Biopharmaceutical Sector

Weekly Update – September 5, 2023

STIFEL | Healthcare

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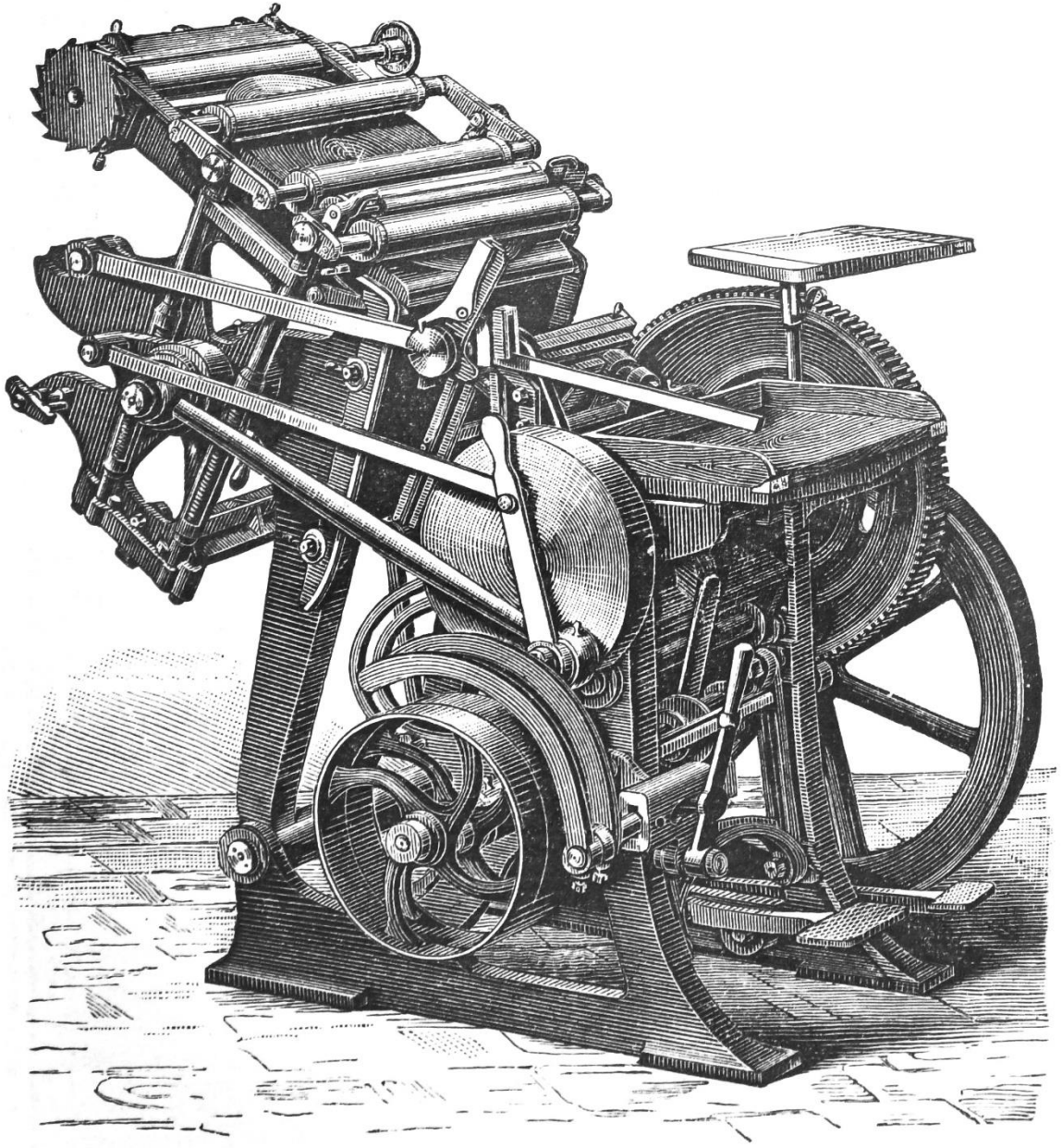
Publication Note

Our publishing schedule has shifted back to a weekly schedule for this Fall. We will be skipping publication during the weeks of Nov 27th and Dec 25th.

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

Recent issues in case you missed and want to read:
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

Old and creaky printing press. Source: Getty Images



Join Us at These Upcoming Events

1

Biotech Hangout held its latest event on August 19th.

Link to the last event: https://twitter.com/BiotechCH/status/1692516364257235376

The next event will be on September 8, 2023.

Please join us.

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

2

SACHS ASSOCIATES

Basel | September 20-21, 2023 (Movenpick Hotel)

23RD ANNUAL BIOTECH IN EUROPE FORUM

The conference will feature more than 15 hours of high-level keynotes and panel discussions. In addition, there will be a global company showcase of 60+ presentations by established public, private, emerging and seed companies, offering innovative solutions and seeking investment and partnering opportunities.

To Learn More
https://www.sachsforum.com/23bef-about.html

3

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/

Join Us at the Stifel Healthcare Conference This Fall

STIFEL | Healthcare

November 14-15, 2023
New York, NY
Lotte Palace Hotel

For registration details contact Natasha Yeung at yeungn@stifel.com.

Macro Update

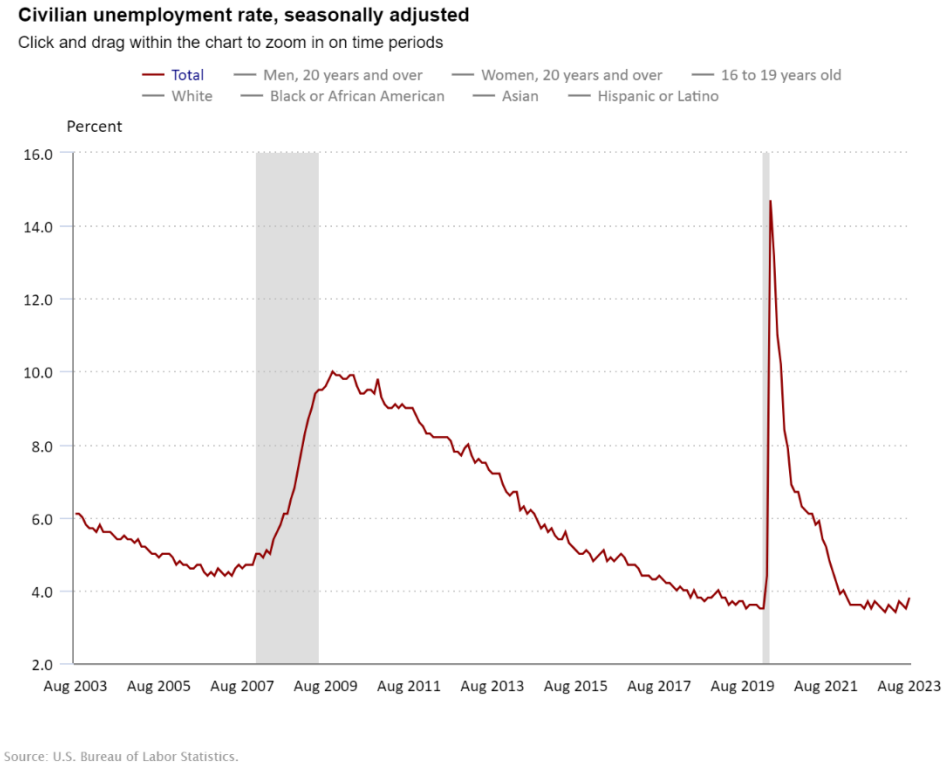
“Goldilocks” Unemployment Numbers Last Week

Last month saw unemployment increase showing that Fed rate increases are having an effect on the real economy, but overall, unemployment remains near historic lows. This is a very good situation. “Goldilocks” refers to a porridge that is neither too hot nor too cold – but, instead, just right.

Bureau of Labor Statistics, Sep 1, 2023

Total nonfarm payroll employment increased by 187,000 in August, and the unemployment rate rose to 3.8 percent, the U.S. Bureau of Labor Statistics reported last Friday (Sep 1).

Employment continued to trend up in health care, leisure and hospitality, social assistance, and construction. Employment in transportation and warehousing declined.



Source: https://www.bls.gov/charts/employment-situation/civilian-unemployment-rate.htm

Market Estimates of Odds of a Fed Rate Increase in September Fell Last Week

Financial Times, September 1, 2023

"The vast majority of investors already expected the central bank to keep rates steady at its next meeting in late September.

But, following Friday's data release, futures markets cut the probability of a rate rise at the subsequent November meeting from just below 50 per cent to roughly 40 per cent. Investors and policymakers are watching closely for signs that the US labour market is cooling, since jobs and wage growth are key contributors to inflation.

In comments responding to Friday's figures, US president Joe Biden pushed back at "experts" who had argued a more severe contraction was needed to bring price rises under control."

Source: https://www.ft.com/content/203c925e-3f65-44b1-b3aa-a86caa416d0c

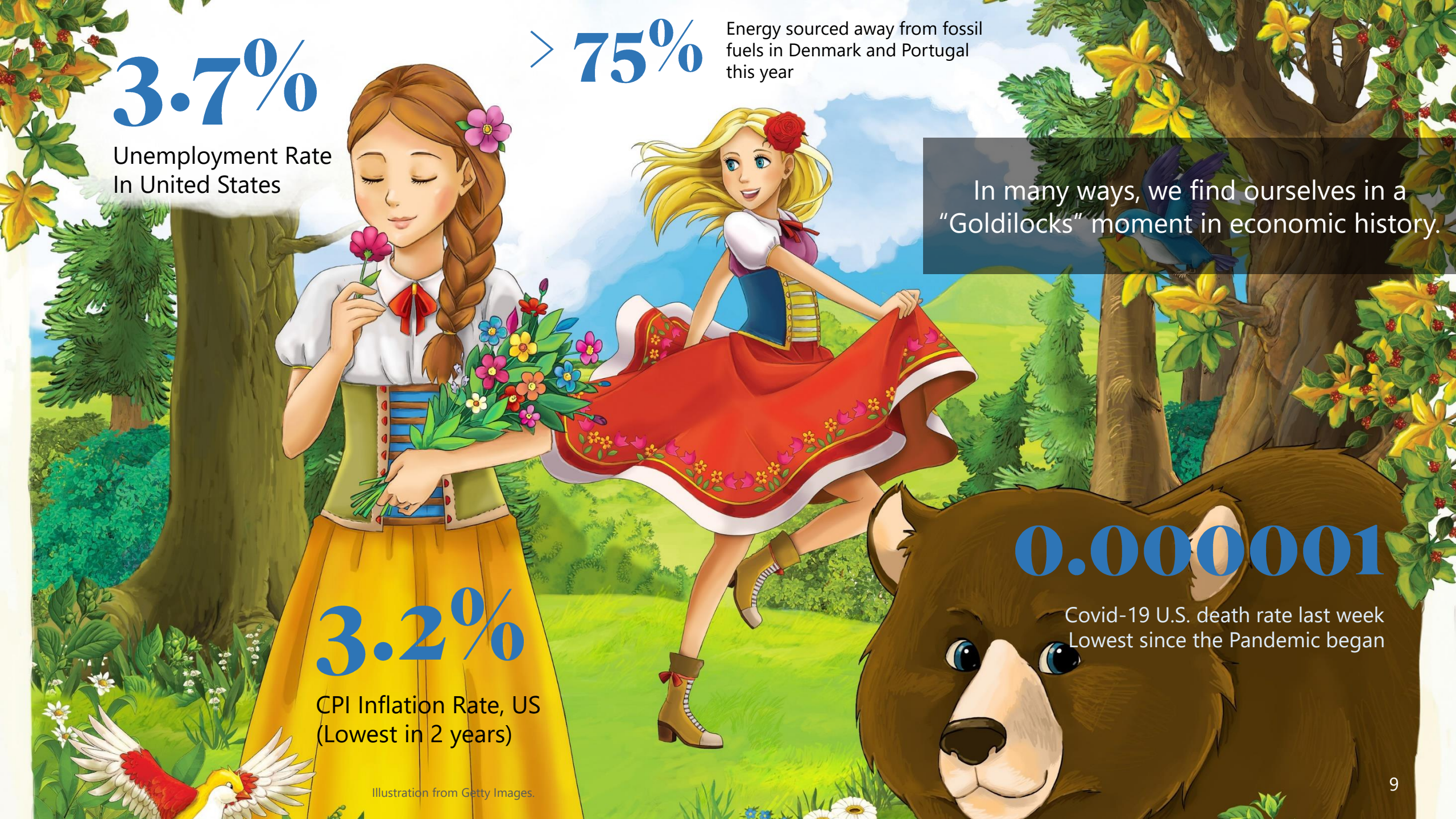


Illustration from Getty Images.

China Takes Aim at Real Estate Crisis

Laura He, *CNN*, September 1, 2023

China has rolled out a new batch of stimulus measures to boost the nation's ailing property market and support a weakening yuan, in its latest attempt to restore confidence in the world's second largest economy.

Cumulatively, the policy announcements — as well signs of a pickup in China's manufacturing sector in August — sent Asian shares modestly higher on Friday.

According to a joint statement by the People's Bank of China (PBOC) and the National Administration of Financial Regulation (NAFR) released Thursday, minimum down payments for mortgages will be cut to 20% for first-time buyers and 30% for second-time buyers nationwide.

Aerial view of real estate in Shenzen, China

Source: https://www.cnn.com/2023/09/01/economy/china-mortgage-stimulus-intl-hnk/index.html

Biopharma Market Update

XBI Up 3% Last Week But Flat Over 12 Months

The XBI was up last week by 3.1% and is now down 2.3% for the year. The overall market, measured by the S&P 500, was up last week in the wake of positive economic news.

Biotech Stocks Up Last Week

Return: August 28 to Sep 2, 2023

Nasdaq Biotech Index: +1.5%
Arca XBI ETF: +3.1%
Stifel Global Biotech (EV): +3.4%*
S&P 500: +2.5%

Return: Jan 1 to Sep 2, 2023

Nasdaq Biotech Index: -1.4%
Arca XBI ETF: -2.3%
Stifel Global Biotech: -7.0%*
Stifel Global Biotech (adjusted): +2.2%*
S&P 500: +17.6%

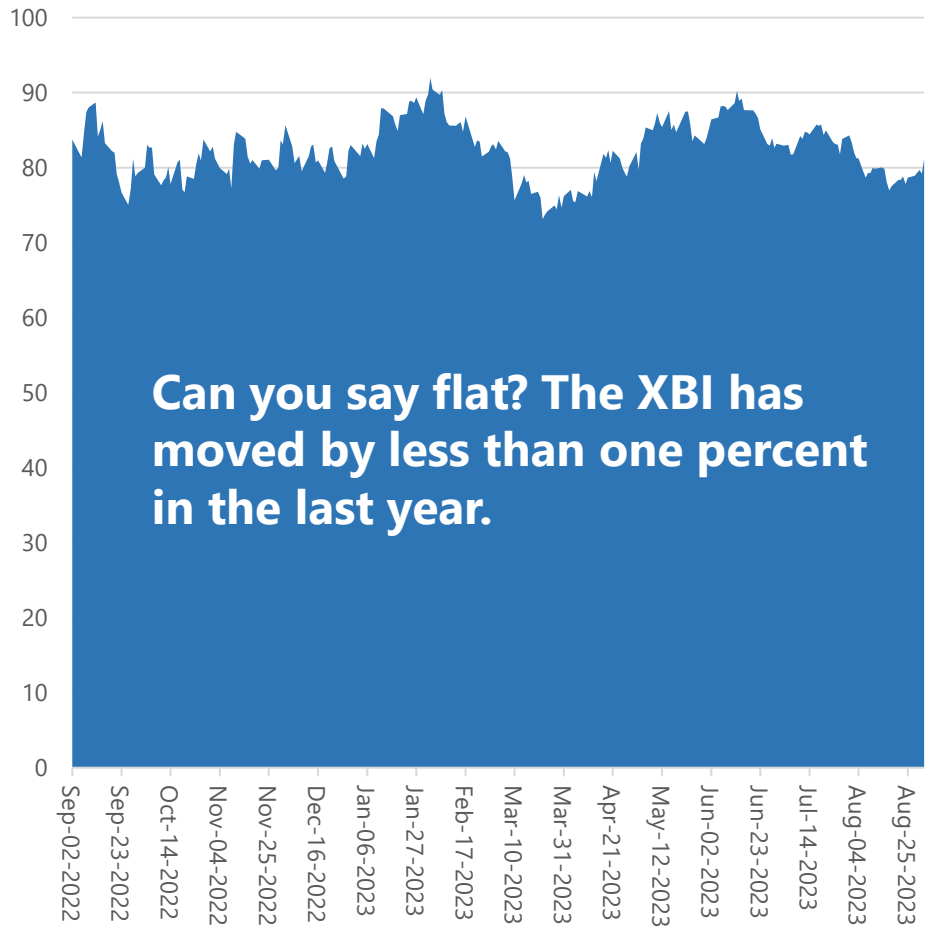
VIX Down

Oct 21: 29.7%
Jan 20: 19.9%
Mar 17: 24.6%
May 26: 18.0%
July 21: 13.6%
Aug 3: 17.1%
Aug 18: 17.3%
Sep 1: 13.1%

10-Year Treasury Yield Flat

Oct 21: 4.2%
Jan 20: 3.48%
Mar 17: 3.39%
May 26: 3.8%
July 21: 3.84%
Aug 3: 4.05%
Aug 18: 4.25%
Sep 1: 4.18%

XBI, Sep 2, 2022 to Sep 1, 2023

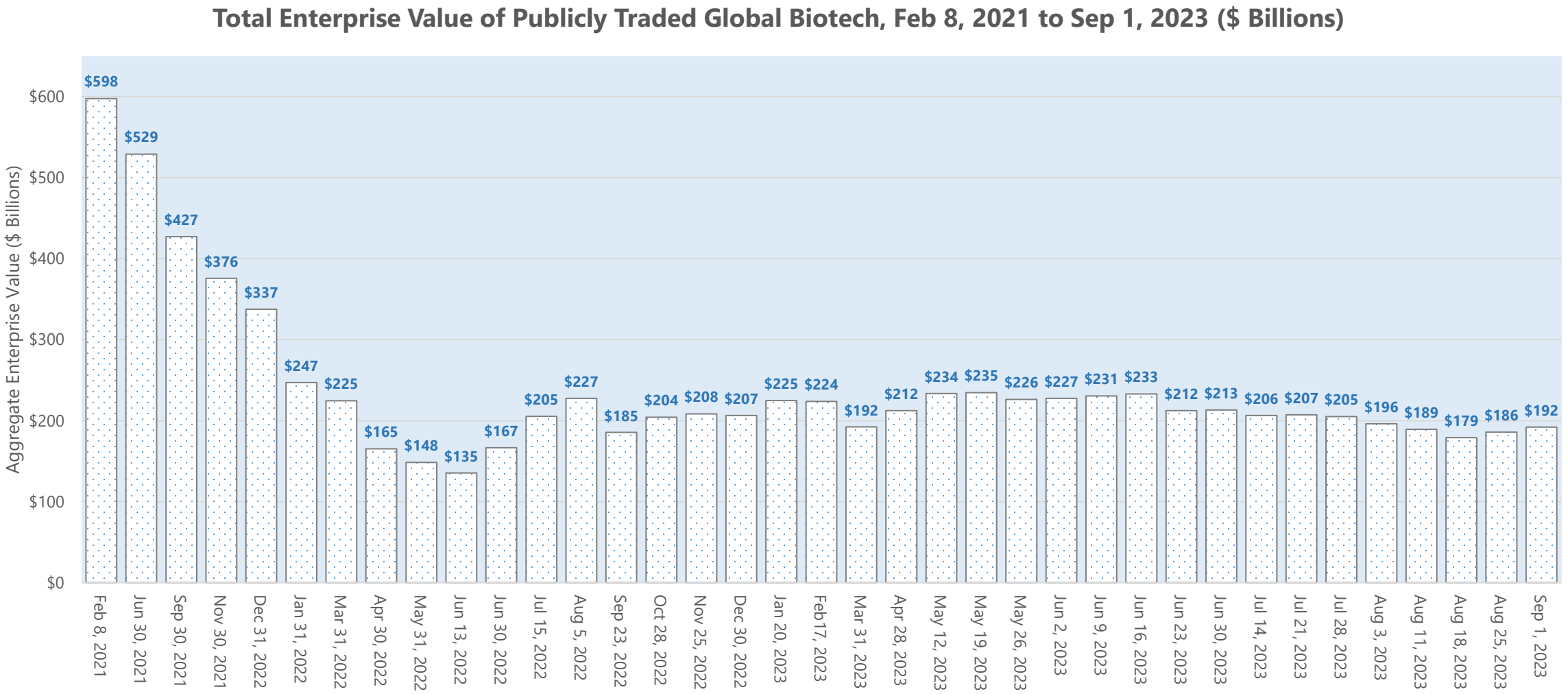


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Up 3.4% Last Week

The total value of the global biotech sector rose 3.4%. If one adjusted out all exits, bankruptcies and IPOs, the biotech market would be up 2% for the year to date.



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

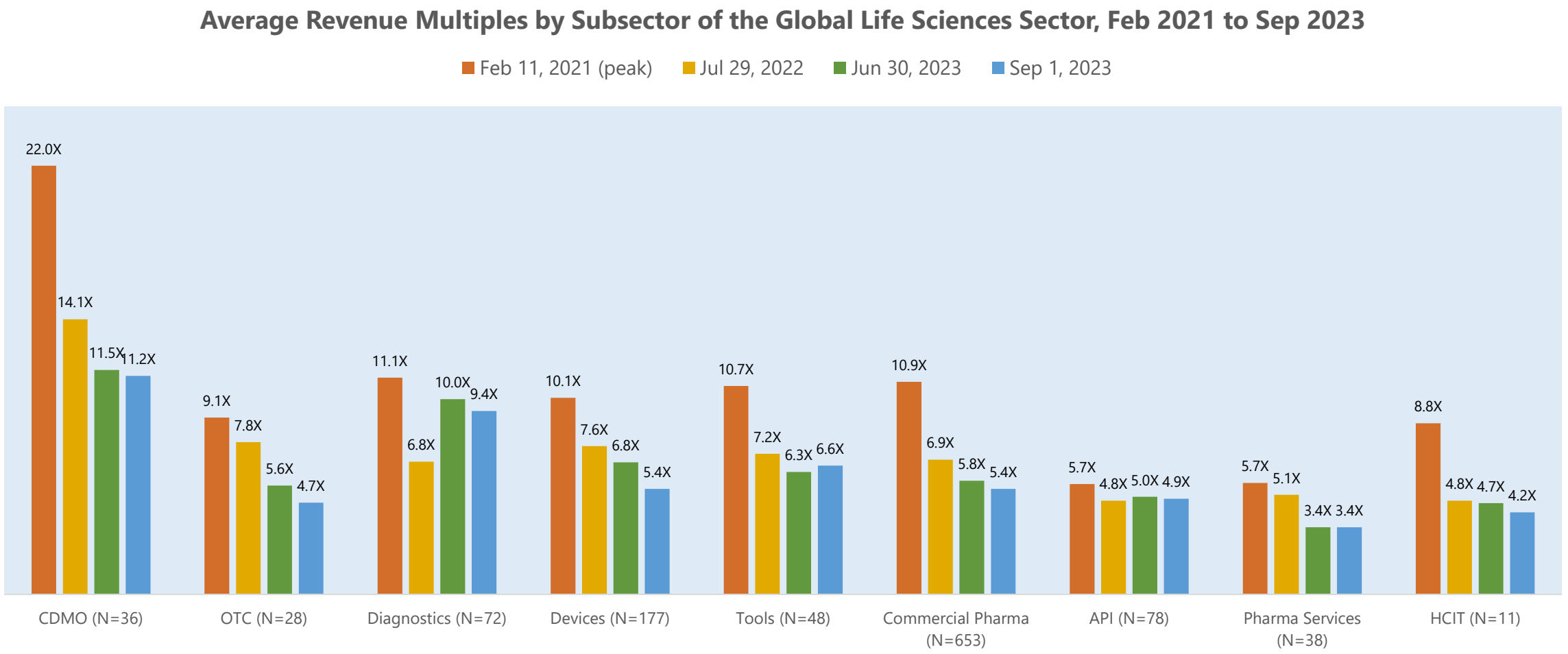
Public Life Sciences Sector Value Rose Last Week

The total enterprise value of the publicly traded life sciences sector rose by 0.9% last week ($80 billion). The sectors that fared best were HCIT, biotech, life science tools and API.

Sector	Firm Count	Enterprise Value (Sep 1, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$78,946	2.7%	-2.6%	-7.9%
Biotech	817	$196,843	3.4%	-2.6%	-5.1%
CDMO	40	$169,314	1.7%	-3.1%	-13.9%
Diagnostics	83	$253,693	2.5%	-5.9%	10.0%
OTC	32	$30,880	-0.5%	0.5%	9.7%
Pharma	725	$5,893,977	0.1%	2.4%	11.0%
Services	41	$216,694	2.3%	1.6%	-2.0%
Tools	54	$726,270	3.0%	0.5%	-3.2%
Devices	182	$1,614,491	1.8%	-2.7%	5.1%
HCIT	11	$24,126	3.6%	-15.6%	-12.6%
Total	**2066**	**$9,205,234**	**0.9%**	**0.7%**	**7.2%**

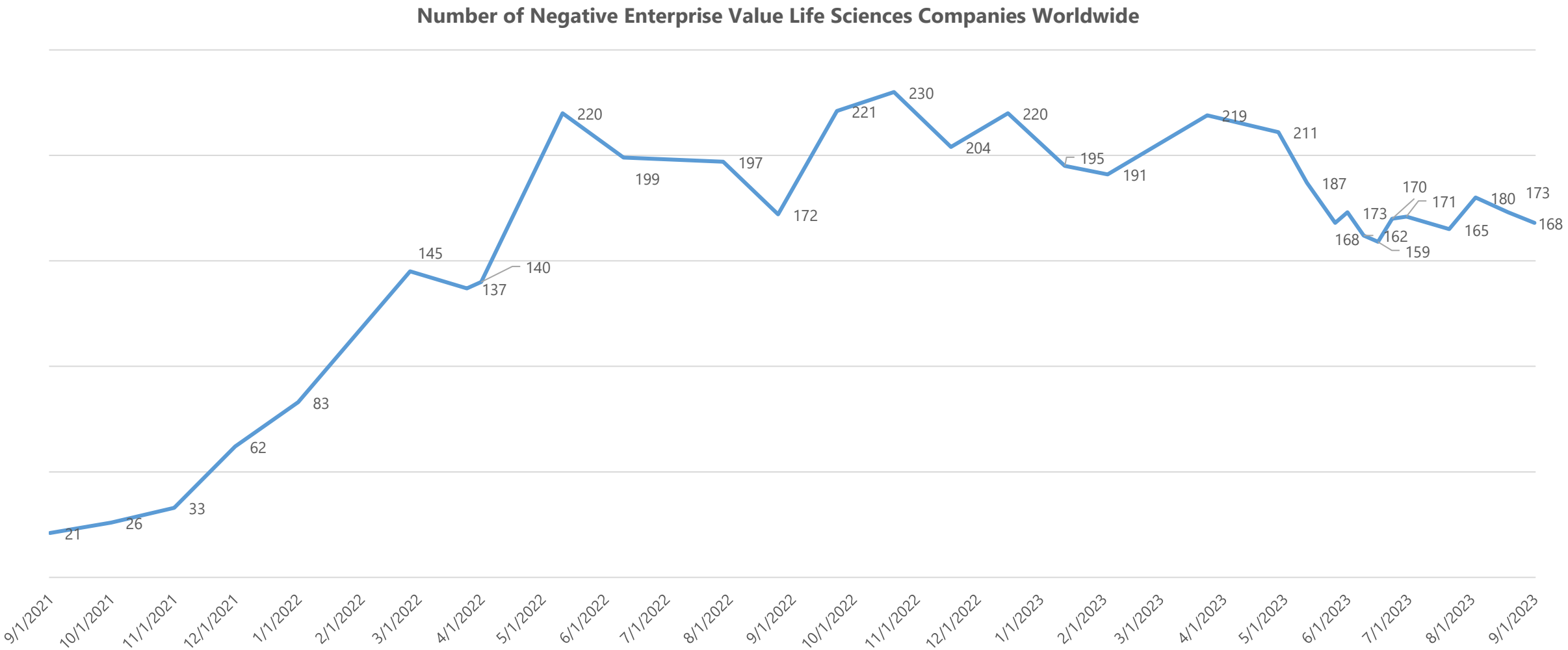
Source: CapitalIQ

Revenue Multiples for Diagnostics, OTC, Commercial Pharma, HCIT and CDMO's Continue to Drop; Tools Bouncing Back



Source: CapitalIQ. Revenue multiple was defined as the ratio of enterprise value to trailing 12 months revenue. Companies with revenue multiples over 100x and below 0.5x were excluded from this analysis.

Number of Negative Enterprise Value Life Sciences Companies Shrunk Slightly in Last Two Weeks



Source: CapitalIQ

Reordering of Largest Players by Value in Life Sciences

Enterprise Value ($mm) of Top Life Sciences Companies, Feb 8, 2021 to Sep 1, 2023

Value Rank (Sep 1 , 2023)	Company	Sep 1, 2023	Value Rank (Jun 30 , 2023)	Jun 30, 2023	Value Rank (June 17, 2022)	Jun 17, 2022	Value Rank (Feb 8, 2021)	Feb 8, 2021
1	Lilly	$516,526	2	$459,931	4	$275,160	8	$199,050
2	novo nordisk	$420,128	3	$360,891	6	$239,281	10	$163,171
3	Johnson & Johnson	$404,788	1	$491,331	1	$446,793	1	$441,136
4	abbvie	$314,239	5	$270,071	2	$310,463	3	$267,777
5	MERCK	$309,303	4	$313,226	7	$236,919	6	$211,317
6	Roche	$262,027	6	$270,006	3	$278,801	2	$301,332
7	ThermoFisher SCIENTIFIC	$249,033	8	$233,280	8	$226,761	7	$207,897
8	AstraZeneca	$233,754	7	$248,828	9	$212,736	11	$150,063
9	NOVARTIS	$226,202	9	$228,384	11	$188,764	5	$231,398
10	Pfizer	$223,175	10	$223,530	5	$273,875	4	$246,412
11	DANAHER	$208,507	11	$192,325	10	$193,248	9	$185,995

Source: CapitalIQ

Lilly has the highest enterprise value of any life sciences company in the world (up from a ranking of #8 on Feb 8, 2021). Last week saw Novo Nordisk sail past J&J by value and is now in the #2 spot. Interestingly, for a while last week, Novo was the most valuable company in Europe, valued even more than LVMH.

J&J, the long-time industry value leader now sits in the #3 spot and, extraordinarily, is worth $112 billion less than Lilly in enterprise value. This is partly due to the recent spinoff of J&J's consumer business, Kenvue.

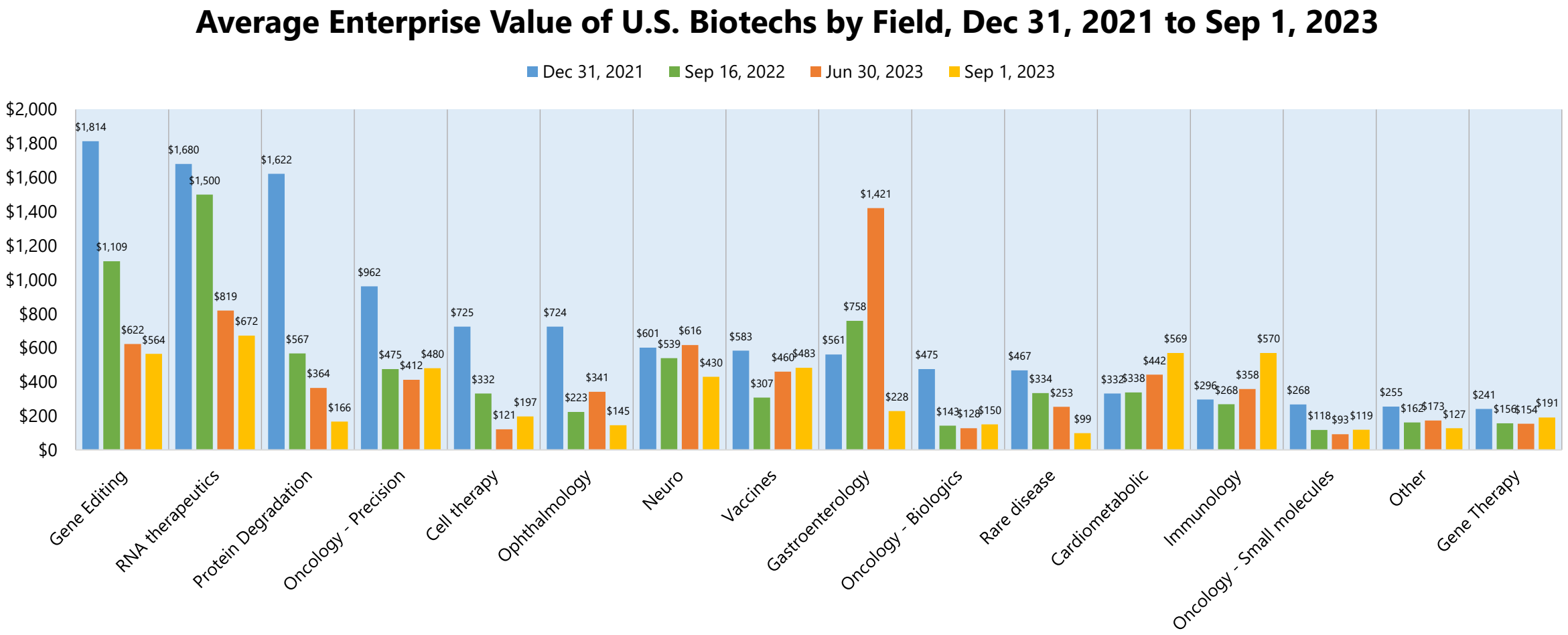
Roche was #2 at the start of the Pandemic and is now #6 as it has failed to overcome drug LOE's with new products fast enough.

In Feb 2021 Novartis was the fifth largest player and dropped to #11 before coming back to #9 over the last year on the strength of new drugs. (see story on p. 40).

We have shifted from a world where obesity and immunology drug performance is shaking up the industry.

The pharma rankings have been massively reshuffled in three years.

Average Biotech Valuations Down in Once "Hot" Areas Like Gene Editing, RNA Therapeutics, Protein Degradation and Precision Oncology. In Contrast, Immunology and Cardio Doing Well

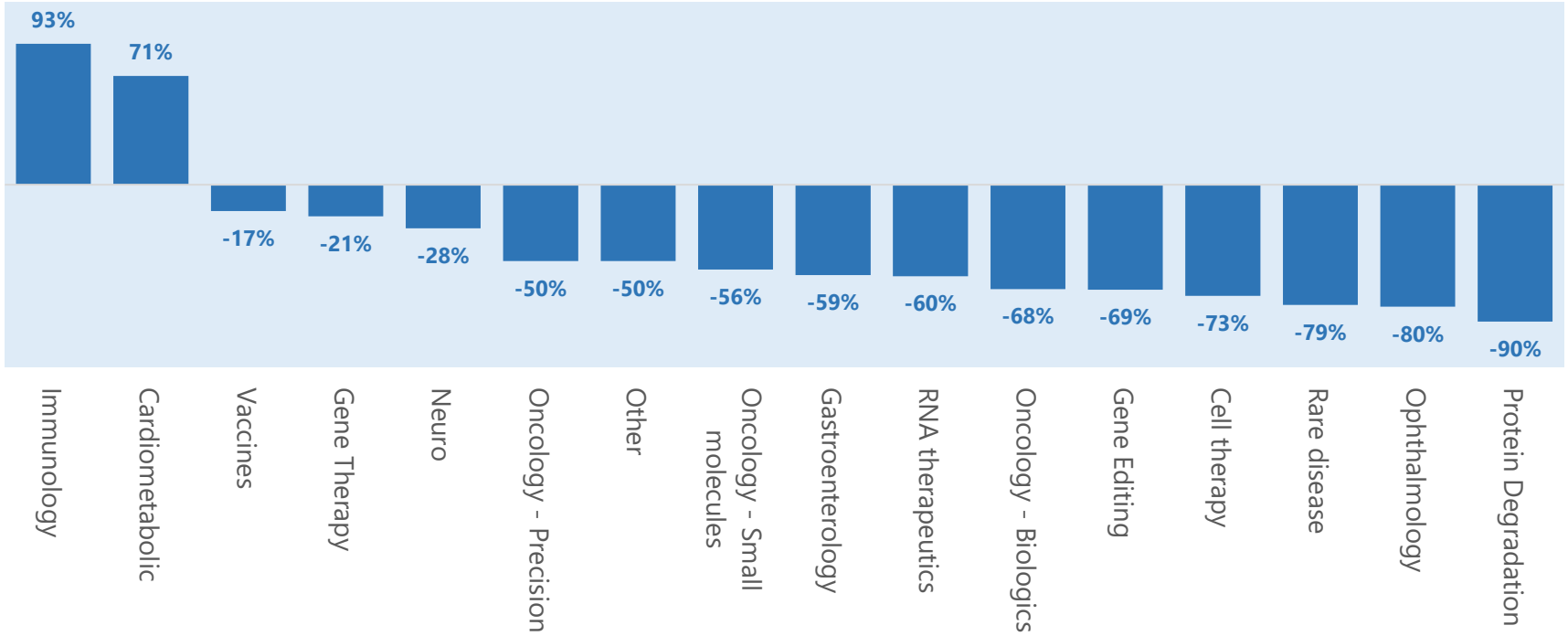


Source: CapitalIQ and Stifel research

Change in U.S. Biotech Average Valuations by Field Over the Last 20 Months

Percent Change in Average Enterprise Value of U.S. Domiciled Biotechs by Lead Asset Therapeutic Area / Modality

Dec 31, 2021 to Sep 1, 2023



Investors' therapeutic tastes have changed quite a lot in the last 20 months.

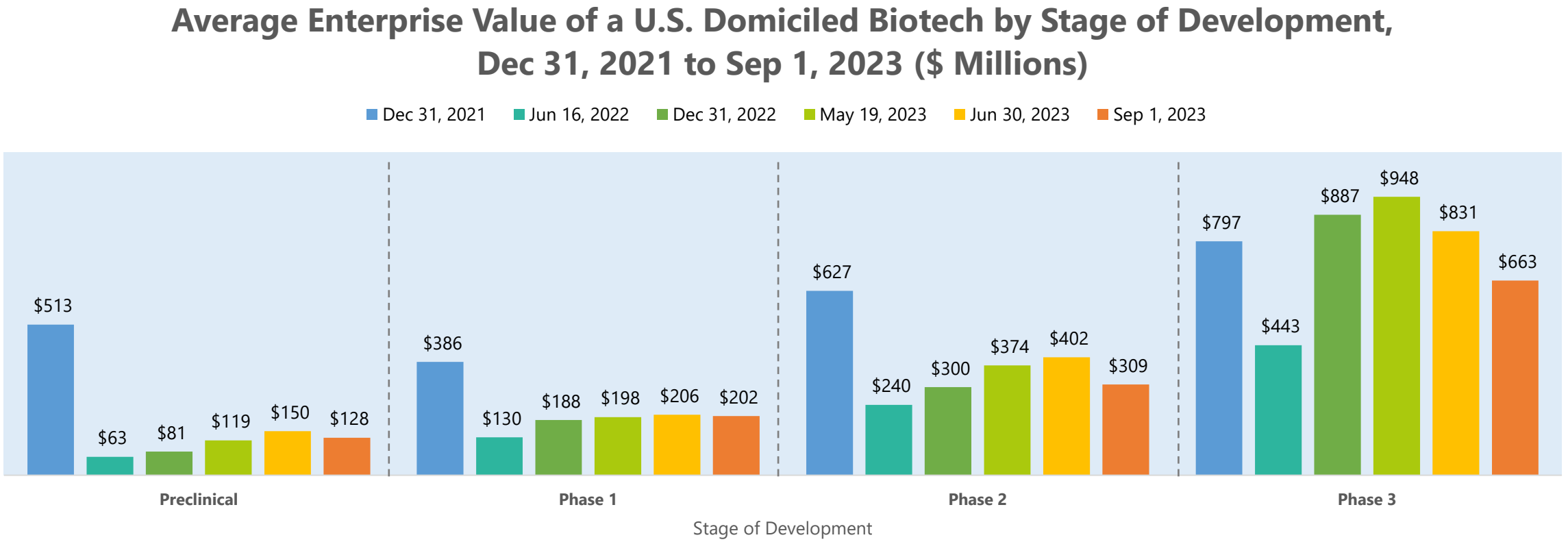
In sympathy with pharma valuations and M&A interest, companies focused on cardiometabolic disease and immunology have seen big jumps in value.

In contrast, companies working in the fields of protein degradation, ophthalmology, rare disease, cell therapy and gene editing have fared less well. There have also been across the board declines in the field of oncology.

Source: CapitalIQ and Stifel research

U.S. Biotech Average Valuations by Stage of Development of Lead Compound, Last 18 Months

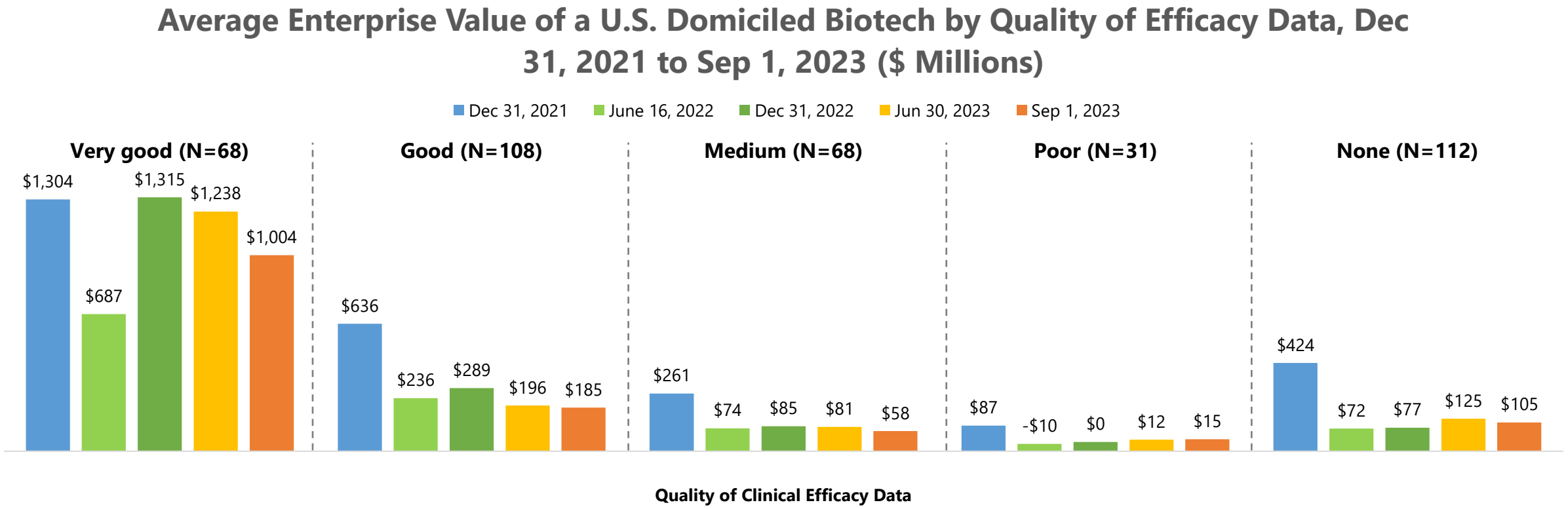
Declines in value have been far greater for preclinical companies than those which are late stage. Early companies remain far below their Pandemic valuations. Phase 2 companies, on average, are also down from their Pandemic peak. While Phase 3 companies rose in value substantially, the premium on being late stage (P2/P3) is clearly down since Q2 of this year. This partly reflects the disappearance of Bellus, Chinook and Prometheus, but also reflects real change in how the market is valuing biotechs.



Notes: These data are sourced from CapitalIQ and based on Stifel research on the company's development stage. We required that the company have data in that stage. So, for example, if a company was dosing a Phase 1 study but had not yet reported data, we classified the company as preclinical.

U.S. Biotech Average Valuations by Quality of Data for Lead Compound, Last 18 Months

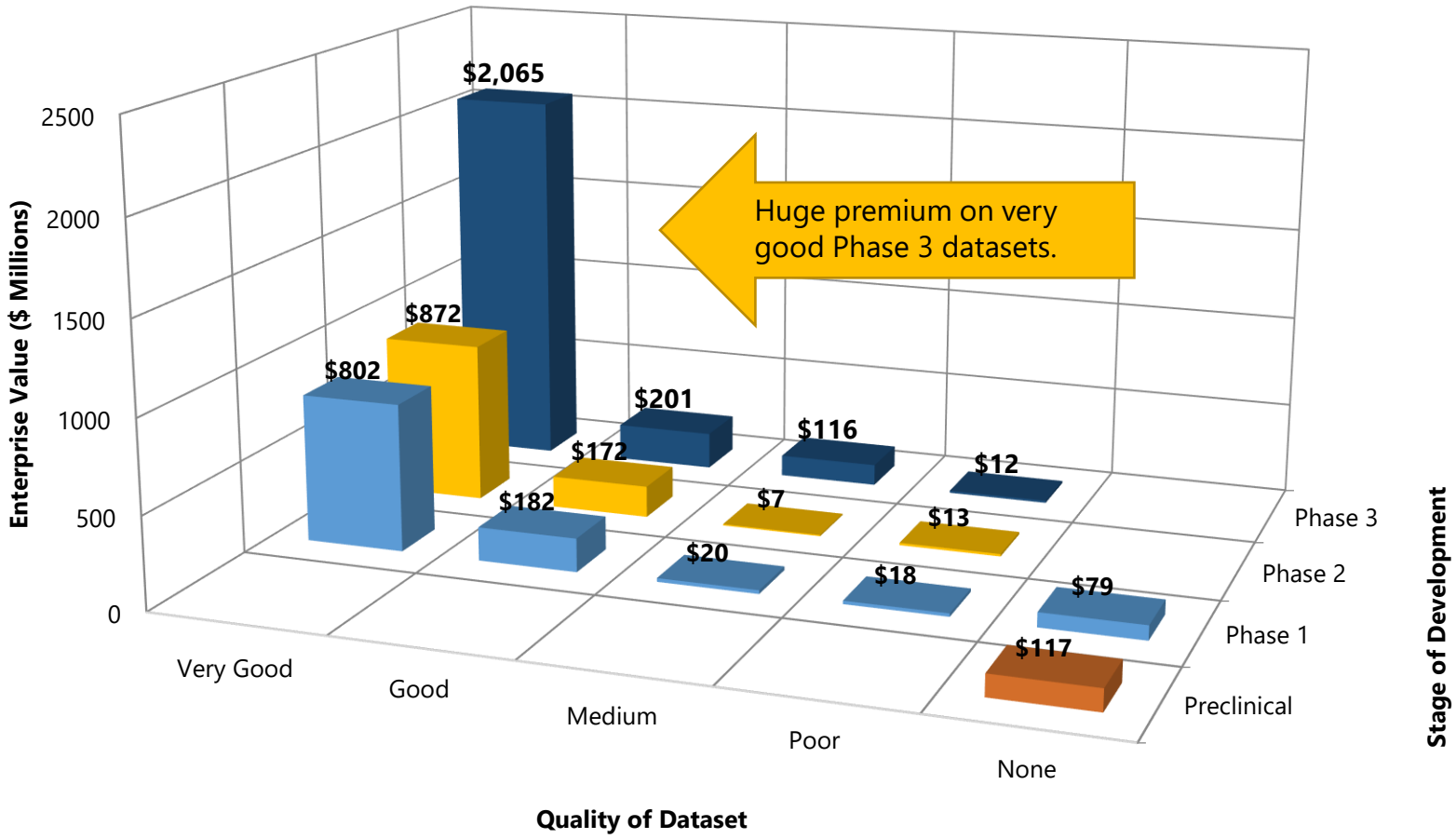
Companies with very good datasets have held their value since the Pandemic period. There has been a bit of a drop in the value associated with having a great dataset – in part because prior incumbents like Bellus and Prometheus have been bought. Companies with good datasets are down almost 70% since the Pandemic peak. Similarly, those with medium quality, poor datasets or no data are down quite substantially. The companies recovering the most in 2023 are those with no data. We saw quality platform companies bounce back quite a bit through the end of June (think Beam, Sana, Verve etc.). However, the last two months have not been kind to such companies.



Notes: These data are sourced from CapitalIQ and based on Stifel research on the dataset quality for a company's lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as "very good". We classified "good" data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial.

The Market is Rewarding Late-Stage Companies with Great Datasets Today. Those with Weaker Data or No Data Are Trading at Much Lower Valuations.

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Sep 1, 2023 ($ Millions)



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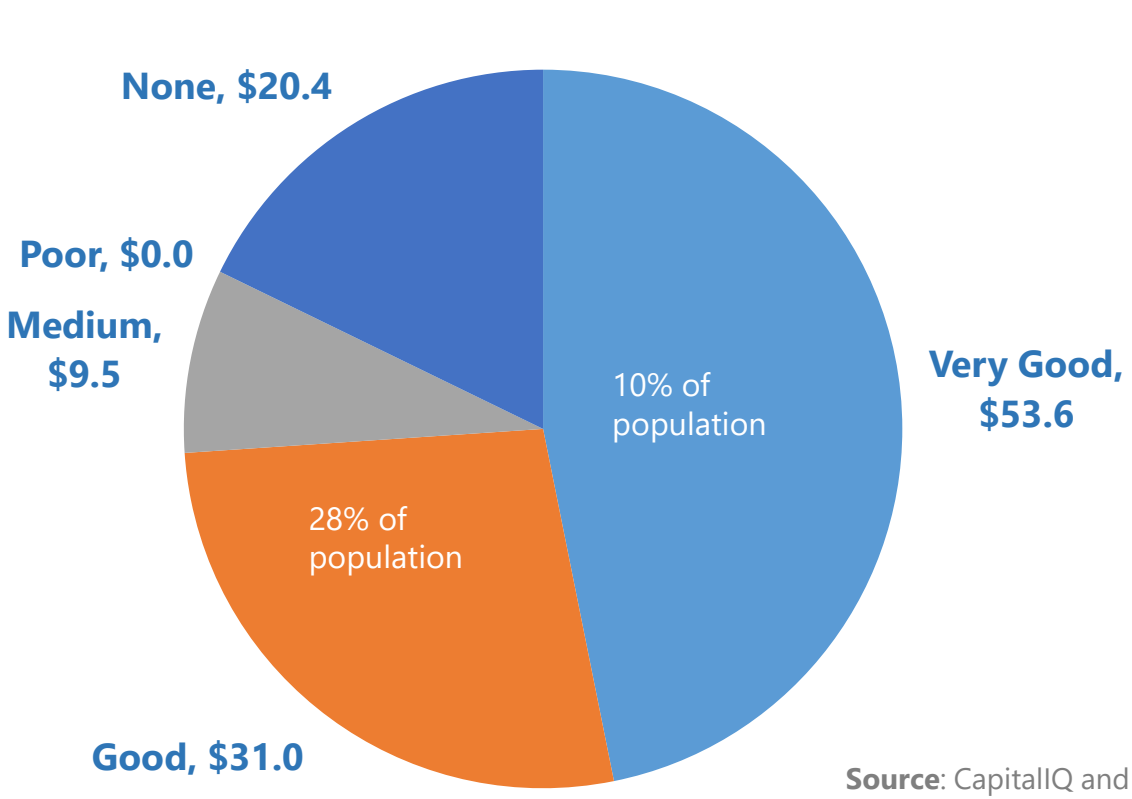
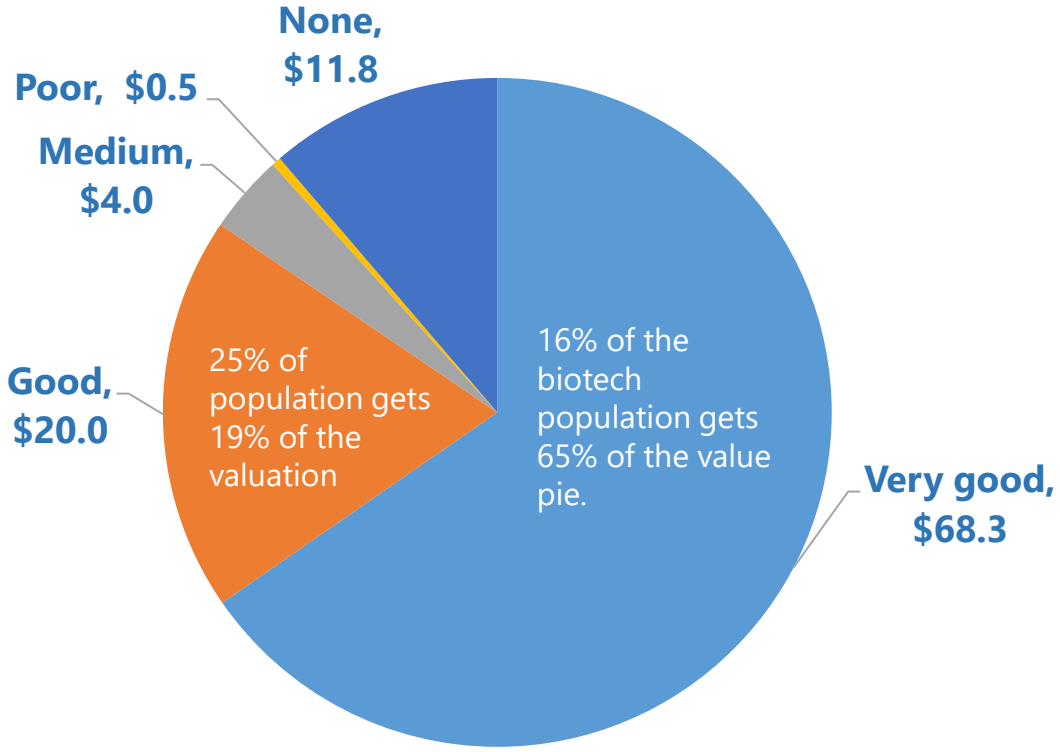
Data Quality is Very Important in Today's Biotech Market

Roughly 60 percent of the public U.S. biotech population has no clinical data yet, poor or medium quality clinical data. These companies get little of the value pie. In contrast, just 16% of the U.S. biotech population has a very good dataset (defined as clear clinical evidence of potential superiority over the standard of care for a disease) and enjoys 65% of the market's total valuation. The market places a high premium on the quality of data – which presumably is linked to probability of approval and market size.

Total Enterprise Value ($ billions) of the U.S. Biotech Sector by Quality of Dataset on Last Completed Stage of Development, Nov 30, 2022



Total Enterprise Value ($ billions) of the U.S. Biotech Sector by Quality of Dataset on Last Completed Stage of Development, Sep 1, 2023



Source: CapitalIQ and Stifel analysis of company press releases.

FTC Settles Antitrust Case with Amgen

FTC Headquarters
Washington DC

Amgen / Horizon Get Green Light to Proceed with Merger

Biopharmaceutical Giant Amgen to Settle FTC and State Challenges to its Horizon Therapeutics Acquisition

FEDERAL TRADE COMMISSION
PROTECTING AMERICA'S CONSUMERS

Amgen will be prohibited from leveraging its drug portfolio to disadvantage rivals and will be required to seek prior approval before acquiring related products

September 1, 2023

The Federal Trade Commission reached a proposed consent order with Amgen Inc. to address the potential competitive harm that would result from Amgen's $27.8 billion acquisition of Horizon Therapeutics plc. As part of a nationwide settlement of their challenge to the acquisition, the FTC and attorneys general from six states – California, Illinois, Minnesota, New York, Washington, and Wisconsin – also will dismiss the related federal court preliminary injunction action.

"Consolidation in the pharmaceutical industry has given companies the power and incentive to engage in exclusionary rebating practices, which can lead to sky-rocketing prices on essential medications," said Henry Liu, Director of the FTC's Bureau of Competition. "Today's proposed resolution sends a clear signal that the FTC and its state partners will scrutinize pharmaceutical mergers that enable such practices, and defend patients and competition in this vital marketplace."

Under the proposed order, Amgen is prohibited from bundling an Amgen product with either Tepezza or Krystexxa, Horizon's medications used to treat thyroid eye disease (TED) and chronic refractory gout (CRG), respectively. In addition, Amgen may not condition any product rebate or contract terms related to an Amgen product on the sale or positioning either one of these drugs. Amgen also is barred from using any product rebate or contract term to exclude or disadvantage any product that would compete with Tepezza or Krystexxa.

Source: https://www.ftc.gov/news-events/news/press-releases/2023/09/biopharmaceutical-giant-amgen-settle-ftc-state-challenges-its-horizon-therapeutics-acquisition

Checkmate: Amgen Legal Strategy Highly Effective Against FTC

Amgen effectively challenged the FTC on its suit to block its merger with Horizon. Key steps by Amgen: (1) agree early on not to bundle – no big concession since bundling is not how one exercises market power anyway in the market, (2) refuse to settle with the FTC early on – play out the case, (3) file a devastating counterattack challenging the constitutionality of the FTC's process, (4) playing out the drama in August just when government employees would rather not be in court and (5) waiting right until the case went forward in the Northern Illinois district court, effectively forcing the FTC to call a halt to the case.

Amgen's $27.8 Billion Deal for Horizon Therapeutics Clears Key Hurdle

Dave Michaels and Joseph Walker, *Wall Street Journal*, Sep 1, 2023 (excerpt)

"House Republicans recently lambasted Khan over her expansive merger-enforcement program, including a string of losses the agency suffered in court. Three GOP-led House committees are investigating her leadership of the FTC.

Khan said Friday the FTC hadn't challenged a proposed pharmaceutical merger in more than 14 years. The agreement is "a major advancement" for its enforcement program and addresses practices that "may work together to deprive Americans of access to affordable drugs."

Eric Grannon, an antitrust attorney at White & Case LLP, said the resolution doesn't require Amgen to give up anything significant and allows the FTC to bow out of litigation rather than risk a loss in district court. "The FTC's theory of harm here had little chance of success," he said.

The FTC's theory for blocking Amgen's deal triggered strong opposition from Amgen and business groups such as the U.S. Chamber of Commerce and National Association of Manufacturers.

"This concession by the FTC represents a substantial victory for all companies considering procompetitive mergers," said Sean Heather, the chamber's senior vice president for antitrust. "The FTC has, at least for the moment, abandoned its effort to advance a theory of antitrust based entirely on hypothetical and speculative harms."

The FTC has stumbled in court several times after filing aggressive merger challenges. It recently lost a federal-court case in which it sought to block Microsoft from buying Activision Blizzard. A judge also rejected its challenge of Meta Platforms' acquisition of a virtual-reality company."

Source: https://www.wsj.com/business/ftc-settles-with-amgen-over-27-8-billion-deal-for-horizon-therapeutics-b96a2d69

Comment on Amgen / Horizon Case

If one reads the FTC's press release last week it sounds like they won a great victory.

In reality, the FTC got Amgen to agree to not bundle products from Horizon – a concession that Amgen had agreed to many months ago. And the agreement not to acquire further products in gout or Graves' orbitopathy is a non-concession. If you have the best biologic in a category, why would you want to buy another one?

The truth is that the FTC was heading into court in the Northern District of Illinois and their case didn't look good at all. On top of the weak case, Amgen had raised the stakes by arguing that the FTC's entire legal process for challenging mergers was unconstitutional. Within ten days of the memo filed by the Amgen side on this constitutional challenge, the FTC indicated that it was standing back on its suit to block the merger.

This is a story of a zealous government agency that picked the wrong fight with the wrong party at the wrong time. Amgen has a legendary legal department and did not scrimp on its strategy with Horizon, hiring not one but two top antitrust firms (Cravath *plus* Sullivan & Cromwell) to take care of the litigation matter.

The FTC was facing not just a loss on its antitrust strategy but also a potential major challenge to its authority on constitutional grounds.

The FTC knew that Amgen could take its challenge all the way to the Supreme Court where it would likely have a friendly audience.

We have previously argued that making bad antitrust challenges is not good for antitrust policy – because the regulator risks weakening its overall authority.

It's the same idea with nations. You never want to start a war that you can't win. Starting a war and losing involves a loss of credibility and can embolden your enemies.

At this point, Amgen has laid out a clear path for others to challenge the FTC on constitutional grounds in the future.

The implications are straightforward. Not only has the FTC backed off on a flimsy bundling merger challenge but it has now put itself in a weak position to challenge further pharma mergers.

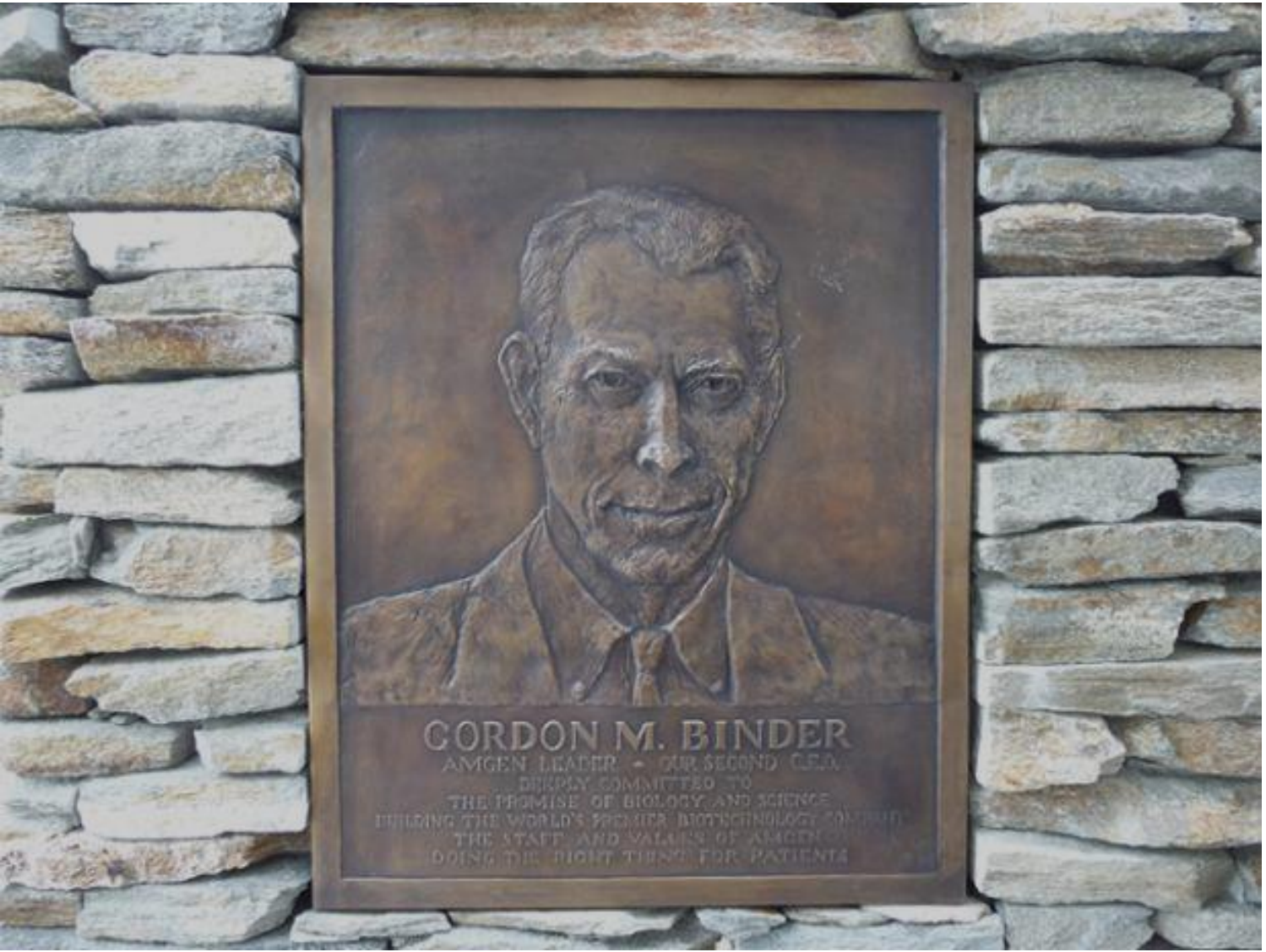
We would expect that the Pfizer / Seagen merger will go forward without challenge. Pfizer would have a field day with the FTC in court and is now incentivized to make few concessions in any pre-approval talks.

Further, the chilling effect of "FTC risk" on large pharma industry mergers may be less today than it was a few years ago.

Of course, one can worry that as long as Lina Khan heads the FTC, further merger challenges are possible. But the ability of the agency to block all but the most egregious large horizontal M&A deals at this point is highly limited.

As a result, we expect to see M&A activity in our industry ramp up in the months and years ahead.

Gordon Binder Quip

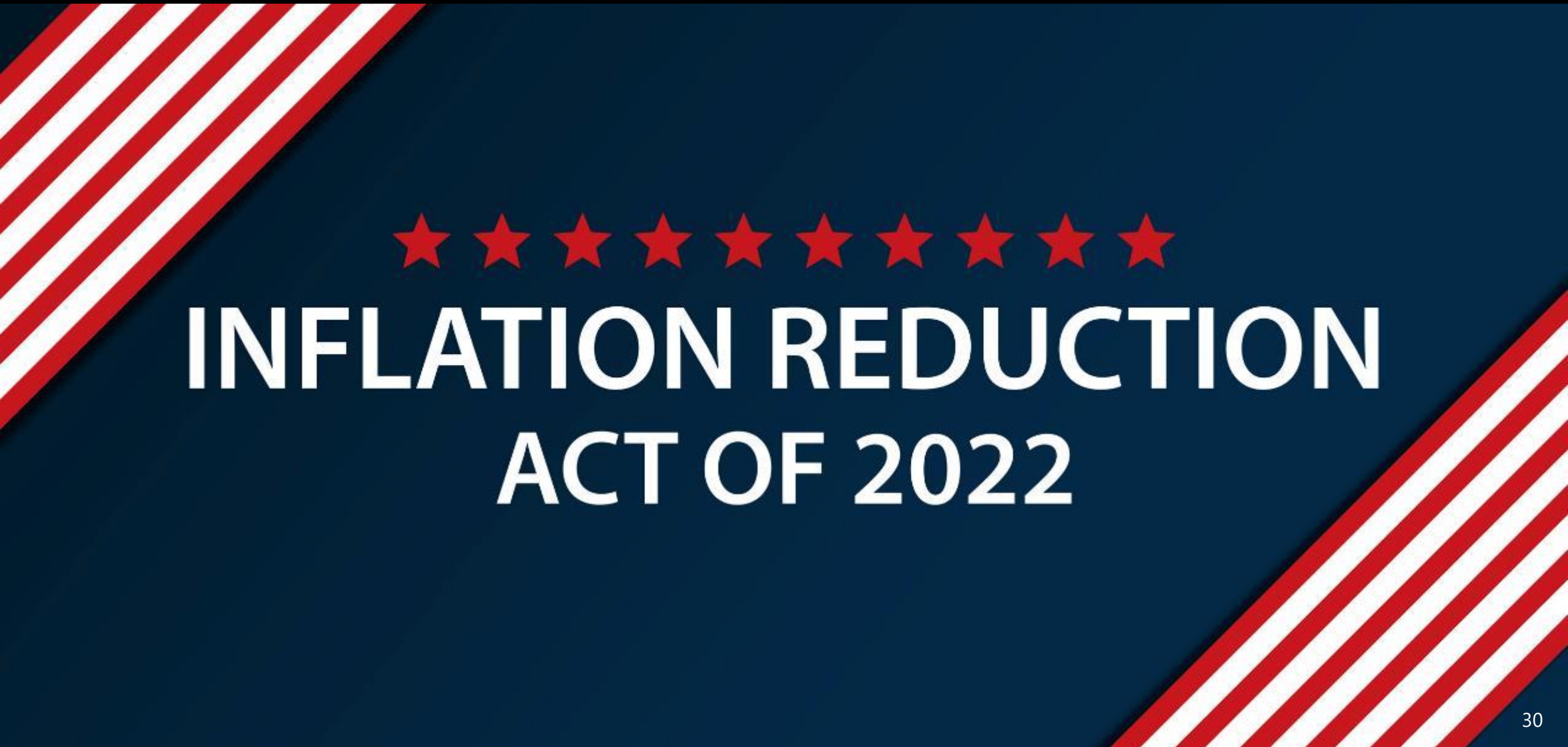


"Few realize that within Amgen lies a really good law firm."

Gordon Binder, Second CEO, Amgen, 1993*

* Amgen's investments in a strong internal legal team were no accident. In Binder's book, *Science Lessons*, he describes two life or death lawsuits that Amgen had to win in order to launch Epogen. One was against Genetics Institute. The other was against J&J.

HHS Announces First Ten Drugs for IRA Price Negotiations



IRA: First Ten Drugs Up For "Negotiation" Announced With Promises for Even More to Come

Karissa Waddick, "Lawmakers are already gunning for more dramatic drug pricing reforms," *PharmaVoice*, Aug 31, 2023

"All eyes were on Medicare this week as the agency took the first step toward implementing the drug pricing provisions laid out in the Inflation Reduction Act (IRA). But more storm clouds could be brewing for the industry on the legislative front as Democratic lawmakers push for additional changes to drug policy.

In a fact sheet announcing the first-ever Medicare pricing list on Tuesday, the Biden administration highlighted a proposal in the president's 2024 budget to build upon the IRA by doubling the number of treatments subject to negotiation per year and shortening the timeframe for when a drug is eligible for negotiation to five years after launch."

Medicare Drug Price Negotiation Program: Selected Drugs for Initial Price Applicability Year 2026

MEDICARE DRUG PRICE NEGOTIATION PROGRAM
CENTERS FOR MEDICARE & MEDICAID SERVICES

In August 2022, President Biden signed the Inflation Reduction Act of 2022 (P.L. 117-169) into law. The new law makes improvements to Medicare by expanding benefits, lowering drug costs, and improving the sustainability of the Medicare program for generations to come. The law provides meaningful financial relief for millions of people with Medicare by improving access to affordable treatments and strengthening Medicare, both now and in the long run.

For the first time, the law provides Medicare the ability to directly negotiate the prices of certain high expenditure, single source drugs without generic or biosimilar competition. Below is the list of 10 drugs covered under Medicare Part D selected for negotiation for initial price applicability year 2026, based on total gross covered prescription drug costs under Medicare Part D and other criteria as required by the law.

Drug Name	Commonly Treated Conditions	Total Part D Gross Covered Prescription Drug Costs from June 2022-May 2023	Number of Medicare Part D Enrollees Who Used the Drug from June 2022-May 2023
Eliquis	Prevention and treatment of blood clots	$16,482,621,000	3,706,000
Jardiance	Diabetes; Heart failure	$7,057,707,000	1,573,000
Xarelto	Prevention and treatment of blood clots; Reduction of risk for patients with coronary or peripheral artery disease	$6,031,393,000	1,337,000
Januvia	Diabetes	$4,087,081,000	869,000
Farxiga	Diabetes; Heart failure; Chronic kidney disease	$3,268,329,000	799,000
Entresto	Heart failure	$2,884,877,000	587,000
Enbrel	Rheumatoid arthritis; Psoriasis; Psoriatic arthritis	$2,791,105,000	48,000
Imbruvica	Blood cancers	$2,663,560,000	20,000
Stelara	Psoriasis; Psoriatic arthritis; Crohn's disease; Ulcerative colitis	$2,638,929,000	22,000
Fiasp; Fiasp FlexTouch; Fiasp PenFill; NovoLog; NovoLog FlexPen; NovoLog PenFill	Diabetes	$2,576,586,000	777,000

Note: Numbers are rounded to the nearest thousands.

Source: https://www.pharmavoice.com/news/Congress-expand-Medicare-drug-pricing/692380/; https://www.cms.gov/files/document/fact-sheet-medicare-selected-drug-negotiation-list-ipay-2026.pdf

FT Editorial: The World Will Need to Stop Piggybacking on US Pharma

Brooke Masters, *Financial Times*, September 1, 2023 (excerpt)

Unlike most of Europe, the US government has not previously controlled medicine prices. Last year's Inflation Reduction Act authorised Medicare, the taxpayer-funded healthcare system for retirees, to bargain directly with drugmakers. It plans to seek cuts of 25 per cent or more to list prices, focusing on top-selling drugs nearing the end of patent protection. This is expected to save Medicare nearly $100bn over the course of a decade, while reducing out-of-pocket costs for many older Americans.

Drug companies, which must negotiate or pay punitive taxes, have questioned whether this is constitutional; some have sued. They expect private insurers will try to push down what they pay too, sharply cutting revenue. As the list of covered medications expands, the industry warns this will put pressure on R&D budgets and limit the number of drugs in development that it can back.

Price caps may also make it harder to attract venture capital investment because the potential pay-off will be lower. This is particularly concerning because so much early stage drug research is now done by start-ups that later sell out to Big Pharma.

The impact is already starting to be felt beyond America's shores. "We have decided that we are not going to do certain trials, or that we are not going to do a merger or acquisition or licensing [deal] because it is becoming financially not viable," Thomas Schinecker, chief executive of Swiss drugmaker Roche, said on a recent media call.

Manufacturers may also benefit from another prong of the IRA reforms that caps out-of-pocket costs for drugs. Some 30 per cent of Medicare patients do not fill new cancer prescriptions because of cost concerns. "They might make up in an increase in volume for the decrease in price," explains Stacie Dusetzina, a Vanderbilt University professor.

The US has several years to work out the kinks in its new system: the first negotiated prices will not go into effect until 2026. But the upheaval should serve as a wake-up call for both Americans and everybody else.

Sky-high US prices are not the only way to fund global medical progress. Other countries will have to contribute more, but it does not have to be expensive for patients. Governments can give drugmakers a leg up by funding research into the causes of disease as well as the pathways and receptors that can be targets for treatment. They can also reduce risk by helping fund clinical trials and guaranteeing sales. Recent experience with Covid vaccines demonstrates that this can work.

The US drug industry's size, wealth and scientific prowess mean that it will always play a big role. But it should no longer be the only gorilla in the room.

Source: https://www.ft.com/content/0c20c518-60a8-4dd0-87be-f03adc8ec0e1

Forty Percent of Targeted Drugs are For Diabetes

Last week's "big reveal" of the top ten drugs targeted for HHS price negotiations was not a huge surprise.

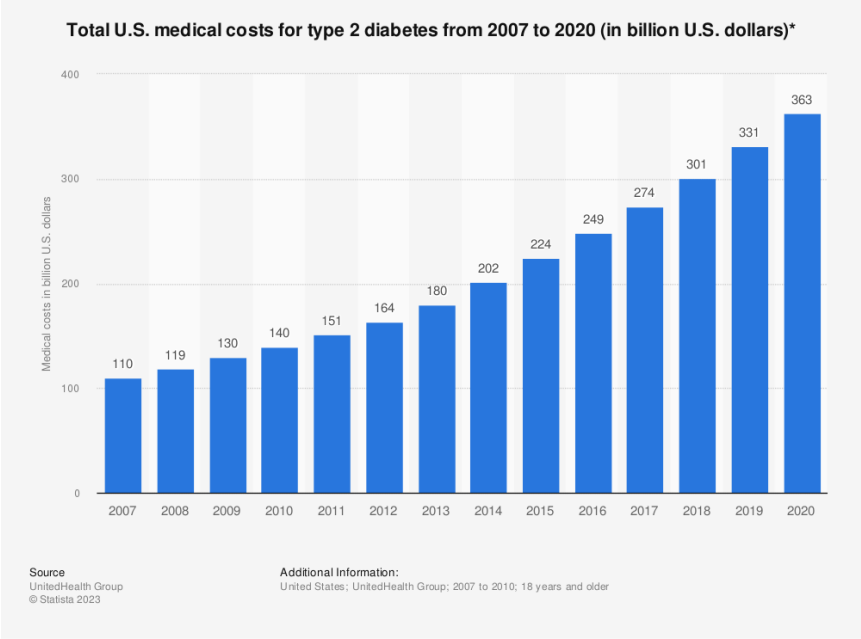
Nonetheless, we were taken aback to see that four of ten targeted drugs are treatments for Type 2 diabetes.

The negative implications are obvious. If pharmas were incentivized not to develop small molecule treatments for this disease before, they certainly have got the message now. It's already been a tough area because there is so much branded competition and so many good generics on the market.

By definition, T2DM is such a large disease that any successful drug that is sold at non-concessionary prices is likely to end up on the "ten most expensive drugs for Medicare" list.

We can't imagine that many R&D heads are lining up to develop small molecule therapies in diabetes at this point. And, we can't remember the last venture round done for a small molecule targeted T2DM.

We hasten to note that T2DM is costing our society ever more ($363 billion as of 2020 according to the chart at right). So, with the IRA negotiations, perhaps the $16 billion spent on the targeted drugs (the two leading SGLT2s, the leading DPP4 and a Novo insulin) gets cut back by $8 to $10 billion. It's a drop in the bucket on society's diabetes bill. But the negative incentive effect could be profound as one of our best hopes to take down the atrocious bill for this disease will be pharmaceutical industry innovation.



One can easily argue that the recent move to target four diabetes drug is penny wise and pound foolish from a societal cost perspective.

Double Whammy: IRA Hits Diabetes Drugs After Sponsors Forced to Carry Out CVOT Trials

Sharma A, Pagidipati NJ, Califf RM, McGuire DK, Green JB, Demets D, George JT, Gerstein HC, Hobbs T, Holman RR, Lawson FC, Leiter LA, Pfeffer MA, Reusch J, Riesmeyer JS, Roe MT, Rosenberg Y, Temple R, Wiviott S, McMurray J, Granger C. Impact of Regulatory Guidance on Evaluating Cardiovascular Risk of New Glucose-Lowering Therapies to Treat Type 2 Diabetes Mellitus: Lessons Learned and Future Directions. *Circulation*. 2020 Mar 10;141(10):843-862.

On the basis of accumulated data up to 2007, questions were raised about the cardiovascular safety of rosiglitazone. In response to the safety concern of an increased risk of MI associated with rosiglitazone and safety issues related to other glucose-lowering therapies, the FDA (adopted December 2008) and European Medicines Agency (adopted November 2012) issued guidance calling for the evaluation of the cardiovascular safety of glucose-lowering therapies. The 2008 FDA guidance required long-term cardiovascular outcome trial (CVOT) evidence (or other equivalent evidence) to rule out increased risk of a major adverse cardiovascular event (MACE) for all new T2DM glucose-lowering therapies. As of September 18, 2019, 18 CVOTs have been completed since the issuance of the guidance, and >200 000 patients with T2DM have been studied. Overall, 16 trials were designed as noninferiority trials and 2 as superiority trials. The completed trials conducted in response to the regulatory guidance in patients with T2DM have examined a variety of patient populations and classes of glucose-lowering therapies, including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

In 2008, the FDA informed those developing diabetes drugs that future approvals would require extremely expensive cardiovascular outcomes trials ("CVOT") to achieve approval.

Several sponsors went ahead and carried out these studies at great cost (Lilly with Jardiance®, Merck with Januvia® and AZ with Farxiga®).

We wonder if these sponsors would have footed the bill for these studies had they known that they would have been targeted for HHS price negotiations in 2023.

Source: https://pubmed.ncbi.nlm.nih.gov/31992065/

T2DM Facts

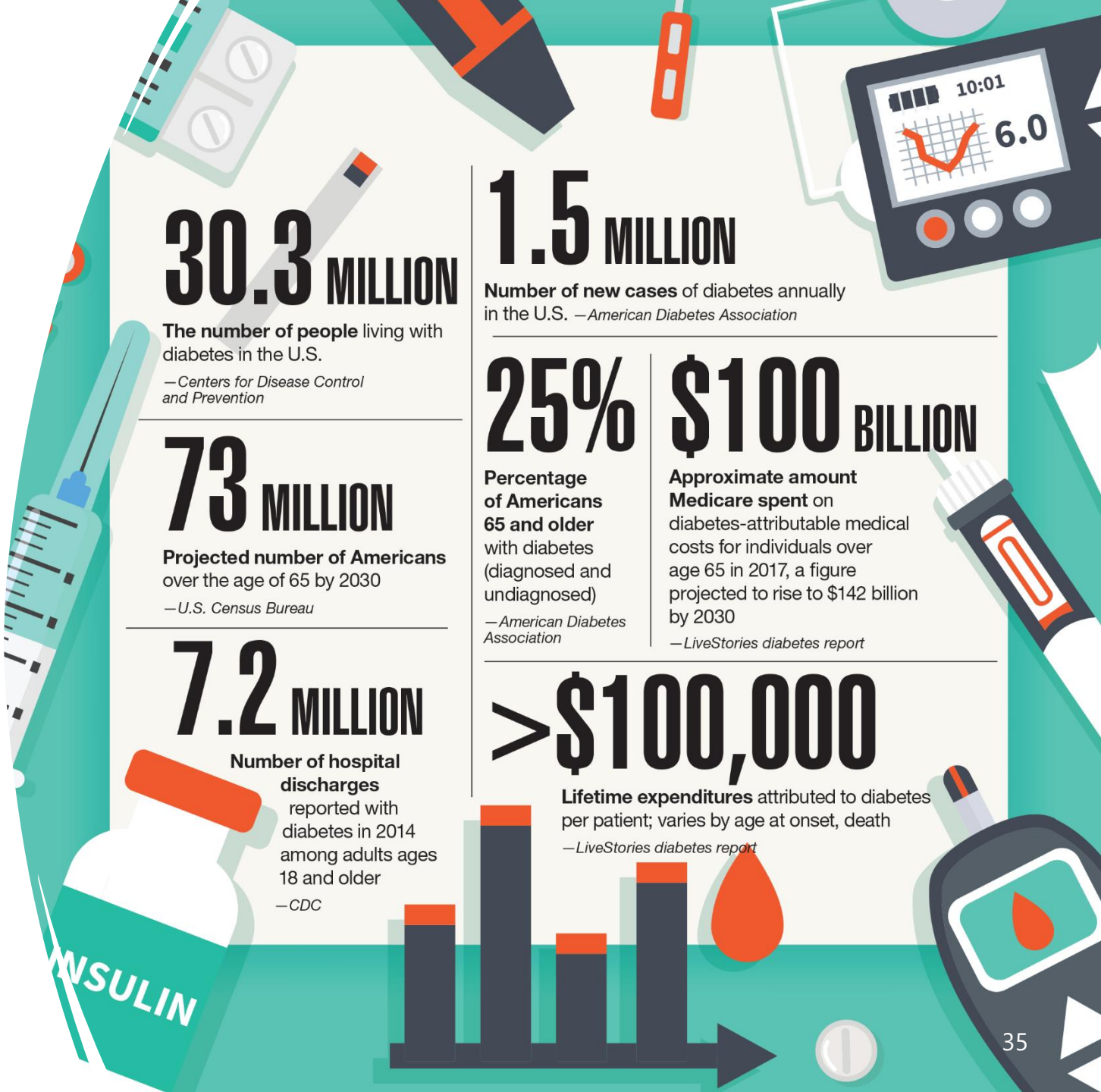
25% of all U.S. healthcare dollars are spent on diabetes and its complications.

30 million people are living with this disease today in U.S.

$100,000 lifetime spend on a T2DM patients in U.S.

Spending on pharmaceutical innovation for this drug category does not appear to be increasing recently.

We doubt that spending is going to be increasing in the future given the recent IRA moves.



Source of chart: American Diabetes Association

Industry News

Use of Expedited Regulatory Programs and Clinical Development Times for FDA-Approved Novel Therapeutics

Wong AK, Mooghali M, Ramachandran R, Ross JS, Wallach JD. Use of Expedited Regulatory Programs and Clinical Development Times for FDA-Approved Novel Therapeutics. JAMA Netw Open. 2023 Aug 1;6(8):e2331753.

Table 2. Duration Between Investigational New Drug Application and New Drug Application (NDA) or Biologics License Application (BLA) Approval Date for Novel Therapeutics Approved by the US Food and Drug Administration From 2015 to 2022

		Approvals using no expedited programs		Approvals using ≥1 expedited programs		
	Total No. (%)	No. (%)	Median (IQR), y	No. (%)	Median (IQR), y	*P* value
Overall	340 (100)	144 (42.4)	8.3 (6.5-11.4)	196 (57.6)	7.0 (4.8-9.0)	<.001
Therapeutic type						
BLA	96 (28.2)	33 (34.4)	8.4 (7.1-11.4)	63 (65.6)	7.2 (4.8-9.1)	.007
NDA	244 (71.8)	111 (45.5)	8.1 (6.4-11.1)	133 (54.5)	6.9 (4.7-9.0)	<.001
Therapeutic area						
Cancer and hematology	120 (35.5)	28 (23.3)	7.7 (6.5-12.0)	92 (76.7)	6.3 (4.7-8.6)	.004
Infectious disease	44 (12.9)	9 (20.5)	9.5 (2.8-11.9)	35 (79.5)	8.7 (4.5-11.2)	.75
CVD, diabetes, and hyperlipidemia	22 (6.5)	14 (63.6)	7.0 (6.0-9.0)	8 (36.4)	8.2 (7.6-12.-0)	.33
Autoimmune, musculoskeletal, and dermatology	41 (12.1)	25 (61.0)	7.8 (6.9-8.7)	16 (39.0)	6.7 (5.0-8.1)	.07
Neurology and psychiatry	46 (13.5)	30 (65.2)	8.7 (6.9-11.2)	16 (34.8)	6.0 (4.6-8.3)	.02
Other[a]	67 (19.7)	38 (56.7)	8.5 (6.8-11.9)	29 (43.3)	7.2 (4.7-8.6)	.007

Abbreviation: CVD, cardiovascular disease.

[a] Other included endocrinology (excluding diabetes) and metabolic disorders; gastroenterology; gynecology; nephrology; opthalmology; pulmonology; and therapeutics for the treatment of amyloidosis, prevention of nausea and vomiting (after surgery or delayed phase chemotherapy–induced), induction and maintenance of procedural sedation, reversing effects of neuromuscular blocking drugs during surgery, treatment of submental fat, and management of acute pain.

We found that FDA approvals using expedited regulatory programs had shorter clinical development times and combined clinical development and review times by approximately 1 to 2 years, demonstrating the association of these programs with faster therapeutic clinical testing and approval.

Source: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2808944

UK Biotech Market Growth Hindered by Pension Rules

Jim Armitage, *The Times,* September 3, 2023

But last week's $5.7 billion sale of the Cambridge biotech group Abcam to Danaher of the US led to renewed concerns in the City and Westminster about Britain's inability to keep its homegrown science businesses from falling into American hands. It follows a host of promising tech firms which have made the pilgrimage across the Atlantic in search of funding.

Paul Nurse, the chief executive of biotech research body the Francis Crick Institute, compared overseas takeovers of UK science businesses to China stealing breakthroughs from laboratories. "Both result in us losing valuable stuff overseas," he said. "The result is the same — a loss of potential UK jobs and wealth for the country."

British universities are highly prized for their groundbreaking discoveries in the realm of life sciences, but the ecosystem supporting them is far behind their peers in Boston and the San Francisco Bay Area.

There, deep-pocketed investment funds staffed by experts in drug discovery work closely with research institutions to fund every stage of the process, from the germ of an idea in a lab through to clinical trials and, finally, launches to the public.

Martin Murphy, a life sciences venture capitalist, set up an early stage investment firm called Syncona in 2012 alongside the Wellcome Trust science foundation. A Cambridge biochemistry PhD with stints at McKinsey and 3i under his belt, he said: "We have got this incredible research engine in our universities and institutions like Wellcome Trust and Cancer Research UK. Over the last 10 or 20 years, we have shown we can spin out technology from that really well. But it's the next stage where we need more funds."

Why do British investors not back homegrown biotech? Largely because the biggest — the pension funds — are curbed by their investment rules from risking pensioners' money on private projects. In Quell's case, one of its current investors is the fund manager Fidelity. This is a major, and well-known pension player in the UK, with some 2,500 staff in Surrey and the City, but Quell had to go to its US parent company for the money.

Syncona's Murphy said: "The real hope will be that more of this pension fund money goes into life sciences. Because at the moment, the UK is really underperforming. Firms at the $1 billion to $20 billion [funding level] are going to the US."

Source: https://www.thetimes.co.uk/article/34063796-49a5-11ee-9ab6-ca60439104a6?shareToken=1c5c0bc9486b567c8fdacee1f07d2df0

Significant Differences in Children's Healthcare Utilization by Community Wealth in the United States

Neighborhood Context and Children's Healthcare Utilization and Health Outcomes: A Comprehensive Descriptive Analysis of National Survey Data

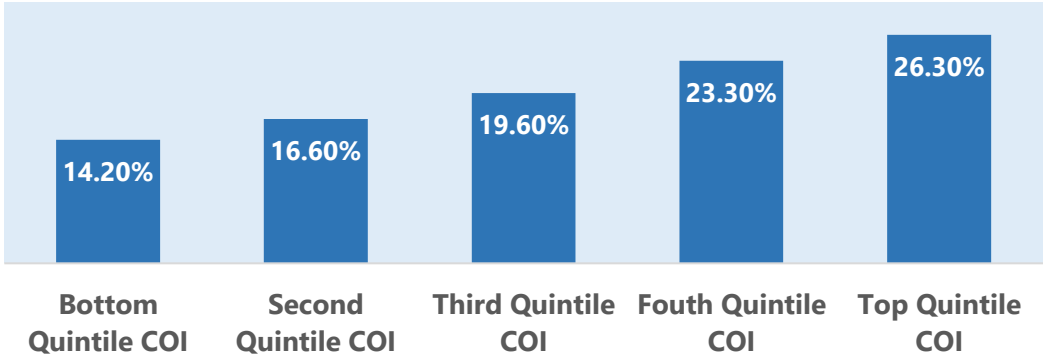
Izabela E Annis, MS, Neal A de Jong, MD, Robert B Christian, MD, Scott A Davis, PhD, Phillip M Hughes, MS, Kathleen C Thomas, PhD

Health Affairs Scholar, qxad038, https://doi.org/10.1093/haschl/qxad038
Published: 24 August 2023 **Article history**

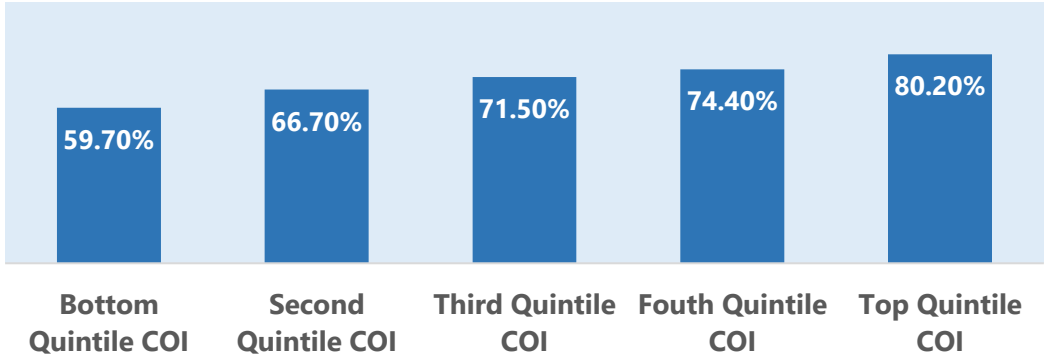
Using the nationally representative sample of children from pooled 2013-2017 Medical Expenditure Panel Survey data linked to the census-tract level Child Opportunity Index (COI) 2.0, a composite measure of neighborhood health, education, and socio-economic conditions, we described US children's socio-economic characteristics, healthcare utilization and expenditures, and health-related outcomes across the spectrum of child neighborhood opportunity levels. We found that neighborhood level of child opportunity was associated with almost all of children's health status, healthcare utilization, expenditures, access to care and satisfaction with care outcomes. **Children living in lower opportunity neighborhoods had the highest rates of poor physical and mental health status and fewest ambulatory care visits but accounted for the highest share of emergency department visits.** Our findings underscore the myriad harms to children of gaps in health, education, and financial resources at the community level and provide targets for public investments to improve child-focused outcomes."

Source: https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxad038/7250150

Share of Ambulatory Visits by Community Child Opportunity Index, 2013-2017, United States



Excellent Child Physical Health by Community Child Opportunity Index, 2013-2017, United States



How Novartis's CEO Learned From His Mistakes and Got Help From an Unlikely Quarter

Jared Hopkins, Wall Street Journal, Sep 3, 2023 (excerpt)

Monday afternoons at Swiss drugmaker Novartis now feature the Ronny Gal Show.

Starting at 2:30 p.m. in Basel, an industry news and intelligence report written by Gal hits the inboxes of 250 senior officials, who rush to read which deals the chief company strategist says Novartis should pursue, what science it should investigate and what rivals are doing.

Gal, a hard-charging Israeli-American who was an outspoken Wall Street analyst, never worked in pharma before a year ago. Now he—and his no-holds-barred reports—are helping propel the remodeling of one of the world's biggest and most hidebound drugmakers.

Among the moves triggered by the reports was a recent multibillion-dollar deal for promising kidney drugs.

While working remotely from his son's bedroom overlooking the Rhine in Basel, Narasimhan contemplated the company's disappointing performance and met virtually with Novartis's largest investors. They said the company wasn't living up to its potential, he recalls. Narasimhan tapped Fiona Marshall, a veteran of Merck & Co., to lead the company's research hub in Cambridge, Mass. Novartis has rejigged how its scientists work, dialing back their budgets for noncore research and tying their bonuses to the start of pivotal testing, not the completion of earlier studies.

The company also pared back by nearly half the number of disease areas it would target, focusing on lucrative conditions like cancer and immunology. It decided to dial back in eye-care, selling off dry-eye drug Xiidra for roughly half of what it paid for the medicine four years earlier.

In its areas of focus, Novartis decided to step up its hunt for drugs in earlier stages of development, and pursue deals that would add candidates to the company's own and increase the odds of one working out.

Hiring Gal was the most unconventional move. During his 18 years at Sanford Bernstein, Gal built a reputation as a pushy yet astute analyst willing to call out sensitive subjects like high drug prices and hefty deal premiums.

Gal's team had been tracking kidney disease research, and then a Seattle company called Chinook because Novartis has its own experimental kidney drug. The team first mentioned Chinook in a report on Jan. 15, which detailed the small company's research efforts and described its lead drug candidate as promising.

Gal said the weekly reports, which kept calling out the promise of Chinook's kidney drug research, put the company on the radar of Novartis officials, accelerated their interest in an acquisition and helped lead to a $3.2 billion deal announced in June.

Narasimhan said Novartis will remain active in deal making, though more selective than a few years ago.

Source: https://www.wsj.com/health/pharma/how-novartiss-ceo-learned-from-his-mistakes-and-got-help-from-an-unlikely-quarter-b087ebbb

The Disruptive Power of Weight Loss Drugs Is Being Felt Beyond Pharma

Vivienne Walt and Lauren Hirsch, *New York Times*, Sep 2, 2023 (excerpt)

As they do every summer, publicly traded companies posted their second-quarter results while Americans were baring their bodies on the beach. But this year, the timing was apt. On several earnings calls in August, chief executives reassured investors that the Ozempic revolution had not left them in the dust, and that they could somehow share in the blazing success of new diabetes and weight loss drugs.

"It puts us in a good position to be a solution for those who are on the drugs," said Dan R. Chard, the chief executive of Medifast, which makes diet products like shakes and protein bars, adding: "They're looking for guidance." He told analysts this even while explaining that new-generation drugs had helped pummel earnings, down 34.7 percent year on year.

"We will continue to study this," Michael Johnson, the chief executive of the nutritional supplement maker Herbalife, told investors. "And when we see an opportunity to capitalize on it, we will."

In theory, that opportunity — both for making profits and for losing fortunes — could be vast not only for the companies behind these drugs but also for some in completely different industries.

And the full potential isn't even clear yet. The market for weight loss drugs is huge: There are roughly 750 million obese people worldwide, including about 42 percent of adults in the United States, where obesity-related illnesses incur billions of dollars in health care costs each year. But Novo says GLP-1 drugs could eventually have other uses, like helping prevent cardiovascular disease among obese adults. There are signs they could treat addiction and even Alzheimer's, too.

"The market potential is very, very significant," Novo's chief financial officer, Karsten Knudsen, told me when I visited the company in June. "We're operating in kind of unusual territory."

Diet companies are bracing for disruption. For decades, weight loss companies have relied on branded, prepackaged meals and lifestyle programs. Some, like WeightWatchers and Noom, have raced to sell GLP-1 drugs themselves, while others still hope their products can survive the Ozempic era. Jenny Craig shut its weight loss centers in May after 40 years. And Simply Good Foods, which distributes Atkins diet products like frozen meals and cookies, will market Atkins as "a perfect complement to people thinking about using the drugs," the company's chief executive at the time, Joe Scalzo, told analysts in June.

The ripple effects are widening. Retailers like Walmart, Kroger and Rite Aid say GLP-1 prescriptions are bringing more people into stores, where they make other purchases. Walmart's chief executive, Doug McMillon, told analysts in August that its executives "expect consumables, and health and wellness, primarily due to the popularity of some GLP-1 drugs, to grow as a percent of total."

Source: https://www.nytimes.com/2023/09/02/business/dealbook/weight-loss-drugs-diet-companies-ozempic.html

Natalie Holles: Biotech Leadership by Pattern Recognition and Adaptation

Growth Mindset for the "Crystallized Intellect"

Posted August 30th, 2023

by Natalie Holles, in Bioentrepreneurship, From The Trenches, Leadership

Life Sci VC

Recovering scientist turned early stage VC A biotech optimist fighting gravity

So we go through our careers, and we take it all in. It's through those years of moving from sitting in the chairs on the edge of the room, to sitting in the chairs at the table, to sitting in the chair at the head of the table, that the patterns establish themselves for us – what works, what's going to lead to disaster, how to be, how not to be, to make it all go. We get to the leadership years of our career, and that pattern recognition is what drives much of our decision making and our sense of what it means to be a good leader. The fluid intelligence of our younger years "crystallizes" (this has always felt like euphemism) into the experience-based intelligence we largely rely upon to drive the bus.

But is this all there is to leadership?

For me as a CEO, this question hit me smack in the face this year when my company went from being what I thought I had signed up for – clinical stage, aggressive pace, build mode – to something much different – early stage, uncertain path forward, batten-down-the-hatches mode. In living and leading through a really rough transition period, I had to acknowledge that some of my personal leadership principles, the ones that I've held for years as this-is-what-makes-me-good-at-this table stakes, weren't working in our new set of circumstances. I needed to adapt. This old dog needed to learn new tricks.

Source: https://lifescivc.com/2023/08/growth-mindset-for-the-crystallized-intellect/

The internal tension wasn't over realizing that I needed to be better – I am always trying to be better at my job. The tension was around the fact that the pattern recognition upon which I had relied, on which I had counted so fundamentally to drive my leadership, might be falling short right when I needed it most. And that, my friends, felt like yet another failure. Another loss. I had a very pivotal discussion with my
executive coach, in which I acknowledged that I had to do things differently, and I remember telling her "You have to let me mourn this."

In follow-up to that tough conversation, she sent me the Harvard Business Review article I quote above, which delves into the question of how a leader can be "authentic" as the ethos of today demands, but also be open to changing how she defines herself. The thought-provoking tagline of the article reads "Why feeling like a fake can be a sign of growth." Huh.

I realized I had to be open to doing something that felt completely unnatural to me as a leader, to "try on" new behaviors that might be better suited to this company, this team, at this time in our evolution. So awkward. We all know what they say about old dogs and new tricks. But if as the article suggests, I chose to look at it with an almost playful mindset, as practicing something about which I'm passionate, to improve my skill level and elevate my performance, that I could wrap my head around.

Increasing Awareness of Nociplastic Pain

Science and technology | A new world of hurt

Some forms of chronic pain are particularly mysterious

***Economist*, Aug 30, 2023**

Nociplastic pain is thought to arise when the body's own pain-processing network gets rewired to overreact to incoming stimuli. Such sensitisation can arise when sustained pain signals permanently change a nerve's ion channels, making even mild sensations indistinguishable from painful ones. Alternatively, it can occur when the body's natural painkillers, neurotransmitters such as endorphins that dampen the flow of pain signals, are less readily manufactured. This often signals some damage to the Descending Pain Modulating System (dpms), a network of brain regions that can provide pain relief if appropriately stimulated. Among its best-known functions is the placebo effect, where a patient can feel better after simply being given the impression of being treated. Another set of mechanisms, known as pain inhibits pain, is what allows the discomfort of nails digging into palms to alleviate the pain of a dental drill being used on teeth.

It is not just the nervous system that can be at fault. Andreas Goebel, a pain researcher at the University of Liverpool, had long hypothesised that antibodies, which patrol the bloodstream to identify and draw attention to pathogens, could also mistakenly attack a patient's nerves. In experimental results published in 2021, he demonstrated that a type of antibody known as immunoglobulin g could, if taken from individuals with fibromyalgia, a condition characterised by severe pain across the body (as well as a host of related symptoms such as tiredness and cognitive problems), induce similar sensitivities when they were injected into mice. This suggests that variations in the immune system may contribute to the onset of nociplastic pain. He intends to conduct similar studies on long covid, as that is a condition also associated with nociplastic pain.

Although unrealistic expectations can make matters worse, ways to relieve nociplastic pain may yet be found. Most interest now lies in harnessing the brain's flexibility for good. "Neuroplasticity can actually go both ways," says Dr Munglani. Psychedelics such as psilocybin, for example, are thought to act on certain neurons in ways that disrupt their existing connections, making it easier to reform faulty circuits or to establish new connections between different parts of the brain. Such new patterns of brain activity have been tentatively linked with an easing of depression, and could potentially help with nociplastic pain. Later this summer, Peter Hendricks at the University of Alabama will begin a clinical trial testing psilocybin on patients with fibromyalgia in order to monitor changes to their level of pain and quality of life. Tryp Therapeutics, a Canada-based biotech company, is also planning to trial the effects of a synthetic form of psilocybin on patients with fibromyalgia and irritable bowel syndrome.

Source: https://www.economist.com/science-and-technology/2023/08/30/some-forms-of-chronic-pain-are-particularly-mysterious

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Phase 3 Trial of Concizumab in Hemophilia with Inhibitors

Matsushita T et al. DOI: 10.1056/NEJMoa2216455

NEJM, Aug 31, 2023

CLINICAL PROBLEM

In patients with hemophilia with inhibitors, subcutaneous prophylaxis may reduce treatment burden as compared with intravenous bypassing agents. Concizumab, a monoclonal antibody that inhibits the anti–tissue factor pathway, is under investigation for subcutaneous prophylaxis in all hemophilia subtypes.

CLINICAL TRIAL

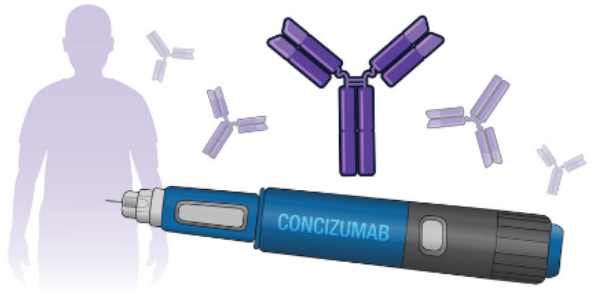
Design: A phase 3a, multicenter, open-label trial that included two randomization groups and two nonrandomization groups evaluated the efficacy and safety of daily concizumab prophylaxis, as compared with no prophylaxis, among patients with hemophilia A or B with inhibitors.

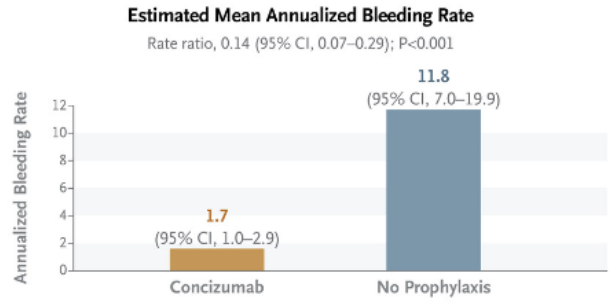
Intervention: 52 patients ≥12 years of age receiving on-demand hemophilia treatment were randomly assigned in a 1:2 ratio to continue on-demand treatment for ≥24 weeks (group 1) or to receive daily concizumab prophylaxis for ≥32 weeks (group 2); after week 24, patients in group 1 could receive concizumab. An additional 81 patients were assigned to concizumab prophylaxis (groups 3 and 4). The primary end point analysis compared treated spontaneous and traumatic bleeding episodes among the patients in groups 1 and 2. Safety was also assessed.

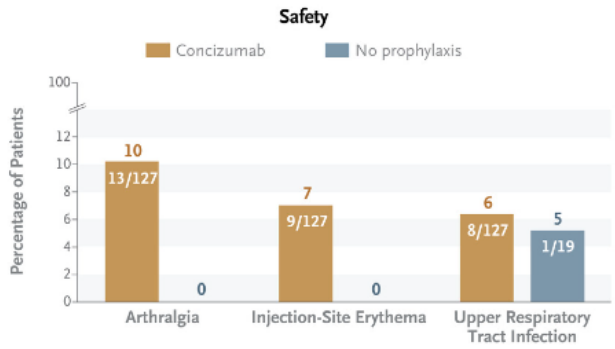
RESULTS

Efficacy: The annualized rate of treated spontaneous and traumatic bleeding episodes was significantly lower with concizumab prophylaxis than with no prophylaxis.

Safety: A serious thromboembolic event occurred in one concizumab recipient in this trial (and in two recipients in a related trial). The trial was paused, risk-mitigation measures were implemented, and treatment was restarted; there were no subsequent thromboembolic events. The most frequently reported adverse events with concizumab included arthralgia, injection-site erythema, and upper respiratory tract infection.







EDITORIAL SCIENCE BEHIND THE STUDY

Hemostasis — A Balancing Act

H. Marijke van den Berg, M.D., Ph.D., and Alok Srivastava, M.D.

Although the findings of Matsushita et al. represent an advance in the management of hemophilia, the ramifications of rebalancing hemostasis, particularly during stress or inflammatory conditions, are not well understood and warrant further investigation. Furthermore, data on the safety and efficacy of concizumab in early childhood are required. In situations in which additional factor VIII or IX replacement may be needed to enhance hemostasis, even though factor VIII or IX assays can be performed, the clinical implication of their combined effect with concizumab is unclear. The subcutaneous delivery of concizumab provided by pen is certainly more convenient than intravenous infusions but involves daily administration. Protocols for restarting concizumab after dose interruptions also need clarification. The clinical effect of anti-TFPI and the recently reported similar clinical efficacy through reduction of antithrombin by small interfering RNA technology11 provide evidence that effective and sustained hemostasis can also be achieved by restoring a balance between procoagulant and anticoagulant factors in hemophilia.

In the bigger picture, these new treatment options need to be weighed against the possibility of cure of hemophilia through gene therapy: two adeno-associated virus (AAV) vector–based products have been approved for clinical use, and more are in the pipeline. The durability of the gene therapy–mediated factor production is being defined. Long-term follow-up of patients receiving gene therapy has documented declines in the expression of the clotting factors over time. Given the strong antibody response to AAV vector–based gene therapy, repeated doses are currently not possible. Therefore, an abundance of therapeutic options such as concizumab, other non–factor-replacement products, and a multitude of clotting factor products will play a large role in prevention of bleeding in hemophilia for the foreseeable future.

Sources: https://www.nejm.org/doi/full/10.1056/NEJMoa2216455, https://www.nejm.org/doi/full/10.1056/NEJMe2304535

Corcoran RB. "A single inhibitor for all KRAS mutations," *Nat Cancer*, 2023 Aug;4(8):1060-1062.

Pan-KRAS inhibitor https://doi.org/10.1038/s43018-023-00615-x

A single inhibitor for all KRAS mutations

Ryan B. Corcoran

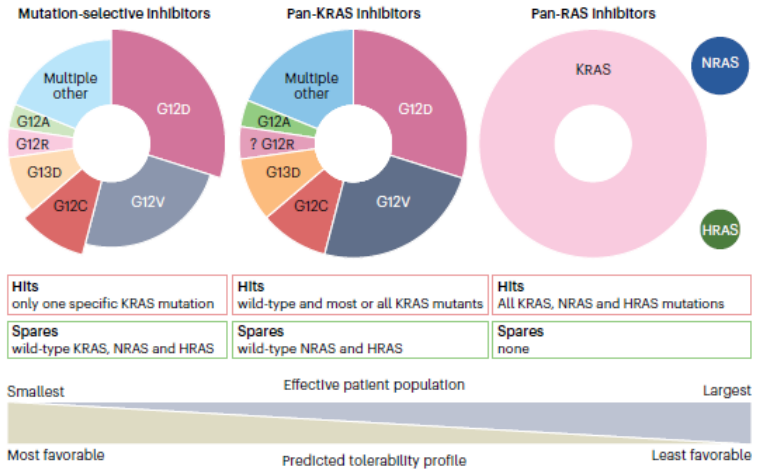
Check for updates

The recent design of mutation-selective KRAS inhibitors has led to US Food and Drug Administration approval of two inhibitors of KRAS(G12C), sotorasib and adagrasib. A study published in *Nature* reports the development of a first-in-class pan-KRAS-selective inhibitor. Here we comment on the current status of KRAS-targeting approaches.

KRAS – the most commonly mutated oncogene – is altered in about 20% of all cancers, but was considered undruggable for more than 3 decades[1]. *KRAS* is a member of the RAS family of protooncogenes, which also includes *NRAS* and *HRAS*. Recent clinical data with KRAS inhibitors that are selective for KRAS(G12C) due to a covalent interaction with the mutant cysteine residue, have demonstrated favorable response rates in non-small-cell lung cancer and other tumor types[2,3], leading to the approval of sotorasib and adagrasib. Recent studies have also suggested that inhibitors that selectively target other KRAS mutations may show similar promise.

KRAS inhibitors that are selective for KRAS mutations including G12D, G12S and G12R have been identified[4–6], and several G12D-selective inhibitors are currently in clinical trials. Similar to KRAS(G12C) inhibitors, these molecules are designed to target only the mutant KRAS protein – sparing wild-type KRAS, NRAS and HRAS – to provide a tractable therapeutic index. However, mutation-selective KRAS inhibitors each bind to a single KRAS mutation, and although some mutations are frequent (such as G12D, which is present in around 25% of cancers with KRAS alterations), nearly 20% of *KRAS*-mutated cancers involve alleles with frequencies of 2% or less. Thus it may be impractical to achieve broad efficacy by developing a specific mutation-selective inhibitor for every *KRAS* allele (Fig. 1).

A selective inhibitor that targets the full spectrum of KRAS mutations while sparing RAS signaling in normal cells would enable a favorable therapeutic index. Mouse genetic studies suggest that there is considerable redundancy in RAS isoform signaling in normal tissues. Although late embryonic heart development is functionally dependent on KRAS4B, no clear phenotype is observed with knockout of any RAS isoform in the adult mouse (reviewed in ref. 7). This redundancy underlies the rationale for developing a new class of pan-KRAS inhibitors (also known as pan-KRAS-selective inhibitors) that inhibit the majority of wild-type and mutant KRAS isoforms, but not NRAS and HRAS.



Pan-KRAS Inhibitor?

This paper by Ryan Corcoran, published in *Nature Cancer* on August 24th, is quite exciting, particularly at a time when many investors eyes are on Revolution Medicines.

Mr. Corcoran reviews the ongoing collaboration between Memorial Sloan Kettering and Boehringer-Ingelheim and their development of BI-2865, a pan-KRAS inhibitor.

He notes:

"The clinical impact of a single inhibitor that can target almost every KRAS mutation with a favorable therapeutic index would be profound. As most mechanisms of acquired resistance to mutation-specific KRAS inhibitors seem to involve secondary activating KRAS mutations, this new class of pan-KRAS-selective inhibitors might provide an additional benefit by preventing the outgrowth of secondary KRAS mutations. A critical caveat for the clinical application of pan-KRAS-selective inhibitors is the lack of knowledge about the consequences of inhibiting wild-type KRAS in humans."

The secret sauce of the new compound is that "BI-2865 requires KRAS to be in the GDP-bound OFF state, indicating that an OFF-state KRAS inhibitor has the potential to inhibit the vast majority of KRAS mutations".

Corcorant concludes: "In summary, Kim et al. present the first example of a novel class of pan-KRAS-selective inhibitors, which have the potential to target around 95% of KRAS alterations with a single molecule. Due to their high selectivity for KRAS over NRAS and HRAS, pan-KRAS-selective inhibitors appear to be well-tolerated in mice, although clinical trials will be needed to determine the consequences and tolerability of inhibition of wild-type KRAS in humans."

Source: https://www.nature.com/articles/s43018-023-00615-x. Also see: https://www.mskcc.org/news/potential-drug-shows-promise-targeting-range-of-kras-driven-cancers-in-lab

ADC Landscape Review

Maecker H, Jonnalagadda V, Bhakta S, Jammalamadaka V, Junutula JR. Exploration of the antibody-drug conjugate clinical landscape. MAbs. 2023 Jan-Dec;15(1):2229101.

The antibody–drug conjugate (ADC) field has undergone a renaissance, with substantial recent developmental investment and subsequent drug approvals over the past 6 y. In November 2022, Elahere™ became the latest ADC to be approved by the US Food and Drug Administration (FDA). To date, over 260 ADCs have been tested in the clinic against various oncology indications. Here, we review the clinical landscape of ADCs that are currently FDA approved (11), agents currently in clinical trials but not yet approved (164), and candidates discontinued following clinical testing (92). These clinically tested ADCs are further analyzed by their targeting tumor antigen(s), linker, payload choices, and highest clinical stage achieved, highlighting limitations associated with the discontinued drug candidates. Lastly, we discuss biologic engineering modifications preclinically demonstrated to improve the therapeutic index that if incorporated may increase the proportion of molecules that successfully transition to regulatory approval.

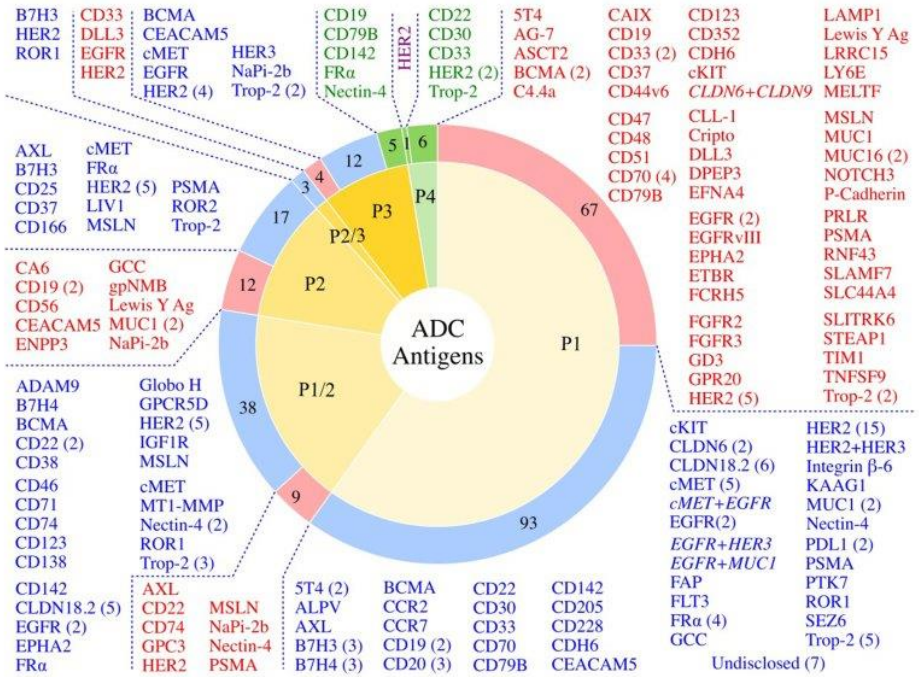


Figure 4. Antigen Targets of the Clinically Tested ADCs. Of the 267 clinically tested ADCs, 260 have known antigens (7 are undisclosed). Numbers of ADCs targe given tumor antigen in various stages of clinical testing (Phase 1-Phase 4, P1-P4) are shown in the categories of FDA Approved ADCs (green sectors, green text), ADCs (blue sectors, blue text), and Discontinued ADCs (red sectors, red text). Dual antigen targeting ADCs are shown in italics. The Phase 4 HER2 candidate sho purple text is disitamab vedotin, that has been approved in China and is not yet approved by the FDA.

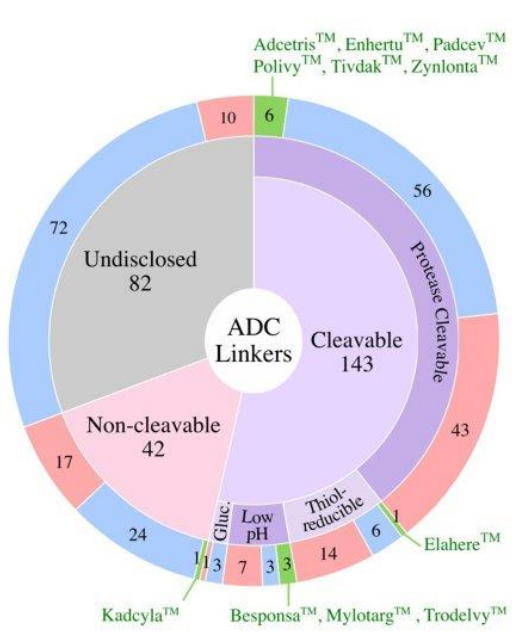


Figure 6. Linkers Used in Clinically Tested ADCs. Numbers of ADCs utilizing different linker classes are shown in the outer ring for the FDA-approved ADCs (green), active ADCs (blue), and discontinued ADCs (red). FDA approved ADCs are shown alongside their respective linkers. Gluc., α-Glucuronide.

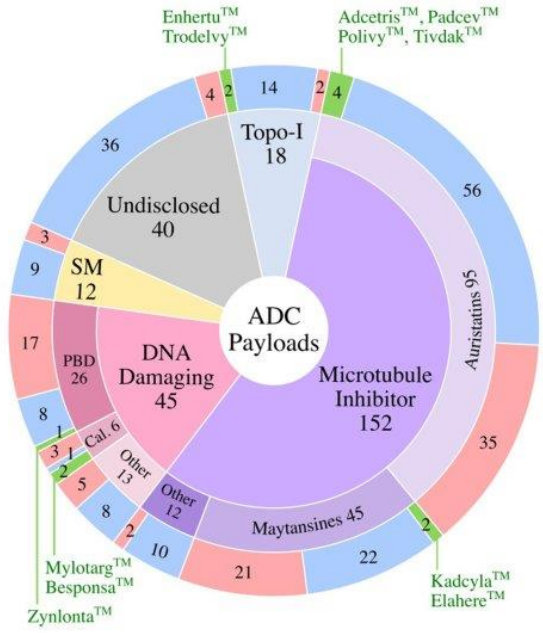


Figure 7. Payloads Used in Clinically Tested ADCs. Numbers of ADCs corresponding to the type of payload are shown are shown in the outer ring for the FDA-approved ADCs (green), active ADCs (blue), and discontinued ADCs (red) sectors. Topo-I, Topoisomerase I Inhibitor; SM, targeted small molecules; PBD, pyrrolobenzodiazepine; Cal., calicheamicin.

Source: https://www.tandfonline.com/doi/full/10.1080/19420862.2023.2229101

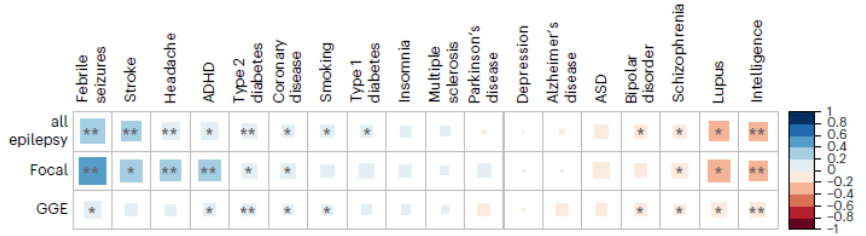
Multiple Genetic Regions Impact Epilepsy

International League Against Epilepsy Consortium on Complex Epilepsies, "GWAS meta-analysis of over 29,000 people with epilepsy identifies 26 risk loci and subtype-specific genetic architecture," *Nature Genetics*, Aug 31, 2023

Epilepsy is a highly heritable disorder affecting over 50 million people worldwide, of which about one-third are resistant to current treatments. Here we report a multi-ancestry genome-wide association study including 29,944 cases, stratified into three broad categories and seven subtypes of epilepsy, and 52,538 controls. We identify 26 genome-wide significant loci, 19 of which are specific to genetic generalized epilepsy (GGE). We implicate 29 likely causal genes underlying these 26 loci. SNP-based heritability analyses show that common variants explain between 39.6% and 90% of genetic risk for GGE and its subtypes.

Subtype analysis revealed markedly different genetic architectures between focal and generalized epilepsies. Gene-set analyses of GGE signals implicate synaptic processes in both excitatory and inhibitory neurons in the brain. Prioritized candidate genes overlap with monogenic epilepsy genes and with targets of current antiseizure medications. Finally, we leverage our results to identify alternate drugs with predicted efficacy if repurposed for epilepsy treatment.

This very large genetic study of epilepsy was produced by 150+ researchers. The work identified 25+ genetic regions that impact epilepsy. This work may lead to novel therapeutic strategies for this widespread disease state. One of the more fascinating findings was that the same genes that make focal epilepsies *more likely*, in turn make lupus *less likely*. See the table below. This shows an interesting potential immunological angle to epilepsy.



Genetic correlations of epilepsy with other phenotypes. The genetic correlation coefficient was calculated with LDSC and is denoted by color scale from −1 (red; negatively (anti-)correlated) to +1 (blue; positively correlated). The square size relates to the absolute value of the corresponding correlation coefficient. Single asterisk indicates two-sided $P < 0.05$ and double asterisk indicates two-sided $P < 0.0009$ (Bonferroni corrected).

Source: https://www.nature.com/articles/s41588-023-01485-w

CD39+ T-Cell Distance to Tumor Matters

Koppensteiner L, Mathieson L, Pattle S, Dorward DA, O'Connor R, Akram AR. Location of CD39+ T cell subpopulations within tumors predict differential outcomes in non-small cell lung cancer. *J Immunother Cancer*. 2023 Aug;11(8):e006770.

Purpose: An improved mechanistic understanding of immunosuppressive pathways in non-small cell lung cancer (NSCLC) is important to develop novel diagnostic and therapeutic approaches. Here, we investigate the prognostic significance of the ectonucleotidases CD39 and CD73 in NSCLC.

Experimental design: The expression and localization of CD39, CD73 and CD103 was digitally quantified in a cohort of 162 early treatment naïve NSCLC patients using multiplex-immunofluorescence and related to patient outcome.

Results: We demonstrate that flow cytometry of early untreated NSCLC patients shows an upregulation of CD39 expression in the tumor tissue among natural killer (NK) cells, fibroblasts and T cells. CD73 expression is mainly found among fibroblasts and Epcam+cells in the tumor tissue. Multiplex Immunofluorescence in a cohort of 162 early untreated NSCLC patients demonstrates that CD39 expression is mainly localized in the tumor stroma while CD73 expression is equally distributed between tumor nest and stroma, and high expression of CD39 and CD73 in the tumor stroma is associated with poor recurrence-free survival (RFS) at 5 years. Additionally, we find that CD8+T cells located in the tumor nest express CD103 and the density of CD39+CD103+CD8+ T cells in the tumor nest predicts improved RFS at 5 years. Targeted RNA-Seq shows that the tumor microenvironment of NSCLC upregulates regulatory pathways in CD4+ T cells and exhaustion in CD8+ T cells, and analysis of a single cell RNA sequencing dataset shows that CD39+CD4+ cells are enriched in Treg signature gene-sets, and CD39+CD103+ cytotoxic T lymphocyte show gene signatures indicative of an exhausted cytotoxic phenotype with upregulated expression of CXCL13.

In a recent report we noted that the T-cell exhaustion and associated lack of effector function is a key issue in combating tumors.

This paper by a group of researchers at the University of Edinburgh shows that the number of CD39+ T-cells near a tumor is highly relevant in treating lung cancer.

Unexpectedly, the *spatial location* of the cells relative to tumor tissue also turns out to be important.

Source: https://www.nature.com/articles/s41588-023-01485-w

TREM1 Highly Relevant Target in Tumor Immunology

Science Translational Medicine, Aug 29, 2023

TREM1 activation of myeloid cells promotes antitumor immunity

Vladislava Juric[1], Erin Mayes[1], Mikhail Binnewies[1], Tian Lee[1], Pamela Canaday[1], Joshua L. Pollack[1], Joshua Rudolph[1], Xiaoyan Du[1], Victoria M. Liu[1], Subhadra Dash[1], Rachael Palmer[1], Nadine S. Jahchan[1], Åsa Johanna Ramoth[1], Sergio Lacayo[1], Shilpa Mankikar[1], Manith Norng[1], Chris Brassell[1], Aritra Pal[1], Christopher Chan[1], Erick Lu[1], Venkataraman Sriram[1], Michel Streuli[1], Matthew F. Krummel[2], Kevin P. Baker[1]*, Linda Liang[1]*

Myeloid cells in the tumor microenvironment (TME) can exist in immunosuppressive and immunostimulatory states that impede or promote antitumor immunity, respectively. Blocking suppressive myeloid cells or increasing stimulatory cells to enhance antitumor immune responses is an area of interest for therapeutic intervention. Triggering receptor expressed on myeloid cells-1 (TREM1) is a proinflammatory receptor that amplifies immune responses. TREM1 is expressed on neutrophils, subsets of monocytes and tissue macrophages, and suppressive myeloid populations in the TME, including tumor-associated neutrophils, monocytes, and tumor-associated macrophages. Depletion or inhibition of immunosuppressive myeloid cells, or stimulation by TREM1-mediated inflammatory signaling, could be used to promote an immunostimulatory TME. We developed PY159, an afucosylated humanized anti-TREM1 monoclonal antibody with enhanced FcγR binding. PY159 is a TREM1 agonist that induces signaling, leading to up-regulation of costimulatory molecules on monocytes and macrophages, production of proinflammatory cytokines and chemokines, and enhancement of T cell activation in vitro. An antibody against mouse TREM1, PY159m, promoted antitumor efficacy in syngeneic mouse tumor models. These results suggest that PY159-mediated agonism of TREM1 on tumoral myeloid cells can promote a proinflammatory TME and offer a promising strategy for immunotherapy.

Myeloid cell populations control immunosuppression in the tumor microenvironment (TME), and targeting the TME is a promising approach for immunosuppressed tumors. To this end, Juric et al. developed an afucosylated humanized monoclonal antibody, PY159, against triggering receptor expressed on myeloid cells-1 (TREM1), a proinflammatory receptor expressed on many myeloid cells. Treatment of a syngeneic mouse models with PY159m promoted antitumor efficacy, suggesting a promising strategy for future immunotherapy.

Source: https://www.science.org/doi/epdf/10.1126/scitranslmed.add9990

A Potential Universal CAR-t Approach to Liquid Tumors

Science Translational Medicine, Aug 31, 2023

CANCER IMMUNOTHERAPY

Epitope base editing CD45 in hematopoietic cells enables universal blood cancer immune therapy

Nils Wellhausen[1], Ryan P. O'Connell[2], Stefanie Lesch[1], Nils W. Engel[1], Austin K. Rennels[1], Donna Gonzales[1], Friederike Herbst[1], Regina M. Young[1], K. Christopher Garcia[3,4], David Weiner[2], Carl H. June[1,5,6]*, Saar I. Gill[1,7]*

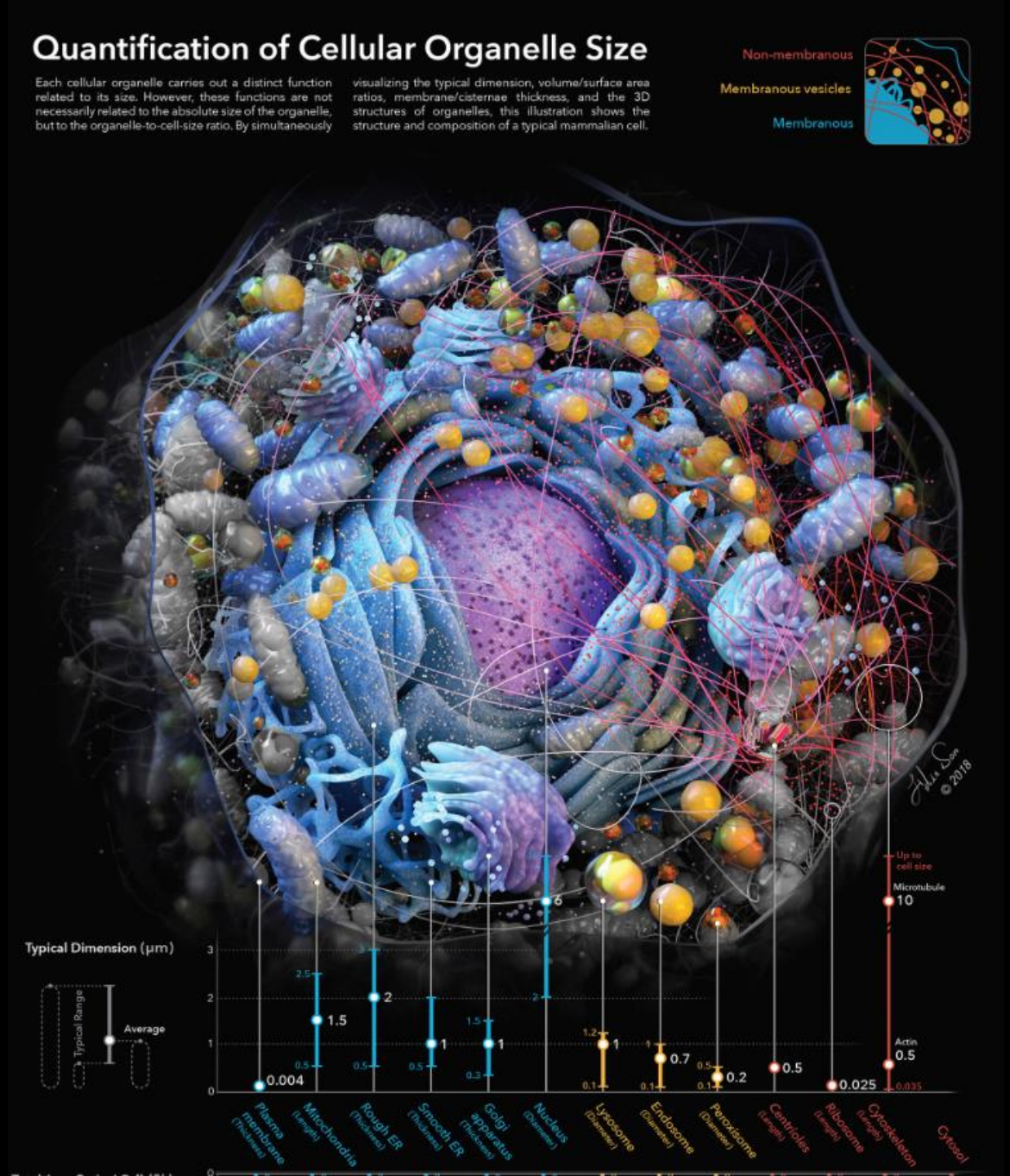
In the absence of cell-surface cancer-specific antigens, immunotherapies such as chimeric antigen receptor (CAR) T cells, monoclonal antibodies, or bispecific T cell engagers typically target lineage antigens. Currently, such immunotherapies are individually designed and tested for each disease. This approach is inefficient and limited to a few lineage antigens for which the on-target/off-tumor toxicities are clinically tolerated. Here, we sought to develop a universal CAR T cell therapy for blood cancers directed against the pan-leukocyte marker CD45. To protect healthy hematopoietic cells, including CAR T cells, from CD45-directed on-target/off-tumor toxicity while preserving the essential functions of CD45, we mapped the epitope on CD45 that is targeted by the CAR and used CRISPR adenine base-editing to install a function-preserving mutation sufficient to evade CAR T cell recognition. Epitope edited CD45 CAR T cell were fratricide-resistant and effective against patient-derived acute myeloid leukemia, B cell lymphoma, and acute T cell leukemia. Epitope edited hematopoietic stem cells (HSCs) were protected from CAR T cells and, unlike CD45 knockout cells, could engraft, persist, and differentiate in vivo. Ex vivo epitope editing in HSCs and T cells enables the safe and effective use of CD45-directed CAR-T cells and bispecific T cell engagers for the universal treatment of hematologic malignancies and might be exploited for other diseases requiring intensive hematopoietic ablation.

This paper led by a group from the University of Pennsylvania proposes a universal CAR-t approach to liquid tumors. The approach works by targeting CD45 which is expressed on all hematopoietic cells. The novel idea here is to cloak non-cancerous hematopoietic cells with a base editing approach.

The data for this approach in animals was quite encouraging.

Very impressive.

Source: https://www.science.org/doi/epdf/10.1126/scitranslmed.add9990



Designed for undergraduate students, this illustration visualizes the quantification of organelles of a typical mammalian cell. Scale at the sub-cellular level is often misrepresented in textbook illustrations, which may lead to students developing misconceptions about the structure of cells. Furthermore, information about the scale and properties of organelles is fragmented and difficult to find. This illustration aims to provide students with a more complete understanding of the structure and composition of a typical mammalian cell.

To achieve this goal, I built the 3D model of the cell and organelles based on proportions and dimensions as published in Cell Biology by the Numbers (Milo and Phillips, 2015), and recent articles. A graphical legend and colour-coding scheme were designed to link the central visual with the scientific data, and a simple black background was incorporated to draw attention on the data visualization.

Source: https://felixvis.artstation.com/projects/v1OlWO

JAMA Report on Psilocybin and Depression

Original Investigation

JAMA

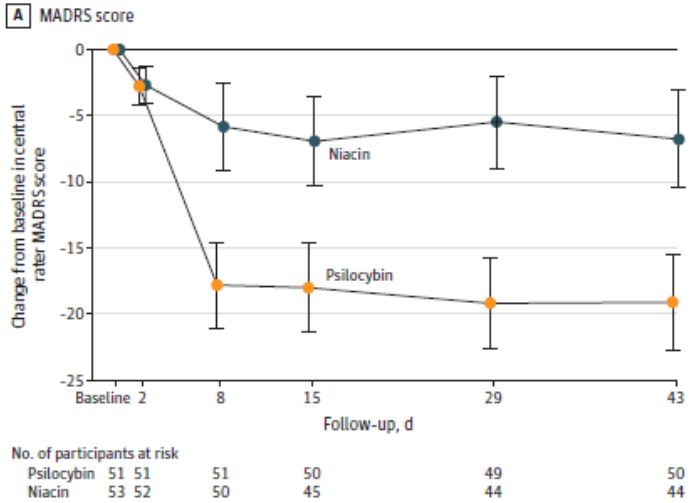
August 31, 2023

Single-Dose Psilocybin Treatment for Major Depressive Disorder

A Randomized Clinical Trial

A total of 104 participants (mean [SD] age, 41.1 [11.3] years; 52 [50%] women) were randomized (51 to the psilocybin group and 53 to the niacin group). Psilocybin treatment was associated with significantly reduced MADRS scores compared with niacin from baseline to day 43 (mean difference,−12.3 [95% CI, −17.5 to −7.2]; P <.001) and from baseline to day 8 (mean difference, −12.0 [95% CI, −16.6 to −7.4]; P < .001).

Figure 2. Change in Montgomery-Asberg Depression Rating Scale (MADRS) Score by Treatment Group

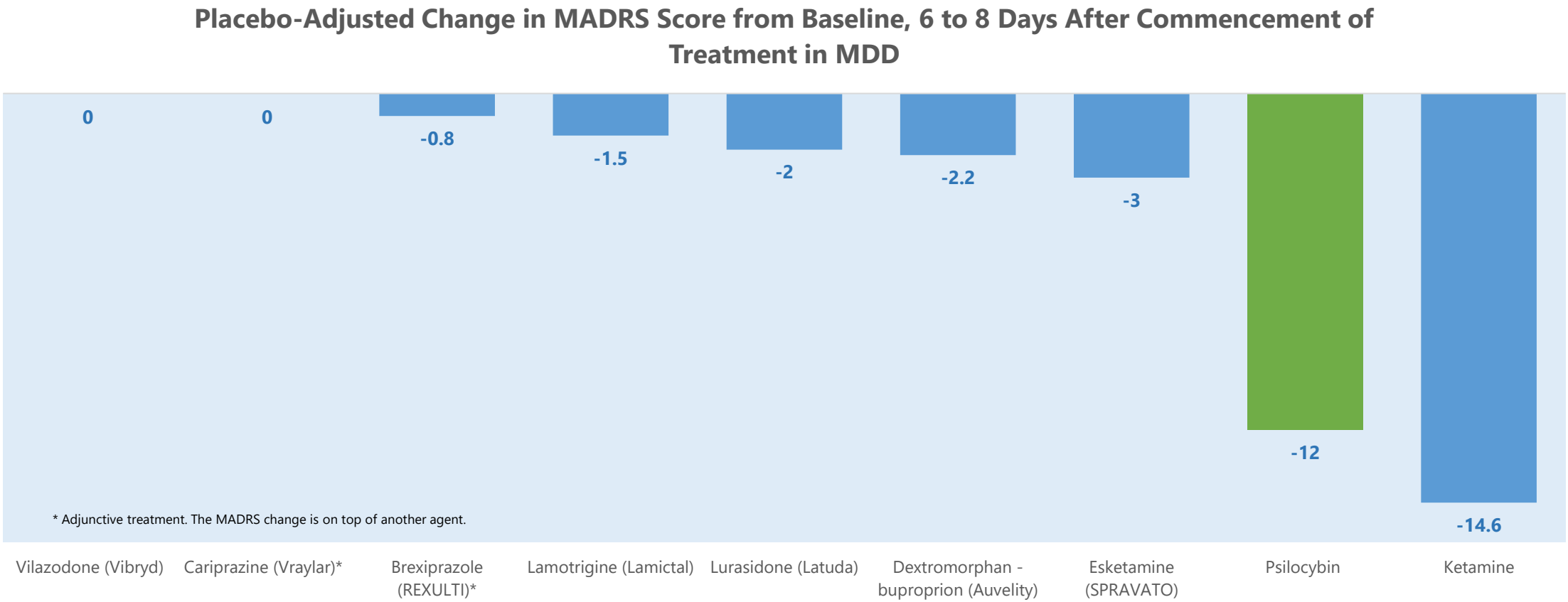


In this phase 2 study, treatment with a 25-mg dose of psilocybin administered with psychological support was associated with a statistically and clinically significant reduction in depressive symptoms compared with a niacin placebo, assessed as change in total MADRS score and as rates of sustained response. The 15.9% difference in sustained remission rates between the groups was not significantly different. Improvements in depression were apparent within 8 days of psilocybin dosing, consistent with a rapid onset of action, and were maintained across the 6-week follow-up period, without attenuation of the effect, and with higher point prevalence rates of MADRS-defined response and remission than has been observed in recent psilocybin studies of TRD.10,14 Although an MCID was not specified a priori for this study, the 12.3-point difference in change in score between the psilocybin and niacin groups is larger than the upper limit active placebo difference in the literature of 9 points and the 19.1-point reduction in MADRS score from baseline to day 43 in the psilocybin group is larger than the 12-point difference shown to reflect substantial clinical improvement in patients with TRD.25 In contrast to prior psilocybin trials for depression,8,14,15 there was not a significant reduction in depressive symptoms or a psilocybin/placebo difference in depressive symptom status at the day 2 assessment (ie, 1 day after dosing) (Figure 2 and Table 2).

Source: https://jamanetwork.com/journals/jama/fullarticle/2808950

Comparison of Psilocybin to Other Agents – One Week

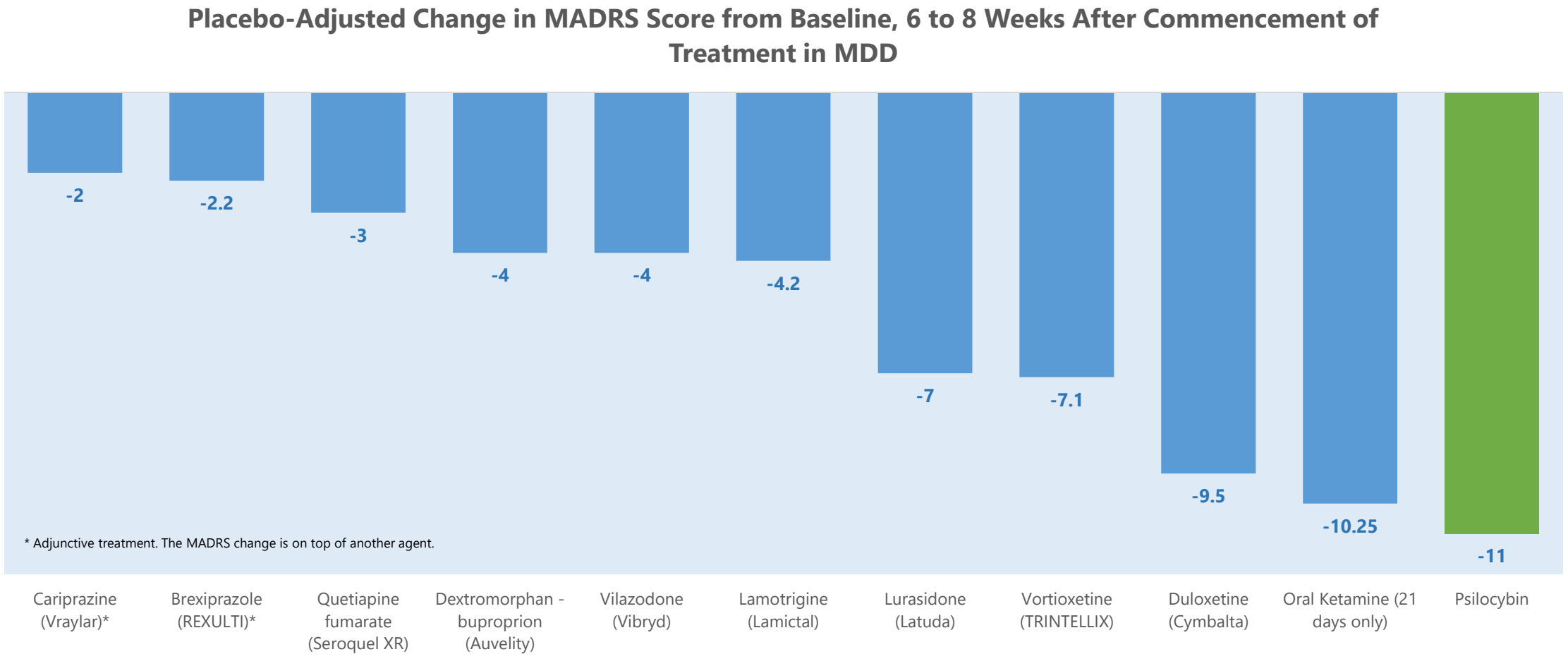
Psilocybin trounces other oral drugs for MDD after one week. The only competitive drug is IV ketamine but this drug is known to have potentially quite serious side effects.



Sources: https://www.psychiatrist.com/jcp/depression/efficacy-safety-vilazodone-major-depressive-disorder/, https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.20220504, https://www.sciencedirect.com/science/article/pii/S0165032717307942, https://www.researchgate.net/figure/MADRS-total-score-over-8-weeks-of-double-blind-treatment-with-lamotrigine-titrated-to_fig2_342047532, https://www.medscape.org/viewarticle/864387_transcript_2, https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.21080800, https://www.researchgate.net/figure/Least-squares-mean-change-SE-in-Montgomery-Asberg-Depression-Rating-Scale-MADRS_fig2_334414555, https://jamanetwork.com/journals/jama/fullarticle/2808950, ttps://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2016.16010037?url_ver=Z39.88-2003

Comparison of Psilocybin to Other Agents – Seven Weeks

Psilocybin does the best of all drugs tested for MDD at 42 to 56 days. Duloxetine and oral ketamine are competitive.



Sources: https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.20220504, https://www.sciencedirect.com/science/article/pii/S0165032717307942, https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.21080800, https://www.psychiatrist.com/jcp/depression/efficacy-safety-vilazodone-major-depressive-disorder/, https://www.researchgate.net/figure/MADRS-total-score-over-8-weeks-of-double-blind-treatment-with-lamotrigine-titrated-to_fig2_342047532, https://www.medscape.org/viewarticle/864387_transcript_2, https://pubmed.ncbi.nlm.nih.gov/24257717/, https://pubmed.ncbi.nlm.nih.gov/30246667/, https://jamanetwork.com/journals/jama/fullarticle/2808950

Psilocybin Use Associated with Increase in Brain Network Integration

Psilocybin increases brain network integration in patients with depression. *Nat Med.* 2022 Apr;28(4):647-648.

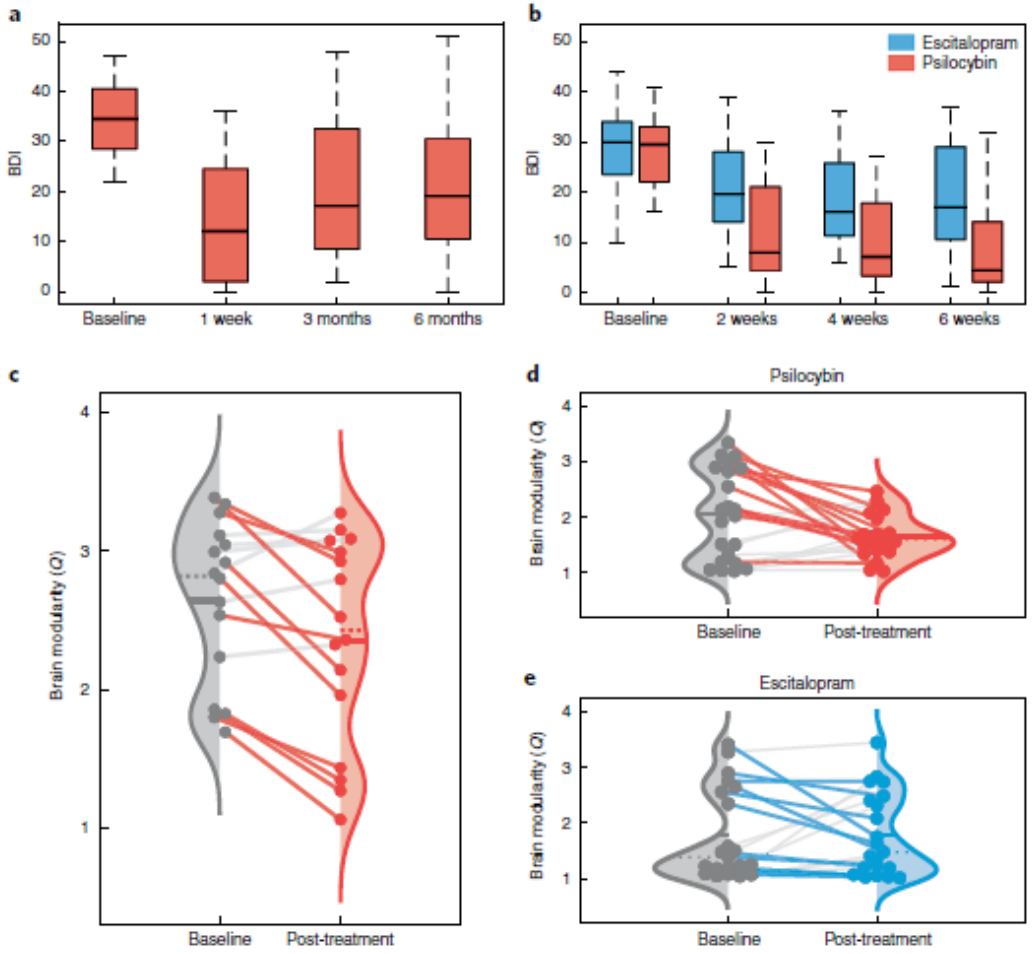


Fig. 1: Psilocybin's antidepressant effect relates to increases in the global integration of brain functional networks.

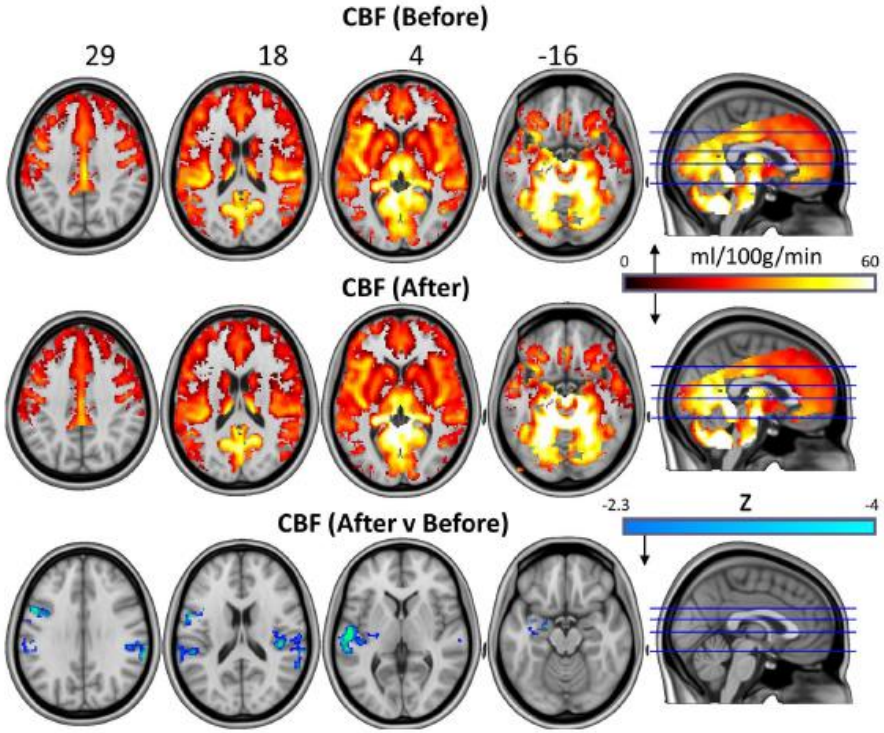
a, Rapid and sustained reduction in depression severity (as determined by Beck's depression inventory (BDI)) after psilocybin therapy in patients with treatment-resistant depression. b, Antidepressant effect similar to that in a, observed in patients with major depressive disorder, in which psilocybin was superior to escitalopram. c,d, Decreased brain network modularity indicates that psilocybin's antidepressant action relates to a global increase in between-network connectivity in patients with treatment-resistant depression (c) or major depressive disorder (d). e, No action such as that in c,d was observed in response to escitalopram.

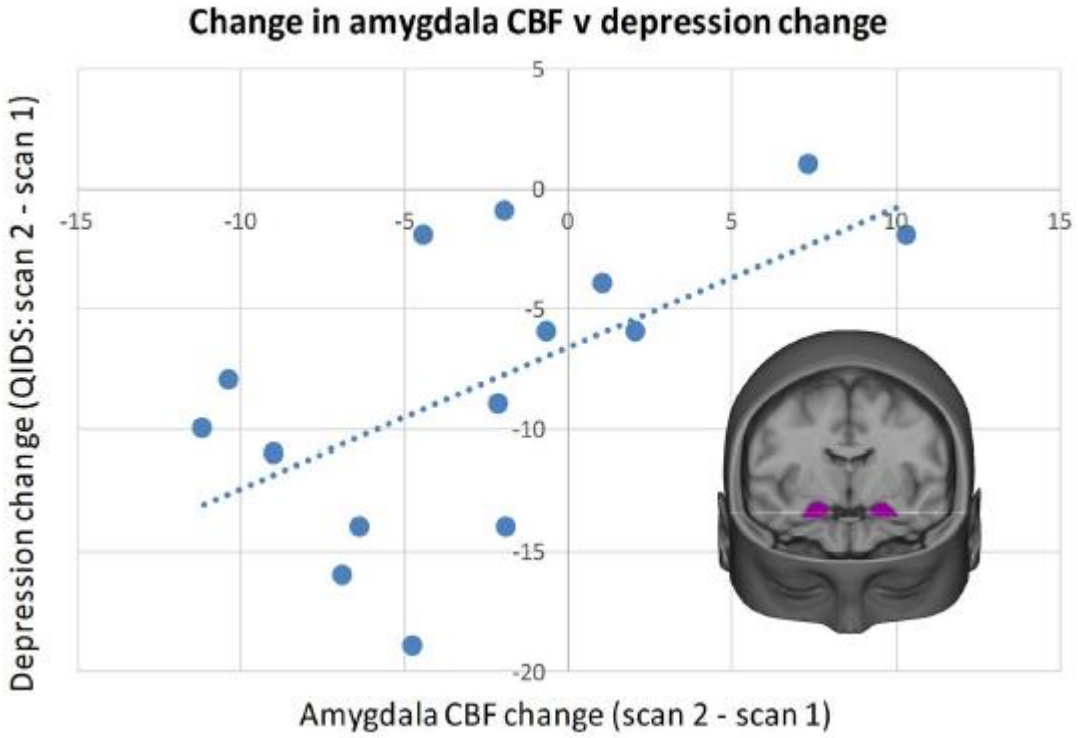
Source: https://www.nature.com/articles/s41591-022-01769-4. Photo from Getty Images.

Psilocybin Use Associated with Reduced Cerebral Blood Flow in Amygdala in Persons with Depression

Carhart-Harris RL, Roseman L, Bolstridge M, Demetriou L, Pannekoek JN, Wall MB, Tanner M, Kaelen M, McGonigle J, Murphy K, Leech R, Curran HV, Nutt DJ. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Sci Rep*. 2017 Oct 13;7(1):13187.

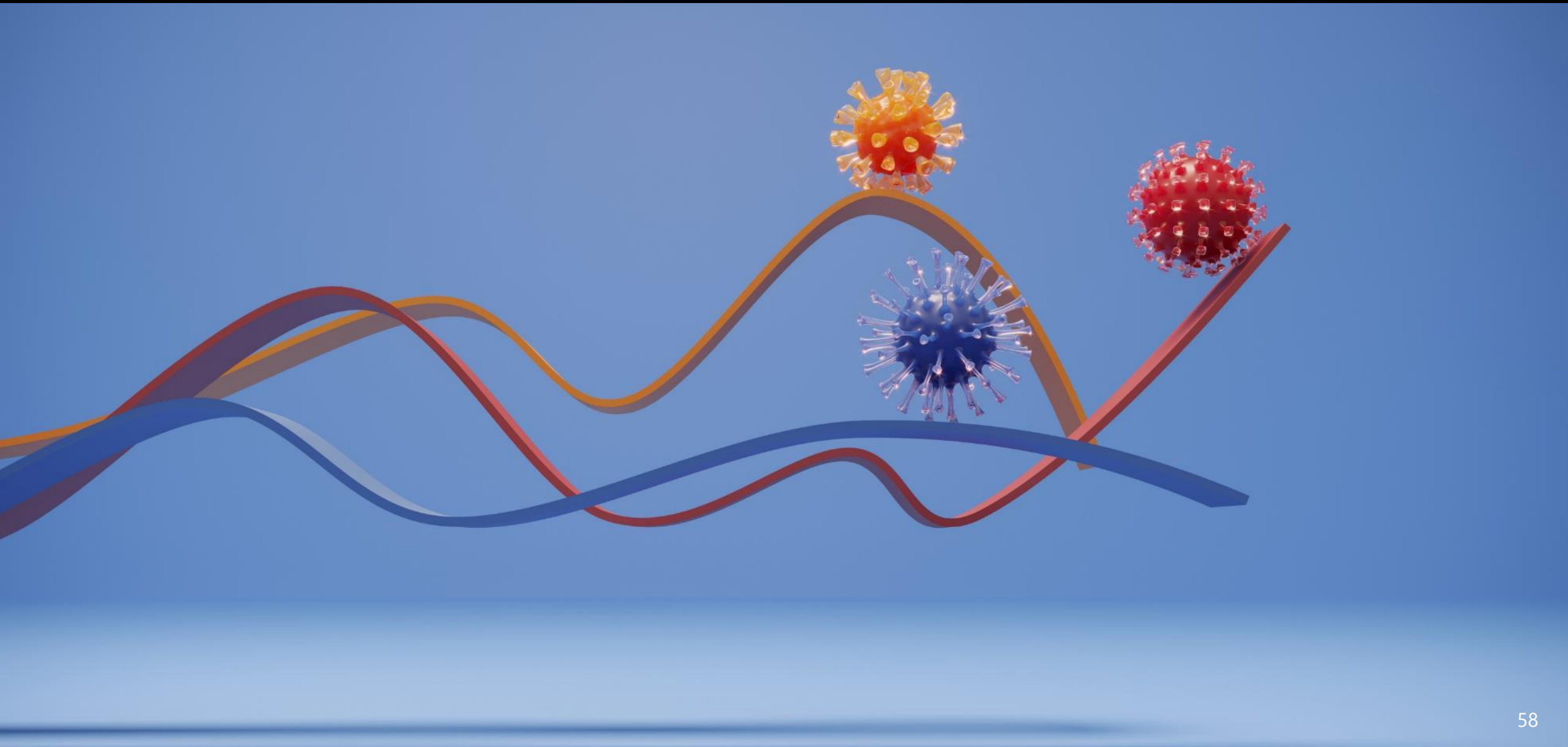
Fig. 1: Whole-brain cerebral blood flow maps for baseline versus one-day post-treatment, plus the difference map (cluster-corrected, $p < 0.05$, $n = 16$). Correlation chart shows post-Treatment changes in bilateral amygdala CBF versus changes in depressive symptoms ($r = 0.59$, $p = 0.01$). One patient failed to completed the scan 2 QIDS-SR16 rating, reducing the sample size to $n = 15$ for the correlation analysis. In all of the images, the left of the brain is shown on the left.





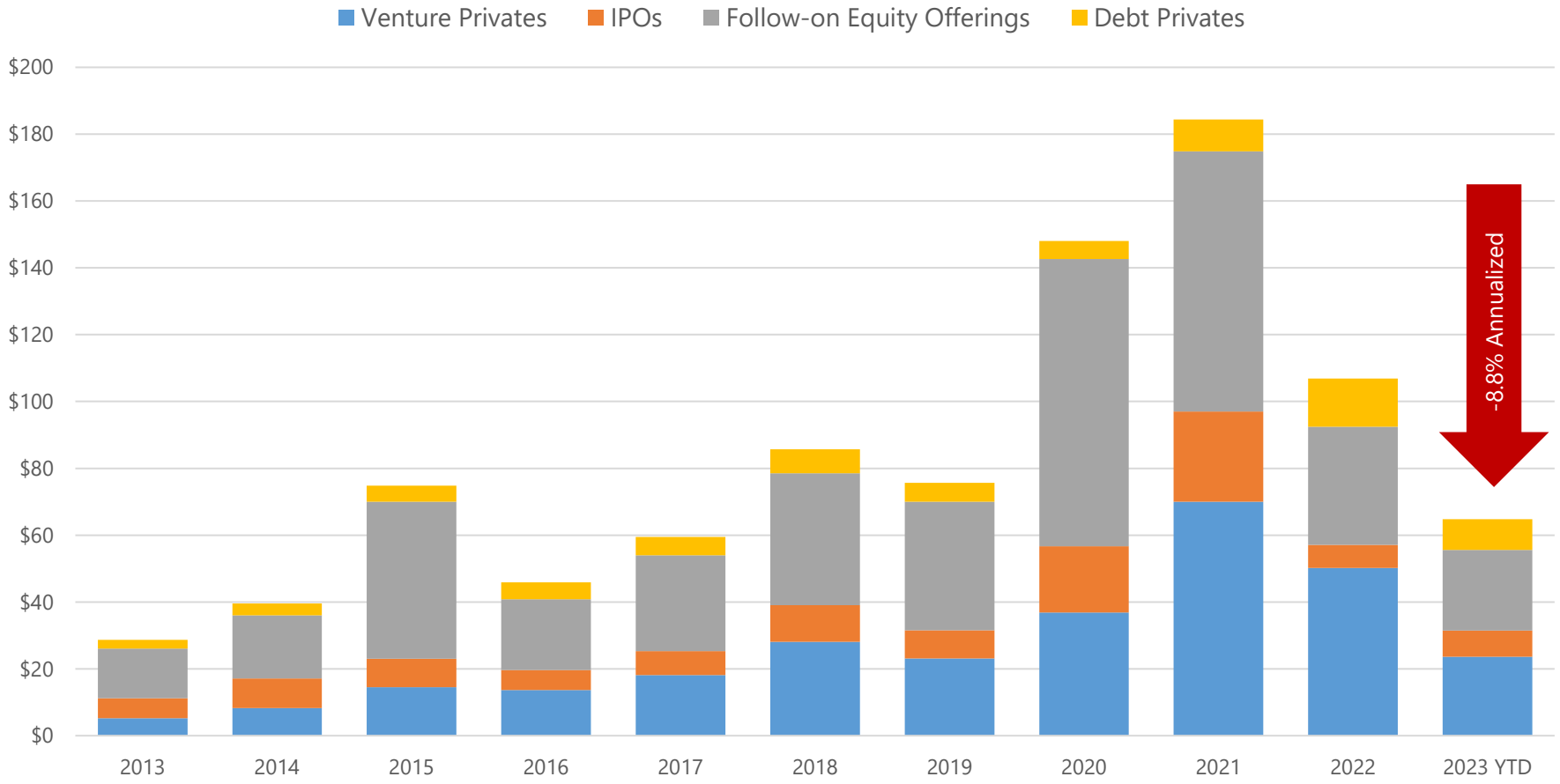
Source: https://pubmed.ncbi.nlm.nih.gov/29030624/

Capital Markets Environment



Overall Biopharma Capital Raised Thus Far in 2023 on an Annualized Basis Is Down 8.8% Versus 2022

Equity Raised, Private Debt Raised in the Biopharma Sector, 2013 - Sep 1, 2023
($ Billions, Worldwide)



Venture privates' volume and IPO volume this year has been down quite substantially compared to 2021 and 2022.

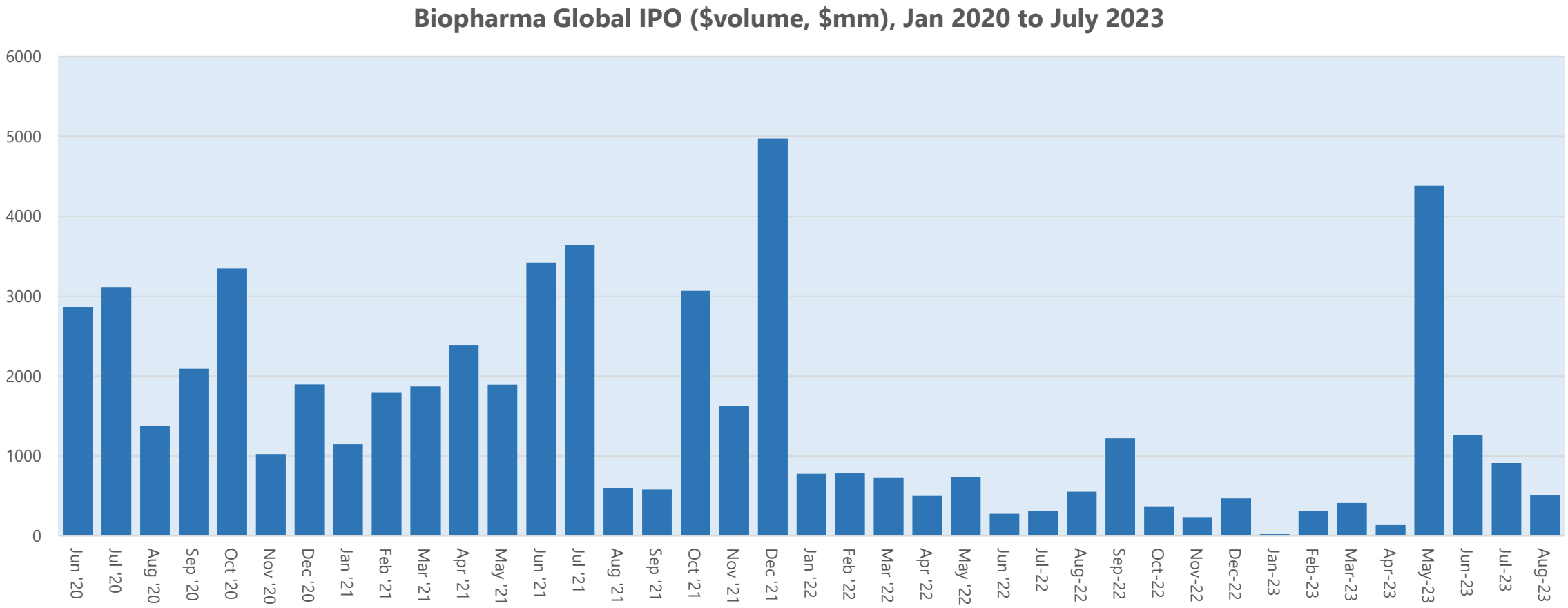
In contrast, the pace of follow-on equity offerings is on pace to exceed that of 2022.

While signs of market improvement have appeared in recent months the markets have been softer in 2023 than in 2021 and 2022.

Source: CapitalIQ and Stifel research

IPO Volume Soft in August

The last two weeks saw no biopharma IPO's get done. August, traditionally, is a very slow month and last month's total volume mirrored low August IPO volume seen in 2021 and 2022. A number of companies are on file to hit the road for IPOs after Labor Day.



Source: Data from CapitalIQ and Stifel research.

Handful of Biotechs Expected to IPO This Fall, But Many Are Stuck in 'Holding Pattern' Until 2024

Kyle LaHucik, Endpoints News, Aug 30, 2023

A pair of late-stage biotechs submitted IPO plans last week as industry insiders gear up for what could be a handful of post-Labor Day public debut pitches.

To repeat: That's a handful of IPOs, not an overflowing basket of filings like the days of 2021 that saw at least 100 biotech IPOs. But any sign of biotechs lining up to ring the trading floor bell could give hope to their privately-held fellows. If members of the fall class and the late July cohort are successful in their first few months of trading, then more startups may have the confidence to pursue public markets next year.

After a brutally quiet first half, the number of biotech IPOs began to inch up this summer. Most experts have pointed to Labor Day as the true start to this year's biotech IPO window, though companies are still grappling with shifting investor appetites, cruelly high interest rates and declining valuations."

The opportunity cost of a dollar for any buyer in biotech right now is really high because the palette of options, the menu of options, is wide, diverse and relatively cheap," said Zavain Dar, co-founder of VC firm Dimension.

Last week's IPO pitches, from brain diseases drugmaker Neumora and radiopharma startup RayzeBio, are both viewed as relatively less risky bets because they have assets in, or about to enter, Phase III trials."

I wouldn't be surprised if people have pumped the brakes just to see how the post-Labor Day market plays out and how Rayze and Neumora trade," said Ray Camahort, partner in Novo Holdings' venture investments group.

Source: https://endpts.com/handful-of-biotechs-expected-to-ipo-this-fall-but-many-are-stuck-in-holding-pattern-until-2024/

Viking to Benefit From Biopharma IPO

Stephen Taub, Institutional Investor, Aug 31, 2023

Another fledgling biopharma company is planning to go public.

And Viking Global Investors is potentially the biggest beneficiary of the offering.

RayzeBio on Friday filed plans for an initial public offering. It did not disclose the number of shares it plans to offer or the price range it is seeking.

The company stated in its filing it is building a radiopharmaceutical therapeutics company whose lead program is currently a Phase 3 clinical trial. "Much like antibody drug conjugates emerged as a new and transformative treatment modality in certain cancers, we see an opportunity for innovative radiopharmaceutical therapeutics to follow a similar path," it elaborated in the filing.

It is currently enrolling its lead drug candidate, RYZ101, in a registrational Phase 3 clinical trial for the treatment of gasteroenteropancreatic neuroendocrine tumors, according to the company.

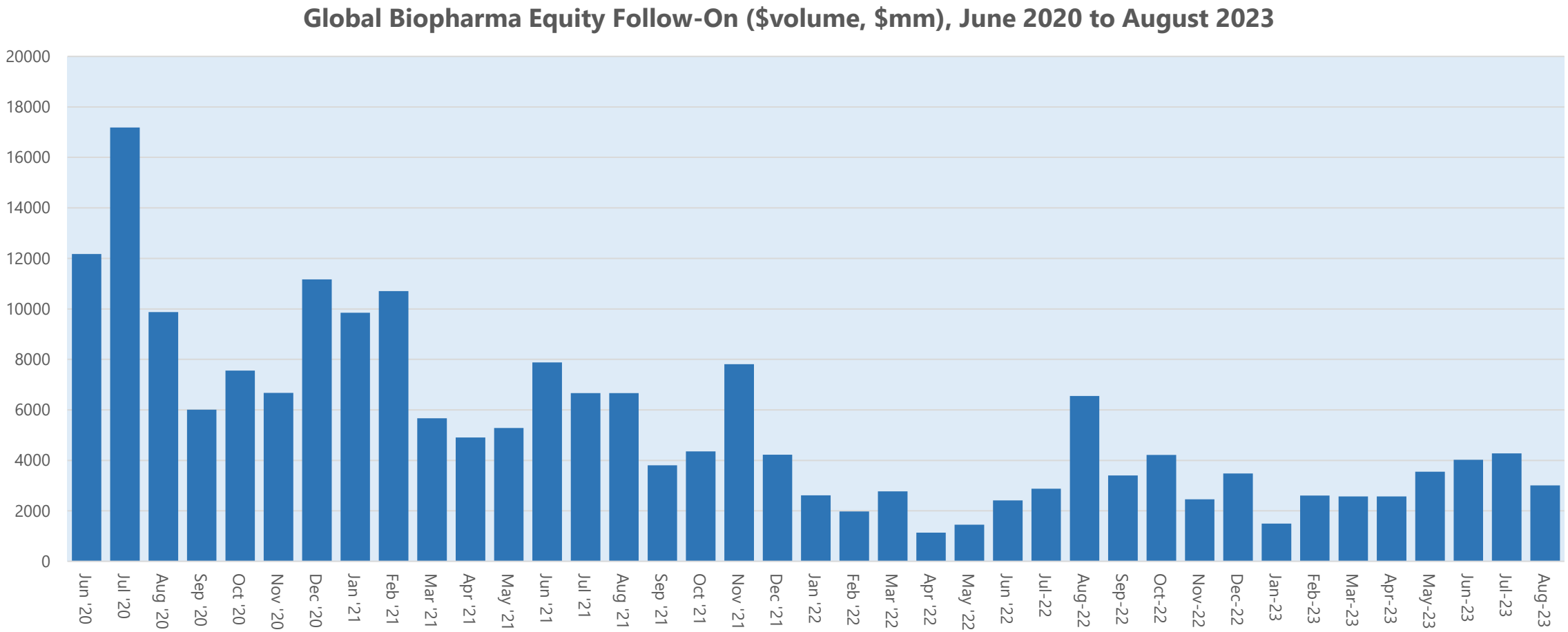
Viking, headed by Tiger Cub O. Andreas Halvorsen, is the largest shareholder with 12.5 percent of the shares, according to the filing.

The fund, which invests in privates and public securities, is up 15.8 percent this year through July, according to a person who has seen the results.

Source: https://www.institutionalinvestor.com/article/2c4pcy9rax65r8ele2mf4/premium/viking-to-benefit-from-biopharma-ipo

Follow-On Offering Volume Down a Bit Last Month

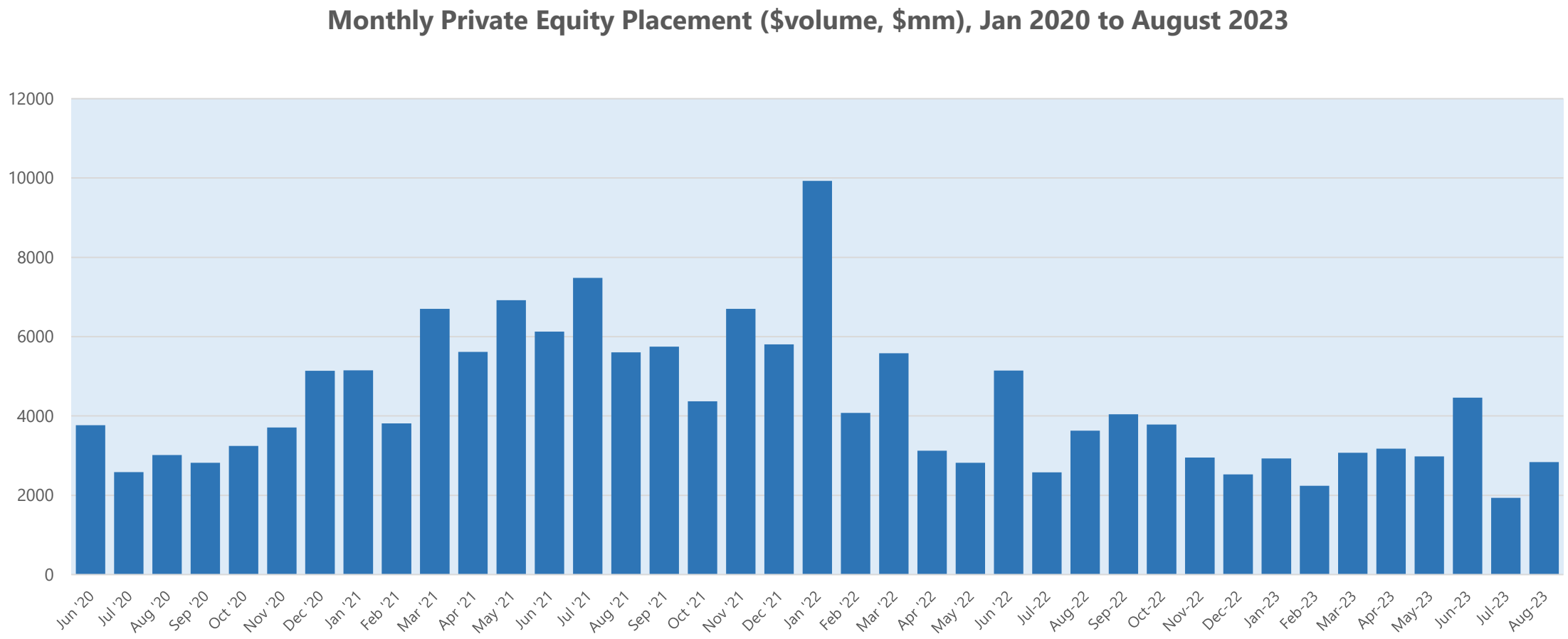
Last month saw $3 billion of follow-on equity financings complete. Volume was down about 25% from June and July. Given current favorable economic conditions, we expect to see a pick up in follow-on volume this Fall.



Source: Data from CapitalIQ and Stifel research.

Monthly BioPharma Private Equity / Venture Placement Volume Was Around $3 Billion in August.

August saw roughly $3 billion get raised in the venture equity marketplace. This pace tracks other months of the year. While volumes are down from 2021 the venture equity market remains open, robust and ready to do business.



Source: Stifel internal database, CapIQ, Crunchbase

Top Biopharma Venture Equity Financings in August 2023

Six announcements in August involved raises over $100mm. Bain and TCGX were the most active investors.

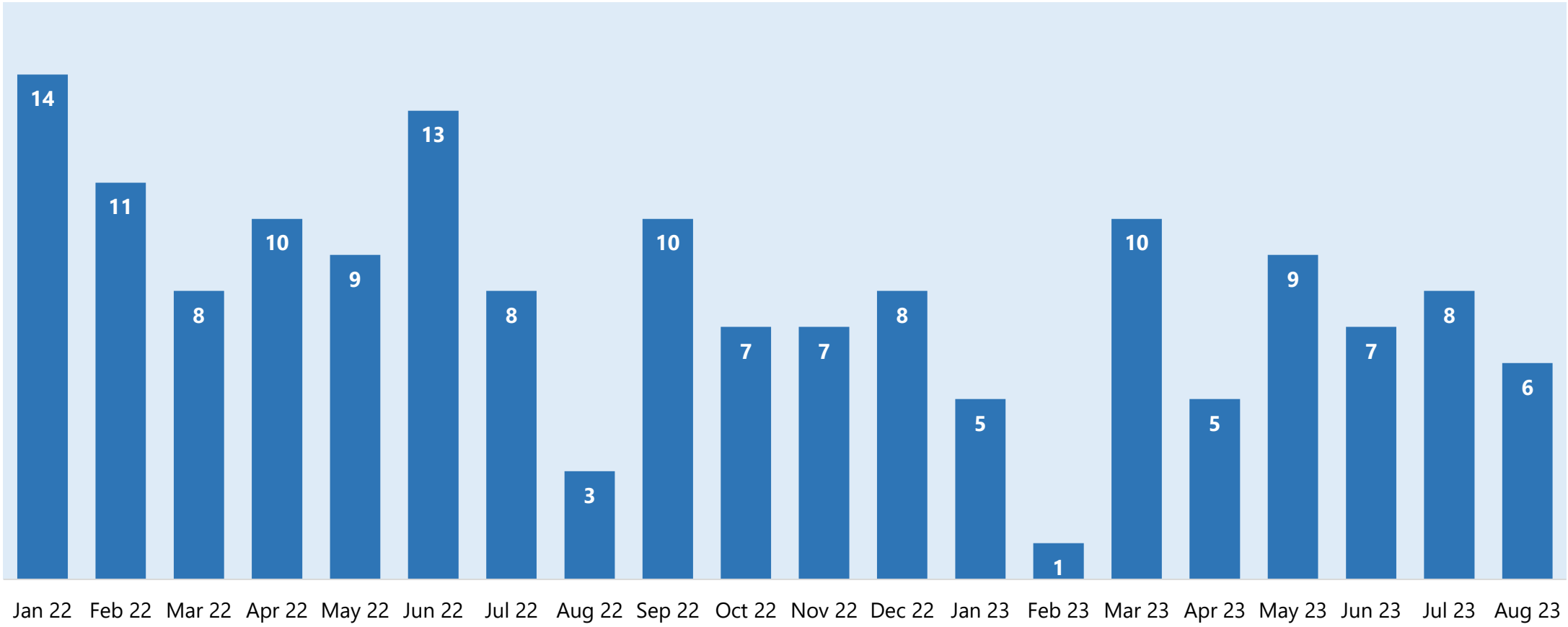
Company	Announcement Date	Amount Raised ($mm)	Round	Lead Investor	Stage at Funding	Primary TA	Company Focus	Modality / Technology	Pre-Money Valuation ($mm)	HQ Country
ADARx PHARMACEUTICALS	8/09/2023	$200	Series C	Bain & TCGX	Platform / Discovery	Rare Disease	siRNA for rare diseases	RNA	NA	United States
Genesis Therapeutics	8/21/2023	$200	Series B	Andreesen Horowitz + undisclosed	Phase II	Cancer and others	3D spatial graph modeling and simulation for drugs	Small Molecule	$56.1	United States
abcuro	8/17/2023	$155	Series B	Redmile and Bain	Phase I	Immunology	KLRG1 mAb for inclusion body myositis	Antibodies	NA	United States
rapport therapeutics	8/23/2023	$150	Series B	Cormorant Asset Management	Phase I	Neurology	Precision neuroscience drugs	Small Molecule	$100	United States
alltrna	8/09/2023	$109	Series B	Flagship	Platform / Discovery	Rare Disease	tRNA platform company for stop codon diseases	RNA	$50	United States
CG ONCOLOGY Attacking Bladder Cancer for a Better Tomorrow™	8/02/2023	$105	Series F	Foresite & TCGX	Phase III	Cancer	Immunotherapy	Oncolytic Virus	$200	United States
Neurophth 纽福斯	8/11/2023	$95	Series C	CMD and others	Preclinical	Ophtha	Gene Therapy for LHON	Gene Therapy	NA	China
Georgiamune	8/09/2023	$75	Series A	General Catalyst, Parker Inst	Phase I	Cancer	Bispecific to trigger immune attack	Antibodies	NA	United States

Source: Data from DealForma, Stifel research for deals where $75mm or more was raised.

Count of Venture Equity Raises of $100mm+ in Last 20 Months

The six announcements in August involved raises over $100mm compared to an average of 6.3 / month this year and 9 / month in 2022.

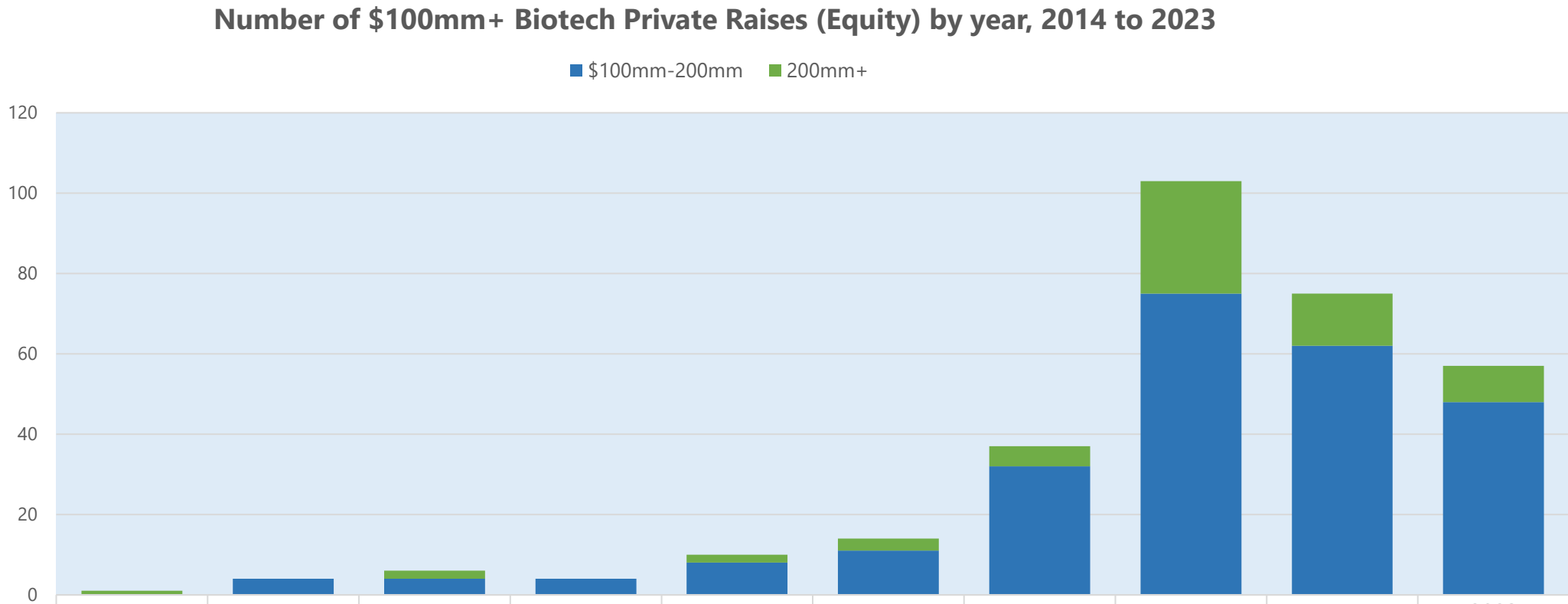
Number of $100 million+ Biotech Private Raises (Equity), January 2022 to August 2023



Source: DealForma

Count of Venture Equity Raises of $100mm+ in Last 10 years

We are at a run rate of around sixty $100mm+ raises a year in 2023. This is well below the pace of 2021 and 2022 but above all other previous years.



	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023 Annualized
200mm+	1		2		2	3	5	28	13	9
$100mm-200mm		4	4	4	8	11	32	75	62	48

Source: DealForma

Saudi Arabia Is Dangling Billions for Research on Aging. Scientists Are Lining Up to Take It.

Stephen Kalin, *Wall Street Journal*, Aug 31, 2023

Crown Prince Mohammed bin Salman, the de facto Saudi ruler, has allocated more than a billion dollars a year to an effort called Hevolution Foundation to develop new treatments for aging. That could dramatically expand the available global funding for research on longevity biology, which now comes mainly from the U.S. National Institute on Aging.

The prospect of a huge surge of funding into the area, whose budgets pale in comparison to research on diseases like cancer, is causing a stir among scientists who study aging.

"People in the field are kind of holding their breath to see how the money is going to be spent," says Steven Austad, a researcher on aging at the University of Alabama at Birmingham and senior scientific director at the American Federation for Aging Research, or AFAR, a U.S. nonprofit that has received $7.76 million in funding from Hevolution.

The Saudi foundation's chief executive, Dr. Mehmood Khan, says much of the initial grant money is likely to end up at universities and startups in the U.S., where scientists are trying to develop treatments that slow, prevent or even reverse the aging process for humans.

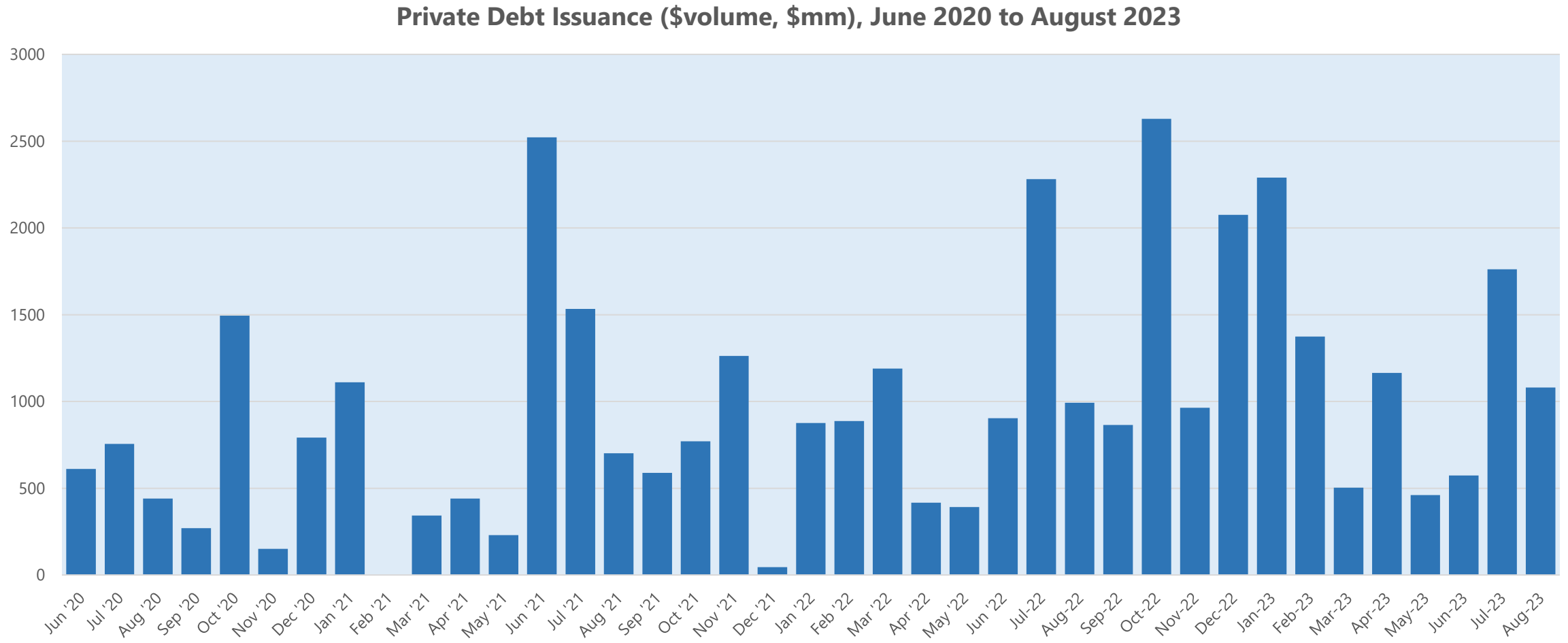
"We're sort of doing the nontraditional approach. Who else might be able to solve the problem?" says Khan, the chief executive. "One of our goals is to actually attract new scientists—in terms of entering science—and scientists from adjacent fields that may not have data but their technologies could be relevant to solving."

Since starting operations in July 2022, the Saudi foundation has focused mostly on establishing itself, dispersing less than $20 million. Khan expects that to ramp up toward $1 billion within the next two to four years. Initially, more of that money will go to research, but eventually the goal is for a roughly even split with investments into antiaging startups, he says.

Source: https://www.wsj.com/science/biology/saudi-arabia-is-dangling-billions-for-research-on-aging-scientists-are-lining-up-to-take-it-7f459eff

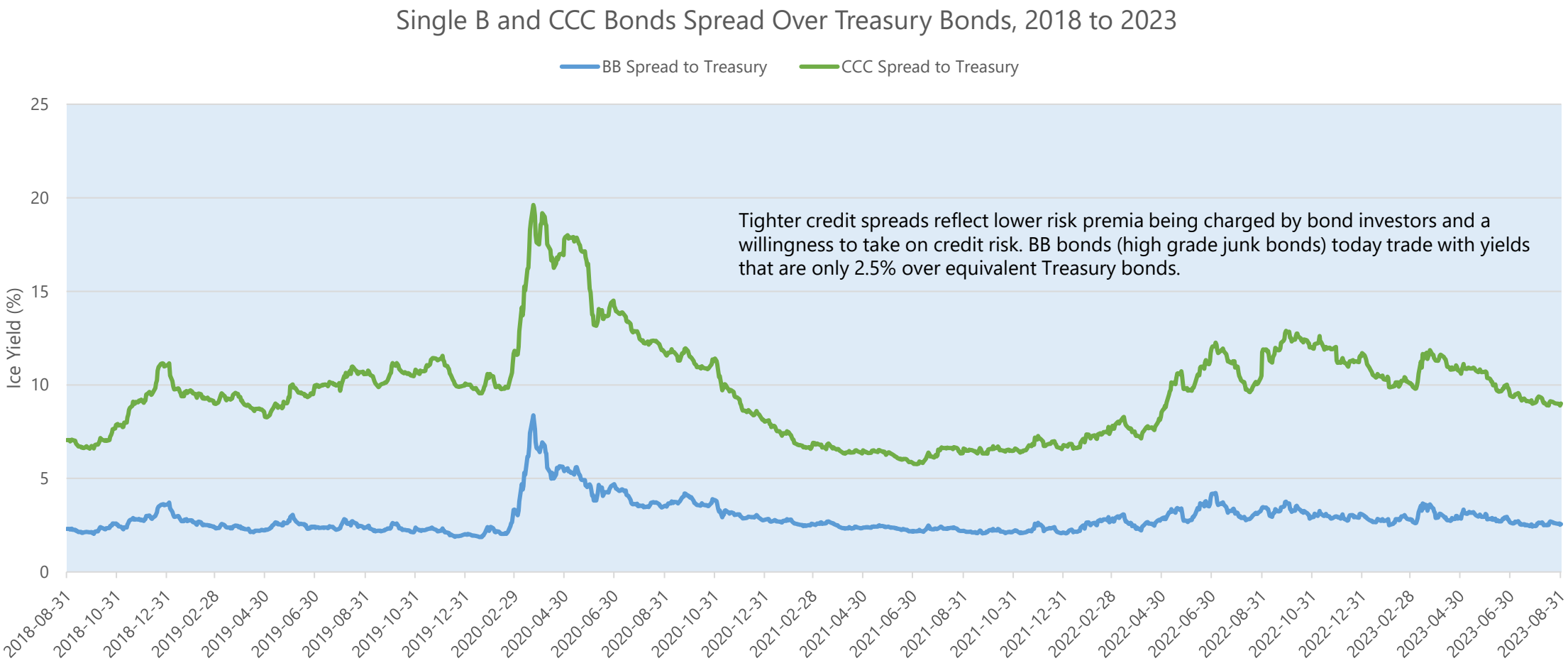
Biopharma Private Debt Volume Solid Last Month

Last month saw over $1 billion in deal volume in the private debt market for biopharmas. This was the fourth strongest month of the year.



Source: Data from CapitalIQ, Crunchbase.

Credit Market Conditions Have Improved Substantially in Recent Months

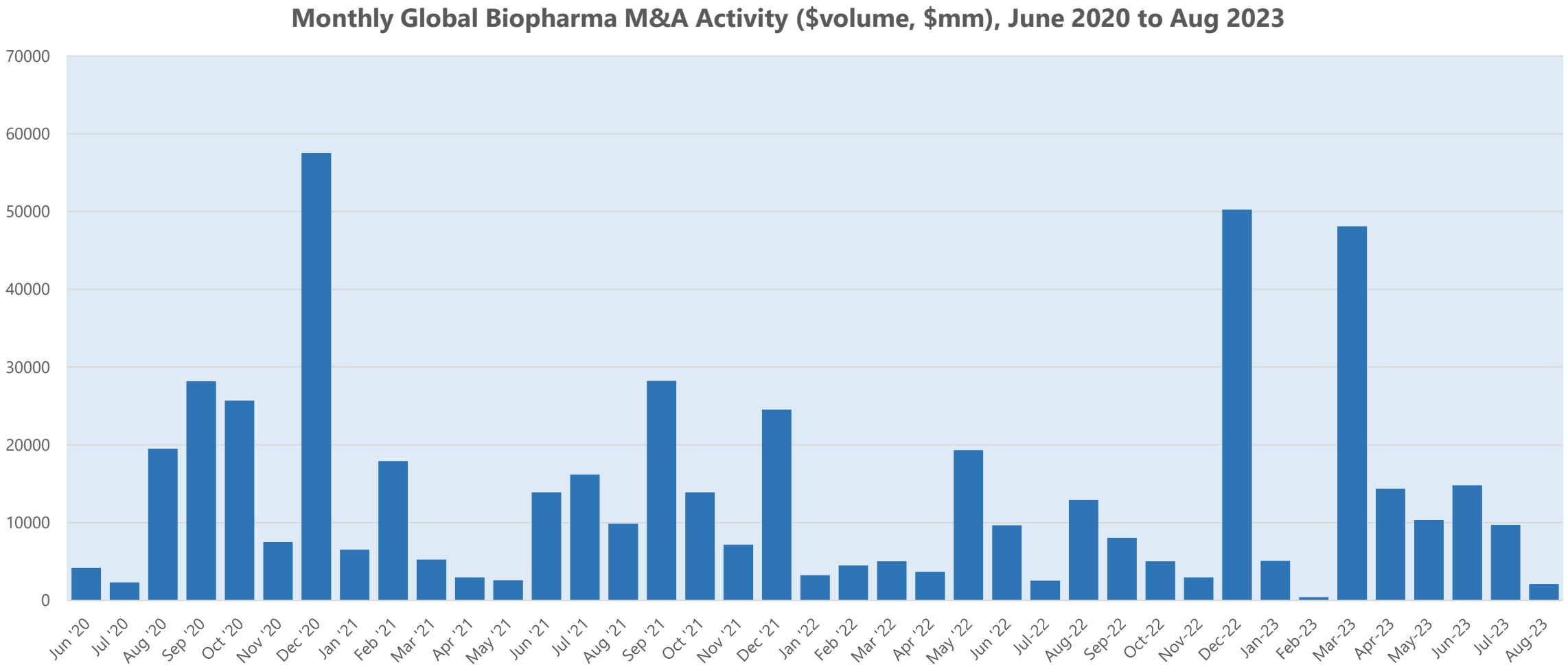


Source: Federal Reserve Bank of St. Louis (FRED)

Deals Update

Last Month Saw $2 Billion in M&A Volume

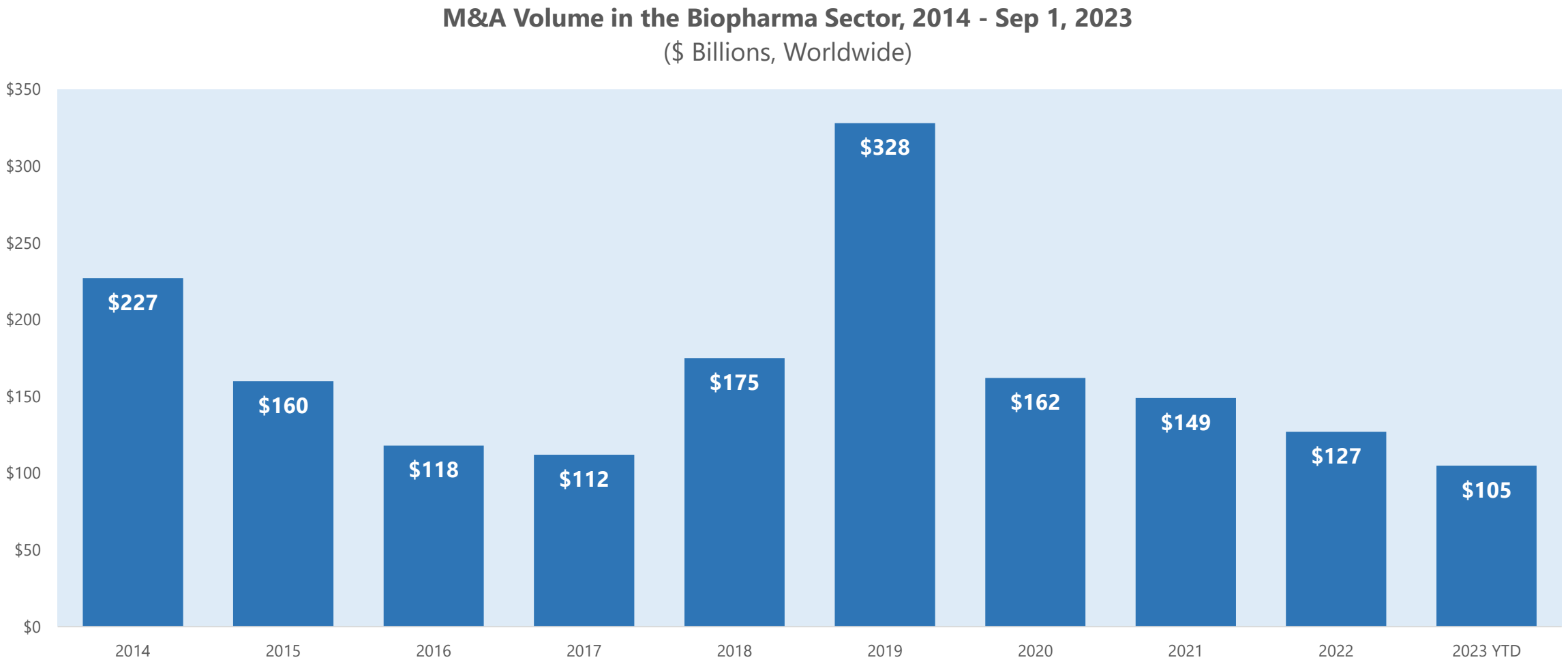
The last two weeks saw very little biopharma M&A volume. Volume for the month of August was down considerably from levels seen earlier in the year.



Source: S&P, CapitalIQ

So Far, We Have Seen $105 Billion in M&A in 2023

We have seen $105 billion in M&A volume (announced deals) so far this year. This puts us on pace for a $158 billion year.



Source: S&P, CapitalIQ

Otsuka Pharmaceutical to Acquire Mindset Pharma for $59 Million

September 1, 2023 -- Otsuka Pharmaceutical Co., Ltd. (Otsuka) and Mindset Pharma, Inc. (Mindset) announce that they have entered into a definitive arrangement agreement pursuant to which Otsuka will acquire Mindset for approximately CAD 80 million in an all-cash transaction. This agreement has been executed through Otsuka America, Inc. (OAI), a wholly owned subsidiary of Otsuka. The Otsuka and Mindset boards of directors have approved the transaction. The acquisition is expected to be completed during the fourth quarter of 2023, subject to required procedures.

Mindset is a drug discovery-based research and development company with exceptional expertise in the research and development of the next generation of therapeutics to help treat psychiatric and neurological disorders with high unmet needs. In January 2022, Mindset and The McQuade Center for Strategic Research and Development, LLC (MSRD), an affiliate of Otsuka that invests in early-stage research programs, entered into a joint development agreement to support Mindset's research and develop a new class of agonists that activate the serotonin 5-HT2A receptor. Since the signing of the joint development agreement between Mindset and MSRD, the two companies have been working together to develop new compounds. The serotonin 5-HT2A agonist being developed through this collaboration is attracting attention as a potential therapy for treatment-resistant depression and post-traumatic stress disorder (PTSD), and is expected to be a major innovation in the field of psychiatric and neurological disorders, where clear unmet medical needs remain.

James Lanthier, CEO of Mindset said, "We are thrilled to announce this all-cash transaction with Otsuka as we believe it maximizes value and is a great outcome for all Mindset stakeholders. We believe Otsuka is ideally positioned to maximize the value of the Mindset assets and IP portfolio to the future benefit of patients."

Source: https://www.otsuka.co.jp/en/company/newsreleases/2023/20230901_1.html

Novo Nordisk Buys Embark for €15mm Upfront

COPENHAGEN, Denmark, Aug. 30, 2023 /PRNewswire/ -- Embark Laboratories announced today that Novo Nordisk has acquired Embark Biotech, including its lead metabolic program, and has entered a three-year research and development collaboration to discover and develop novel pharmaceuticals to treat obesity and related co-morbidities.

Under the acquisition agreement for Embark Biotech, Novo Nordisk receives the full rights to develop and commercialize the lead program, while the Embark shareholders will receive 15 million Euro in an upfront cash payment and are eligible to receive potential development, regulatory, and commercial milestones of up to 456 million Euro.

The research and development collaboration with Embark Laboratories provide Novo Nordisk with the option to acquire selected assets based on the Embark Biotech discoveries across several indications, including obesity and type 2 diabetes.

Brian Finan, Vice President of Obesity Research at Novo Nordisk, said: "Novo Nordisk has been engaged in obesity research for 25 years, and we continuously search for new ways to address this serious chronic disease. We are excited about the opportunity to advance Embark Biotech's lead program and look forward to co-creating novel treatments for cardiometabolic diseases with Embark Laboratories to complement our in-house R&D,".

Zach Gerhart-Hines, Chief Technology Officer at Embark Laboratories commented: "There is a clear strategic fit between the novel biology we have discovered and Novo Nordisk's expertise and focus on developing new drugs in the cardiometabolic space. We are thrilled to pass on the baton for our lead metabolic program to Novo Nordisk. This deal and Embark's success are direct outcomes of the unique and innovative ecosystem in Denmark that has been cultivated by the BioInnovation Institute and the University of Copenhagen and through initiatives from the Novo Nordisk Foundation and the Innovation Fund Denmark".

Source: https://www.prnewswire.com/news-releases/novo-nordisk-acquires-embark-biotech-including-its-lead-asset-targeting-obesity-and-other-cardiometabolic-diseases-301913476.html

Embark Based on Gerhart-Hines Group at University of Copenhagen

From left to right: Camilla Grauslund, David Tandio, Hannes Elofsson, Lucile Chantal Marie Dollet, Zach Gerhart-Hines, Cecilie Kynding Kristensen, Tao Ma, Iuliia Karavaeva, Astrid Linde Basse, Julius Elliot Nyegaard Grothen, Jacob Bondo Hansen, Jeppe Hvidtfeldt Ekberg, Olivia Sveidahl Johansen, Frederike Sass, Fabian Michael Finger

Research Focus: Signals or cues from the environment, diet, circadian clock, and other organs exert substantial control over the plasticity and function of adipose tissue. The overarching goal of my group is to uncover how these diverse 'inputs' converge on adipocytes to uniquely shape adipose tissue biology and coordinate organismal energy metabolism. Specifically, we focus on identifying cell surface receptors, intracellular enzymes, and transporters that represent key regulatory nodes in influencing adipose tissue catabolism. By combining global gene, protein, metabolite, and lipid profiling with cutting-edge *in vivo* physiological phenotyping and pharmacological engineering, we believe we are ideally poised to make transformative breakthroughs in the basic understanding of adipose biology and to develop innovative strategies for counteracting metabolic disease.

Patent filed on TACR2 Agonist Peptides

Summary of invention

The present disclosure relates to an agonist of Tacr2 or a pharmaceutically acceptable salt thereof for use in treatment of diabetes and/or obesity in an individual in need thereof. The inventors have found that agonists of Tacr2, in particular peptide agonists of Tacr2 are able of activating brown and beige/brite adipose tissue independently of norepinephrine (NE)/β-adrenergic receptor signalling. The invention discloses that administration of agonists of Tacr2 to an individual has a multiplicity of effects on brown and beige adipocytes, which are beneficial in treatment of obesity and diabetes. In particular, agonists of Tacr2 cause an increase in oxygen consumption rate, and preferably also in glucose absorption, oxygen consumption rate, energy consumption and heat production in brown and beige adipocytes. Preferably, agonists of Tacr2, in particular peptide agonists of Tacr2, result in activation of brown adipose tissue, without causing deleterious side effects such as elevated blood pressure and heart rate

Sources: https://cbmr.ku.dk/research/research-groups/gerhart-hines-group/, https://patents.google.com/patent/WO2021073742A1

Zevra Therapeutics to Acquire Acer Therapeutics For $15mm Upfront

CELEBRATION, Fla. and NEWTON, Mass., Aug. 31, 2023 (GLOBE NEWSWIRE) -- Zevra Therapeutics, Inc. (NasdaqGS: ZVRA) ("Zevra"), a rare disease company melding science, data and patient need to create transformational therapies for diseases with limited or no treatment options, and Acer Therapeutics Inc. (Nasdaq: ACER) ("Acer"), a pharmaceutical company focused on development and commercialization of therapies for rare and life-threatening diseases, today announced the companies have entered into a definitive agreement pursuant to which Zevra would acquire Acer in a merger transaction having a total potential value for Acer stockholders of up to $91 million, consisting of (i) approximately 2.96 million shares of Zevra common stock valued at $15 million, or 0.121 shares of Zevra's common stock per share of Acer common stock based on the volume weighted average trading price (VWAP) of shares of Zevra's common stock during the 20 consecutive trading days ending on the trading date prior to today, and (ii) up to an additional $76 million in a series of potential cash payments pursuant to non-transferable Contingent Value Rights (CVRs) upon achievement of certain commercial and regulatory milestones for Acer's OLPRUVA (sodium phenylbutyrate) and Acer's EDSIVO (celiprol) within specified time periods. Certain additional cash payments are also possible pursuant to the CVRs with respect to milestones involving Acer's early-stage program ACER-2820 (emetine), as described further below. Zevra has also purchased Acer's secured debt at a discount from Nantahala Capital (Nantahala) through a series of transactions in capital efficient structure. In addition, Zevra has agreed to provide Acer with a bridge loan facility for up to $16.5 million, subject to certain terms and conditions. Both companies are deeply committed to developing and commercializing treatments for rare diseases with a strong focus on patients and remain dedicated to supporting communities with little or no existing therapeutic options. The merger is expected to expand Zevra's rare disease portfolio, as well as increase and diversify its revenues with the addition of a U.S. commercial asset, OLPRUVA, indicated for the treatment of UCDs. The transaction is subject to certain customary closing conditions, including, but not limited to, approval by Acer's stockholders.

Source: https://www.globenewswire.com/news-release/2023/08/31/2735142/16626/en/Zevra-Therapeutics-to-Acquire-Acer-Therapeutics-Expanding-its-Rare-Disease-Portfolio-and-Adding-Commercial-Product.html

Catalent Reaches Settlement with Elliott to Explore Strategic Review

By Svea Herbst-Bayliss, Maggie Fick and Sriparna Roy, Reuters, Aug 29, 2023

Aug 29 (Reuters) - Contract drug maker Catalent Inc (CTLT.N) said on Tuesday it had added four new directors to its board and will conduct a strategic review after reaching a settlement with activist investor Elliott Investment Management.

The company, which has struggled with manufacturing problems at three plants and has been the target of takeover interest from both private equity firms and strategic buyers in recent months, also reported a double-digit drop in quarterly revenue.

"We have the right strategy in place," Catalent Chief Executive Officer Alessandro Maselli said on a call with analysts after the announcement in which executives said more cost-cutting measures would come. The company has been working to improve "rigor and discipline" in its financial forecasting process, he added.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/catalent-revenue-falls-delays-annual-report-2023-08-29/

J&J's $40 Billion Split-Off Sets Stage for Pharma, Medical Tech Expansion

Mark Mauer, Wall Street Journal, September 4, 2023

Johnson & Johnson plans to tap billions in proceeds from the recent split-off of its consumer-health business to fuel growth in pharmaceuticals and medical technology through capital allocation, which could include new acquisitions and investments in product offerings and robotics.

The New Brunswick, N.J.-based healthcare giant in May sold shares in Kenvue, which owns brands such as Band-Aid and Tylenol, through an initial public offering that netted J&J $13.2 billion in cash. In August J&J shed about 80% of its Kenvue shares through a roughly $40 billion split-off, whereby some investors chose to trade in their shares of J&J for Kenvue ones.

The moves marked the conclusion of a multiyear effort, a plan decided upon in 2019 and put into action in 2021 when J&J embarked on untangling its finances and operations for such a split.

The split allows J&J's executives to focus more on developing innovations and expanding the businesses of medical technologies and pharmaceuticals. "We need to be a top-tier medical tech company and a top-tier pharmaceutical company, first and foremost," Chief Financial Officer Joseph Wolk said. "That is what's going to carry us for the medium term."

J&J's targets for acquisitions are businesses with scientific expertise and commercial capabilities that could benefit from J&J's global reach, Wolk said. The company's growth will continue to stem from a 50-50 split between organic, in-house development and expansion through acquisitions and partnerships, as it has historically, he said.

Source: https://www.wsj.com/articles/j-js-40-billion-split-off-sets-stage-for-pharma-medical-tech-expansion-817701c1

India’s Biggest-ever Pharma Deal in the Making? Torrent Seeks Financiers to Buy Cipla Promoters’ Stake, Claims Report

Business Today, Sep 1, 2023

Amedabad-based Torrent Pharma is interested in buying out top shareholder Hamied family's 33.47 per cent stake in Cipla and is trying to put together financing for the purchase, a media report said, citing several people with knowledge of the matter. This would be the largest pharma sector acquisition in the country till date, the report said, adding that the acquisition would include a likely Rs 8,300 crore ($1 billion) equity infusion from one or more private equity players.

The company has reached out to several private equity firms including Advent International, Bain Capital, Warburg Pincus and CVC Capital, for a minority stake in a consortium, The Economic Times reported. Additionally, it is also in talks with foreign banks such as Standard Chartered and JP Morgan for acquisition financing, and domestic shadow banks and mutual funds in share-backed promoter financing, the report added.

Meanwhile, Torrent Pharmaceuticals on Friday said it has no information requiring disclosure under listing regulations.

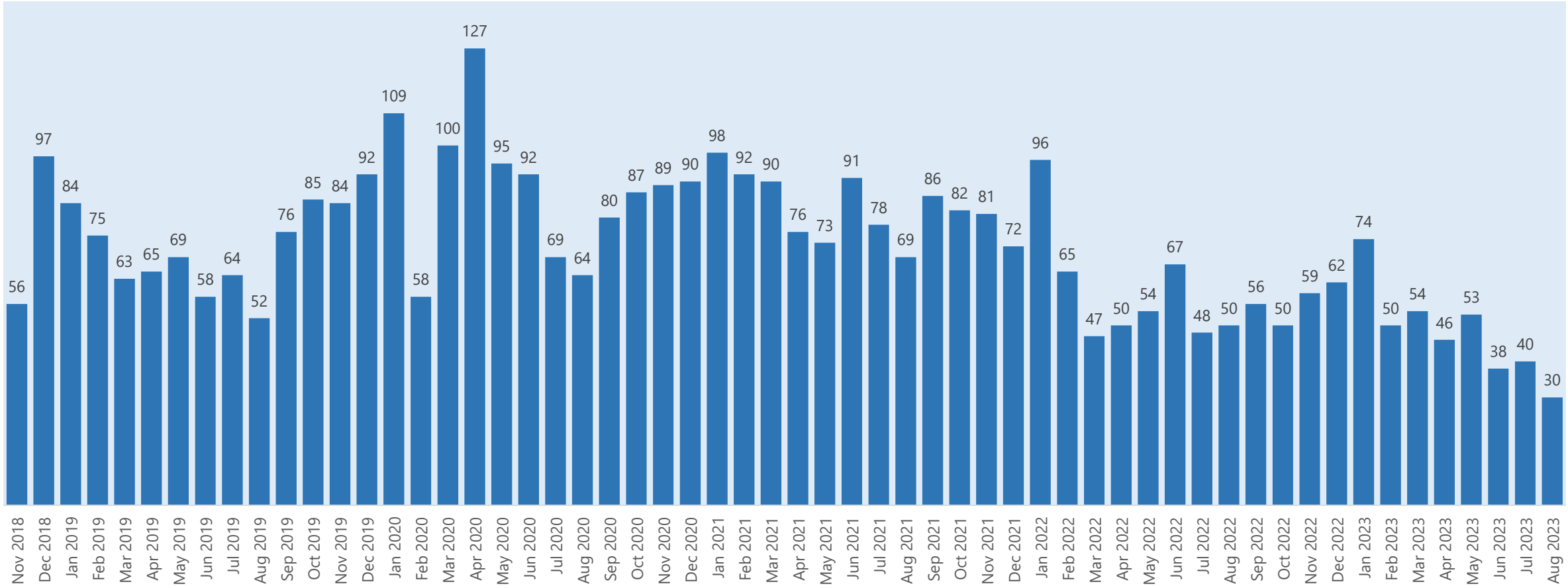
Torrent said it “does not comment on speculative reports in the absence of verified data,” and that it was not in a position to comment on the movement in its share price.

Source: https://www.msn.com/en-in/money/topstories/indias-biggest-ever-pharma-deal-in-the-making-torrent-seeks-financiers-to-buy-cipla-promoters-stake-claims-report/ar-AA1g5iQC

August 2023 Partnership Deal Count the Lowest in a Long Time

Licensing and partnership deal activity in the biopharma sector was unusually low in August. This largely reflects the lack of cross-border activity and withdrawal of mid and small cap companies from the license market.

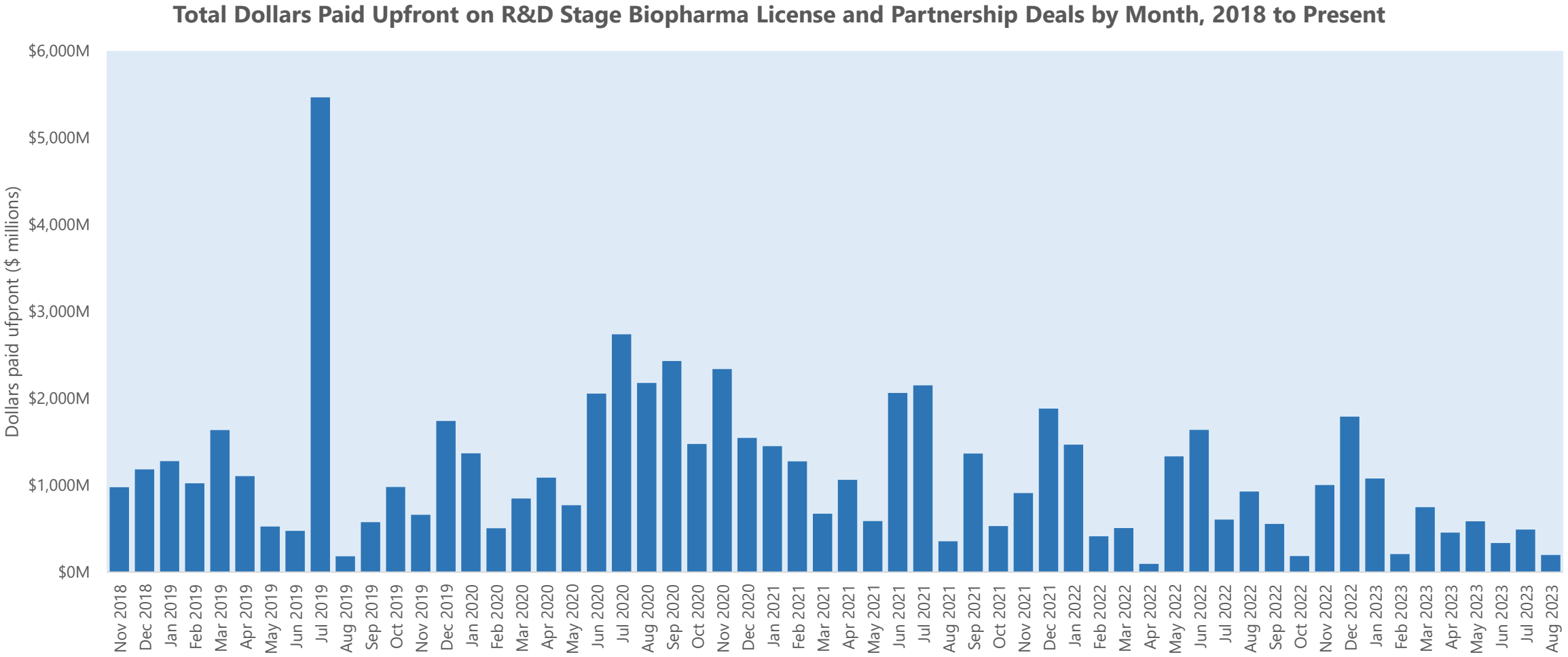
Monthly Count of R&D Stage Biopharma License and Partnership Deals, 2018 to Present



Source: DealForma

August 2023 Saw Less Than $200mm Paid in Licensing Deal Upfronts

Disclosed upfronts paid in licensing / partnership deals were quite light in August reflecting the relatively moribund partnership marketplace.



Source: DealForma

Disclosure

STIFEL | Healthcare

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