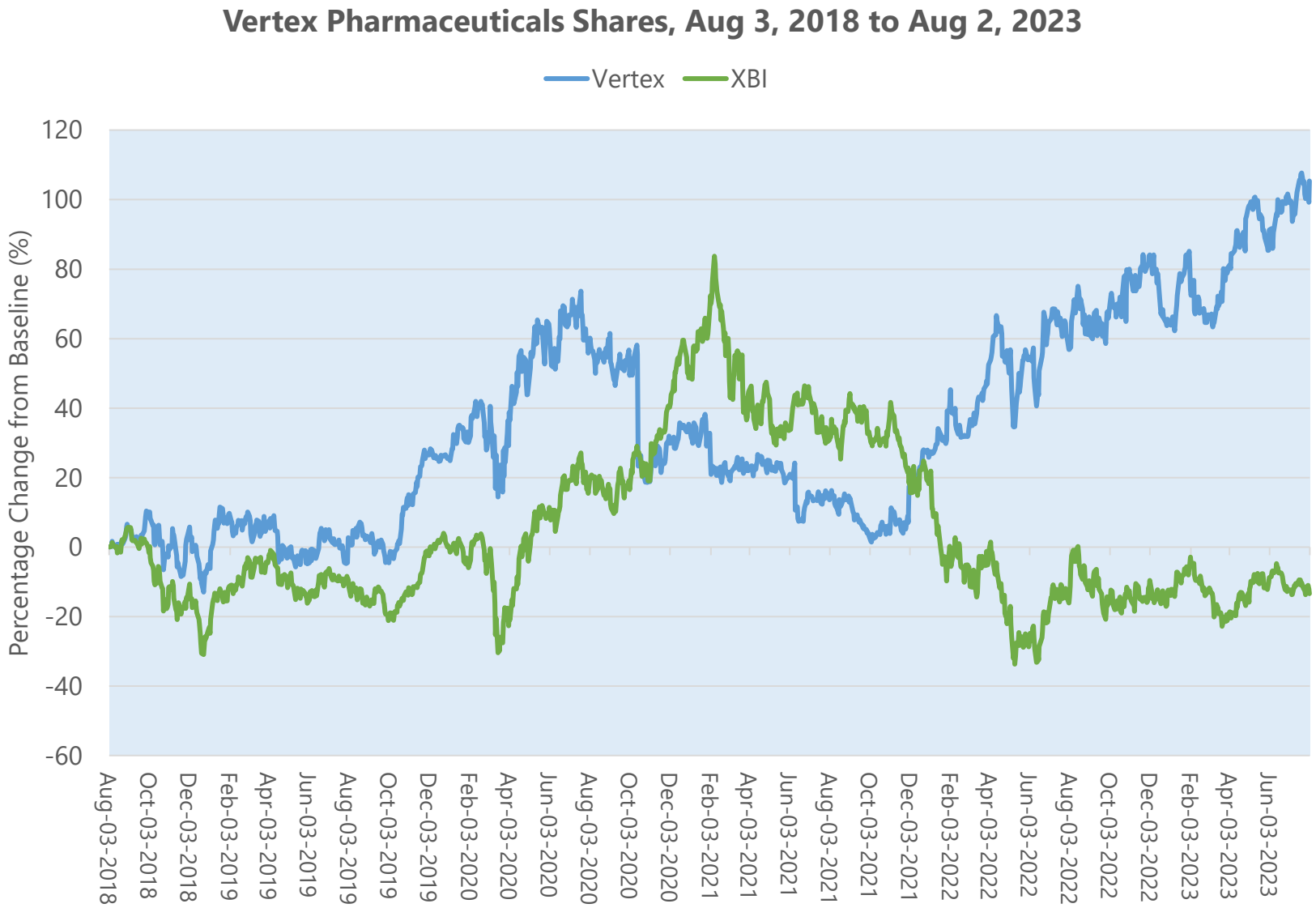
BOSTON--(BUSINESS WIRE)--Aug. 1, 2023-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today reported consolidated financial results for the second quarter ended June 30, 2023 and updated its full year 2023 financial guidance.

"The second quarter of 2023 marked another period of strong progress across our business. We are reaching more patients globally with our cystic fibrosis medicines, advancing our late-stage clinical programs and making rapid progress across our research and development pipeline of transformative medicines," said Reshma Kewalramani, M.D., Chief Executive Officer and President of Vertex. "In the second half of the year, we look forward to expanding our leadership in CF; continuing to prepare for several near-term potential launches, starting with exa-cel; and completing major Phase 3 trials including VX-548 in acute pain and the vanzacaftor triple in cystic fibrosis."

Vertex is raising its full year 2023 CF product revenue guidance to $9.7 to $9.8 billion, from $9.55 to $9.7 billion previously. The increase reflects the expected full-year impact of the strong uptake of TRIKAFTA/KAFTRIO in multiple countries internationally and continued performance of TRIKAFTA in the U.S. This guidance includes an approximately 150-basis-point negative impact from changes in foreign currency rates, inclusive of our foreign exchange risk management program. Vertex is also increasing full year 2023 combined GAAP and non-GAAP R&D, Acquired IPR&D and SG&A expense guidance. The increase accounts for higher acquired IPR&D expenses incurred year-to-date, including a $70 million milestone payment to CRISPR Therapeutics.

Source: https://investors.vrtx.com/news-releases/news-release-details/vertex-reports-second-quarter-2023-financial-results

Vertex Shares Up 105% Over Last Five Years



Vertex Pharma shares have trounced the XBI in the last five years. VRTX is up 105% while the XBI is down 13% over the same period.

VRTX is up 353% over the last 10 years versus 97% for the XBI.

Vertex is now the 14th largest pharma by market cap and has a market cap twice that of Takeda, well ahead of GSK and equal to Gilead.

Source: CapitalIQ

CLINICAL PORTFOLIO IS BROAD, DIVERSE AND RAPIDLY ADVANCING; RESEARCH PIPELINE PROGRESSING TO DELIVER NEXT WAVE OF INNOVATION

Next Wave Discovery Research	Phase 1 In Healthy Volunteers	Phase (1)/2 in Patients	Pivotal Development	Regulatory Submissions Completed	Launched
Vertex hypoimmune cells Type 1 diabetes	**Follow-on small molecules:** • CF • Pain • AMKD • AATD	**VX-880** Type 1 diabetes *PoC achieved*	**VX-548** Acute Pain	**Exa-cel** Sickle Cell Disease	trikafta™
DMD	**VX-634** AATD	**VX-264 cells + device** Type 1 diabetes	**Vanzacaftor triple** Cystic Fibrosis	**Exa-cel** TD Beta Thalassemia	symdeko™
DM1		**VCTX-211 (ViaCyte) hypoimmune cells** Type 1 diabetes	**Inaxaplin** AMKD		ORKAMBI®
Huntington's		**VX-548** Peripheral neuropathic pain			kalydeco®
ADPKD		**VX-864** AATD			
Exa-cel Improved conditioning		**VX-522*** CFTR mRNA			
Na_V 1.7 Pain					

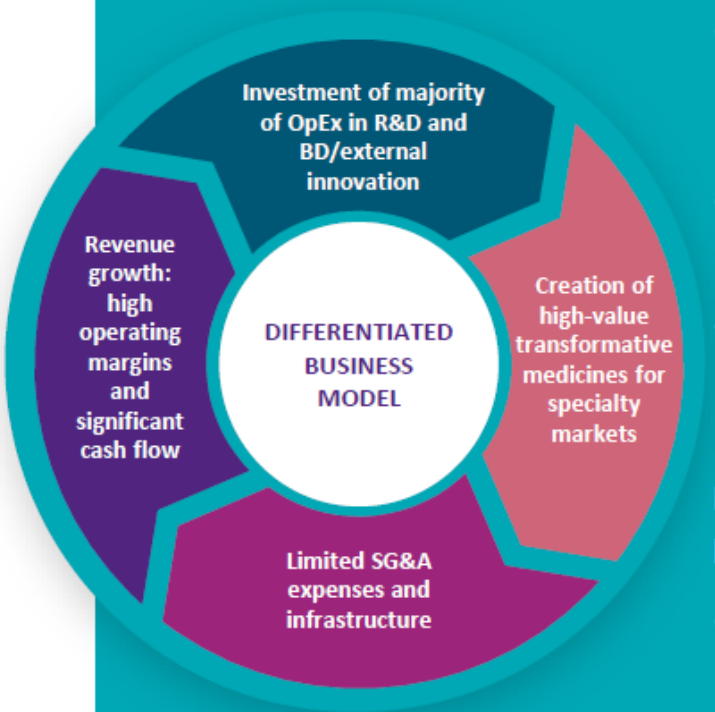
Next Wave = select assets in preclinical development

DMD: Duchenne Muscular Dystrophy; DM1: Myotonic Dystrophy Type 1; ADPKD: Autosomal Dominant Polycystic Kidney Disease; FIH: First In Human

**Phase 1, single ascending dose study in patients with CF*

EXECUTING ON VERTEX BUSINESS MODEL AND R&D STRATEGY WITH RAPID PROGRESS ON A ROBUST PIPELINE

FIVE POTENTIAL LAUNCHES IN THE NEXT FIVE YEARS



We focus on

- **Validated targets** that address causal human biology
- **Predictive lab assays** and clinical biomarkers
- **Rapid path to registration and approval**

In order to deliver a portfolio with

- **transformative benefit,** regardless of modality
- **greater likelihood of clinical success**

4 **Approved medicines in cystic fibrosis**

kalydeco™ ORKAMBI® symdeko™ trikafta™

8 **Programs in mid- or late-stage development**

Near-term commercial opportunities
Exa-cel (SCD)
Exa-cel (TDT)
Vanzacaftor triple (CF)
VX-548 (acute pain)

Mid/late-stage clinical pipeline
Inaxaplin (AMKD) - Post PoC
VX-880 (T1D) - Post PoC
VX-548 (neuropathic pain) – Phase 2
VX-864 (AATD) – Phase 2

PoC: proof of concept; SCD: sickle cell disease; TDT: transfusion-dependent beta thalassemia; AMKD: APOL1-mediated kidney disease; T1D: type 1 diabetes; AATD: Alpha-1 Antitrypsin Deficiency

Vertex Progressing Rapidly With Acute Pain Drug

NEAR-TERM LAUNCH POTENTIAL: VX-548 FOR MODERATE TO SEVERE ACUTE PAIN

ON TRACK TO COMPLETE PIVOTAL PROGRAM BY THE END OF 2023

Significant Unmet Needs

- Millions in the U.S. each year suffer from acute pain
- Existing therapies have challenging side effects and/or abuse potential

Validated Target

- $Na_V1.8$ is genetically and pharmacologically validated
- 5 successful Proof-of-Concept studies across both VX-150 and VX-548 in major pain types

Pivotal Program Ongoing

- Phase 3 pivotal program design, duration and endpoints similar to Phase 2
- **Pivotal program to complete by end of 2023**
- **Results from all three Phase 3 studies expected in late 2023 or early 2024**

Near-Term Commercial Opportunity

- Positive interactions with FDA
- Granted Fast Track and Breakthrough Therapy designations

8

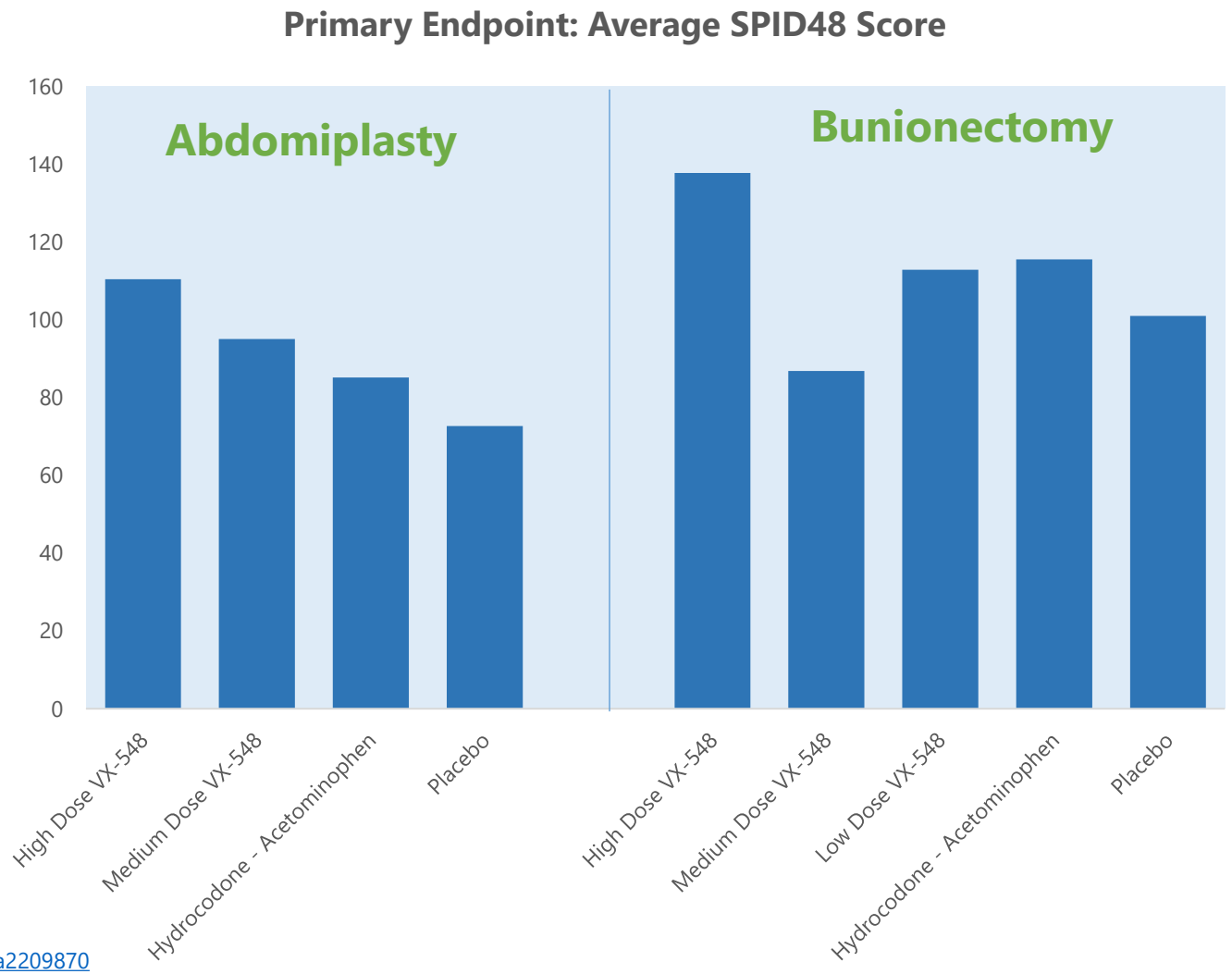
Source: https://investors.vrtx.com/news-releases/news-release-details/vertex-reports-second-quarter-2023-financial-results

Selective Inhibition of $Na_V1.8$ with VX-548 for Acute Pain

Jim Jones, M.D., Pharm.D., Darin J. Correll, M.D., Sandra M. Lechner, Ph.D., Ina Jazic, Ph.D., Xiaopeng Miao, Ph.D., David Shaw, Ph.D., Christopher Simard, M.D., Jeremiah D. Osteen, Ph.D., Brian Hare, Ph.D., Alina Beaton, M.D., Todd Bertoch, M.D., Asokumar Buvanendran, M.D., et al., for the VX21-548-101 and VX21-548-102 Trial Groups*

New England Journal of Medicine, August 3, 2023

SPID-48 is the sum of the pain intensity difference (PID) over the 48-hour time period. A pain intensity score of 0 (no pain) to 10 (worse possible pain) is obtained before starting the study and throughout the 48-time period. In both trials, the primary efficacy end point was the time-weighted sum of the pain-intensity difference (SPID) over a period of 48 hours (SPID48) in a comparison of VX-548 with placebo. We calculated the difference in pain intensity as measured by NPRS scores at each time point as compared with baseline, and the SPID48 values were determined by multiplying a weight factor to each score before summing these values; the weight factor at each of 19 time points was the time elapsed since the previous observation. Because SPID48 is a time-weighted assessment, pain-intensity differences have a greater contribution if they are associated with a longer time interval; higher SPID48 values represent greater reduction in pain.



Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2209870

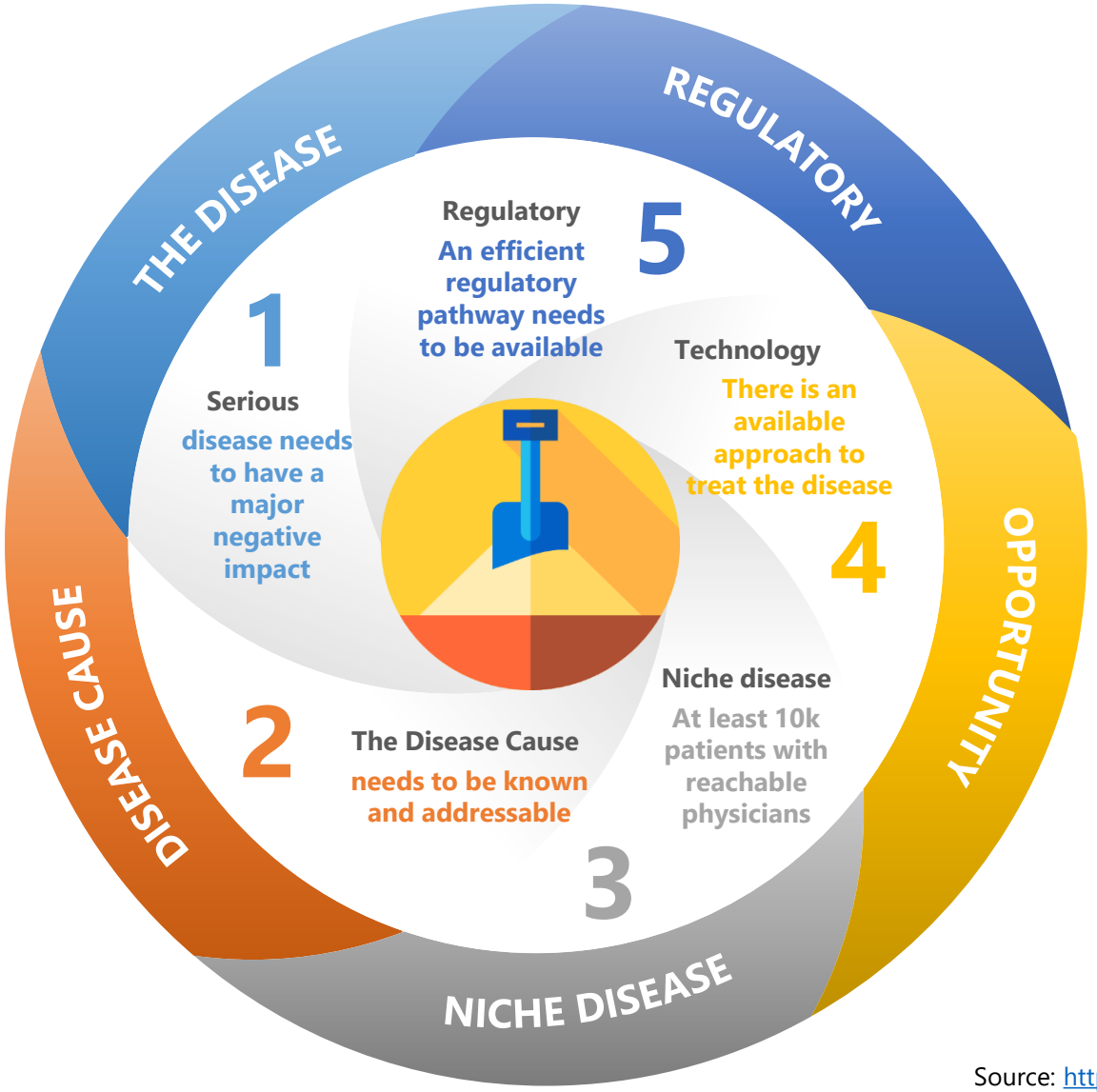
VX-548, a NAV1.8 selective inhibitor, delivered impressive acute pain relief associated with an abdominoplasty. Results for bunionectomy at a high dose of drug were also impressive and competitive against hydrocodone.

Importantly, options for these patients are limited to effective but potentially addictive opioids and less effective drugs like IV meloxicam.

VX-548, indeed, offers high potential for changing the treatment of acute pain. We look forward to Vertex's upcoming Phase 3 data on this topic (late this year or early in 2024).

Vertex Success Built on a Unique Approach

Look for Diseases in the "Sandbox"



Andrew Dunn, *Business Insider*, Oct 4, 2023

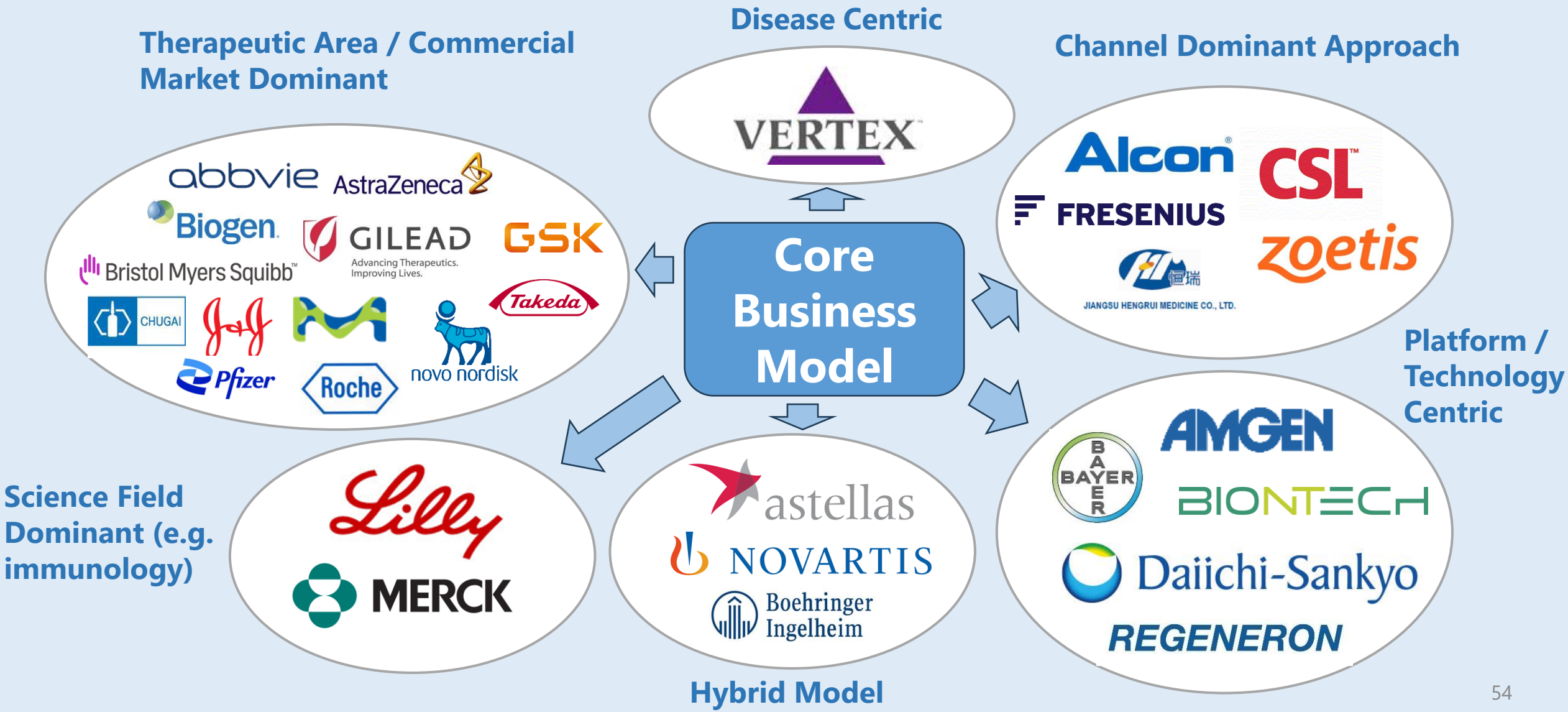
Rather than just maximize profits in CF, Vertex is plowing cash into its unique disease-centric research strategy. While most drugmakers build a pipeline around a key technology or a related group of diseases, Vertex is picking certain diseases like sickle cell or diabetes and then going all in on attempts to transform how they're treated.

[CEO Reshma] Kewalramani calls it the "sandbox" approach. Scientists search for diseases that check five boxes, including an understanding of the illness' biology and an efficient regulatory pathway. If a disease fits those criteria, it's considered "in play," or in the sandbox. That has led to going after unrelated diseases like sickle cell, diabetes, muscular dystrophy, kidney disease, and pain. And instead of homing in on one technology the way Moderna focuses on messenger RNA, Vertex is agnostic, partnering with (and sometimes acquiring) other biotechs to gain access to a wide range of tools, including CRISPR-Cas9.

Source: https://www.businessinsider.com/vertex-ceo-interview-on-future-growth-crispr-cures-2022-9

Vertex Business Model Differentiated From Peers

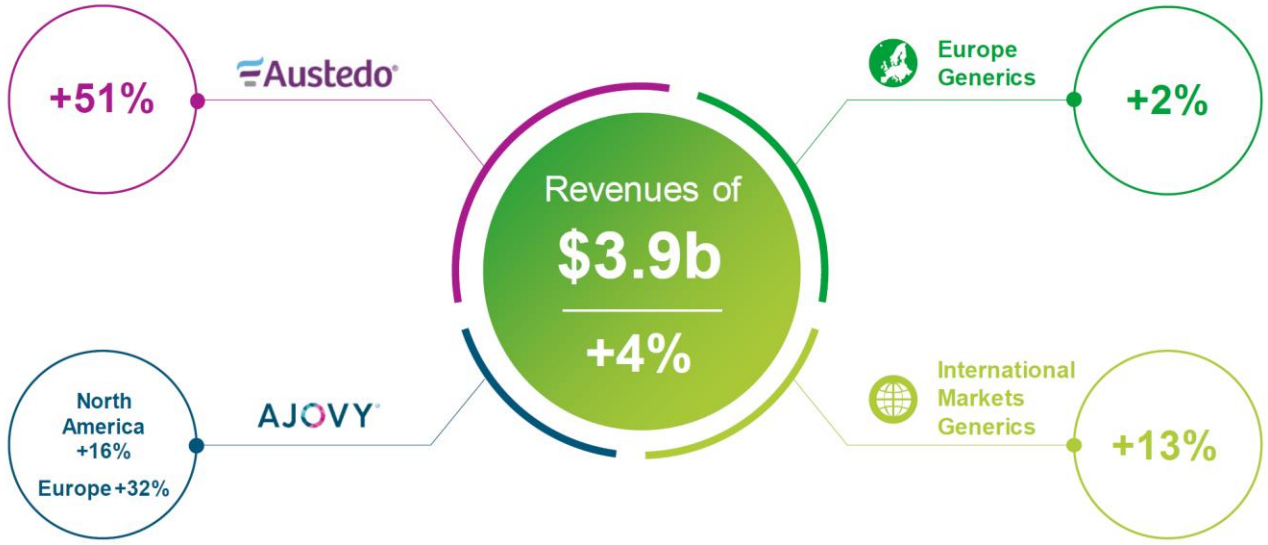
(BioPharma's with $40bn+ Market Caps)



Teva Posts Strong Austedo® Growth

Q2 2023 Solid Performance Driven by our Growth Engines

% In local currency, compared to Q2 2022

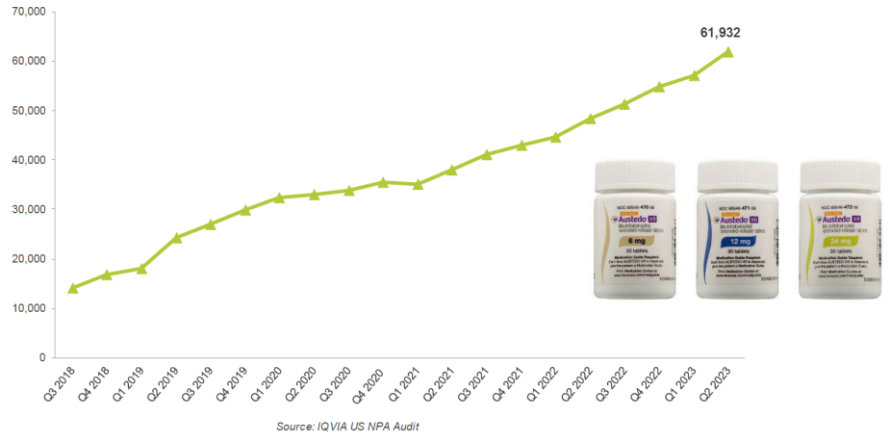


| 5 |

teva

Continued growth of AUSTEDO prescriptions

AUSTEDO quarterly TRx



Source: IQVIA US NPA Audit

AUSTEDO – Reaffirming Goal to Achieve $2.5B by 2027

Austedo

- **Commercial excellence** including increased field force resources
- **Enhanced patient support** to improve conversion & adherence
- **Streamlined titration regimen** and **XR launch**
- **Raised awareness**, e.g., DTC campaigns and medical education
- Investigating **EU market entry** by 2026

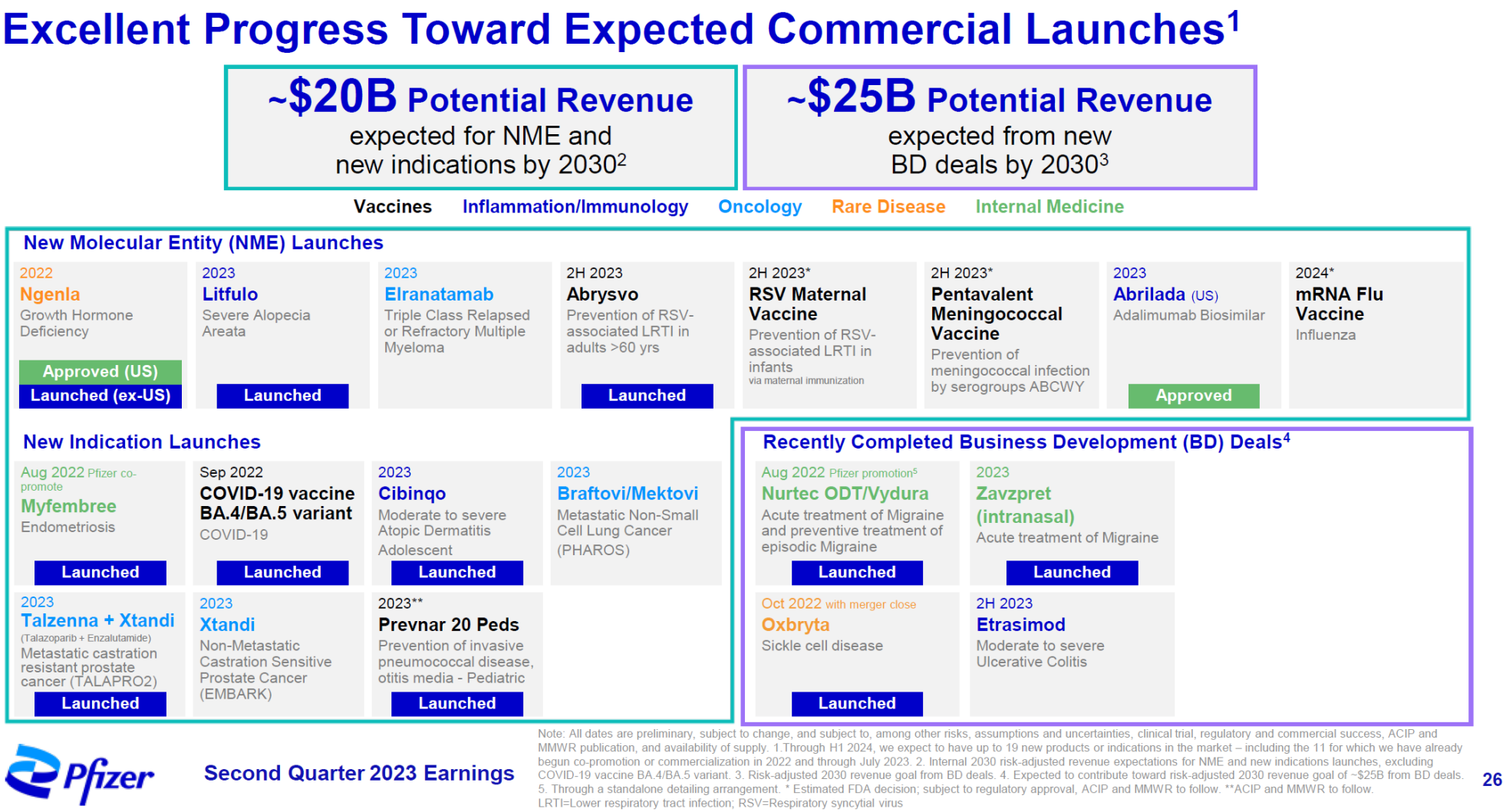
Largely under-treated and under-diagnosed TD market

Number of U.S. tardive dyskinesia patients in thousands (2022)

AUSTEDO growth dynamic in large untapped market supports potential to x 2 revenue by 2027

Source: https://s24.q4cdn.com/720828402/files/doc_financials/2023/q2/2023-08-02-Teva_Q2-2023_Earnings_Presentation-vFINAL.pdf

Pfizer Earnings Call: Good Progress on New Launches

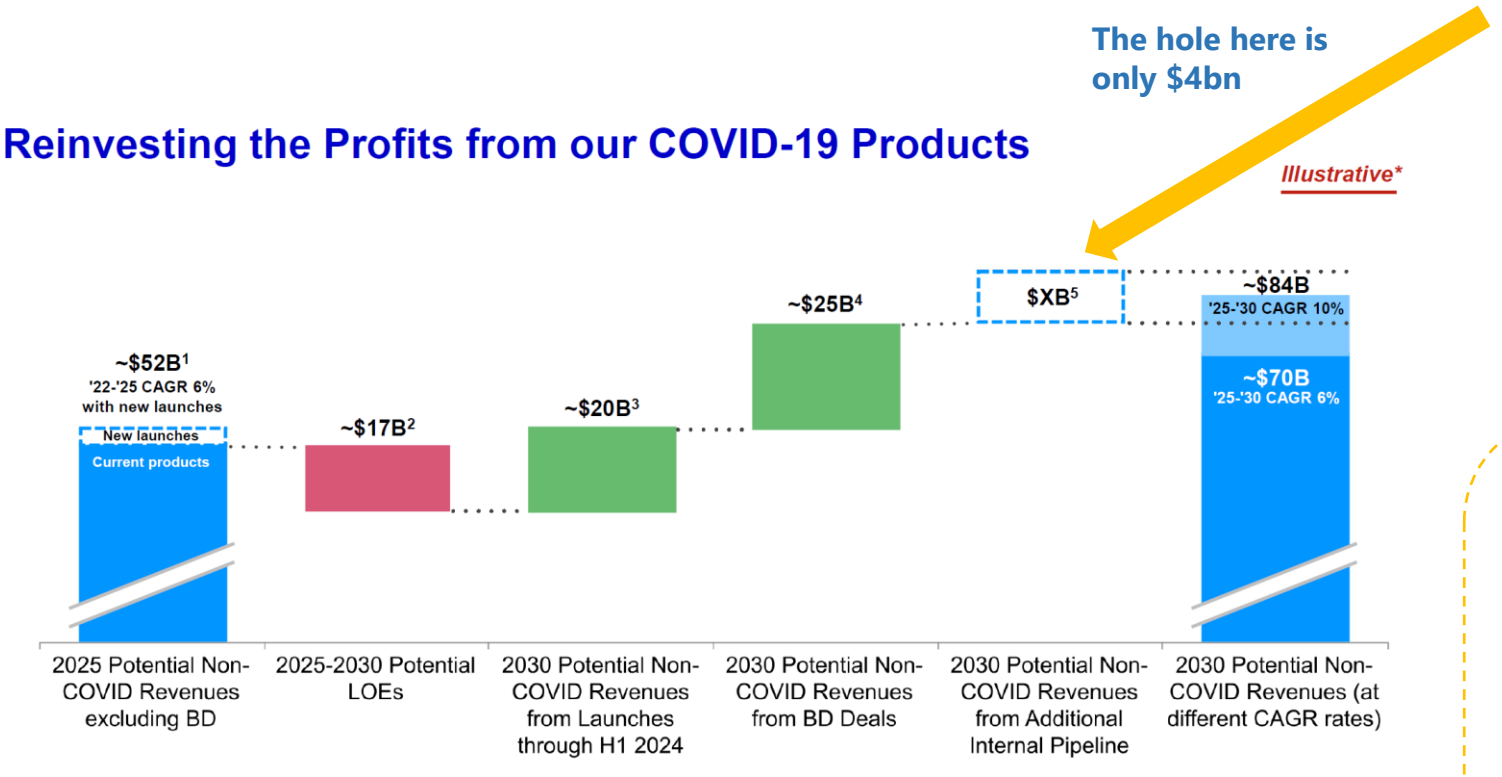


Note: All dates are preliminary, subject to change, and subject to, among other risks, assumptions and uncertainties, clinical trial, regulatory and commercial success, ACIP and MMWR publication, and availability of supply. 1.Through H1 2024, we expect to have up to 19 new products or indications in the market – including the 11 for which we have already begun co-promotion or commercialization in 2022 and through July 2023. 2. Internal 2030 risk-adjusted revenue expectations for NME and new indications launches, excluding COVID-19 vaccine BA.4/BA.5 variant. 3. Risk-adjusted 2030 revenue goal from BD deals. 4. Expected to contribute toward risk-adjusted 2030 revenue goal of ~$25B from BD deals. 5. Through a standalone detailing arrangement. * Estimated FDA decision; subject to regulatory approval, ACIP and MMWR to follow. **ACIP and MMWR to follow. LRTI=Lower respiratory tract infection; RSV=Respiratory syncytial virus

Source: https://s28.q4cdn.com/781576035/files/doc_financials/2023/q2/Q2-2023-Earnings-Charts-FINAL.pdf

Pfizer Earnings Call: Gets Quantitative on 2030 Revenue Plans

Reinvesting the Profits from our COVID-19 Products



*For illustrative purposes only and not intended to be at scale. All values at constant exchange rates. 1. Assumes actual 2022 non-COVID revenues ($43.6B) and 2022-2025 CAGR of 6%. Excludes 2022-2025 BD. 2. Internal expected negative LOE impact from products with a 2022 total revenue base of $18B as shown on slide 32 in Appendix. 3. Internal 2030 risk-adjusted revenue expectations for NME and new indications launches, excluding COVID-19 vaccine BA.4/BA.5 variant, as shown on first two sections of slide 26. 4. Risk-adjusted 2030 revenue goal from BD deals. 5. Potential 2030 risk-adjusted revenues for new product launches as shown on slide 33 in Appendix.
Note: Preliminary, subject to change, and subject to, among other risks, assumptions and uncertainties, clinical trial, regulatory and commercial success and availability of supply. LOE=Loss of Exclusivity; NME=New Molecular Entity; BD=Business Development

Additional Pipeline Potential Launches Through 2030 – Selected Examples

Product Candidate	Anticipated Indication(s)	Expected Potential Launch
New Molecular Entity (NME) Launches		
Danuglipron (oral GLP1)	Type 2 Diabetes, Obesity	>2024
Anti-IFN-β Antibody (PF'3859)	Dermatomyositis, Polymyositis	>2024
COVID / Influenza mRNA Combination Vaccine[1]	COVID-19 & Influenza prevention	>2024
Lyme Disease Vaccine (PF'405)	Lyme disease prevention	>2024
mRNA Shingles Vaccine[1]	Shingles (VZV) prevention	>2024
HemA GTx	Hemophilia A gene therapy	>2024
HemB GTx	Hemophilia B gene therapy	>2024
DMD GTx	Duchenne Muscular Dystrophy gene therapy	>2024
sasanlimab	Non-muscle invasive bladder Cancer	>2024
marstacimab	Treatment of Hem A / Hem B	>2024
Vepdegestrant (ARV-471)	ER+/HER2- BC	>2024
Maplirpacept (TTI-622)	Hematological malignancies	>2024
GBS6 Conjugate Vaccine	Prevention of Group B Streptococcus Infections in Infants via Maternal Immunization	>2024
CDK4, CDK2, and KAT6 inhibitors	HR+/HER2- Breast Cancer	>2024

Note: Expected timing; all dates are preliminary, subject to change, and subject to, among other risks, assumptions and uncertainties, clinical trial and regulatory success and availability of supply.
[1] In collaboration with BioNTech.

Remarkably, Pfizer shares are down 30% in the last 12 months. Today, Pfizer trades with an EV that is 3.2X forward revenue estimates ($66bn for 2024 according to analysts). Analyst consensus revenue today for 2030 is $61 billion. Pfizer's point in this chart (which is getting more specific than before) appears to be that analysts and investors are being too pessimistic about forward performance – perhaps because of this year's falloff in Covid revenues. Pfizer is well on the way to the $25bn in BD revenues and should have little difficulty in generating the $20bn in revenue from products launching through H1 2024 nor in plugging the $4bn revenue hole from its pipeline. Put another way, the market seems to be far off in appreciating what Pfizer's revenue and cash flow in 2030 could be.

Source: https://s28.q4cdn.com/781576035/files/doc_financials/2023/q2/Q2-2023-Earnings-Charts-FINAL.pdf

Merck Q2 Earnings Report Impressive With Strong Keytruda and Gardasil Growth

Strong underlying Q2 performance[1]

Q2 Worldwide Sales

$15.0B

+3%

+14% ex-Exchange, ex-LAGEVRIO[2]

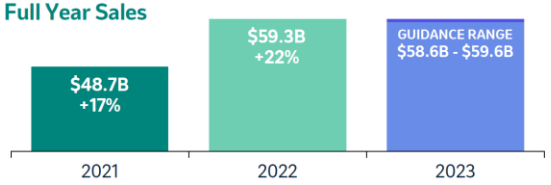
Q2 Non-GAAP LPS[3]

($2.06)

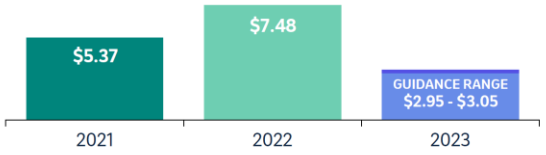
N/M[4]

Includes one-time charge of $4.02 from Prometheus acquisition

Full Year Sales



Full Year Non-GAAP EPS[5]



Strong underlying Q2 worldwide sales growth

Merck

WORLDWIDE SALES[1,2]

$15.0B

+3% growth
+11% ex-LAGEVRIO[3]
+14% ex-exchange, ex-LAGEVRIO[3]

Human Health

$13.5B

+6% growth
+14% ex-LAGEVRIO[3]
+17% ex-exchange, ex-LAGEVRIO[3]

Animal Health

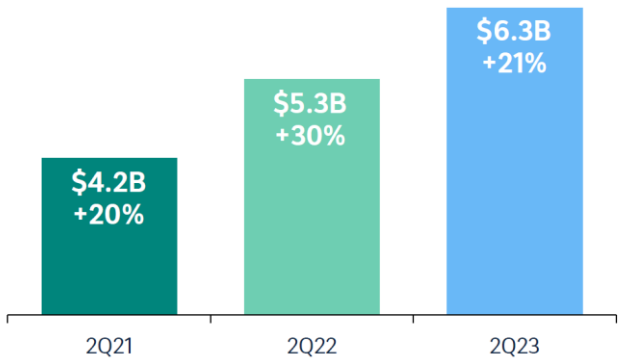
$1.5B

-1% growth
+2% ex-exchange

1. Results attributable to Merck & Co., Inc. 2. Worldwide Sales includes Other Revenue. 3. Excludes Lagevrio sales of $203 million in 2Q23 and $1.2 billion in 2Q22.

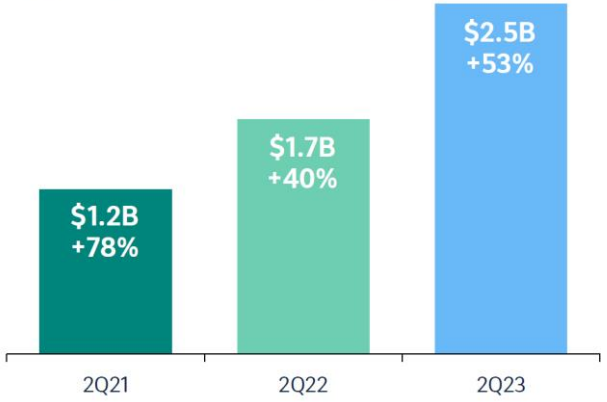
MERCK 10

KEYTRUDA® (pembrolizumab) injection 100 mg



GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]

GARDASIL® 9 [Human Papillomavirus 9-valent Vaccine, Recombinant]



"We continue to have a priority to do business development, so you should not necessarily expect a slowdown. If and when assets that bring important scientific opportunities present themselves—where we see an alignment with strategy and where we can see value creation—we have the capacity and we will be willing to act on those."

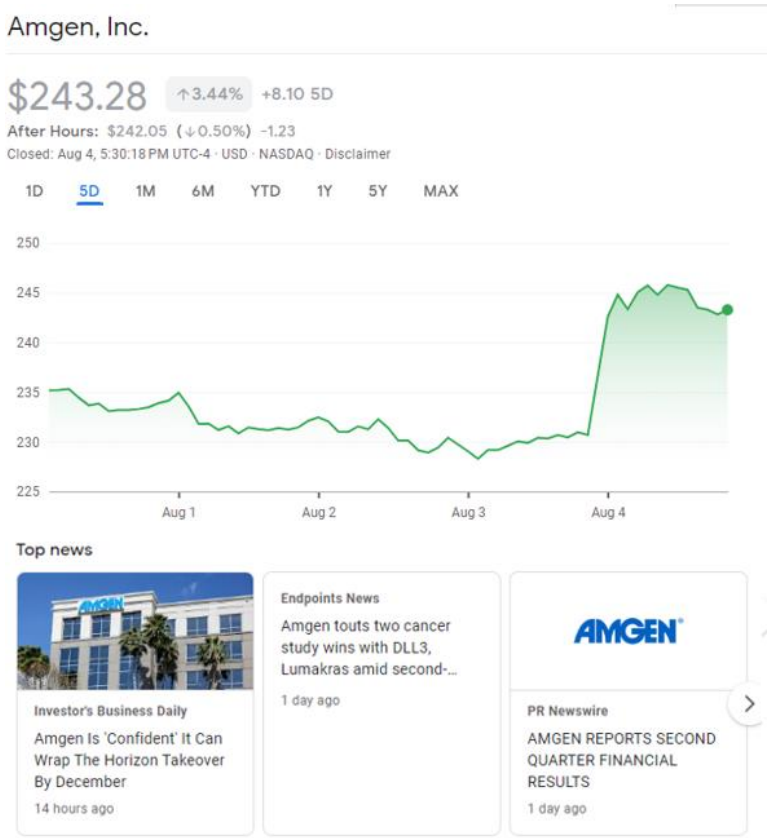
Rob Davis
Chief Executive Officer

"Wow Factor" in Q2 Earnings from Amgen

Amgen stock rose 3.4% for the week on the back of impressive earnings and nice DLL3 BiTe data in SCLC.

We Achieved Record Results, Reported Positive Pipeline Data and Raised Our Full-Year Outlook

- Delivered record revenues and non-GAAP earnings per share
- Delivered 11% volume growth, with record sales for 9 brands
- Expanded our international footprint, with 16% ex-U.S. volume growth (46% in Asia Pacific)
- Positive top-line data for tarlatamab in small cell lung cancer
- Positive top-line data for LUMAKRAS® (sotorasib) plus Vectibix® (panitumumab) in metastatic colorectal cancer
- Expect to close our announced acquisition of Horizon Therapeutics by mid-December of this year



Provided August 3, 2023, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.

AMGEN

Sources: https://investors.amgen.com/static-files/7db6d721-8c83-4676-a4fa-9f33eeecce52 and Google Finance.

Amgen Comments on Earnings Call

Prolia story impressive on osteoporosis. Confident on close of Horizon deal. AMG 133, Amgen's promising obesity drug, has a name for the first time: maridebart cafraglutide (say that fast 10 times!)

Nine of our medicines generated record sales in the quarter. This is consistent with my comments from our first quarter call in April when I said we see the potential for many of our currently marketed products to reach significantly more patients over time and to contribute substantially to our long-term growth. In April, I spoke about Repatha and the growing contribution it's making in the fight against cardiovascular disease. Today I'll highlight **Prolia**, which achieved $1 billion in quarterly sales for the first time, up 11%. Prolia is one of the first biologics to be widely prescribed by primary care physicians to treat a chronic disease, something we expect to see replicated over time in other categories like cardiovascular disease. For all of Prolia success though we know that osteoporosis remains an underdiagnosed and undertreated disease placing millions of elderly women at risk for life-changing fractures. With recently generated real world data, we've established that Prolia is superior to alendronate, the most frequently prescribed bisphosphonate treatment in the U.S. in reducing fractures, and not by a little, but by a lot. To give you one data point, in May we announced that in a real world study, Prolia reduced the risk of hip fracture by 36% compared to alendronate. That's superior. Prolia and EVENITY, which achieved 47% sales growth in the quarter give us a powerful one two punch against osteoporosis, a disease that will only become more prevalent as the world grows older.

Turning to our planned acquisition of Horizon Therapeutics, we remain very enthusiastic about what our companies can achieve together for patients suffering from rare serious diseases. Horizon has certainly accomplished a great deal as an independent company. Amgen's global commercial manufacturing and R&D capabilities, especially for biologic products, will enable Horizon's medicines to reach even more patients more quickly than Horizon could have achieved on its own. As you know, this combination has been approved by regulators around the world, with the exception of the Federal Trade Commission in the United States. **The FTC's arguments in this case are based on speculation and hypothetical notions. Their arguments are not grounded in long established antitrust law. Notwithstanding that in choosing to pursue this case, they've ignored the commitments we made to address their stated concerns.**

In general medicine, we are advancing our cardiovascular franchise and emerging portfolio of obesity molecules with a focus on clinical trial execution. The Phase 3 outcomes study of Olpasiran are potentially best-in-class Lp(a) targeting small interfering RNA molecule and atherosclerotic cardiovascular disease is enrolling well as is a Phase 2 study of **maridebart cafraglutide** formerly known as AMG 133 in patients with obesity with or without diabetes and related comorbidities. The goal of the Phase 2 study is to generate data that will provide broad optionality to design a Phase 3 program leveraging the unique properties of maridebart cafraglutide that will deliver strong sustainable weight loss.

Source: https://investors.amgen.com/events/event-details/q2-2023-amgen-earnings-conference-call

Amgen Obesity Drug Update

Amgen Obesity Drug Update in Q2 Earnings Report

General Medicine

Maridebart cafraglutide (formerly AMG 133) – multispecific GIPR inhibitor and GLP-1 receptor agonist

- A Phase 2 study in overweight or obese adults with or without type 2 diabetes mellitus continues to enroll patients.

AMG 786 – small molecule obesity program (target not disclosed)

- Continuing to enroll patients in a Phase 1 study.
- This molecule has a different target than AMG 133 and is not an incretin-based therapy.

GIPR= Gastric inhibitory polypeptide receptor; GLP-1= Glucagon-like peptide-1.

Source: https://investors.amgen.com/static-files/7db6d721-8c83-4676-a4fa-9f33eeecce52

As highlighted in Stifel's recent obesity drug report, we think AMG 133, now maridebart cafraglutide, has the potential to be one of the largest drugs in history as it is currently the leader in 12-week weight loss.

This drug is working its way through a Phase 2 study which will most likely report out in H1 2024.

Separately, Amgen's AMG 786 is in a Phase 1 study, and we should be seeing data before long.

Mysteriously, the target is not disclosed but Amgen gives a hint that this is not an incretin-based therapy.

We are going to take a guess as to what this is on the next page. We found a patent disclosure from Amgen that was published by USPTO in May 2023 that sounds like the drug. We reasoned, how many small molecule, non-incretin obesity drugs could Amgen have a patent on? We found one. Time will tell if our guess is correct.

If we are right, Amgen could be on to something even bigger than AMG 133.

Our Guess on the Identity of AMG 786

Our guess is that AMG 786 is a D5D Inhibitor that prevents formation of arachidonic acid.

(19) **United States**
(12) **Patent Application Publication** (10) **Pub. No.: US 2023/0159560 A1**
ALLEN et al. (43) **Pub. Date: May 25, 2023**

(54) **METHODS OF USING HETEROCYCLIC COMPOUNDS AS DELTA-5 DESATURASE INHIBITORS**

(71) Applicant: **AMGEN INC.**, Thousand Oaks, CA (US)

(72) Inventors: **Jennifer R. ALLEN**, Newbury Park, CA (US); **Michela BELTRANI**, Verona (IT); **Matthew P. BOURBEAU**, Woodland Hills, CA (US); **Teodora P. DAMYANOVA**, Verona (IT); **Iain LINGARD**, Verona (IT); **Ana E. MINATTI**, Los Angeles, CA (US); **Paolo Vincetti**, Verona (IT)

(21) Appl. No.: **18/056,863**

(22) Filed: **Nov. 18, 2022**

Related U.S. Application Data

(62) Division of application No. 17/103,389, filed on Nov. 24, 2020, now Pat. No. 11,512,097.

(60) Provisional application No. 62/939,821, filed on Nov. 25, 2019.

Publication Classification

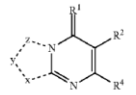
(51) **Int. Cl.**
C07D 513/04 (2006.01)
A61P 3/04 (2006.01)
C07D 487/04 (2006.01)
C07D 498/04 (2006.01)

(52) **U.S. Cl.**
CPC ***C07D 513/04*** (2013.01); ***A61P 3/04*** (2018.01); ***C07D 487/04*** (2013.01); ***C07D 498/04*** (2013.01)

(57) **ABSTRACT**

The present disclosure provides compounds useful for the inhibition of Delta-5 Desaturase ("D5D"). The compounds have a general Formula I.

I

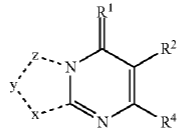


wherein the variables of Formula I are defined herein. This disclosure also provides pharmaceutical compositions comprising the compounds, uses of the compounds, and compositions for treatment of, for example, a metabolic or cardiovascular disorder. Further, the disclosure provides intermediates useful in the synthesis of compounds of Formula I.

What is claimed is:

1. A method of reducing the body weight or the body-mass-index of a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula I

I



or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer,

[0008] The FADS1-3 locus has been associated with many metabolic traits in human genome-wide association studies including fasting glucose, plasma lipids, and body weight. Fumagalli M et al., 2015. Willer C J et al., 2013. Dupuis J et al., 2010. An increase or elevation of each metabolic trait is associated with the FADS1-3 locus is also associated with an increase in the activity of D5D as estimated by AA:DGLA ratios. Fumagalli M et al., 2015. Merino D M et al., 2011.

[0009] In addition to human genetic evidence supporting a role of FADS1/D5D in metabolic disorders, FADS1 knock out ("KO") mice also show a phenotype with protection from diet-induced obesity including low body fat content, improved glycemic control, and decreased circulating lipid levels. Powell D R et al., 2016, page 197. In addition, the FADS1 KO mice are resistant to the development of arterial atheromatous plaque. Id.

[0010] Desaturase enzyme activity has been linked to a variety of diseases, in particular metabolic and cardiovascular diseases, such as obesity, diabetes, nonalcoholic steatohepatitis ("NASH"), dyslipidemia, and coronary artery disease. Tosi F et al., 2014; Kroeger J and Schulze M B, 2012; and Merino D M et al., 2010. Therefore, the pharmacological inhibition of D5D is a target of interest for treating metabolic, cardiovascular and other diseases. Powell D R et al., 2016, page 197.

[0011] Despite some progress in the area of small molecule therapeutics (for example, Miyahisa I et al., 2016; Yashiro H et al., 2016; and Baugh S D et al., 2015), a need for inhibitors of D5D, which may be suitable for use as therapeutic agents, remains in view of the significant continuing societal burden caused by, for example, metabolic and cardiovascular diseases (for example, Haidar Y M and Cosman B C, 2011; Mendis S et al., 2007; Chopra M et al., 2002; and Monteiro C A et al., 2004).

Amgen filed a provisional patent on Nov 25, 2019, for a group of delta-5 desaturase inhibitors for the treatment of obesity. Their DIO mouse data are disclosed and are highly impressive.

As noted in the text at left, there is strong GWAS rationale for hitting this target. And the target is clearly linked to obesity and the formation of cardiac plaque.

Delta-5 desaturase is also known as FADS1 or D5D.

Source: https://patents.google.com/patent/US20230159560A1

Amgen DIO Mouse Data After Getting a High Fat Diet and a Delta-5 Desaturase Inhibitor

TABLE 17

	measurement day	Vehicle	Example 2	Example 2
Dose (mg/kg)			10	30
Body weight (g)	84	53.1 ± 1.1	38.1 ± 1.0*	32.3 ± 0.9*
Blood glucose (mg/dL)	81	201.6 ± 10.2	165.3 ± 4.6*	152.1 ± 6.1*
Insulin (ng/mL)	84	15.8 ± 2.3	1.8 ± 0.3*	1.4 ± 0.2*
Cholesterol (mg/dL)	84	341.3 ± 17.2	224.5 ± 7.3*	207.5 ± 4.8*
LDL cholesterol (mg/dL)	84	110.2 ± 9.5	85.9 ± 3.8*	80.6 ± 3.9*
Triglycerides (mg/dL)	84	29.9 ± 3.6	14.3 ± 1.2*	12.8 ± 1.0*
Fat mass (g)	78	22.9 ± 0.6	11.4 ± 0.6*	5.7 ± 0.6*
Lean mass (g)	78	29.5 ± 0.7	26.4 ± 0.6*	26.1 ± 0.4*
Food consumption(g/day)	0-2	2.7 ± 0.1	2.5 ± 0.2	2.5 ± 0.2
Food consumption(g/day)	70-72	2.8 ± 0.1	2.5 ± 0.1*	2.7 ± 0.1
Liver weights (g)	84	2.7 ± 0.2	3.0 ± 0.2	3.2 ± 0.1
inguinal WAT (g)	84	2.7 ± 0.1	1.2 ± 0.1*	0.5 ± 0.1*
epididymal WAT (g)	84	1.5 ± 0.2	1.2 ± 0.1	0.75 ± 0.1*
mesenteric WAT (g)	84	1.1 ± 0.1	0.4 ± 0.0*	0.2 ± 0.0*
DGLA (μg/mL)	81	80.0 ± 4.4	167.8 ± 11.1*	137.7 ± 6.5*
AA (μg/mL)	81	175.2 ± 7.7	14.5 ± 0.9*	10.7 ± 0.6*
Adiponectin (ng/mL)	84	42.0 ± 23.0	48.3 ± 17.7	51.0 ± 24.4
Leptin (ng/mL)	84	21.9 ± 6.2	10.7 ± 3.6	3.2 ± 1.6
Resisten (ng/mL)	84	1.7 ± 0.4	0.9 ± 0.2	0.7 ± 0.2

*P < 0.05 vs. vehicle, one-way ANOVA with Dunnett's posthoc test

Source: https://patents.google.com/patent/US20230159560A1

The big unmet needs in obesity drugs are for an oral, a drug that avoids nausea, a drug that is lower cost, a source of lasting weight loss and a drug that avoids muscle loss.

The D5D inhibitor in example 2 was associated with a 39.2% weight loss vs placebo (vehicle) in 84 days. Almost all the weight loss was in fat rather than lean mass.

Yet food consumption dropped little when comparing those on drug to placebo.

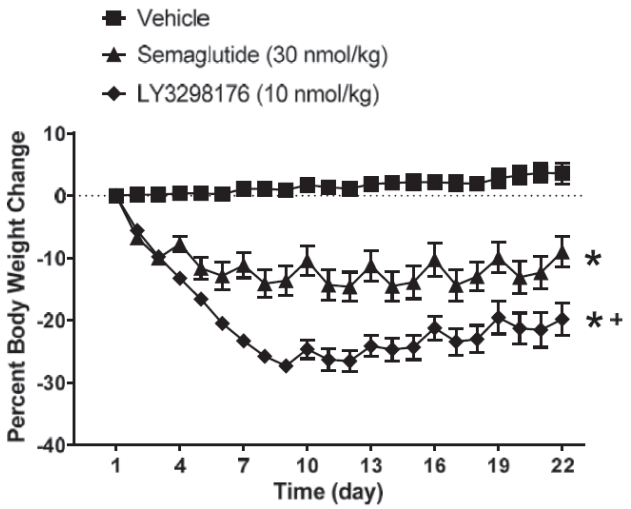
Insulin levels were massively decreased (91%) as were levels of leptin (down 85%).

This is holy grail stuff. You can eat normally, keep muscle mass but not create fat while doing so. Hamburger time?

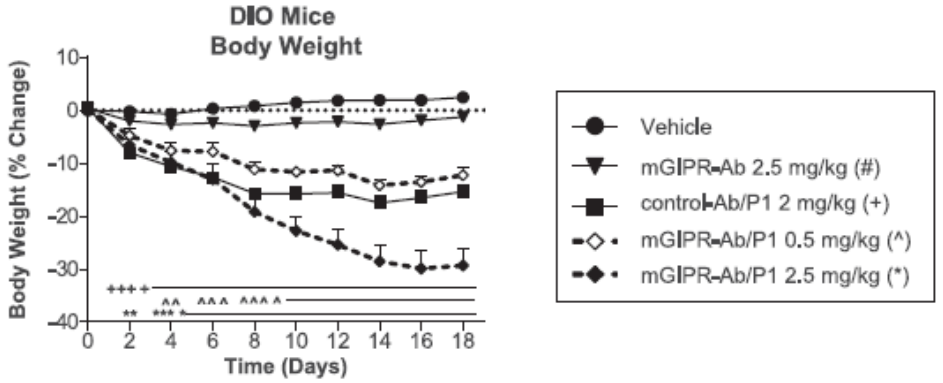
In general DIO mouse data replicate in humans but with a lessened effect. We think that the AMG 786 trial has a good chance of showing strong efficacy, particularly for an oral. The key unknown is safety. Notably, there are no major known safety issues with the relevant FADS1 knockout mouse and Amgen has been enrolling its Phase 1 AMG 786 trial since July 2022 (ClinicalTrials.gov).

DIO Mouse Weight Loss Benchmarks

DIO Model with Mounjaro (LY3298176) and Wegovy (Semaglutide)



AMG 133 (Gipr Antagonist coupled to GLP-1 agonist)



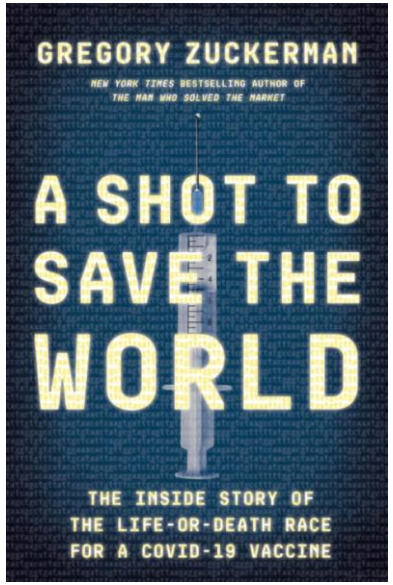
"All the lab mice look so fit these days!"

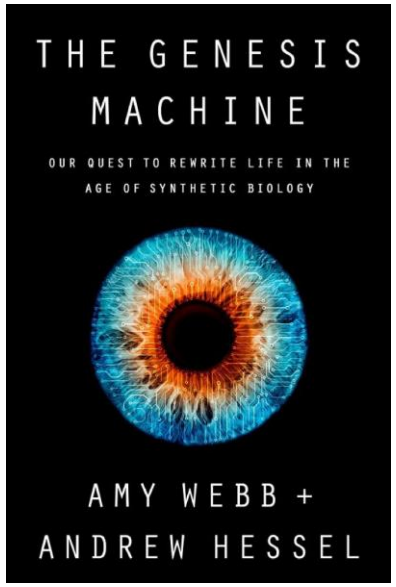
Sources: (1) Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, Cui X, Briere DA, Cabrera O, Roell WC, Kuchibhotla U, Moyers JS, Benson CT, Gimeno RE, D'Alessio DA, Haupt A. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. Mol Metab. 2018 Dec;18:3-14. (2) Lu SC, Chen M, Atangan L, Killion EA, Komorowski R, Cheng Y, Netirojjanakul C, Falsey JR, Stolina M, Dwyer D, Hale C, Stanislaus S, Hager T, Thomas VA, Harrold JM, Lloyd DJ, Véniant MM. GIPR antagonist antibodies conjugated to GLP-1 peptide are bispecific molecules that decrease weight in obese mice and monkeys. Cell Rep Med. 2021 Apr 30;2(5):100263.

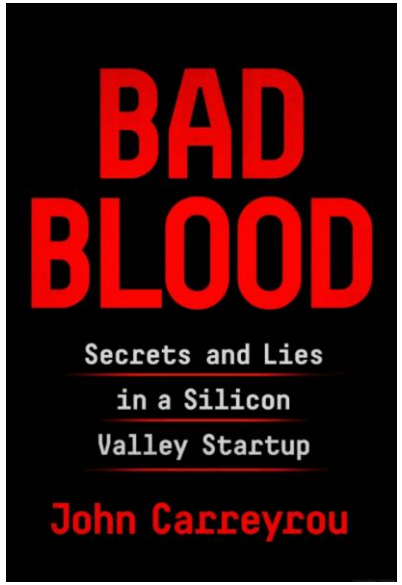
Summer Reading

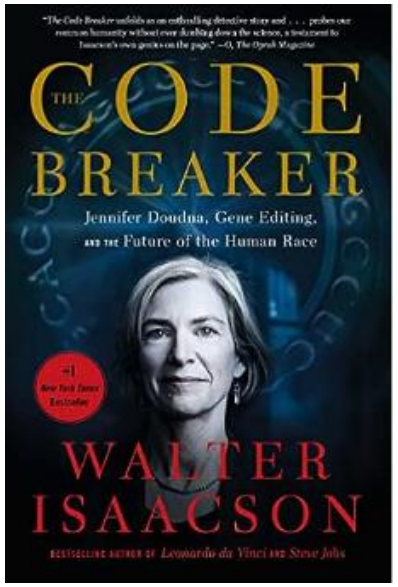
Summer Reading: The Top Five Biotech Books of All Time

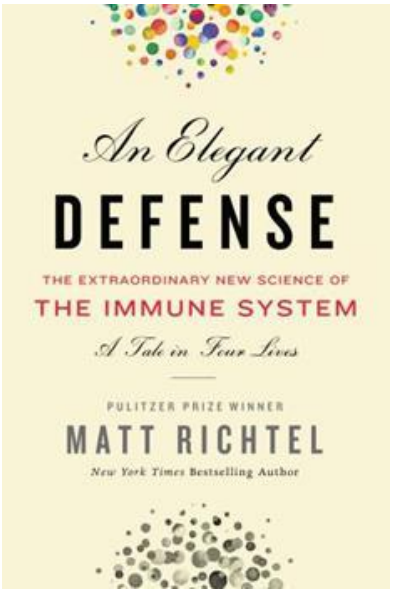
By Roohi Mariam Peter, *LabBiotech*, August 1, 2023











You can see Ms. Peter's full list of 46 suggested books to read at https://www.labiotech.eu/best-biotech/top-biotech-books-of-all-time/

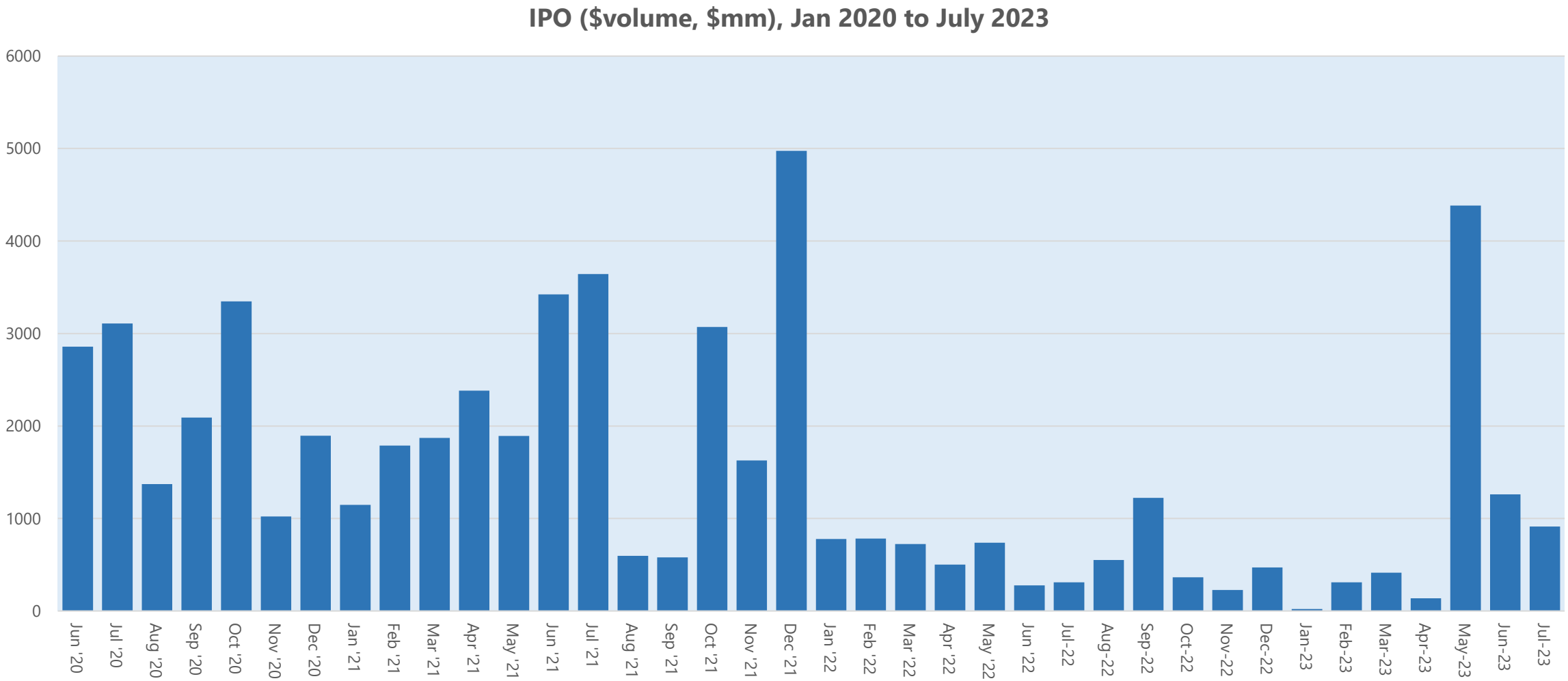
25 Biotech Books that We Have Enjoyed

1. *The Gene*, by Siddhartha Mukherjee (insanely well-written and informative)
2. *Extra Life: A Short History of Living Longer* by Stephen Johnson (and PBS Series – one of our absolute favorites)
3. *The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race* by Walter Isaacson (can a book on science be a page-turner? yes)
4. *Bad Blood: Secrets and Lies in a Silicon Valley Startup* by John Carreyrou (gets you inside what can go very wrong in a startup)
5. *For Blood and Money: Billionaires, Biotech, and the Quest for a Blockbuster Drug* by Nathan Vardi
6. *The End of Medicine* by Andy Kessler (funny book by an industry outsider that makes you think quite deeply about our sector)
7. *The Emperor of All Maladies*, by Siddhartha Mukherjee (history of cancer research - also recent book "Song of the Cell" amazing)
8. *Moonshot: Inside Pfizer's Nine-Month Race to Make the Impossible Possible* by Albert Bourla (a personal, engaging story from Pfizer's leader)
9. *The Great Secret* by Jennet Conant (history of mustards for chemo coming out of a WWII disaster – well written – also enjoyed her *Tuxedo Park*)
10. *Unhealthcare*, Hemant Taneja and Stephen Klasko (visionaries on where healthcare needs to go)
11. *The Great American Drug Deal: A New Prescription for Innovative and Affordable Medicines*, by Peter Kolchinsky (highly current – distinct point of view)
12. *De Humani Corporis Fabricus* by Andreas Vesalius (ok, so we don't read Latin but the pictures and story are mind-boggling)
13. *An Elegant Defense: The Extraordinary New Science of the Immune System: A Tale in Four Lives* by Matt Richtel (you might think immunology is fun after this)
14. *DNA: The Secret of Life* by Jim Watson and Andrew Berry (very good exposition on genetics)
15. *Reinvent: A Leaders Playbook for Serial Success* by Fred Hassan (about corporate culture in our industry)
16. *Black Edge* by Sheelah Kokhatkar (Elan insider trading scandal)
17. *The Perfect Predator* by Steffanie Strathdee and Thomas Patterson (page-turner that introduces bacteriophage therapeutics)
18. *The Billion Dollar Molecule: One Company's Quest for the Perfect Drug* by Barry Werth (also *Antitode* by same author on history of Vertex Pharma)
19. *What is Life?*, By Erwin Schrodinger (highly prescient thinker)
20. *From Alchemy to IPO* by Cynthia Robbins-Roth (published in 2000 – still relevant)
21. *VC: An American History* by Tom Nicholas (takes you back to how whaling expeditions were financed – and the history of venture capitalists)
22. *Genentech: The Beginnings of Biotech* by Sally Smith Hughes
23. *Being Mortal*, by Atul Gawande
24. *Science, the Endless Frontier* by Vannevar Bush (foundations of science as a national enterprise – came right after the Manhattan Project)
25. *The Long Shot: The Inside Story of the Race to Vaccinate Britain* by Kate Bingham and Tim Hames

Capital Markets Environment

IPO Market Continues Uptrend in July

While the last two weeks have been quiet, July was the third month running with more than a half billion in biopharma IPO volume. This a sharp contrast with the feeble volumes seen between October 2022 and April 2023.



Source: Data from CapitalIQ and Stifel research.

Nasdaq Biotech IPOs in 2023 Continuing to Trade Well

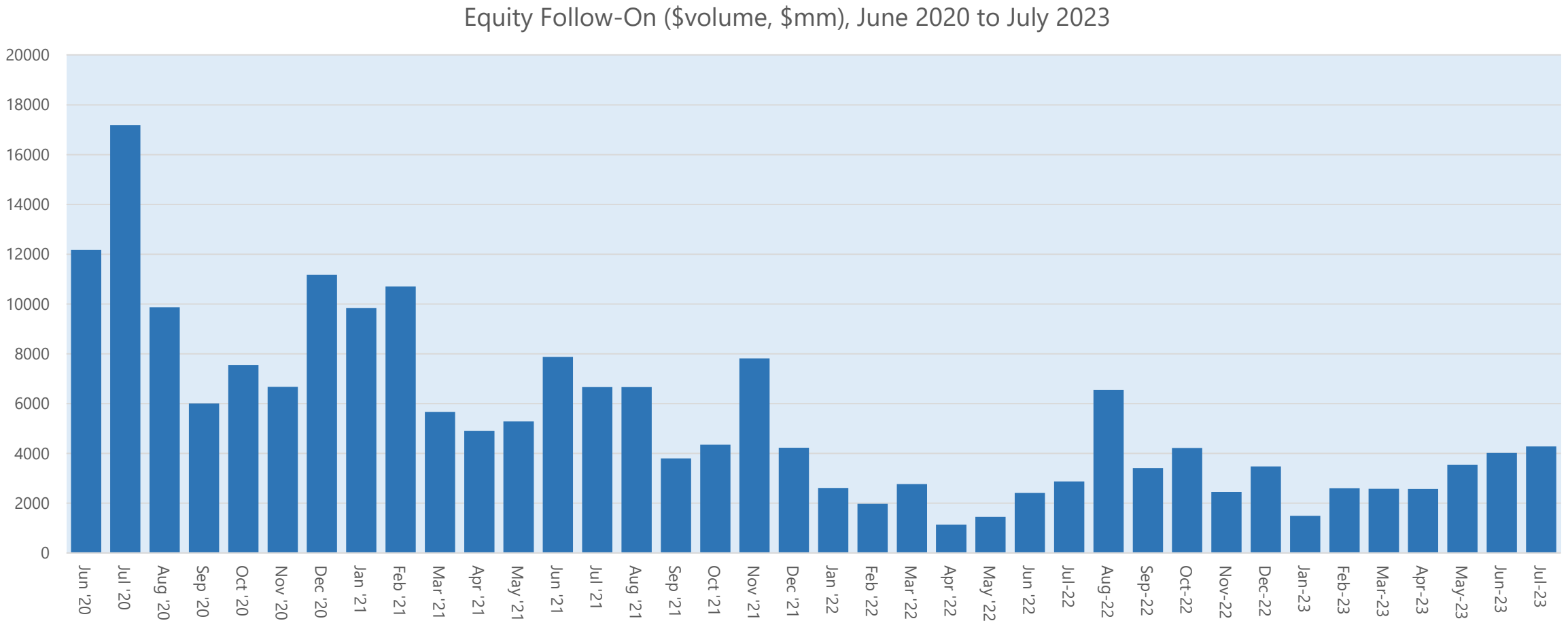
The average current/offer of the six IPO's that have priced this year is 22%, driven mainly by strong aftermarket performance of Structure Therapeutics, Acelyrin and Apogee.

Offer Date	Target/Issuer	Amount Raised ($mm)	Issue Price	Price at Offer Date Close	Price Aug 3, 2023	Current / Offer
07/20/2023	Turnstone Biologics	$80	$12.0	$11.0	$11.5	-4.3%
07/13/2023	Sagimet Biosciences	$85	$16.0	$16.0	$16.1	0.6%
07/13/2023	Apogee Therapeutics	$300	$17.0	$21.2	$20.7	21.8%
05/04/2023	Acelyrin	$540	$18.0	$23.5	$24.5	35.9%
02/14/2023	Mineralys Therapeutics	$192	$16.0	$18.0	$13.3	-16.9%
02/07/2023	Structure Therapeutics	$161	$15.0	$23.3	$29.3	95.0%
Average		$226mm				22.0%
Median		$177mm				11.2%

Source: Data from CapitalIQ and Stifel research. Photo from Getty Images. NASDAQ offerings of $50mm or more included.

Last Month Was the Most Active of the Year for Follow-On Offerings

July was the first month in ten months with more than $4 billion in follow-on market. Monthly volume in follow-on biopharma offerings has nearly tripled from the nadir month of January 2023.



Source: Data from CapitalIQ and Stifel research.

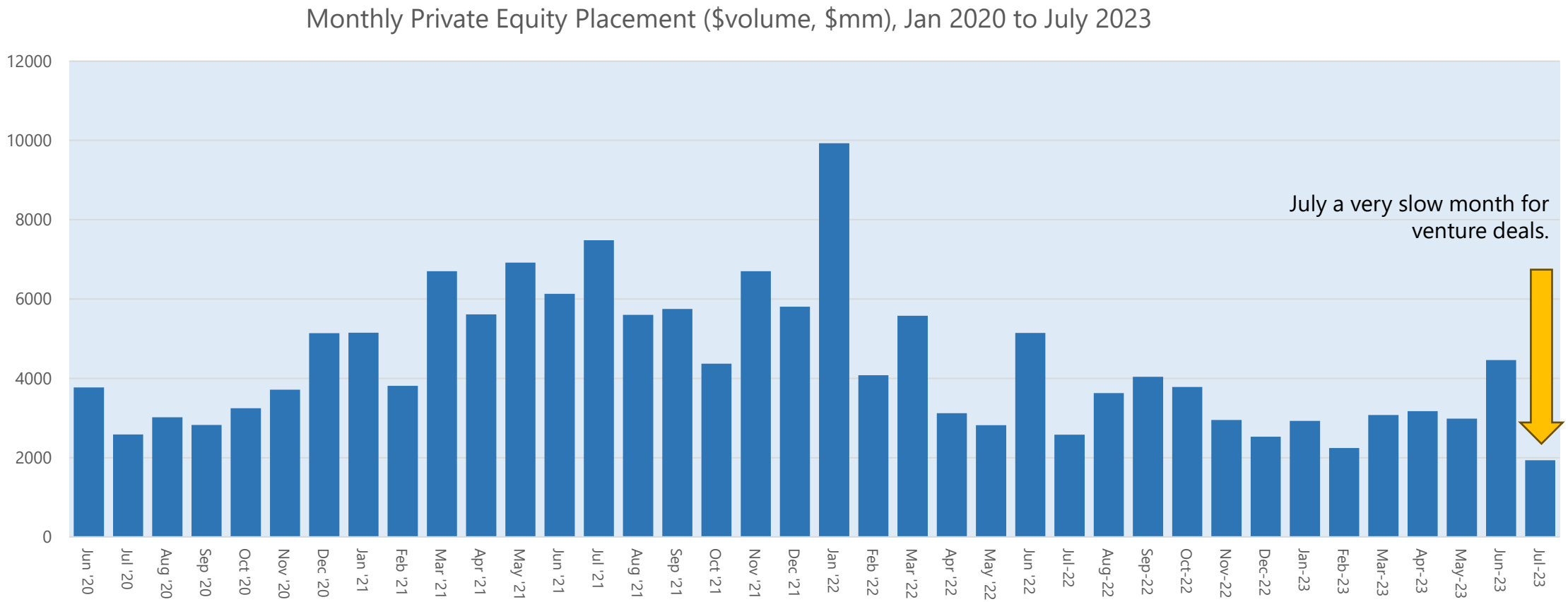
Tarsus Raises $100mm After FDA Approval of its XDEMVY® Drug for Blepharitis

IRVINE, Calif., Aug. 01, 2023 (GLOBE NEWSWIRE) -- Tarsus Pharmaceuticals, Inc. (Nasdaq: TARS) (the "Company" or "Tarsus"), whose mission is to focus on unmet needs and apply proven science and new technology to revolutionize treatment for patients, starting with eye care, today announced the pricing of an underwritten public offering of 5,714,285 shares of its common stock at a public offering price of $17.50 per share, before underwriting discounts and commissions. In addition, Tarsus has granted the underwriters a 30-day option to purchase up to an additional 857,142 shares of common stock at the public offering price, less underwriting discounts and commissions. The gross proceeds from the offering, before deducting underwriting discounts and commissions and other offering expenses payable by Tarsus, are expected to be approximately $100.0 million, excluding any exercise of the underwriters' option to purchase additional shares. The offering is expected to close August 4, 2023, subject to the satisfaction of customary closing conditions.

Source: https://ir.tarsusrx.com/news-releases/news-release-details/tarsus-announces-pricing-1000-million-underwritten-public

Venture Equity Market is Continuing to Slow Down

July was an incredibly slow month for venture equity privates. We saw $1.9 billion in deal volume get announced. Compare this to average monthly volume of $3.1bn this year and $4.1 billion in 2022.



Source: Data from CapitalIQ, Crunchbase.

CG Oncology Announces $105 Million Oversubscribed Crossover Financing

August 2, 2023: IRVINE, Calif.--(BUSINESS WIRE)--CG Oncology, Inc. today announced the close of an oversubscribed $105 million crossover financing round, co-led by new investors Foresite Capital and TCGX, with participation from Avidity Partners, BVF Partners and Janus Henderson Investors, as well as existing investors including Acorn Bioventures, Ally Bridge Group, Decheng Capital, Longitude Capital, Malin Corporation and RA Capital Management.

"We have been impressed and encouraged by the significant progress the team at CG Oncology has made to demonstrate the efficacy of oncolytic immunotherapy cretostimogene grenadenorepvec, which has shown clear signals of activity as a single agent and in combination," said Michael Rome, Ph.D., Managing Director, Foresite Capital. "A significant unmet need remains in bladder cancer, and the CG team is moving with great urgency and focus to deliver potential new treatment options that could elevate the standard of care in this difficult-to-treat patient population."

The proceeds will support the continued advancement of clinical programs in bladder cancer towards FDA approval including BOND-003, a fully enrolled, single-arm, Phase 3, monotherapy study for cretostimogene grenadenorepvec as a potential treatment for high-risk non-muscle invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette-Guerin (BCG).

"Cretostimogene grenadenorepvec has the potential to address resistance mechanisms to approved immunotherapies and substantially improve outcomes for bladder cancer patients," said Giuliano Marostica, Principal, TCGX. "We are excited to partner with CG Oncology to develop this transformational therapy that addresses a high unmet medical need in bladder cancer."

"We are excited to welcome leading life science investors who share our vision of developing cutting-edge therapeutics addressing unmet medical needs in bladder cancer. Our lead asset, cretostimogene grenadenorepvec, continues to make significant clinical progress in bladder cancer in both monotherapy and in combination studies and we are encouraged to see our treatments get closer to being available to bladder cancer patients worldwide."

Arthur Kuan
Chief Executive Officer
CG Oncology

Source: https://www.businesswire.com/news/home/20230802677533/en/CG-Oncology-Announces-105-Million-Oversubscribed-Crossover-Financing-to-Advance-Clinical-Stage-Bladder-Cancer-Pipeline

Alvotech Completes $100 Million Convertible Bond Private Placement

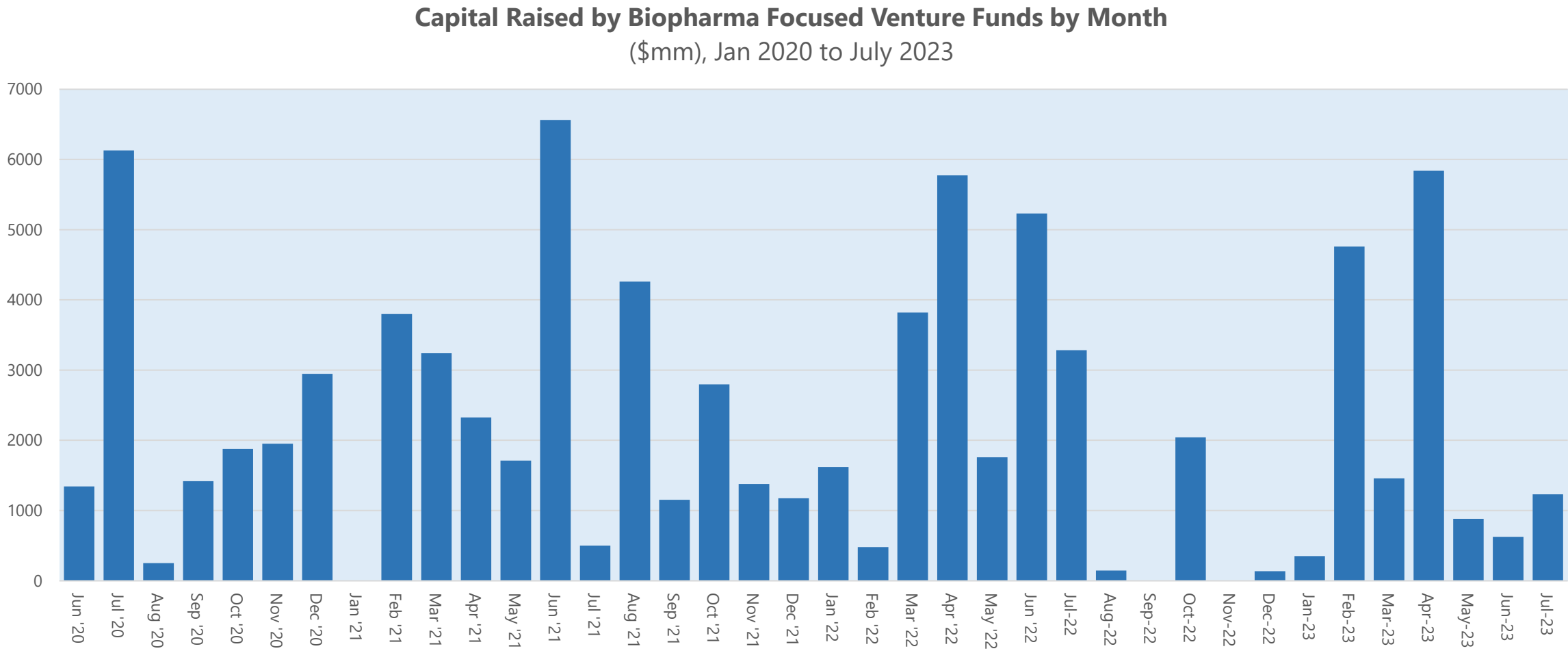
REYKJAVIK, Iceland, July 31, 2023 (GLOBE NEWSWIRE) -- Alvotech (NASDAQ: ALVO), a global biotech company specializing in the development and manufacture of biosimilar medicines for patients worldwide, today announced the completion of a private placement, in an overseas directed offering directed solely into Iceland to professional clients or eligible counterparties, of subordinated convertible bonds denominated in Icelandic krona (ISK) and US dollar (the "Bonds") for a par value of $100 million. Alvotech expects to use the proceeds for continued development of its biosimilars pipeline.

ATP Holdings ehf., which is affiliated with Aztiq Pharma Partners S.a.r.l. the largest shareholder of Alvotech, previously entered into an agreement with Alvotech under which ATP Holdings ehf. committed to acquiring any of the Bonds which were not sold to other investors in the private placement. The value of ATP Holdings ehf. total commitment was up to the total par value of the Bonds offered, or $100 million. Offers for Bonds for a total par value of $70.1 million at current exchange rates were received from qualified investors and ATP Holdings ehf. Will acquire all the remaining Bonds. Settlement of the private placement is expected to take place on August 11, 2023.

Alvotech will issue the Bonds, with a maturity date on December 20, 2025, pursuant to a convertible bond instrument dated December 20, 2022. The ISK denominated tranche is registered on the Nasdaq First North Growth Market in Iceland. Holders of the Bonds may elect, at their sole discretion, to convert all or part of the principal amount and accrued coupon into Alvotech ordinary shares, at a fixed conversion rate of $10 per share, on December 31, 2023, or June 30, 2024.

Source: https://investors.alvotech.com/news-releases/news-release-details/alvotech-completes-100-million-convertible-bond-private

July an Active Month for Funds Flowing Into Biopharma Focused Venture Capital



Source: Data from Stifel venture capital sector tracker.

Emerson Collective Health Spins Off to Form New Investment Fund, Yosemite

SAN FRANCISCO, Aug. 1, 2023 /PRNewswire/ -- Today, Yosemite announced it has launched as a new standalone entity, spinning off from Emerson Collective to form an independent investment firm focused on opportunities across the oncology ecosystem—the new fund launches with an oversubscribed first close of $200M+. Yosemite will deploy a differentiated strategy that employs both grantmaking and venture investing as a catalyst for scientific breakthroughs to become viable cancer patient solutions.

Since 2015, Emerson Collective Health has been breaking down silos to reach its goal of making cancer non-lethal in our lifetime. In spinning off as an independent fund, Yosemite offers a tailored focus on its proven model of creative collaboration.

Composed of the Emerson Health team, Yosemite continues its investment strategy of providing grants to emerging research along with flexible funding for incubation and early-translation investments in therapeutics, diagnostics, and digital health.

Yosemite brings an impressive track record of identifying emerging scientists and budding entrepreneurs on the cusp of scientific breakthrough. Yosemite leaders have supported hundreds of researchers and invested in dozens of therapeutic and diagnostic companies across the U.S., Europe, and Israel.

"Yosemite is uniquely positioned to meet cutting edge academic science where it is to accelerate translation to biotech innovation," said David Hallal, Founder of ElevateBio, an Emerson Health portfolio company. "ElevateBio has been a direct beneficiary of Yosemite's dual-strategy, having partnered with two Yosemite grantees from leading academic centers, as well as having the team involved through their direct venture investment in our most recent few rounds of financing. Yosemite has rightfully earned a reputation for advancing the discoveries of many of the world's great scientists with the goal of discovering and developing innovative therapies for patients and families suffering with devastating diseases."

"We're on a mission to lead the next chapter in the fight against cancer and forming our own standalone entity provides us the flexibility to best propel great ideas until they're at scale."

Reed Jobs
General Partner
Yosemite

Source: https://www.prnewswire.com/news-releases/emerson-collective-health-spins-off-to-form-new-investment-fund-yosemite-announces-first-close-of-oversubscribed-200m-fund-to-accelerate-transformative-cancer-ventures-301890424.html

Coatue Launches VC Fund

COATUE

The Tiger Cub continues to target early-stage financings.

Stephen Taub, *Institutional Investor*, August 2, 2023

Coatue Management has closed on a new venture capital fund.

According to a regulatory filing, the Tiger Cub headed by Philippe Laffont has raised $331 million for Coatue Ventures III. The fund's first sale was in September 2022. As is usually the case, the filing does not disclose much more information.

According to *The Information*, Coatue was seeking to raise as much as $500 million for the new fund. The shortfall isn't particularly surprising, given that both the venture capital market and the initial public offering market have shriveled from their peak less than two years ago, as valuations for private companies have been cut and it has become all but impossible to bring a company public.

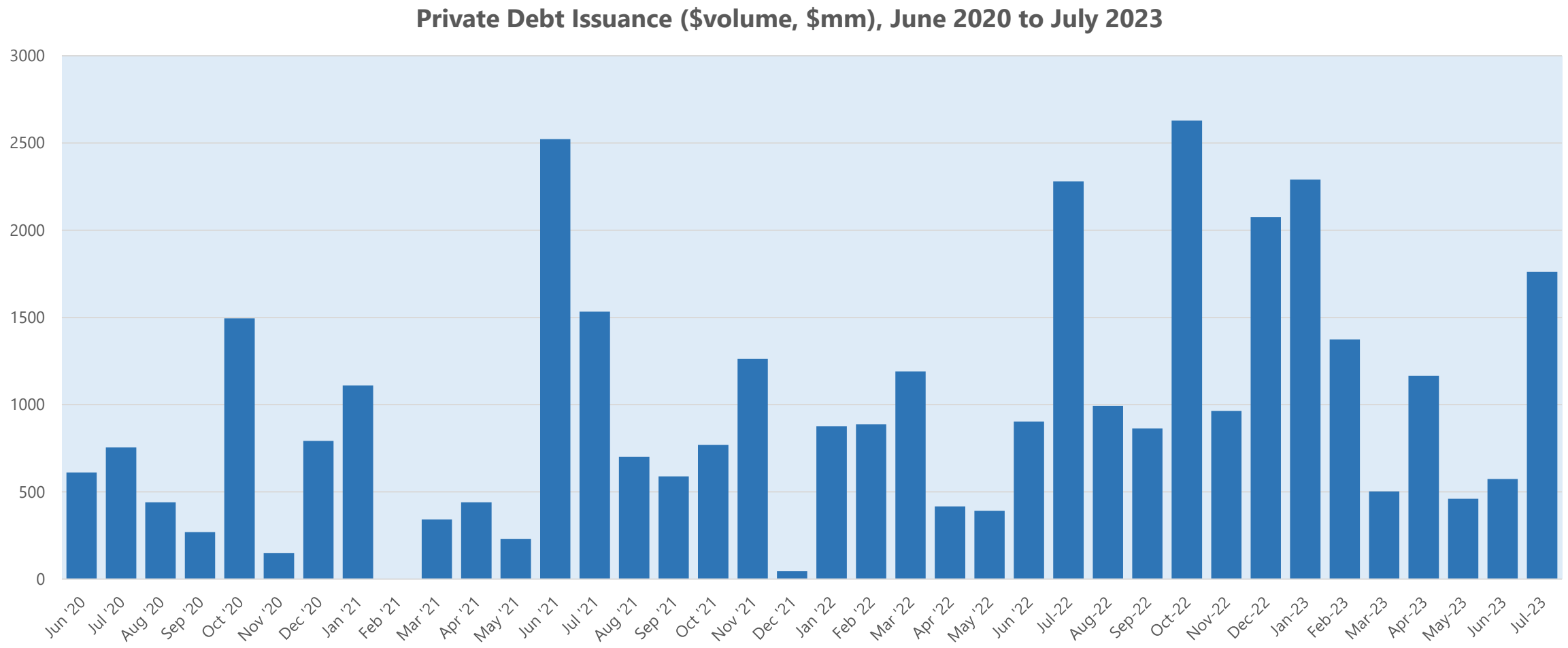
This is Coatue's third VC fund targeting early-stage financings. It had previously raised $500 million for a similar fund in 2021 and $750 million for its first early-stage fund, according to *The Information*.

Until recently, Coatue was the second most active firm in the VC market among firms also known for their hedge fund arms, behind Tiger Global Management.

Source: https://www.institutionalinvestor.com/article/2c040kp9ofq4zqrgbueio/premium/coatue-launches-vc-fund

Private Debt Market Picked Up Nicely in July

The private debt market had its strongest month since January with issuers raising around $1.7 billion in this market.



Source: Data from CapitalIQ, Crunchbase.

X4 Pharma Takes Down $22.5 Million in Venture Debt from $115 Million Facility

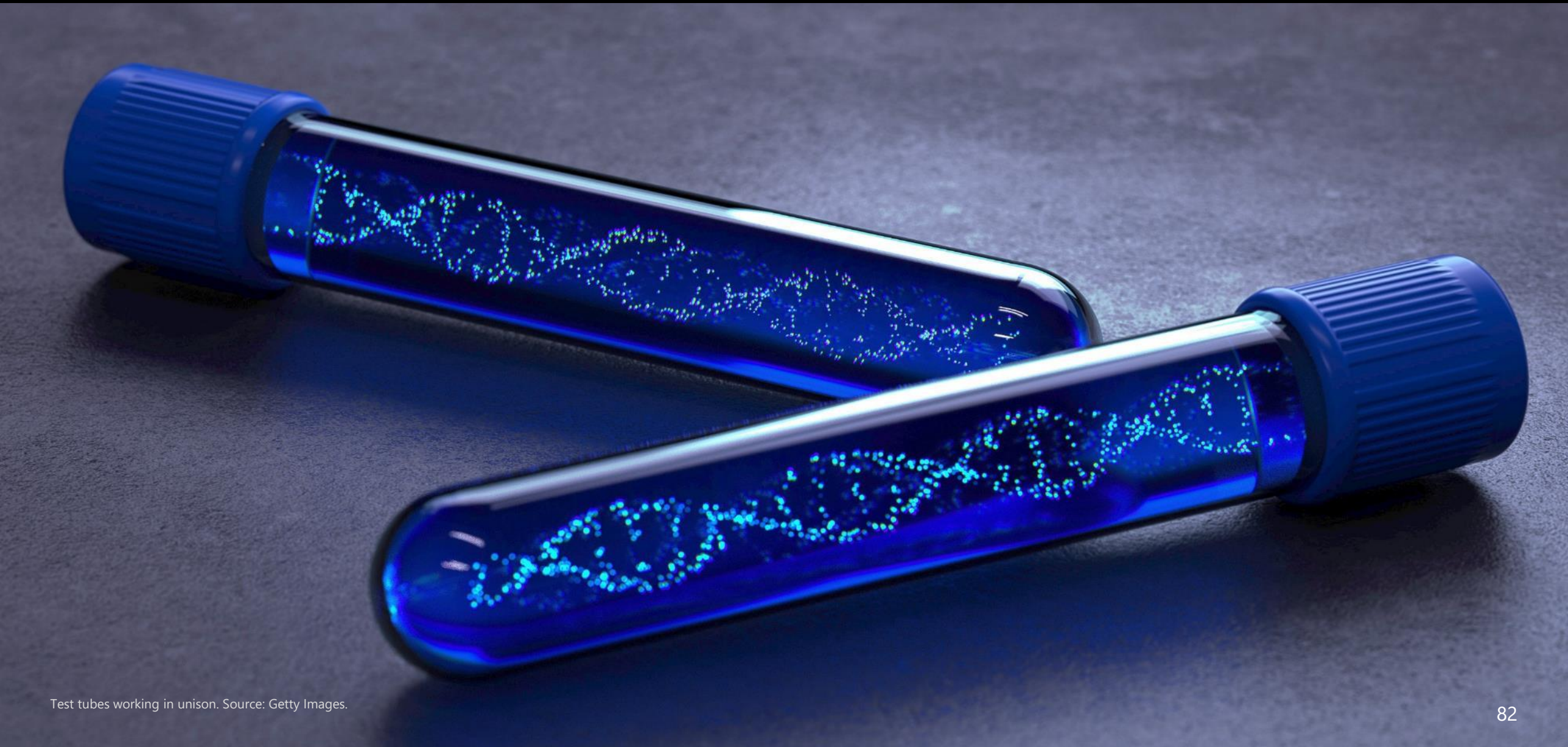
BOSTON, Aug. 03, 2023 (GLOBE NEWSWIRE) -- X4 Pharmaceuticals (Nasdaq: XFOR), a leader in the discovery and development of novel small-molecule therapeutics to benefit people with rare diseases of the immune system, today announced the closing of a $115 million loan facility with Hercules Capital, Inc. (NYSE: HTGC) ("Hercules"). The company also announced that it drew down $22.5 million upon the transaction's closing.

"This expanded loan facility creates significant financial flexibility for X4 as we continue preparations for the potential commercial launch of mavorixafor in individuals with WHIM syndrome and continue to advance mavorixafor for certain chronic neutropenic disorders," said Adam Mostafa, Chief Financial Officer of X4 Pharmaceuticals. "The initial draw down not only strengthens our balance sheet on a non-dilutive basis and extends our projected cash runway into 2025, but the overall transaction also creates expanded, future optionality beyond the equity capital markets as we potentially commence product sales and monetize a priority review voucher next year."

The term loan facility provides for up to $115 million of term loans in the aggregate, available to be funded in multiple tranches. In addition to its initial drawdown, X4 may, for a period of time following U.S. approval of mavorixafor in individuals with WHIM syndrome, draw an additional tranche of up to $20 million. An additional tranche will be available to X4 in the amount of up to $7.5 million for a period of time following achievement of a certain clinical development-related milestone. The availability of a final tranche of up to $32.5 million in support of X4's growth initiatives is subject to the approval of the lenders. In addition, the availability of each tranche is subject to certain customary conditions to drawing. The facility refinances $32.5 million in outstanding principal indebtedness and extends the initial interest-only period and maturity of existing and future borrowings. X4 is under no obligation to draw funds in the future.

Source: https://investors.x4pharma.com/news-releases/news-release-details/x4-pharmaceuticals-closes-115-million-loan-facility-hercules

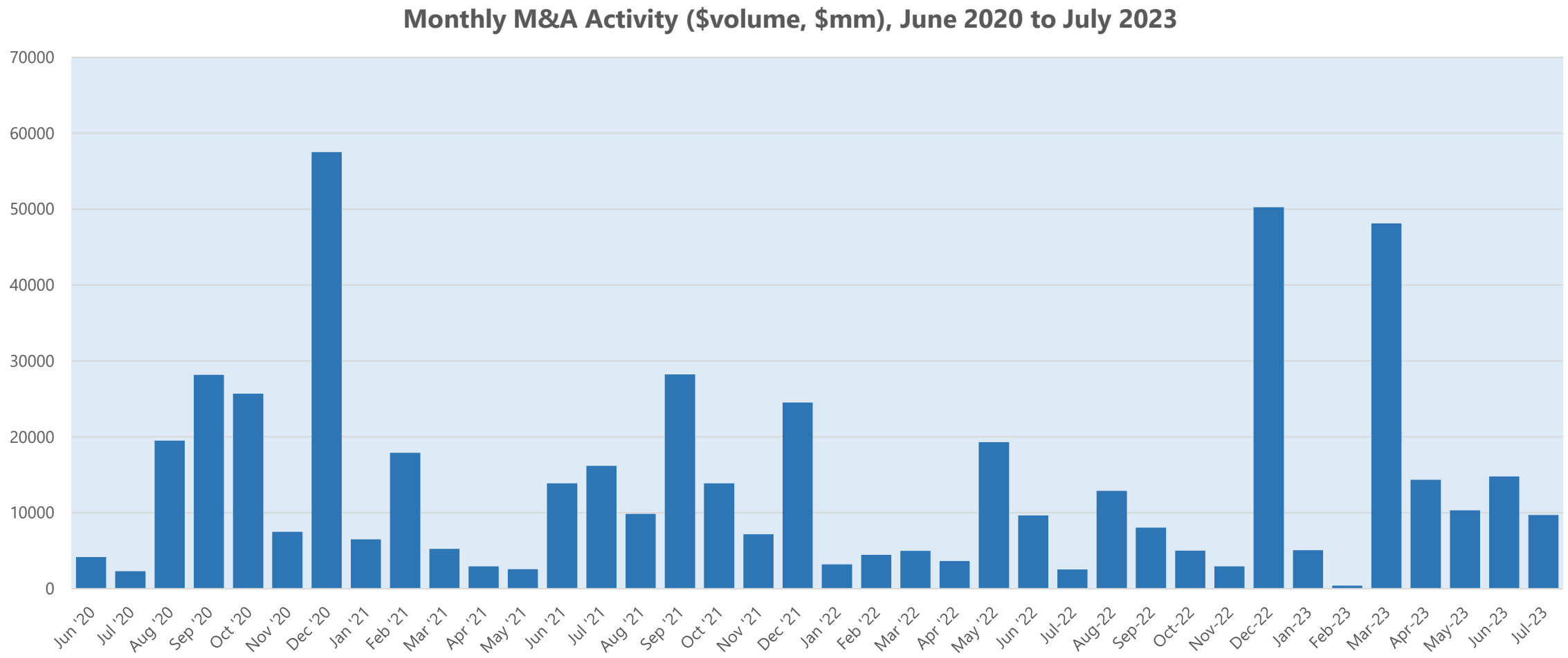
Deals Update



Test tubes working in unison. Source: Getty Images.

July Was a $10 Billion Month for Biopharma M&A

July was quite a strong month for M&A anchored by Biogen's announced acquisition of Reata.



Source: S&P, CapitalIQ

Revolution Medicines, Inc. to Acquire EQRx, Inc. in All-Stock Transaction to Gain More Than $1 Billion in Additional Capital

REDWOOD CITY, Calif. and CAMBRIDGE, Mass., Aug. 01, 2023 (GLOBE NEWSWIRE) -- Revolution Medicines, Inc. ("Revolution Medicines" or the "Company") (Nasdaq: RVMD), a clinical-stage oncology company developing targeted therapies for RAS-addicted cancers, and EQRx, Inc. ("EQRx") (Nasdaq: EQRX) today announced a definitive agreement through which Revolution Medicines plans to acquire EQRx in an all-stock transaction intended to add more than $1 billion in net cash to Revolution Medicines' balance sheet. The total number of shares of Revolution Medicines common stock to be issued to EQRx security holders will be determined in close proximity to the closing of the stockholder votes on the transaction based on the formula described below (see Transaction Details section). The deal, which was overseen by independent committees of Revolution Medicines' and EQRx's respective boards of directors, has been approved by the directors of each company. The transaction, which is subject to customary closing conditions, will enhance Revolution Medicines' efforts to fulfill its vision to discover, develop and deliver pioneering RAS(ON) Inhibitor drugs on behalf of patients with RAS-addicted cancers.

This proposed transaction is intended to reinforce and sustain Revolution Medicines' parallel development approach for its extensive RAS(ON) Inhibitor pipeline in multiple RAS-driven cancers by enhancing its balance sheet, increasing financial certainty in a challenging macroenvironment. With encouraging data trends thus far for its RASMULTI(ON) Inhibitor RMC-6236, planning is underway for one or more single agent pivotal clinical trials potentially to begin in 2024. Likewise, with encouraging initial clinical experience with its KRASG12C(ON) Inhibitor RMC-6291, planning is underway for a Phase 1/1b clinical trial to evaluate the combination of RMC-6236 and RMC-6291 potentially to begin in early 2024, while continuing single agent evaluation of RMC-6291. Revolution Medicines' acquisition of EQRx reflects both companies' confidence in Revolution Medicines' ability to deploy this amount of capital effectively. With the additional capital, Revolution Medicines will be positioned to maximize the potential clinical impact of its targeted drug pipeline across multiple oncology indications, and thereby offers the potential for shareholder value creation while retaining strategic control of its RAS(ON) Inhibitor pipeline.

Transaction Details

Under the terms of the merger agreement, Revolution Medicines will acquire EQRx in an all-stock transaction. The stock exchange ratio formula in the merger agreement uses a blended average to account for developments in Revolution Medicines' ongoing business and potential movement in its stock price. Approximately 80% of the stock exchange ratio is based on Revolution Medicines' public market stock price measured in close proximity to the EQRx stockholder vote and the remaining 20% of the exchange ratio is a determined price per share of Revolution Medicines' stock as of the signing of the merger agreement. Specifically, at closing, EQRx stockholders will receive the number of shares of Revolution Medicines common stock equal to the sum of 7,692,308 Revolution Medicines shares (determined as $200 million divided by $26.00 per share) plus a number of shares equal to $870 million divided by a price that is a 6% discount to the 5-day volume-weighted average Revolution Medicines share price measured in close proximity to the stockholder vote.

Source: https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-inc-acquire-eqrx-inc-all-stock-transaction

How the FTC's Proposed Merger Guidelines Might Affect Biopharma

Adrianna Nine, Biospace, Aug 2, 2023 (article summary)

The U.S. Federal Trade Commission (FTC) has introduced new draft merger guidelines that could have significant implications for the biopharmaceutical industry. Unlike the agency's historical focus on protecting direct competition, the proposed guidelines have a broader scope, potentially enabling the FTC to scrutinize concentration, negotiation, or displacement within specific markets. This has raised concerns among biotechnology, pharmaceutical, and medical technology companies, as the guidelines could make resources and exits more challenging to obtain, particularly for smaller firms.

The proposed guidelines aim to prevent issues such as coordination risks, elimination of potential entrants in concentrated markets, significant increases in market concentration, and the entrenchment or extension of dominant positions. The FTC's recent concerns over mergers like Amgen's attempted $26.4 billion merger with Horizon Therapeutics and IQVIA's acquisition of Propel Media indicate the agency's increased commitment to preventing such potential anticompetitive effects.

If the guidelines are implemented as they are, biopharmaceutical companies already under scrutiny, such as Pfizer in its $43 billion buyout of Seagen, may face even more extensive reviews and delays in the approval process. The FTC's current Democratic makeup without opposition voices arguing for modifications or limits on the guidelines could contribute to the comprehensive approach taken with the new draft guidelines. As a result, proposed deals can be expected to undergo lengthier reviews, with almost no issue deemed too insignificant for investigation.

Source: https://www.biospace.com/article/how-the-ftc-s-proposed-merger-guidelines-might-impact-biopharma-/

Apollo chief warns private equity industry ‘in retreat’ as rates rise

Financial Times, Aug 3, 2023

A lucrative age for private equity buyouts has ended, prompting an abrupt shift in the $4tn industry where returns will no longer be fuelled by rising valuations, the chief executive of Apollo Global Management warned on Thursday.

“In the [private] equity business, this year has really marked the end of an era,” said Marc Rowan, whose Apollo is one of the world’s biggest private equity groups with $617bn in assets.

A decade of “money printing”, fiscal stimulus and low interest rates that had pulled forward economic demand “is in retreat”, he added. His warning comes as investors face a period of lower growth and higher interest rates, which have raised the buyout industry’s cost of borrowing to take companies private.

Private equity groups enjoyed an extraordinary run of profitability in the past decade as low financing costs and buoyant financial markets made it easy to sell investments for a gain. Private equity firms would be forced “to go back to investing in the old-fashioned way. They’ll actually have to be very good investors,” Rowan said. Similar warnings have come from other top executives in private capital.

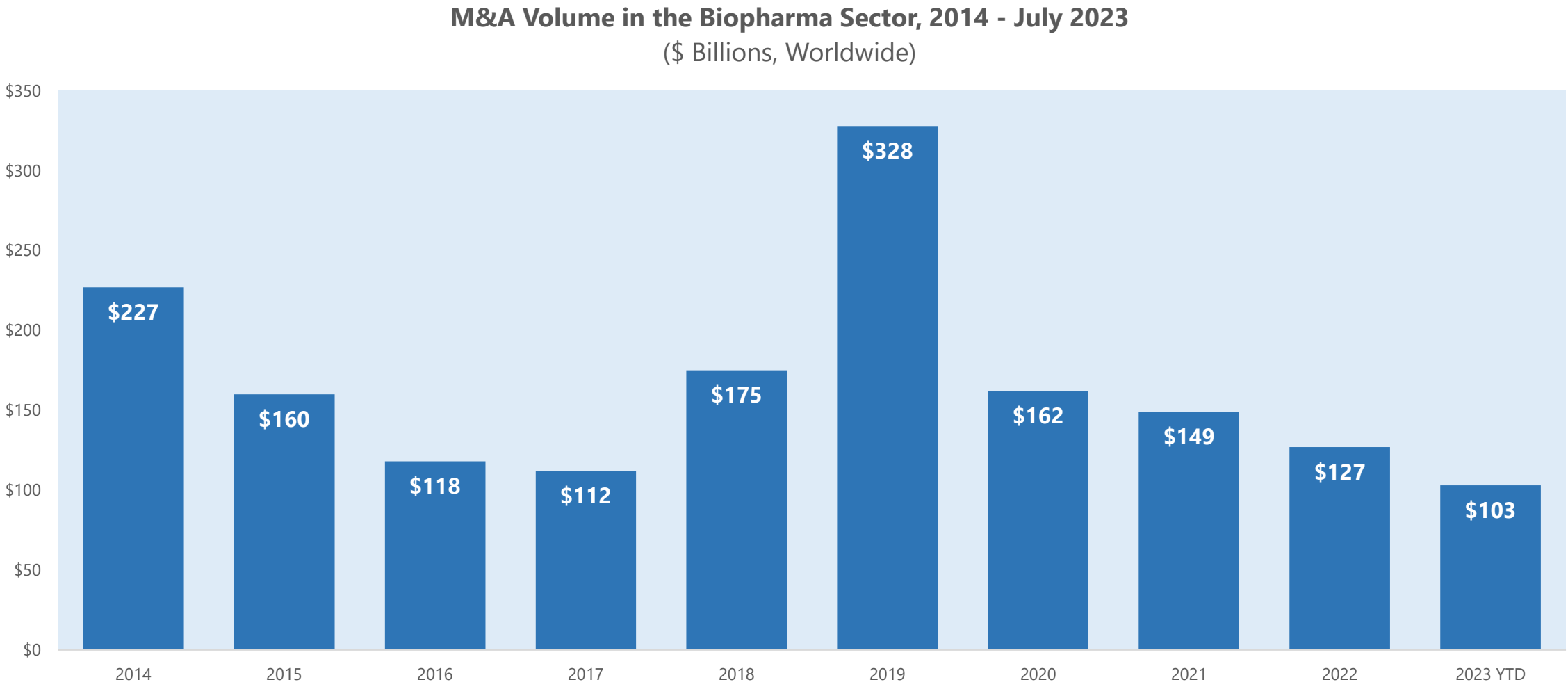
Chip Kaye, chief executive of Warburg Pincus, told the Financial Times last year that an era of geopolitical calm that had provided a tailwind to asset prices was reversing, complicating the investment outlook.

Marc Rowan, CEO, Apollo

Source: https://www.ft.com/content/7d24db29-9046-42d3-a221-efb9e54db702

$103 Billion of Biopharma M&A So Far in 2023

We are tracking to a $177bn M&A year which would exceed historical volumes except for 2014 and 2019.

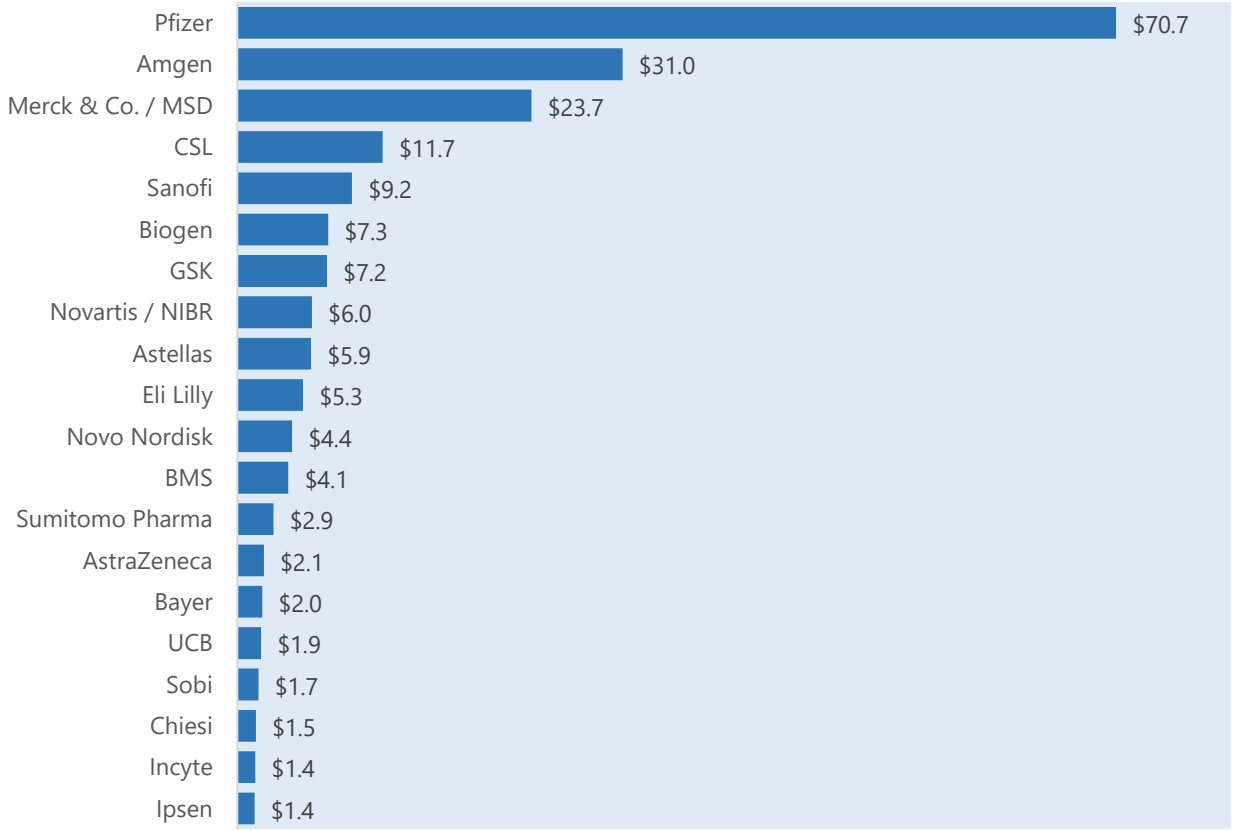


Most Active M&A Buyers in Biopharma

Pfizer has been leading by dollar volume and number of transactions.

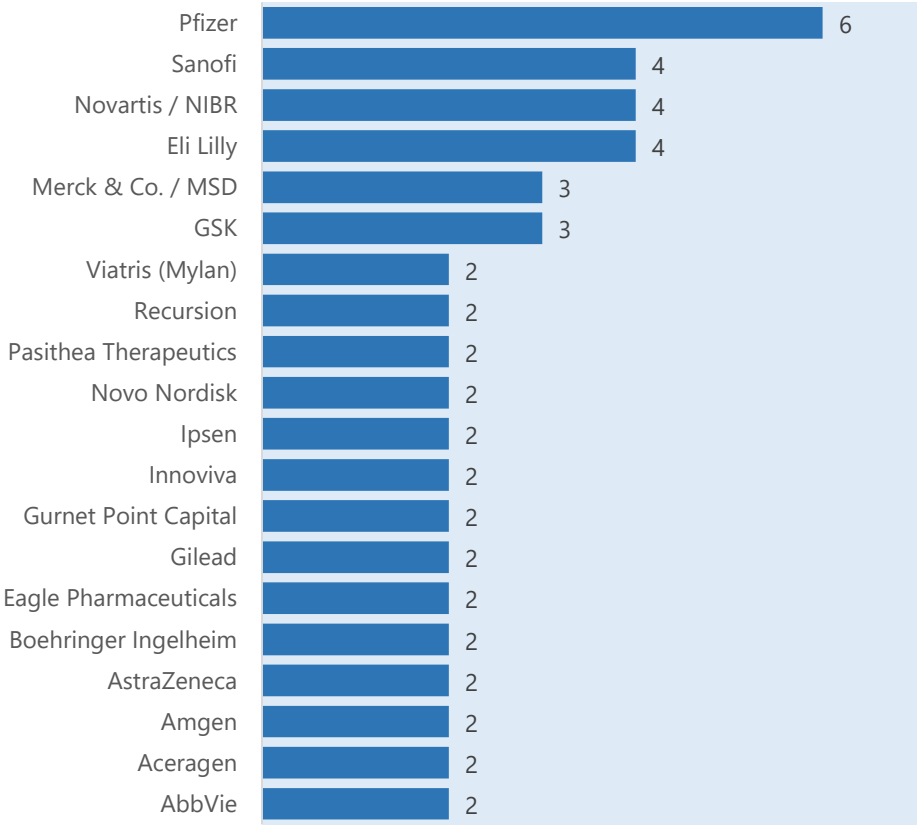
Top 20 M&A Buyers in Biopharma Last Two Years by Dollar Volume of Upfronts ($ Billions)

Aug 4, 2021 to Aug 3, 2023



Top 20 M&A Buyers in Biopharma Last Two Years by Number of Transactions

Aug 4, 2021 to Aug 3, 2023



Source: DealForma

Samsung Bioepis Said to Acquire U.S. Biogen's Biosimilar Unit

SEOUL, Aug. 2 (Yonhap) -- Samsung Bioepis Co., a biosimilar medicine developer under Samsung Group, has been in talks with Biogen Inc. to buy the U.S. biotech firm's biosimilar business unit, industry sources said Wednesday.

Through the deal with the Nasdaq-listed firm, Samsung Bioepis seeks to secure a direct sales network in the United States, according to the sources.

Biogen is a co-founder of Samsung Bioepis, which was established in 2012 as a 50-50 joint venture with Samsung Biologics Co., and has been cooperating in selling Samsung Bioepis' products in the U.S.

The Massachusetts-based firm has recently announced plans to sell its biosimilar business as part of its restructuring process.

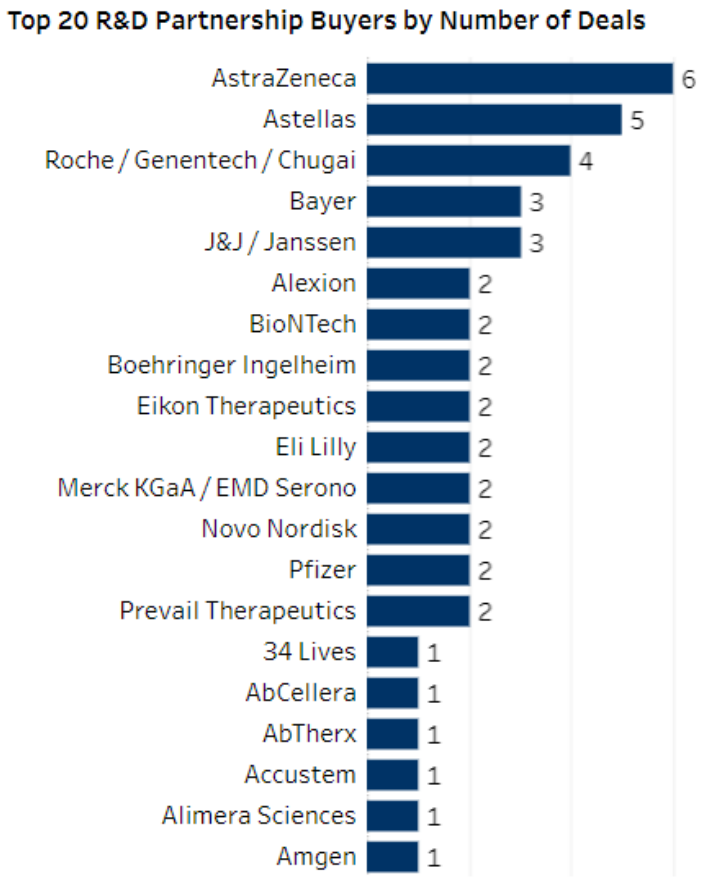
But Samsung Bioepis said nothing has been decided yet, denying some news reports that the company has completed due diligence.

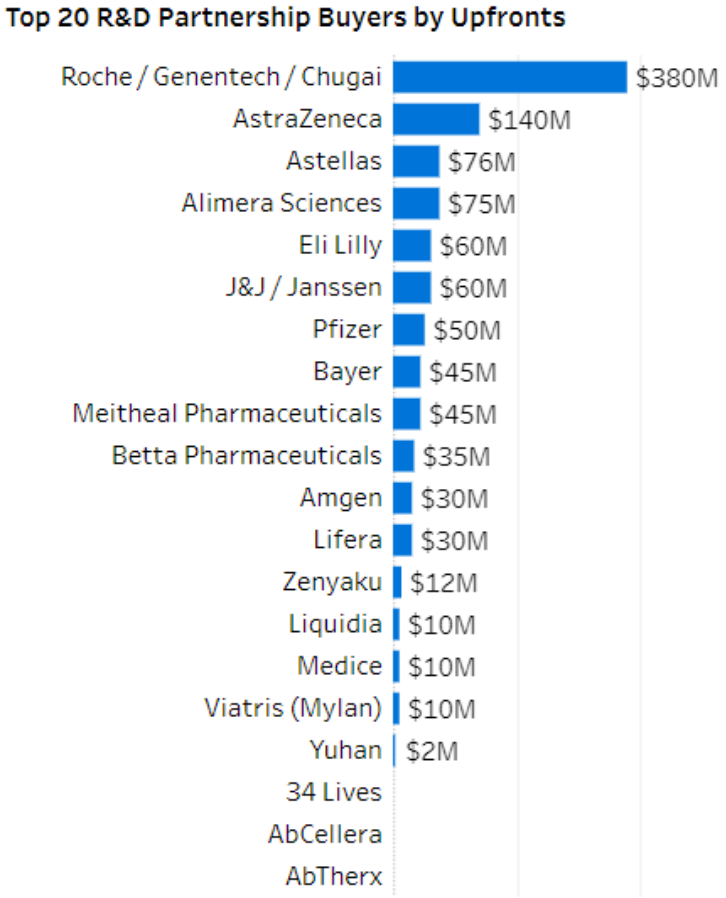
"When it comes to the acquisition, nothing has been set," a company official said. "We are reviewing various strategies to secure our biosimilar production capability at a global level and are now focusing on expanding our R&D on competitive pipelines and our sales networks."

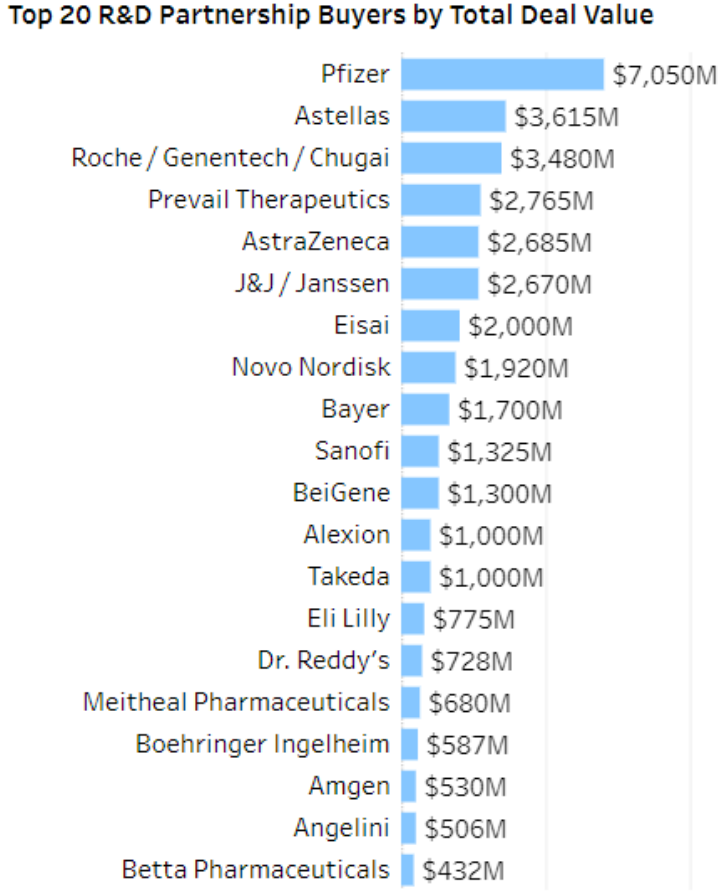
Source: https://en.yna.co.kr/view/AEN20230802006100320?section=news

In-Licensing Leaders Last Three Months (May 3, 2023 to Aug 3, 2023)

AZ, Astellas and Roche have been the most active players on the BD front lately.







Source: DealForma

License Deals of Note Last Week

Alnylam development and commercialization deal with Agios for TMPRSS6

Licensor
Alnylam Pharmaceuticals Inc.
Cambridge, Massachusetts, United States

Licensee
Agios Pharmaceuticals Inc.
Cambridge, Massachusetts, United States

Announced: August 2023

Stage at Signing: Preclinical / IND

Primary TA / Indication: Hematologic / Hematologic (General)

Primary Technology: RNA

DealForma Synopsis:
Alnylam granted Agios Pharmaceuticals exclusive, worldwide rights to develop and commercialize Alnylam's TMPRSS6, a siRNA-targeting therapy by combining Alnylam's siRNA platform with Agios' scientific expertise for the treatment of polycythemia vera (PV). Alnylam will be responsible for Phase I manufacturing while Agios will be responsible for further manufacturing activities. Agios will receive $17.5M up front and is eligible for up to $130M in development and regulatory milestones, and undisclosed commercial milestones, plus tiered royalties.

Financial Highlights:

Total Deal Value
$147.5M

Upfront Cash
$17.5M

Total Milestones
$130M

Royalty
Undisclosed

August 3, 2023

BlueRock research partnership with bit.bio with an option to license T cell (Treg) therapies

Research Partner
bit.bio (Bit Bio, formerly Elpis Biomed)
Cambridge, United Kingdom

Research Partner
BlueRock Therapeutics LLC (Bayer)
Cambridge, Massachusetts, United States

Announced: August 2023

Stage at Signing: Platform / Discovery

Primary Technology: Artificial Intelligence (AI) / Machine Learning (ML)

Secondary Technology: Cell Therapy

DealForma Synopsis:
BlueRock Therapeutics signed a research partnership with bit.bio to discover transcription factor (TF) combinations to reprogramme iPSCs into Tregs using bit.bio's machine learning discovery platform for the treatment of undisclosed diseases. BlueRock will have an exclusive, worldwide option to license the development and commercialization of resulting Treg therapies and opti-ox cell programming technology. bit.bio will receive an undisclosed upfront payment and is eligible for development, regulatory, and commercial milestones, plus royalties.

Financial Highlights:

Total Deal Value
Undisclosed

Upfront Cash
Undisclosed
Upfront Equity Investment
Undisclosed

Total Milestones
Undisclosed

Royalty
Undisclosed

August 3, 2023

Source: DealForma

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