Biopharmaceutical Sector

Weekly Update – November 6, 2023

STIFEL | Healthcare

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STIFEL | Healthcare

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Past Issues / Mailing List

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:

October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Changing Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

Join Us at These Upcoming Events

Biotech Hangout held its latest event on November 3rd.

The next event will be on November 10, 2023.

Some links:

November 3rd Replay: https://twitter.com/i/spaces/1dRJZEwjBAMGB

November 10th Session: https://twitter.com/i/spaces/1PlJQDwrWLNGE

Please join us.

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

BIO-Europe convenes over 5,500 attendees, representing 60 countries and 2,220+ companies, making the event the industry's largest gathering of biopharma professionals in Europe.

To Learn More
https://informaconnect.com/bioeurope/

Macro Update

Positive Jobs Report

Talmon Joseph Smith, *New York Times*, Nov 3, 2023 (excerpt)

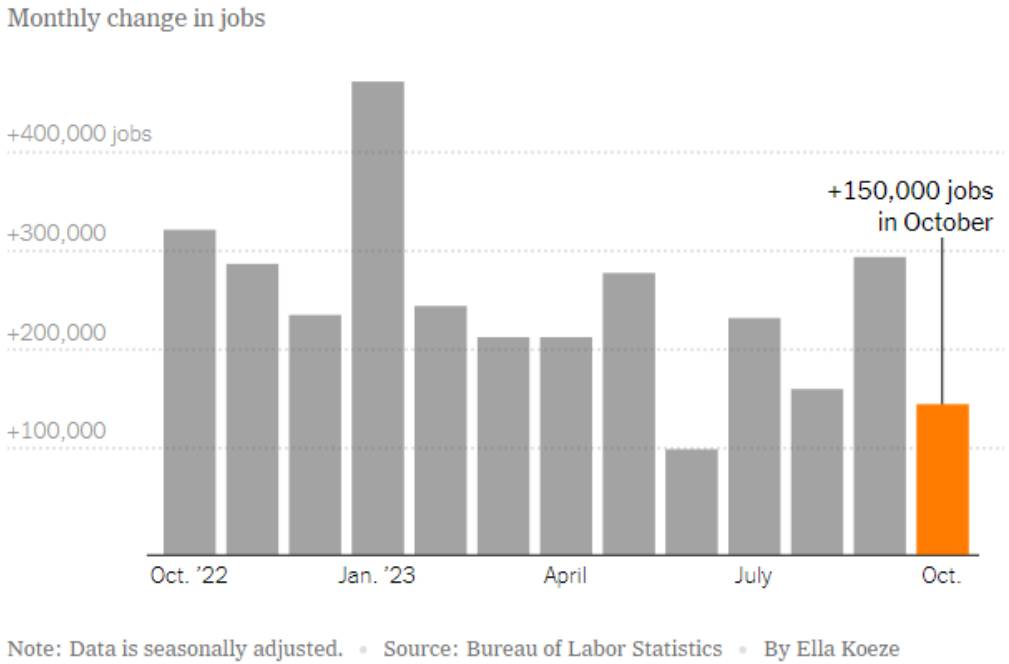
The labor market has been relentlessly hot since the U.S. economy began to recover from the shock of the pandemic. But there are signs of cooling as the holidays approach.

Employers added 150,000 jobs in October on a seasonally adjusted basis, the Labor Department reported on Friday, a number that fell short of economists' forecasts.

Hiring figures for August and September were revised downward, subtracting more than 100,000 jobs from earlier reports. And the unemployment rate, based on a survey of households, rose to 3.9 percent from 3.8 percent in September.

Markets reacted positively to the news. The signs of recent cooling reinforced expectations that the Federal Reserve would hold off on further interest rate increases in its fight against stubborn inflation. Bond prices rose, and stocks delivered a fifth straight day of gains.

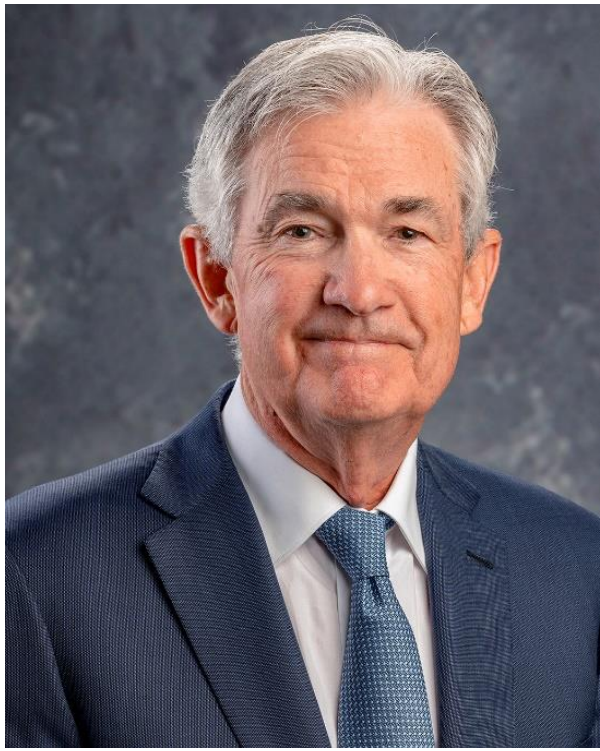
Because they worry that rapidly growing incomes can spur higher prices, Fed policymakers have been encouraged by recent decelerations in wage growth. The Labor Department report showed average hourly earnings up 0.2 percent in October from the previous month, slightly less than expected, and 4.1 percent higher than a year earlier.



Source: https://www.nytimes.com/2023/11/03/business/economy/jobs-report-october-2023.html

Federal Reserve Leaves Its Key Rate Unchanged But Keeps Open Possibility of a Future Hike

Christopher Rugaber, *AP News*, Nov 1, 2023 (excerpt)



WASHINGTON (AP) — The Federal Reserve kept its key short-term interest rate unchanged Wednesday for a second straight time but left the door open to further rate hikes if inflation pressures should accelerate in the months ahead.

The Fed said in a statement after its latest meeting that it would keep its benchmark rate at about 5.4%, its highest level in 22 years. Since launching the most aggressive series of rate hikes in four decades in March 2022 to fight inflation, the Fed has pulled back and has now raised rates only once since May.

The central bank's latest statement noted that the economy "expanded at a strong pace" in the July-September quarter and that job gains "remain strong." And it reiterated that future rate hikes, if the Fed finds them necessary, remain under consideration.

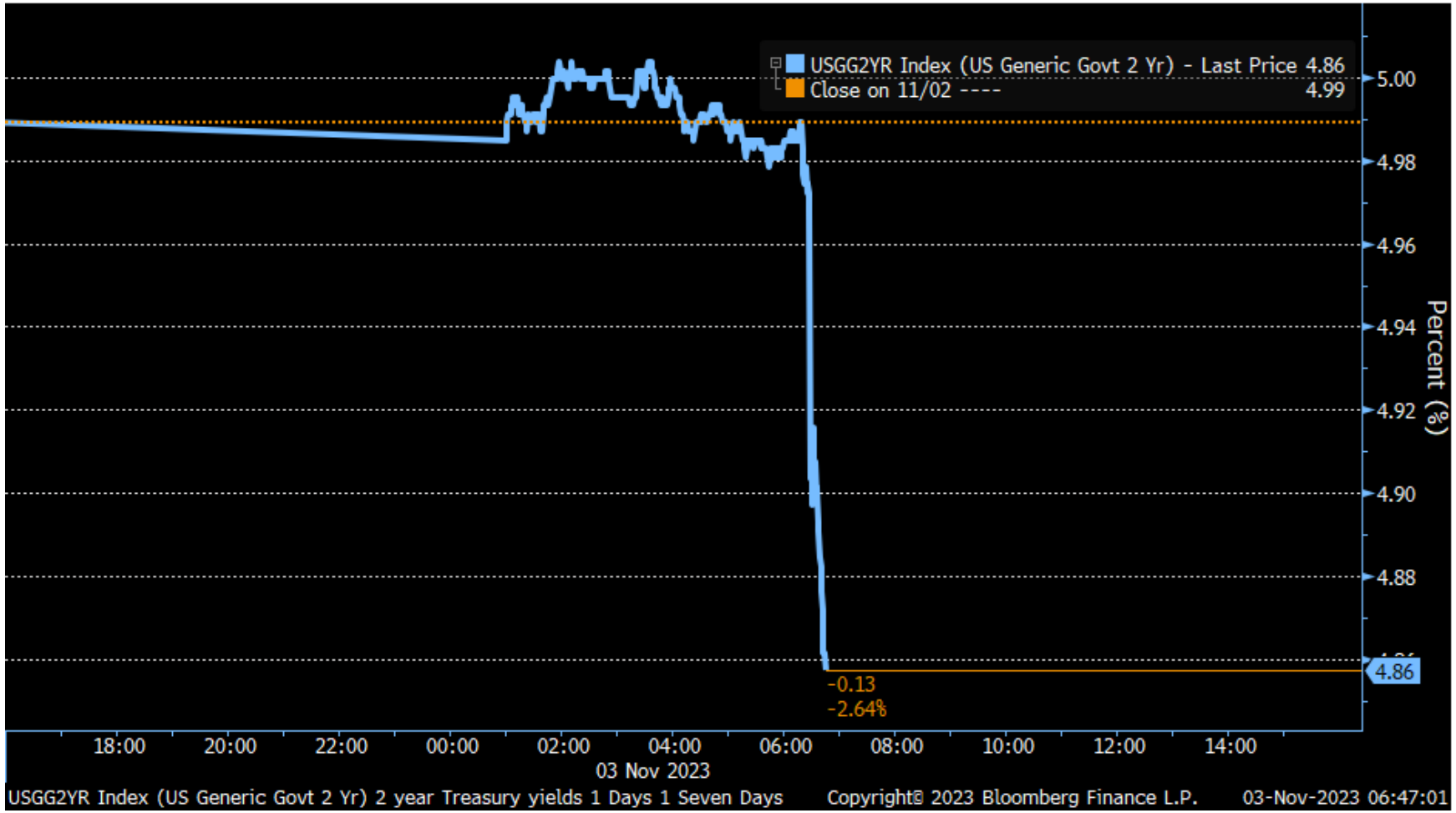
But it also acknowledged that recent tumult in the financial markets has sent interest rates on 10-year Treasury notes to near 16-year highs and contributed to higher loan rates across the economy — a trend that helps serve the Fed's goal of cooling the economy and inflation pressures.

At a news conference, Chair Jerome Powell suggested that the Fed was edging closer to the end of its rate-hiking campaign. He noted that the sharply higher longer-term rates could help lower inflation without necessarily requiring further rate hikes from the Fed. And he highlighted a steady decline in pay increases, which tends to ease inflation because companies may find it less necessary to offset their labor costs by raising prices. The Fed chair expressed confidence that inflation, despite some signs of persistence in the most recent monthly data, is still heading lower even as the economy is still growing.

"The good news," Powell said, "is we're making progress. The progress is going to come in lumps and be bumpy, but we are making progress."

Source: https://apnews.com/article/inflation-interest-rates-prices-economy-federal-reserve-63f5a7ed041d6b55c7aa773d071a05fb

Two Year Treasury Yields Plummet on Jobs Report News



Two-Year Treasury yields plummeted on Friday.

The market is saying the Fed is done with raising rates.

This is obviously a huge positive for biotech.

Source: Bloomberg

Fed Hiking Cycle Looks Done After US Jobs Report Shows Cooling

Steve Matthews, *Bloomberg*, Nov 3, 2023

A cooling US job market gives the Federal Reserve room to keep interest rates on hold in December and reinforces market views that the US central bank is done with the most aggressive hiking campaign in four decades.

Nonfarm payrolls increased 150,000 last month, less than expected, following a downwardly revised 297,000 advance in September, a Bureau of Labor Statistics report showed Friday. The unemployment rate climbed to 3.9%, and monthly wage growth slowed.

"Put a fork in it – they are done," said Jay Bryson, Wells Fargo & Co. chief economist. "If you are an FOMC official, this is what you wanted to see. This is very good news for the Fed."

The US central bank's policy-setting Federal Open Market Committee voted on Wednesday to hold interest rates at a 22-year high for a second straight meeting. Fed Chair Jerome Powell told reporters in a press briefing that it's an open question whether the central bank would need to hike again, and that it's "proceeding carefully," an assessment that's often suggested a reluctance to raise rates in the near term.

Source: https://www.bloomberg.com/news/articles/2023-11-03/fed-hiking-cycle-looks-done-after-us-jobs-report-shows-cooling?srnd=premium

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

Biopharma Market Update

XBI Closed at 71.5 Last Week (Up 11.4%)

The XBI was up big last week (finally). The XBI is down 13% for the year (vs -21% last week). The dovish Fed meeting and positive jobs report has made a huge difference and generated a powerful three-day market rally.

Biotech Stocks Up Last Week

Return: Oct 28 to Nov 3, 2023

Nasdaq Biotech Index: 7.5%
Arca XBI ETF: 11.4%
Stifel Global Biotech EV (adjusted): -2.7%*
S&P 500: +5.8%

Return: Jan 1 to Nov 3, 2023

Nasdaq Biotech Index: -13.7%
Arca XBI ETF: -12.9%
Stifel Global Biotech EV (adjusted): -17.9%*
S&P 500: +13.5%

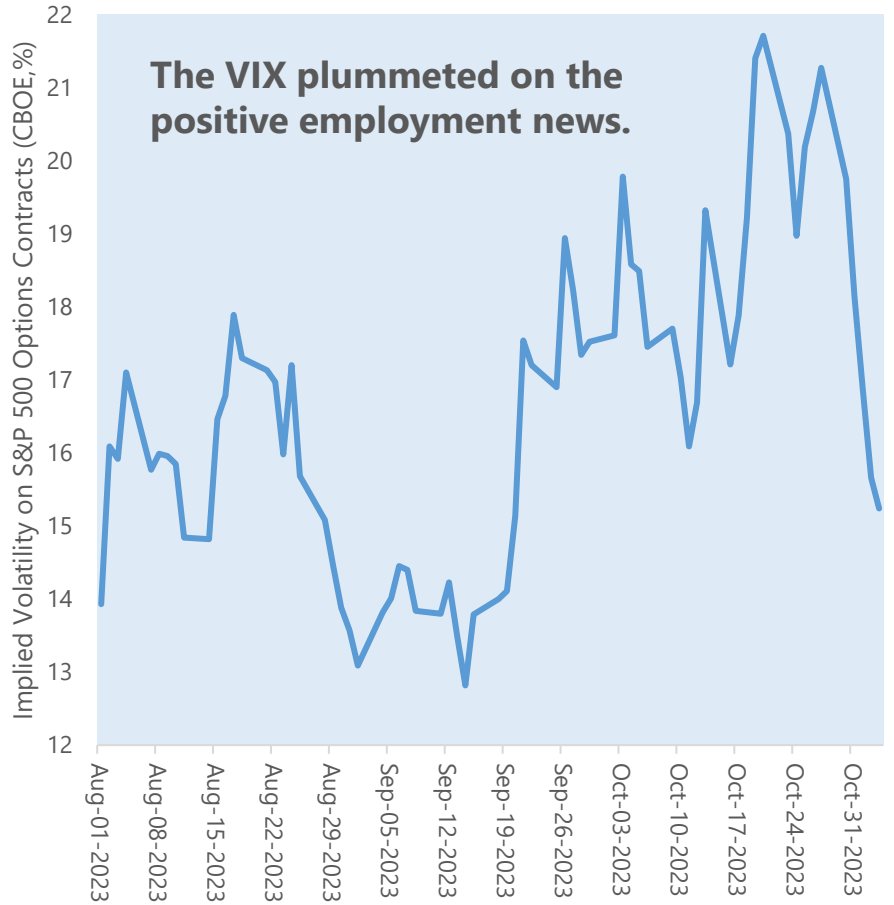
VIX Down Big

Oct 21: 29.7%
Jan 20: 19.9%
May 26: 18.0%
July 21: 13.6%
Sep 29: 17.3%
Oct 20: 21.7%
Oct 27: 21.2%
Nov 3: 15.2%

10-Year Treasury Yield Down

Oct 21: 4.2%
Jan 20: 3.48%
May 26: 3.8%
July 21: 3.84%
Sep 29: 4.59%
Oct 20: 4.98%
Oct 27: 4.86%
Nov 3: 4.57%

VIX, Aug 1 to Nov 3, 2023

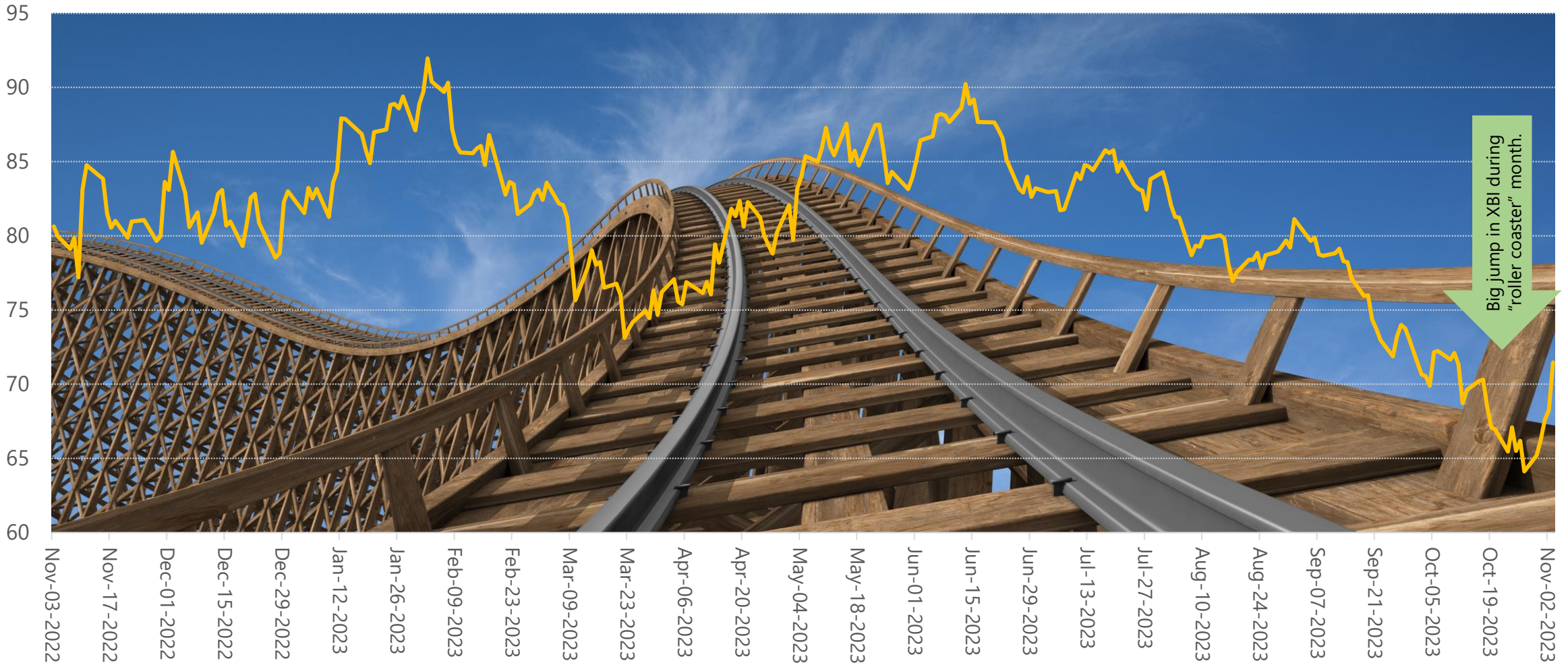


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

XBI Jumped Over Three News Filled Trading Days

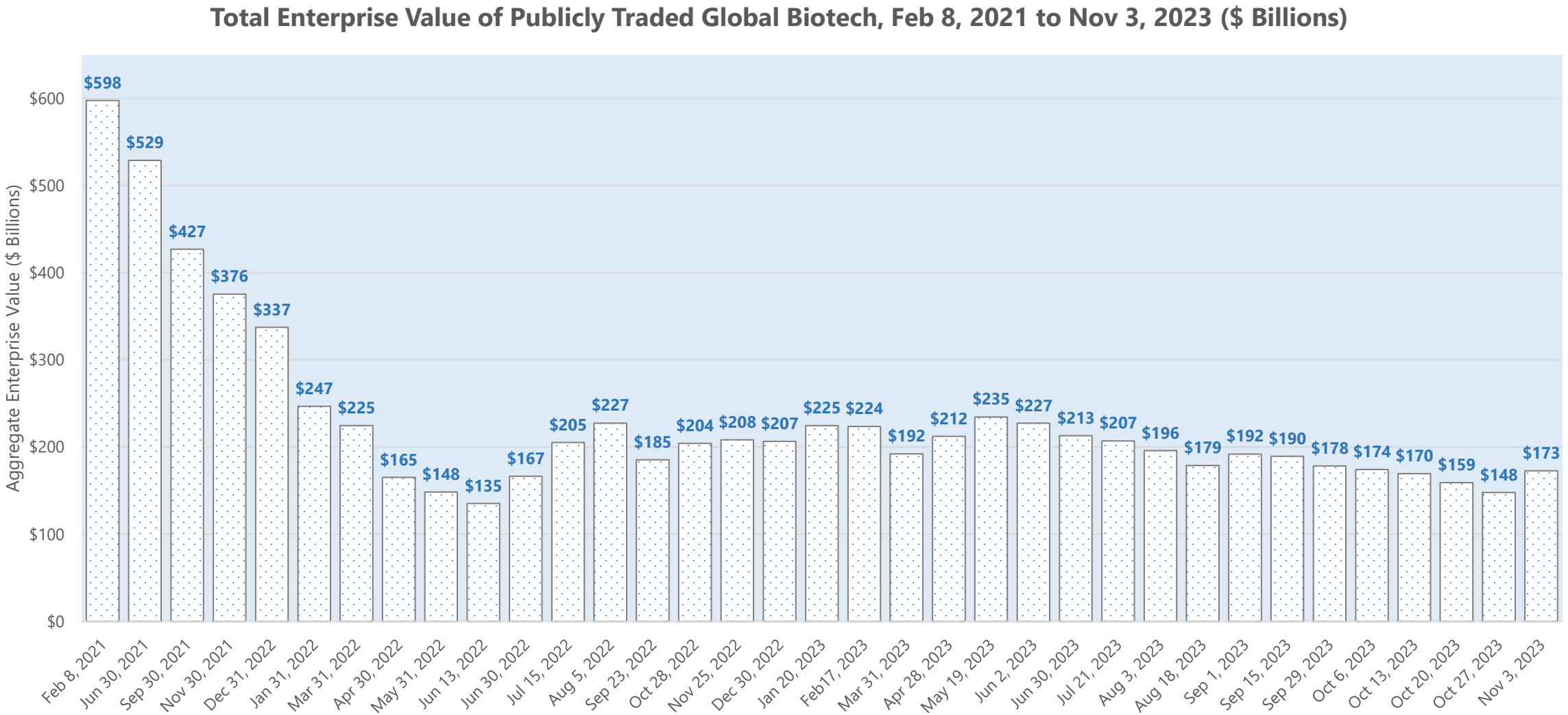
XBI, Nov 3, 2022 to Nov 3, 2023



Source: S&P Capital IQ and Stifel analysis

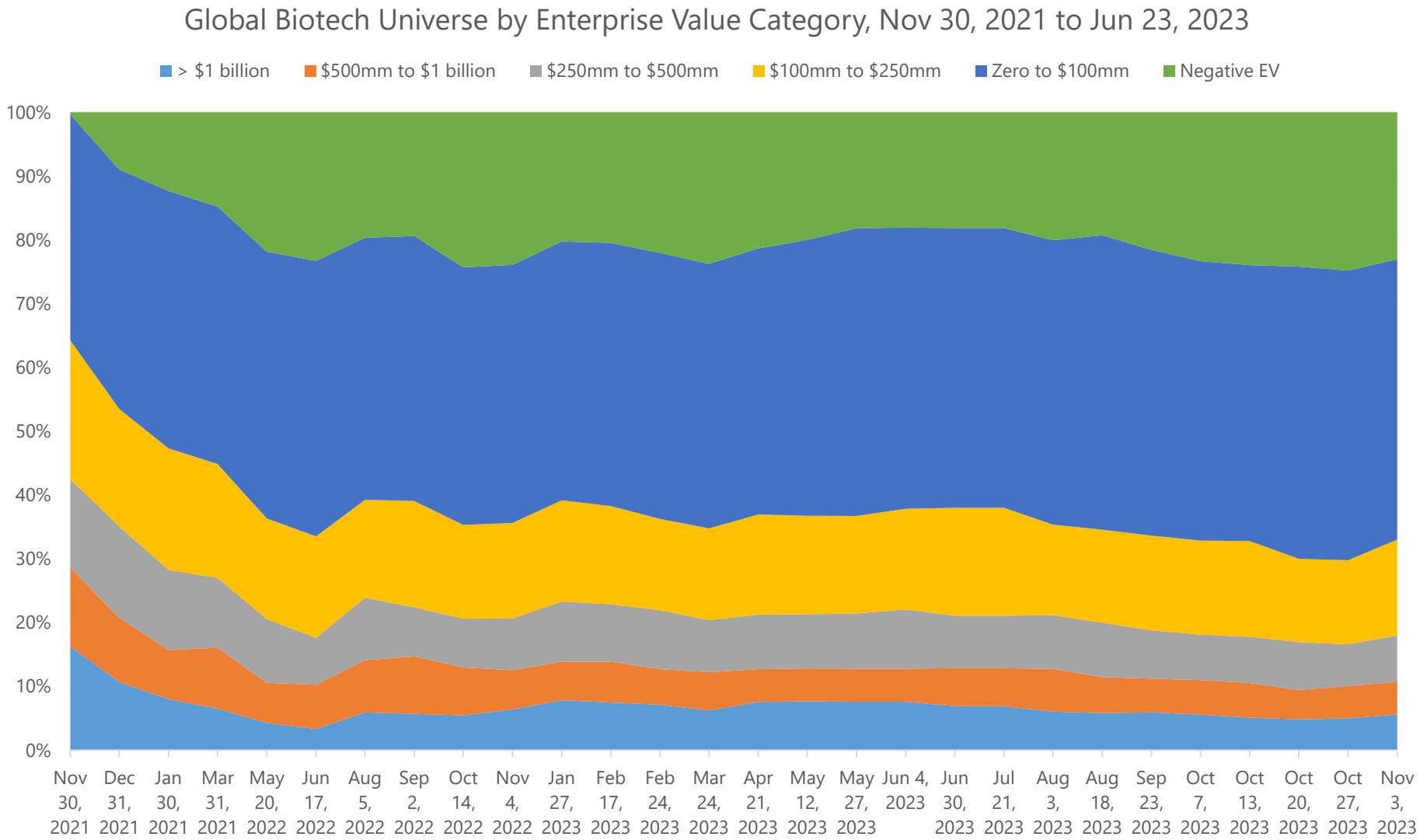
Total Global Biotech Sector Value Up 16.9% in One Week

The total enterprise value of the global biotech sector rose by 16.9% last week (on an adjusted basis) and is now down over 5.8% for the year after adjusting out for exits and entries (versus 17.9% last week)



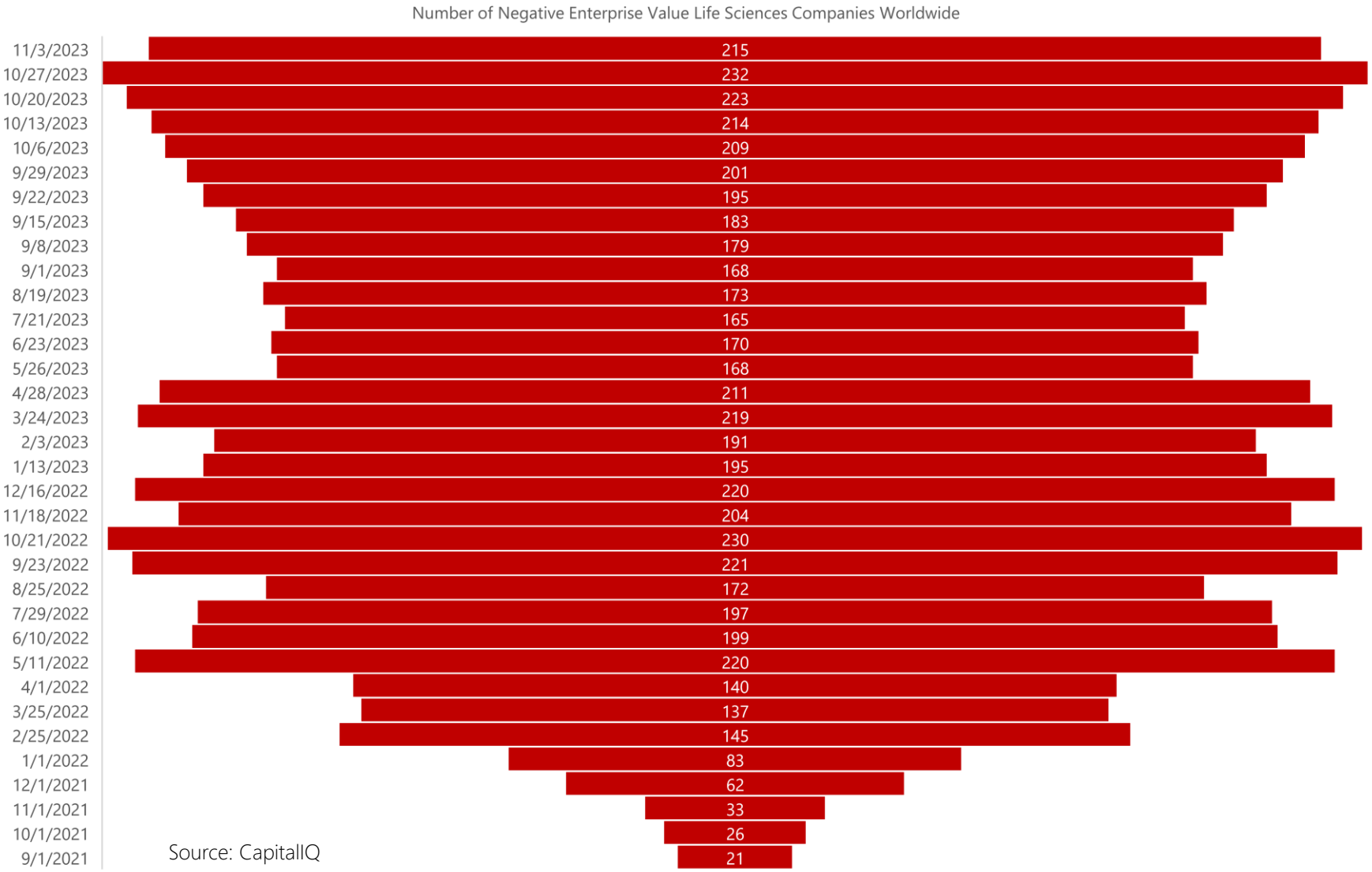
Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange. Last week included a removal of a commercial company with a $7bn value.

A Week Can Make a Big Difference



One can see an abrupt turn across the value spectrum in just one week. The number of companies worth less than $100mm, for example, moved from 70.2% to 67% in three days. We obviously have a long way to go before the bear market in biotech is gone.

Number of Negative Enterprise Value Life Sciences Companies Dropped to 215 in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide fell from 232 a week ago to 215 last Friday.

Public Life Sciences Sector Value Up Big Last Week

Last week saw a massive reversal in the life sciences bear market. The sector's value rose 3.7% ($305 billion). Diagnostics, pharma services, biotech and life science tools rebounded most sharply.

Sector	Firm Count	Enterprise Value (Nov 3, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$79,264	2.0%	-1.6%	-3.5%
Biotech	813	$173,940	16.9%	6.7%	-5.1%
CDMO	40	$147,828	1.4%	-4.1%	-7.5%
Diagnostics	83	$234,055	7.8%	1.9%	1.2%
OTC	31	$27,745	1.5%	-1.9%	-4.6%
Pharma	725	$5,613,120	2.9%	-1.1%	2.5%
Services	40	$198,352	5.2%	0.2%	6.8%
Tools	53	$593,013	5.1%	-7.6%	-14.5%
Devices	181	$1,465,023	4.4%	-1.5%	1.6%
HCIT	11	$21,072	0.0%	-5.2%	-8.2%
Total	**2058**	**$8,547,411**	**3.7%**	**-1.4%**	**0.6%**

Source: CapitalIQ

A Crazy Few Months in Hedge Fund Land

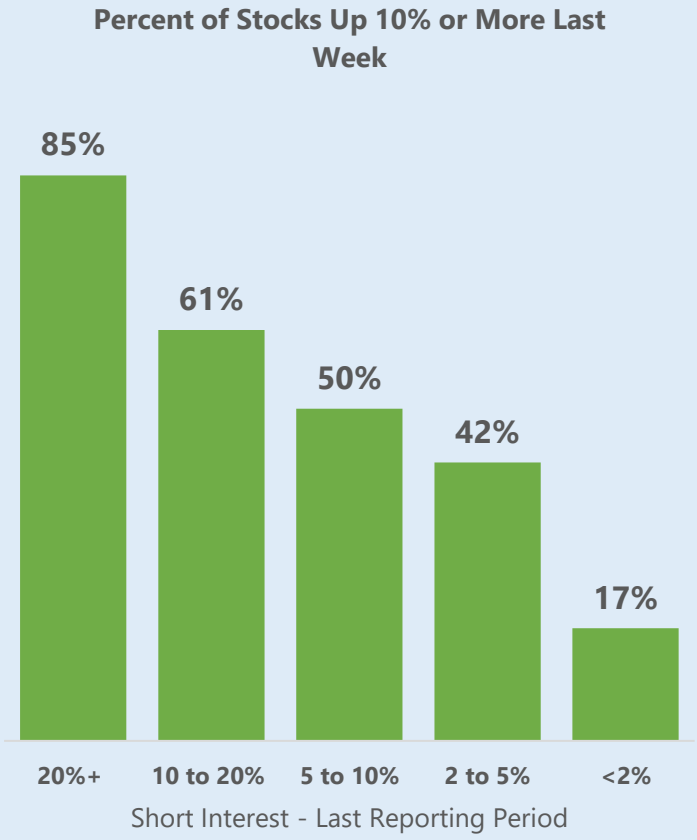
We saw a powerful relief rally hit the biotech sector in the last week. Count us in on the relief part. Whew!

The sentiment was unbelievably bad as the downward grind of the market continued. We'll never fully know what was behind the drop that preceded last week. As we have written previously, the decline was well beyond what one could rationalize by interest rates alone. Stocks with neutral news have been getting hit. Stocks with negative news have been getting savaged. And most positive news has generated little upward bump.

We have been asking around to better understand what might have been happening. Our information is incomplete, but we can report that one observer had collected data on YTD performance of 23 biotech specialist hedge funds as of Aug 30th and noted that 18 were down for the year. Further, several were nearing levels that would imply liquidation. Some funds are set up in pods inside large multi-strategy hedge funds and we understand that at least one pod got shut down in Q3 - triggering portfolio liquidation. After August 30th we went through an unbelievably bad stretch in the market. We don't have fund performance numbers for the last few months but unless a fund was net short things could only have gotten worse relative to August end. This is the time where stock reactions were starting to make less and less sense. We can only surmise that additional pain and liquidations were hitting the sector. Rational players would understand this and would pile on to the short trade. Then, last week we saw unexpected good news. First, Fed Chairman Powell seemed to be in an uncharacteristically jovial mood at his post-FOMC news conference last Thursday. Then, the jobs report on Friday showed a real jump in unemployment and softening of employment growth - the first time in many months. The market read this as an indicator that the Fed is done raising rates. We hope so. Our own guess is that we still have a month or two to go before this is obvious. But whatever the case, this could only have been a bit of a violent week for some hedge fund portfolios as it became clear that this news would reverse the market decline – meaning it was time to cover shorts. And, to do so quickly. This is readily evident in the chart shown at right. Heavily shorted stocks were much more likely to make a big jump last week.

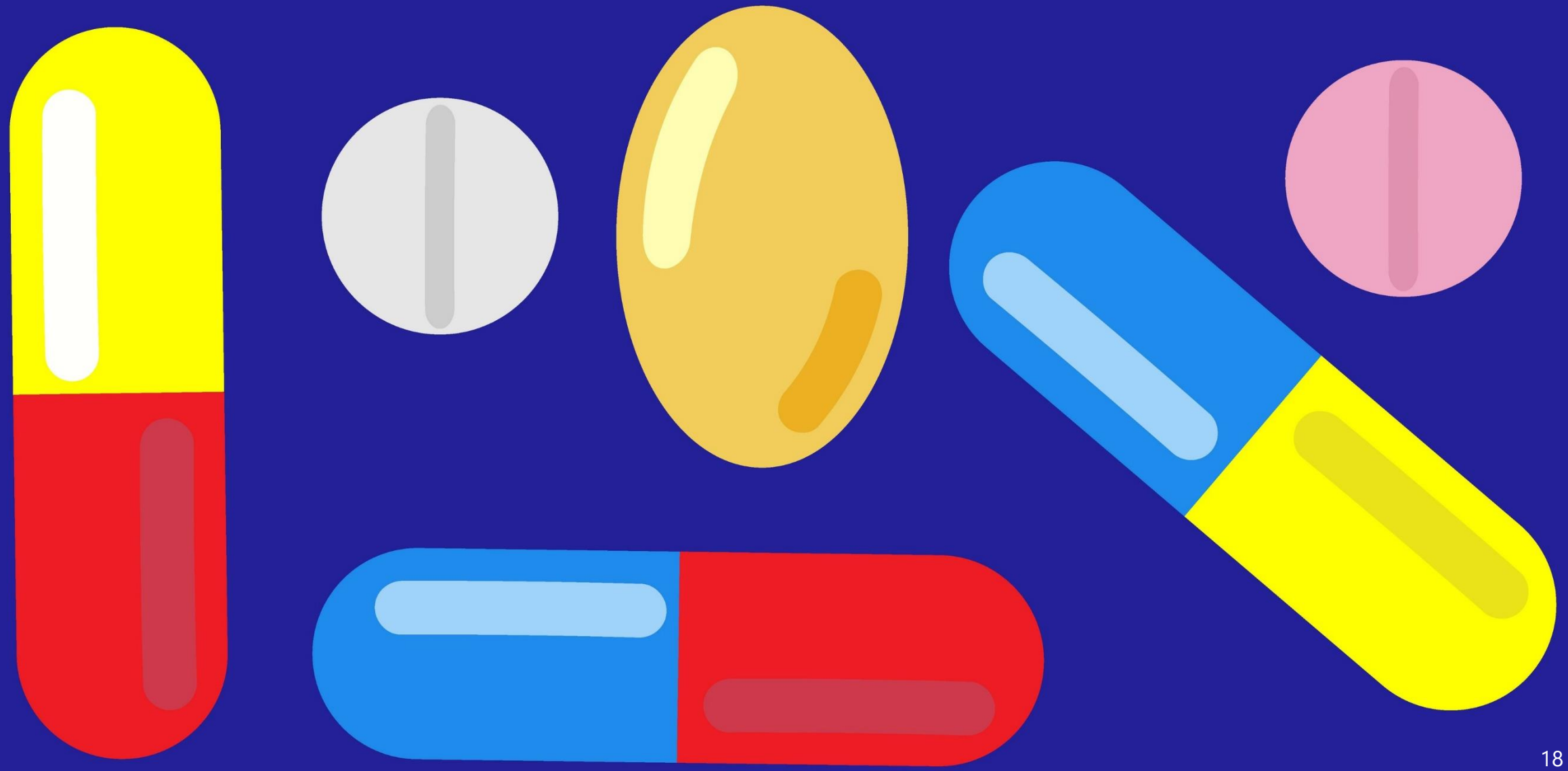
We have seen biotech relief rallies before in this down market (particularly in mid-2022). Short covering doesn't make for a recovery but it's not a bad place to start. We will need to see meaningful fundamental buying in to the market for biotech stocks to recover. Ultimately, we'll need generalists and retail to return to the market. We are still a long way from that.

85% of stocks with 20% or more short interest rose 10% or more last week. In contrast, only 17% of stocks with less than 2% short interest jumped by 10% or more.



Source: CapIQ, Stifel Research

Big Pharma Update



It's Been a Challenging Period for Some in Big Pharma

We have seen eventful earnings reports in recent weeks as many pharmas struggle with the current environment.

Sanofi shares fall 19% after cut to profit outlook

French pharma group announces consumer unit split and increased R&D investment

BMS Reports Q2 Sales Miss Amid Generic Competition, Lowers Full-Year Guidance

Published: Jul 27, 2023 | By Kate Goodwin

Takeda Reports $770M Write-Down, Cuts Profit Forecast by 71% for FY2023

Published: Oct 26, 2023 | By Kate Goodwin

HEALTH AND SCIENCE

Pfizer slashes full-year earnings and revenue guidance as Covid treatment, vaccine sales slump

PUBLISHED FRI, OCT 13 2023•5:47 PM EDT | UPDATED MON, OCT 16 2023•9:53 AM EDT

Matt Gline on Recent Big Pharma Stock Volatility

"It's a wild market out there. With the sector in flux, people are probably moving faster and asking questions later. There's a major cataclysmic set of changes happening basically at all of these companies. The market reaction is the tip of the iceberg of just how big the reorientations are. All of this is happening against the backdrop of trying to manufacture their growth story for the next decade."

Matt Gline
CEO, Roivant Sciences

Source: Biotech Hangout, Nov 3, 2023

Last Week Saw Recovery in Big Pharma Valuations

The week before last saw the top 20 pharmas lose $145 billion in value. Most of this came back with a sector gain of $100 billion last week. All stocks but one had a positive return. Sanofi remains down 15% for the month and J&J is down 11%. Novo and Lilly have gained nicely in the last month.

Company Name	Headquarters	Enterprise Value ($mm)	Market Cap ($mm)	Weekly Value Change ($mm)	YTD Value Change ($mm)	Return Year to Date	Monthly Return	Weekly Return
Lilly	United States	$527,899	$510,636	$6,828	$167,521	48.2%	4.9%	1.4%
Novo Nordisk	Denmark	$436,716	$439,746	$20,870	$133,942	44.0%	9.6%	5.0%
Johnson & Johnson	United States	$370,728	$364,318	$13,818	-$97,531	-21.1%	-10.8%	3.9%
AbbVie	United States	$302,272	$249,613	$4,395	-$41,586	-14.6%	-4.1%	1.8%
Merck	United States	$292,911	$262,329	$1,421	-$7,627	-2.7%	-0.2%	0.5%
Roche	Switzerland	$238,327	$212,864	$914	-$70,087	-25.0%	-2.2%	0.4%
AstraZeneca	United Kingdom	$221,378	$197,022	$6,375	-$17,013	-8.1%	-4.1%	3.3%
Novartis	Switzerland	$203,456	$190,772	$16	-$1,188	-0.6%	-3.3%	0.0%
Pfizer	United States	$197,656	$176,493	$6,493	-$91,097	-31.7%	-6.6%	3.8%
Amgen	United States	$170,150	$144,423	$4,509	$2,785	2.0%	1.9%	3.2%
BMS	United States	$138,853	$107,476	$3,663	-$52,059	-32.6%	-8.8%	3.5%
Sanofi	France	$129,264	$114,926	$6,765	-$6,843	-5.7%	-15.3%	6.3%
Gilead	United States	$118,412	$101,662	$6,193	-$6,944	-6.4%	9.2%	6.5%
GSK	United Kingdom	$89,161	$76,722	$4,870	-$4,384	-4.6%	0.3%	6.8%
CSL	Australia	$86,956	$70,066	-$498	-$881	-1.3%	-4.1%	-0.7%
Bayer	Germany	$86,323	$44,374	$2,219	-$2,795	-5.5%	-2.2%	5.3%
Vertex	United States	$85,269	$97,095	$5,399	$20,088	27.1%	5.9%	5.9%
Zoetis	United States	$79,505	$74,482	$2,659	$7,029	10.3%	-5.9%	3.7%
Merck KGaA	Germany	$78,349	$68,331	$2,476	-$15,514	-18.5%	-3.4%	3.8%
Takeda	Japan	$76,065	$43,262	$968	-$6,427	-13.3%	-6.4%	2.3%
Total ($mm)		**$3,929,649**	**$3,546,612**	**$100,352**	**-$90,609**			

Source: CapitalIQ

We Are Raising Our Full Year Outlook and Have Completed the Acquisition of Horizon Therapeutics

- Achieved 11% volume growth, with record sales for 7 brands
- Added Horizon's rare disease medicines; strong strategic fit with our broad innovative portfolio
- Expanded our international footprint, with 12% ex-U.S. volume growth (27% in Asia Pacific)
- Completed enrollment in maridebart cafraglutide (AMG 133) Phase 2 obesity study; topline data expected in 2024
- Delivered robust operating margins while investing ~$1B in internal innovation
- Increased dividend 10% year-over-year

General Medicine

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

- **A Phase 2 study in overweight or obese adults with or without type 2 diabetes mellitus has completed enrollment with topline data anticipated in late 2024.**

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

- **A Phase 1 study is ongoing, with initial data readout anticipated in H1 2024.**
- **This molecule has a different target than AMG 133 and is not an incretin-based therapy.**

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

Clear momentum driving strong year-to-date performance

Delivered 13%[1] sales growth, 14%[1] adj. operating profit growth

Profitable, resilient growth across portfolio:

- Vaccines +21%[1]
- Specialty Medicines +14%[1]
- General Medicines +5%

New products launched since 2017[2] delivered £7.8 billion[1] year to date, with c.80% from Vaccines and Specialty

Q3 2023 performance

Sales
£8.1bn, +10%
+16%[1]

Adj. operating profit
£2.8bn, +15%
+22%[1]

Adj. EPS
50.4p, +17%
+25%[1]

Dividend per share
14p

Full-year 2023 guidance: upgraded[1]

Sales growth: 12-13%
Adj. operating profit growth: 13-15%
Adj. EPS growth: 17-20%

Absolute values at actual exchange rates (AER); changes at CER, unless stated otherwise.
1. Excluding COVID-19 solutions 2. Product approvals since 2017 include: *Zejula, Trelegy, Shingrix, Juluca, Dovato, Duvroq, Rukobia, Blenrep, Cabenuva, Jemperli, Apretude, Arexvy*

Source: https://www.gsk.com/en-gb/investors/quarterly-results/

Spotlight on prevention: Vaccines are a strong, durable growth business

Launched world's first RSV vaccine, £709m in Q3

AREXVY (RESPIRATORY SYNCYTIAL VIRUS VACCINE, ADJUVANTED)

- Approved in US, EU, Canada, Japan
- Positive data in 50–59-year-old adults

Shingrix £825m +15% in Q3

SHINGRIX (ZOSTER VACCINE RECOMBINANT, ADJUVANTED)

- 100% efficacy in large, study in China
- Partnership with Zhifei expands potential in China
- Launched in 39 countries

Large vaccines pipeline with outstanding capabilities in technology platforms

- 18 vaccines in clinical development
- Substantial innovation and comprehensive suite of vaccine platform technologies, including next-generation mRNA and MAPS

Source: https://www.gsk.com/en-gb/investors/quarterly-results/

STRATEGIC DELIVERABLES

PROGRESS SINCE THE LAST EARNINGS CALL

Invest in Current Portfolio

- **Gross Margin**: Non-GAAP gross margin of 81.7% in Q3
- **SG&A**: 12% increase in Q3 primarily driven by launches of new products and indications as well as compensation and benefit costs

Invest in Future Innovation

- **R&D**: 34% increase in Q3 driven primarily by late-stage assets and early-stage research
- **Business Development**: Completed the acquisitions of DICE Therapeutics, Versanis Bio, Emergence Therapeutics and Sigilon Therapeutics; announced the potential acquisition of POINT Biopharma

Deliver Revenue Growth

- Excluding the olanzapine portfolio and COVID-19 antibodies[1], revenue grew 24% in Q3
- Together, New Products and Growth Products[2] contributed approximately 17 percentage points of volume growth in Q3

Speed Life-Changing Medicines

- FDA approval of **Omvoh**™ for the treatment of adults with moderately to severely active ulcerative colitis and **Jardiance**®[3] for the treatment of adults with chronic kidney disease at risk of progression
- Positive CHMP opinion in the EU and CRL in the U.S. for **lebrikizumab** for the treatment of moderate-to-severe atopic dermatitis
- Positive results in the Phase 3 VIVID-1 study of **mirikizumab** in moderately to severely active Crohn's disease

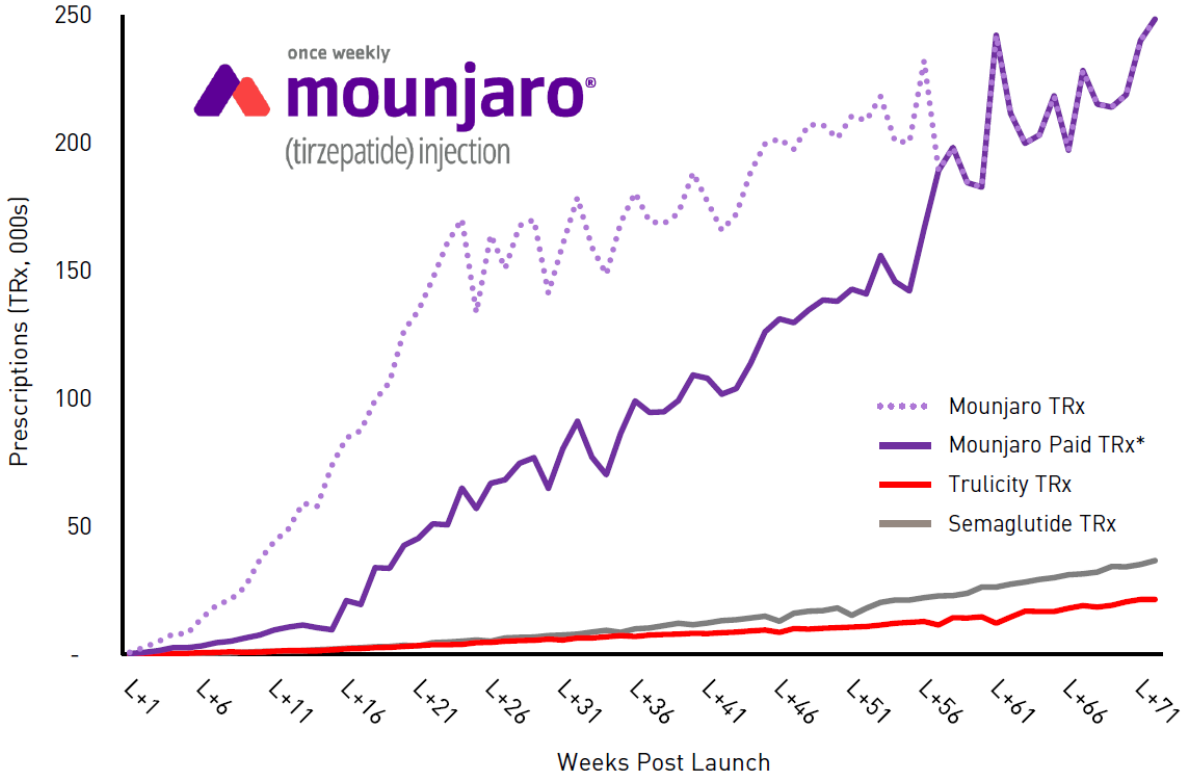
Return Capital to Shareholders via:

- **Dividend**: Distributed over $1 billion in Q3
- **Share Repurchase**: $750 million YTD

[1] Sales for COVID-19 antibodies include bamlanivimab, etesevimab and bebtelovimab sold pursuant to Emergency Use Authorization or similar regulatory authorizations
[2] Refer to slide 9 for a list of New Products and Growth Products
[3] Jardiance is part of the Boehringer Ingelheim (BI) and Lilly Alliance, and BI holds the marketing authorization for Jardiance.

Stunning 250,000 Prescriptions of Mounjaro® in Week 71 of Launch

MOUNJARO U.S. LAUNCH PROGRESS

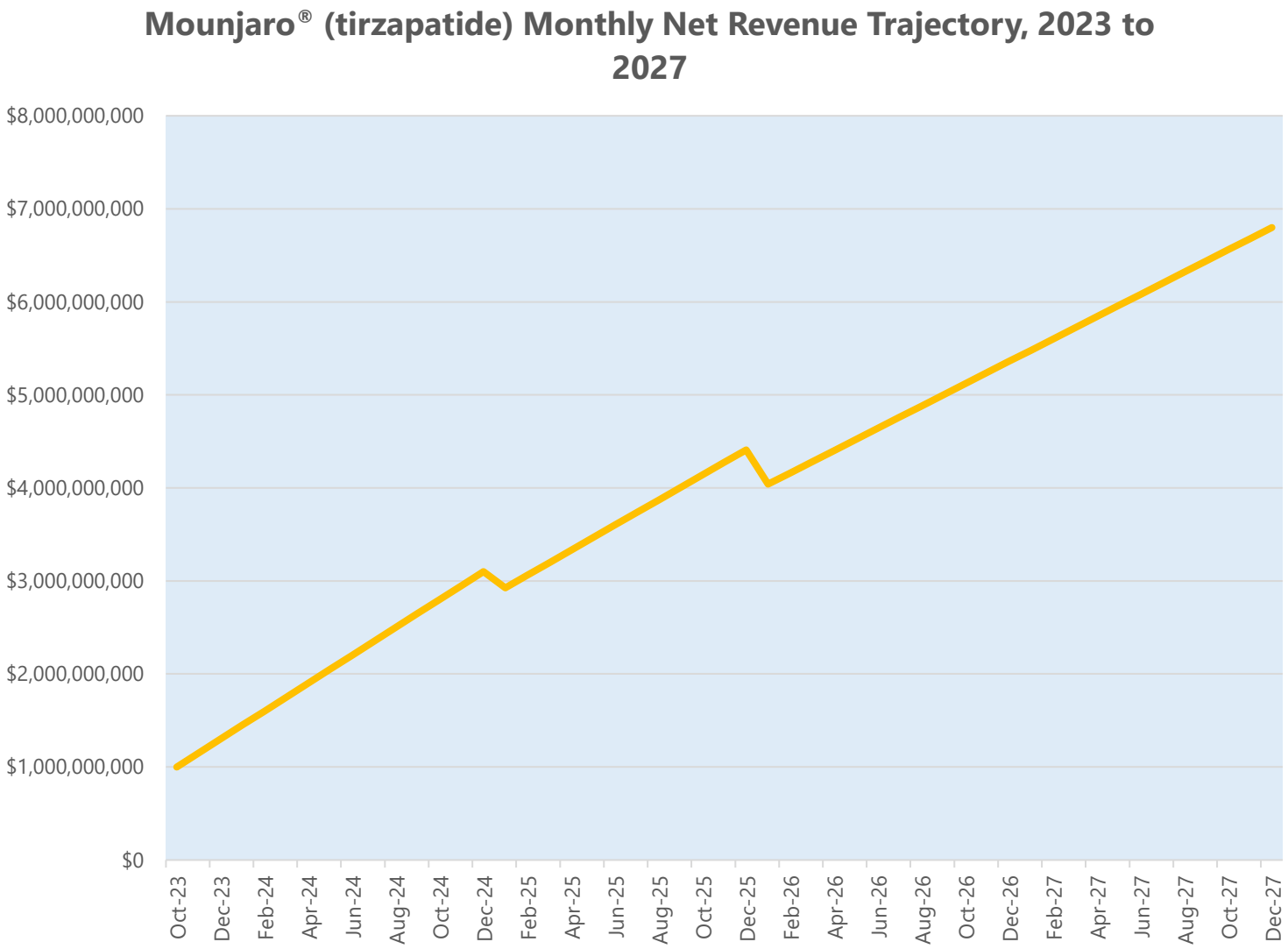


Mounjaro volume has significantly outpaced prior launches in the type 2 diabetes injectable incretin class

- Access on October 1st was 78% for patients with type 2 diabetes across commercial and Part D lives, including 85% in commercial
- Original non-covered $25 copay card expired June 30th; all Q3 prescriptions are considered paid
- All doses are now listed as available on the FDA Drug Shortage Database
- Focused on driving new-to-brand growth with increased access and promotional efforts

*Internal estimate of weekly paid TRx
IQVIA weekly data for week ending Oct 20, 2023 (type 2 diabetes injectable incretin class)

Mounjaro® (Tirzepatide) on Track to be a $73 Billion Product by 2027



It doesn't take a Ph.D. to take Lilly's Mounjaro® growth trajectory and extend it out.

We assume $1000 net price per month today, dropping to $900 in 2025 and then $800 in 2026. We assume that Lilly continues to add 150,000 net patients on the drug per month indefinitely.

This implies that by Dec 2027 there would be 8.5mm people on the drug (not at all implausible in the U.S. alone given the size of the obese population).

Key positives going forward are the build out of capacity and the label – to include obesity shortly. Obviously, there is a huge unexploited global opportunity.

Key negatives are the competitive environment.

The key questions are how fast can Lilly build out capacity here and how fast can true small molecules as opposed to oral peptides (such as Amgen's AMG 786) hit the market.

Implications are 2024 revenue of $27bn, 2026 revenue of $56bn, 2027 revenue of $73bn and 2030 revenue of $126 billion.

The implications for Lilly value are obvious given that large pharmas in our industry trade, on average, at revenue multiples of six times.

This forecast is intended to be indicative of product direction and does not represent a fully-researched Stifel Financial forecast of Mounjaro® revenue.

Eli Lilly 'Aggressively Planning' Manufacturing Expansions, CEO Says, as Mounjaro Soars

Angus Liu, FiercePharma, Nov 2, 2023

Supply of different doses of Mounjaro has become somewhat unpredictable as significant demand outstripped Lilly's output from time to time. During a call with investors Thursday, Lilly's CFO Anat Ashkenazi acknowledged that the company experienced "tight supply" of Mounjaro throughout most of the third quarter.

A regular guest on the FDA's drug shortage list, Mounjaro currently has all six dosing forms available, according to the agency's website. But so was the case back in February, until it came to light in July that Lilly was having trouble providing four solutions [of Mounjaro].

Shipments and inventory at wholesalers in the U.S. have improved, Ashkenazi said, but supply outside the U.S. remains tight "which materially impacted performance in these regions."

Lilly recently invested $450 million in its Research Triangle Park facility in North Carolina with additional drug filling, device assembly and packaging capacity for the company's incretin products, including Mounjaro. With that expansion coming online, **Lilly is on track to achieve its goal of doubling capacity by the end of this year** compared to what it had a year ago, Ashkenazi said.

"We're also continuing to focus on other parts of the supply chain, as demand is expected to remain high and production bottlenecks may shift over time," the CFO added. Besides the North Carolina project, Lilly in April also unveiled an additional $1.6 billion investment in new manufacturing sites in its home state Indiana.

"We're not done with those," Lilly CEO David Ricks said of the manufacturing expansions on Thursday's call, adding that Lilly is **"aggressively planning"** further production build-up. "We think that there is a need to take up parenteral incretin supply pretty dramatically from the current levels. And we plan to do that," Ricks said.

The forecast shown on the previous page would suggest that Lilly will need to deliver 12 million Mounjaro pens a month by the end of 2024 and nearly 60 million pens a month by 2030.

This is obviously massive volume for a complex autoinjector, and Lilly obviously needs to massively scale up its manufacturing capacity to meet demand.

It appears that Lilly is well on the way to doing this.

Source: https://www.fiercepharma.com/pharma/eli-lilly-aggressively-planning-manufacturing-expansions-ceo-says-mounjaro-soars

Key Tirzepatide Clinical Events

SELECT TRIALS – TIRZEPATIDE

Study	Indication*	Title	Phase	Patients	Primary Outcome**	Primary Completion	Completion
NCT04184622	Obesity	A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1)	3	2539	Percent Change from Baseline in Body Weight	Apr 2022	Jul 2024
NCT05822830	Obesity	A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight With Weight Related Comorbidities (SURMOUNT-5)	3	700	Percent Change from Baseline in Body Weight	Nov 2024	Nov 2024
NCT06075667	Obesity	A Study of Tirzepatide (LY3298176) Once Weekly in Adolescent Participants Who Have Obesity, or Are Overweight With Weight-Related Comorbidities (SURMOUNT-ADOLESCENTS)	3	150	Percent Change from Baseline in Body Mass Index (BMI)	Feb 2026	Dec 2026
NCT06047548	Obesity	A Study of LY3298176 (Tirzepatide) For the Maintenance of Body Weight Reduction in Participants Who Have Obesity or Overweight With Weight-Related Comorbidities (SURMOUNT-MAINTAIN)	3	400	Percent Maintenance of Body Weight (BW) Reduction Achieved during the 60-Week Weight Loss Period	May 2026	May 2026
NCT05556512	Obesity	A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO)	3	15000	Time to First Occurrence of Any Component Event of Composite (All-Cause Death, Nonfatal Myocardial Infarction (MI), Nonfatal Stroke, Coronary Revascularization, or Heart Failure Events)	Oct 2027	Oct 2027

Lilly will have a lot of new data on the market from SURMOUNT-1/5 next year including effects on comorbidities.

SURMOUNT-MMO is a key clinical trial. Presumably, Lilly will start to show some data from this 15k subject study in 2026. But, by 2027/2028 we should have a panoply of data showing the full effect of Tirzepatide on a broad range of obesity comorbities.

The Big Upcoming Events are the Regulatory Actions on Donanemab for AD and Lebrikizumab for Atopic Dermatitis

POTENTIAL KEY EVENTS 2023

New since last update

Lilly

Phase 3 Initiations

- Basal Insulin-Fc for type 2 diabetes (QWINT-1)
- Tirzepatide for chronic weight management (H2H vs semaglutide 2.4 mg)
- Retatrutide for chronic weight management
- Orforglipron for chronic weight management
- Orforglipron for type 2 diabetes
- Remternetug for early Alzheimer's disease (efficacy trials)

Phase 3 Data Disclosures

- Donanemab for early Alzheimer's disease
- Tirzepatide for chronic weight management (SURMOUNT-2)
- Tirzepatide for chronic weight management (SURMOUNT-3)
- Tirzepatide for chronic weight management (SURMOUNT-4)
- Mirikizumab for Crohn's disease
- Abemaciclib for castrate-resistant prostate cancer (CYCLONE-2)
- Pirtobrutinib for CLL prior BTKi (BRUIN CLL-321)

Regulatory Submissions

- Tirzepatide for chronic weight management (US/EU)
- Lebrikizumab for atopic dermatitis (J)
- Empagliflozin[3] for chronic kidney disease (US/EU/J)
- Donanemab for early Alzheimer's disease [1] (US/EU/J)
- Pirtobrutinib for MCL prior BTKi (J)
- Pirtobrutinib for CLL prior BTKi and BCL2i [2]

Regulatory Actions

- Donanemab for early Alzheimer's disease [2] (US)
- Lebrikizumab for atopic dermatitis (US/EU)
- Mirikizumab for ulcerative colitis (US/EU/J)
- Pirtobrutinib for MCL prior BTKi (US [2]/EU)
- Empagliflozin[3] for chronic kidney disease (US/EU/J)
- Tirzepatide for chronic weight management (US)
- Pirtobrutinib for CLL prior BTKi and BCL2i [2]

[1] Under the traditional approval pathway
[2] Under the FDA Accelerated Approval Program
[3] Jardiance is part of the company's alliance with Boehringer Ingelheim. Lilly reports as revenue royalties received on net sales of Jardiance.

Note: donanemab is an investigational antibody against amyloid beta.

Lebrikizumab is an antibody against IL-13.

Novo Nordisk Focused on Raising Bar on Diabetes, Obesity, Chronic Diseases and Rare Disease

Strategic Aspirations 2025 | Highlights first nine months of 2023

Light blue indicates developments in Q3 2023

Purpose and sustainability (ESG)

Progress towards zero environmental impact
- Carbon emissions decreased by 28% vs first 9M 2019[1]

Adding value to society
- Medical treatment to ~40 million people with diabetes
- Reached more than 46,000 children in Changing Diabetes® in Children programme
- Partnership with Aspen to produce human insulin for Africa

Being recognised as a sustainable employer
- Share of women in senior leadership positions has increased to 41% from 38% at end of September 2022

Innovation and therapeutic focus

Further raise innovation bar for Diabetes treatment
- Regulatory submission of once-weekly insulin icodec
- Initiation of phase 3 trial with CagriSema T2D
- FLOW stopped for efficacy based on interim analysis

Develop superior treatment solutions for obesity
- Regulatory submission of SELECT CVOT

Strengthen and progress Rare Disease pipeline
- Concizumab approved for HAwI/HBwI in Japan

Establish presence in other serious chronic diseases
- Acquisition of ocedurenone within CVD

Commercial execution

Diabetes value market share increased by 1.8%-points to 33.3%[2]

Obesity care sales of DKK 30.4 billion (+174% at CER)

Rare disease sales of DKK 12.6 billion (-18% at CER)

Financials

Sales growth of 33% (CER) and operating profit growth of 37% (CER)

Operational leverage reflecting sales growth

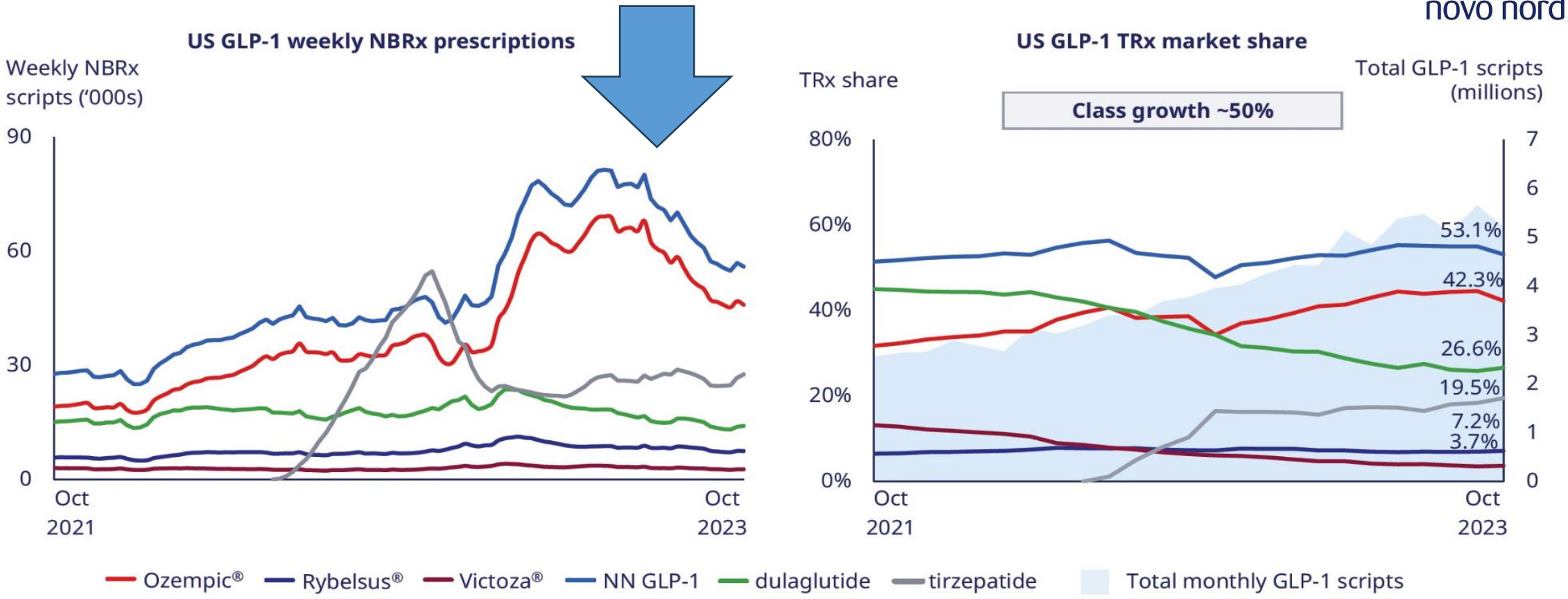
Free cash flow of DKK 75.6 billion and DKK 52.0 billion returned to shareholders

[1]Scope 1,2 and partial scope 3 limited to CO2 emissions from business flights and product distribution; [2]MAT (Moving annual total) value market share
CER: Constant exchange rates; 9M: Nine months; HAwI/HBwI: Haemophilia A/B with inhibitors
Note: The strategic aspirations are not a projection of Novo Nordisk's financial outlook or expected growth

Source: https://investor.novonordisk.com/q3-2023-presentation/

Novo Has 53% of U.S. GLP-1 Prescriptions But Losing Share Due to Capacity Issues

Novo is obviously capacity constrained and is throttling back NRx



NBRx: New-to-brand prescriptions; TRx: Total prescriptions; NN: Novo Nordisk; Scripts: Prescriptions; US: United States
Note: Class growth calculated as Q3 2023 vs Q3 2022
Source: IQVIA Xponent, NBRx data from week ending 13 Oct 2023. TRx data from week ending 13 Oct 2023. Each data points represents a rolling four-week average

Source: https://investor.novonordisk.com/q3-2023-presentation/

Generating evidence with the semaglutide molecule beyond glycaemic control and weight loss

Serious chronic diseases are associated with diabetes and obesity

ILLUSTRATIVE

Millions of patients are affected globally

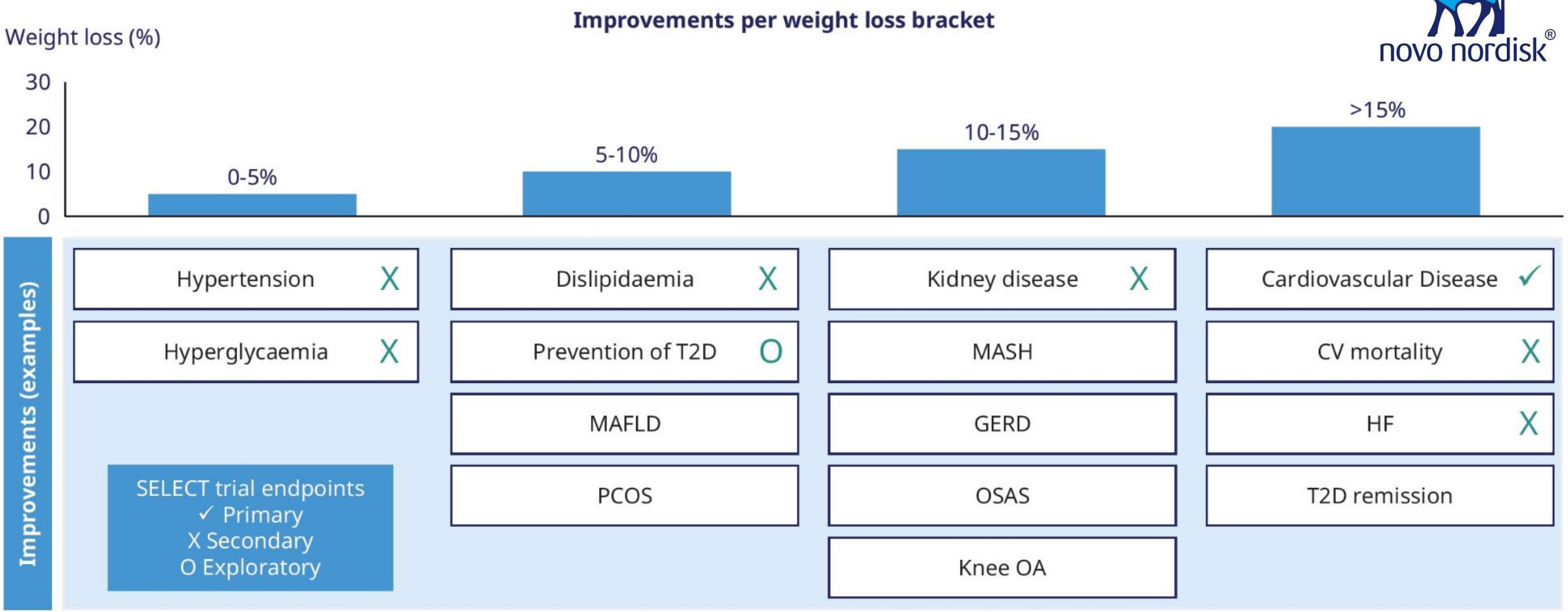
Novo Nordisk is generating evidence to adress the medical unmet need in subpopulations

CKD: ~700 million[3]	**FLOW**
MASH: ~25 million[4]	**ESSENCE**
CVD: ~520 million[5]	**SELECT** **SOUL**
HF: ~64 million[6]	**STEP** HFpEF **STEP** HFpEF-DM
PAD: ~200 million[7]	**STRIDE**
Alzheimer's Disease: ~85 million[8]	**evoke** **evoke+**

[1]International Diabetes Federation: Diabetes Atlas 10th edition, 2021; [2]World Diabetes Atlas 2022; [3]Carney EF. Nat Rev Nephrol 2020;16:251; [4]Estes C et al. Hepatology, 2018; [5]Roth GA et al. J Am Coll Cardiol 2020; [6]Groenewegen A et al. Eur J Heart Fail 2020;22:1342–13561; [7]Fowkes FG et al. Lancet 2013; [8]WHO, Dementia key facts 2022

ASCVD: Atherosclerotic cardiovascular disease; MASH: Metabolic dysfunction-associated steatohepatitis; CVOT: Cardiovascular outcome trial; T2D: Type 2 diabetes; CKD: Chronic kidney disease; PAD: Peripheral arterial disease; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction, HFpEF-DM; Heart failure with preserved ejection fraction with Diabetes; s.c.: Subcutaneous.

The cardiovascular trial, SELECT, addresses many comorbidities that can be improved with weight management



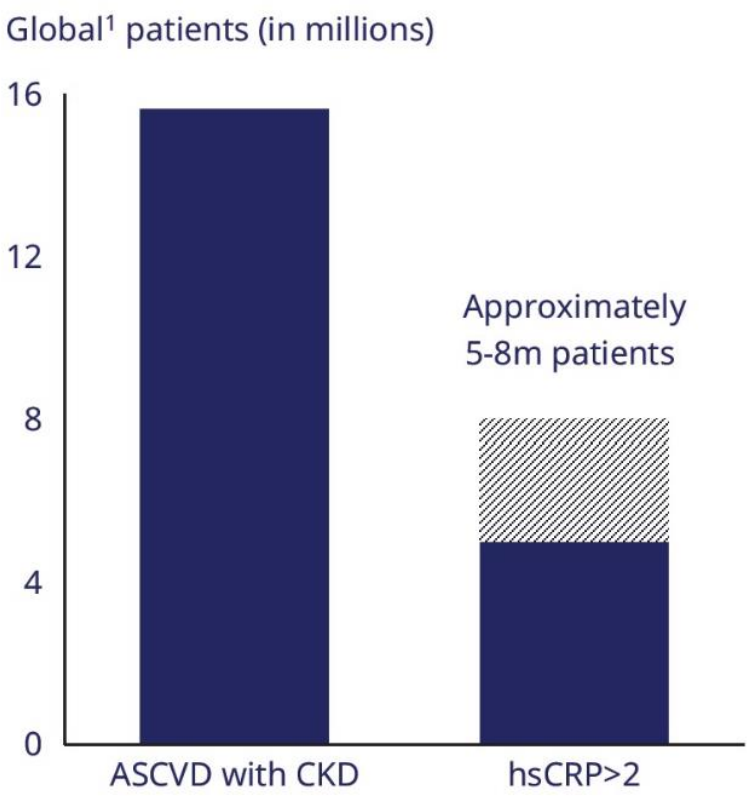
T2D: Type 2 diabetes; MAFLD: Metabolic dysfunction-associated fatty liver disease; PCOS: Polycystic ovary syndrome; MASH: Metabolic dysfunction-associated steatohepatitis; GERD: Gastroesophageal reflux disease; OSAS: Obstructive sleep apnea syndrome; OA: Osteoarthritis HF: Heart failure

Sources: Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; Lean ME et al. Lancet 2018;391:541–5; Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; Sundström J et al. Circulation 2017;135:1577–85., Morales E and Praga M. Curr Hypertens Rep 2012;14:170-176

Source: https://investor.novonordisk.com/q3-2023-presentation/

Ziltivekimab aspires to address an unmet need in more than 5 million people in patients with ASCVD, CKD and inflammation

Ziltivekimab aspires to reduce MACE in people with ASCVD and CKD



Critical success factors to commercialise ziltivekimab

Market building	Focus areas	Investment levels
Targeted HCP outreach and relationship building	• Increase presence with key prescriber base being cardiologists and PCPs • Enhance awareness of inflammatory burden in CVD with KOLs and HCP associations	●
Successful payer engagement	• Utilise ZEUS read-out to quantify anti-inflammatory clinical benefit in ASCVD patients with CKD vs Standard of Care	◑
Integrated evidence generation	• Understand hsCRP and inflammation, epidemiology of disease and socio-economic burden of disease	◑

○ Low ● High

[1] Includes US, EU5 (Germany, France, Spain, Italy, United Kingdom) and Japan
MACE or major adverse cardiovascular events includes CV death, non-fatal MI or non-fatal stroke; ASCVD: Atherosclerotic cardiovascular disease; CKD: Chronic kidney disease; HCP: Healthcare professional; PCP: Primary care physician
KOL: Key opinion leader; hsCRP: High-sensitivity C-reactive protein

Source: https://investor.novonordisk.com/q3-2023-presentation/

Buoyed by GLP-1 Stars, Novo's Sales Soar in Q3. Will Manufacturing Prove a Long-term Hurdle?

Eric Sagonowsky and Fraiser Kansteiner, *FiercePharma*, Nov 2, 2023 (excerpt)

But even as Novo Nordisk hustles to grow its manufacturing footprint, the company expects Wegovy demand to outpace supply, CEO Lars Fruergaard Jørgensen said on a media call, according to the Financial Times and Reuters.

To help get a handle on the surge in demand, Novo Nordisk earlier this year throttled the U.S. rollout of the drug, placing restrictions on starter doses so that existing patients can maintain access.

Those restrictions will remain in place in the U.S. even as capacity for Wegovy is "gradually being expanded," Novo's head of North American operations Doug Langa said on a call with investors Thursday.

The strategy will also influence Novo's launch plans abroad, Langa added.

"While eager to launch Wegovy in more [international] countries, our focus remains to do this in a sustainable manner, for example by capping volumes," he said.

Source: https://www.fiercepharma.com/pharma/buoyed-glp-1-stars-novos-sales-soar-q3-will-manufacturing-capacity-prove-long-term-hurdle

Q3 2023: Continued Strength in Pfizer's Non-COVID Portfolio

ABRYSVO™ (OA)
Respiratory Syncytial Virus Vaccine

$375M * op

U.S. $375M, *

Int'l —, —

Nurtec® ODT (rimegepant)
orally disintegrating tablets 75 mg

Vydura® 75 mg
oral lyophilisate
rimegepant

$233M * op

U.S. $227M, *

Int'l $6M, * op

Oxbryta® (voxelotor)

$85M * op

U.S. $83M, *

Int'l $2M, * op

Vyndaqel® family[1] (tafamidis)

$892M +47% op

U.S. $511M, +55%

Int'l $381M, +36% op

Prevnar family[2]

$1.9B +15% op

U.S. $1.3B, +20%

Int'l $544M, +5% op

7% op growth for non-COVID revenues YTD Q3 2023
On track for expected 6-8% op revenue growth ex-COVID in FY 2023

*Indicates calculation not meaningful.
1. Vyndaqel family includes global revenues from Vyndaqel, as well as revenues for Vyndamax in the U.S. and Vynmac in Japan. 2. Prevnar family includes revenues from Prevnar 13/Prevenar 13 (pediatric and adult) and Prevnar 20/Apexxnar (pediatric and adult).

Excellent Progress Toward Expected Commercial Launches[1]

~$20B Potential Revenue
expected for NME and new indications by 2030[2]

~$25B Potential Revenue
expected from new BD deals by 2030[3]

Vaccines | Inflammation/Immunology | Oncology | Rare Disease | Internal Medicine

New Molecular Entity (NME) Launches

2022	2023	2023	2H 2023	2H 2023	2H 2023**	2023	Beyond 2024*
Ngenla	**Litfulo**	**Elrexfio**	**Abrysvo (OA)**	**Abrysvo (MI)**	**Penbraya**	**Abrilada** (US)	**Next-Generation mRNA Flu Vaccine**
Growth Hormone Deficiency	Severe Alopecia Areata	Relapsed Refractory Multiple Myeloma	Prevention of RSV-associated LRTI in adults >60 yrs	Prevention of RSV-associated LRTI in infants via maternal immunization	Prevention of meningococcal infection by serogroups ABCWY	Adalimumab Biosimilar	Influenza
Launched	Launched	Launched	Launched	Launched	Approved	Approved	Revised

New Indication Launches

Aug 2022 Pfizer co-promote	Sep 2022	2023	2023
Myfembree	**COVID-19 vaccine BA.4/BA.5 variant**	**Cibinqo**	**Braftovi/Mektovi**
Endometriosis	COVID-19	Moderate to severe Atopic Dermatitis Adolescent	Metastatic Non-Small Cell Lung Cancer (PHAROS)
Launched	Launched	Launched	Approved

2023	2023	2023
Talzenna + Xtandi (Talazoparib + Enzalutamide)	**Xtandi**	**Prevnar 20 Peds**
Metastatic castration resistant prostate cancer (TALAPRO2)	Non-Metastatic Castration Sensitive Prostate Cancer (EMBARK)	Prevention of invasive pneumococcal disease, otitis media - Pediatric
Launched		Launched

Recently Completed Business Development (BD) Deals[4]

Aug 2022 Pfizer promotion[5]	2023	Oct 2022 with merger close	2H 2023
Nurtec ODT/Vydura	**Zavzpret (intranasal)**	**Oxbryta**	**Velsipity**
Acute treatment of Migraine and preventive treatment of episodic Migraine	Acute treatment of Migraine	Sickle cell disease	Moderate to severe Ulcerative Colitis
Launched	Launched	Launched	Approved

Note: All dates are preliminary, subject to change, and subject to, among other risks, assumptions and uncertainties, clinical trial, regulatory and commercial success, ACIP and MMWR publication, and availability of supply. 1.Through H1 2024, we expect to have up to 18 new products or indications in the market – including the 13 for which we have already begun co-promotion or commercialization in 2022 and through October 2023. 2. Internal 2030 risk-adjusted revenue expectations for NME and new indications launches, excluding COVID-19 vaccine BA.4/BA.5 variant. 3. Risk-adjusted 2030 revenue goal from BD deals. 4. Expected to contribute toward risk-adjusted 2030 revenue goal of ~$25B from BD deals. 5. Through a standalone detailing arrangement. * Estimated FDA decision; subject to regulatory approval, ACIP and MMWR to follow. **MMWR to follow.
LRTI=Lower respiratory tract infection; RSV=Respiratory syncytial virus

First Ever Demonstration of Efficacy for an mRNA Flu Vaccine Candidate

Primary endpoints achieved in Ph 3 trial's 18-64 yrs. cohort; ≥65 yrs. cohort readout anticipated in 2023

First-Generation modFlu mRNA Vaccine Candidate

Phase 3 18-64 yrs. Cohort

- ***Non-inferiority*** and ***superiority*** vs. licensed influenza vaccine achieved at primary analysis[1]
- ***Efficacy maintained,*** with ***non-inferiority*** vs. licensed influenza comparator achieved at end of season analysis[1,2]
- Safety ***similar to standard*** flu vaccine
- ***Secondary immunogenicity*** endpoints achieved only for ***A strains***, not B strains

≥65 yrs. Age Group

- Phase 3 readout anticipated by ***year-end***
- Some interference was observed against B strains in early Phase studies for humoral responses
- ***Phase 1/2 T cell responses*** against A and B strains were encouraging

1. Primary and end of season analyses considered both influenza A and B cases collectively, though the vast majority of cases recorded in this trial, and during the 2022 / 2023 influenza season overall, were influenza A cases; 2. Superiority vs. the licensed influenza comparator not met at end of season analysis; Ph: Phase

Positive Phase 1/2 Influenza + COVID-19 Combination Vaccine Data[1]

Next-generation mRNA flu + COVID-19 combo candidates met all criteria for advancement to Ph 3

Phase 1/2 Combo Study in Adults Ages 18 – 64

Next-Gen mRNA Flu + COVID-19 Combo
Multiple Formulations and Dose Levels Evaluated

vs.

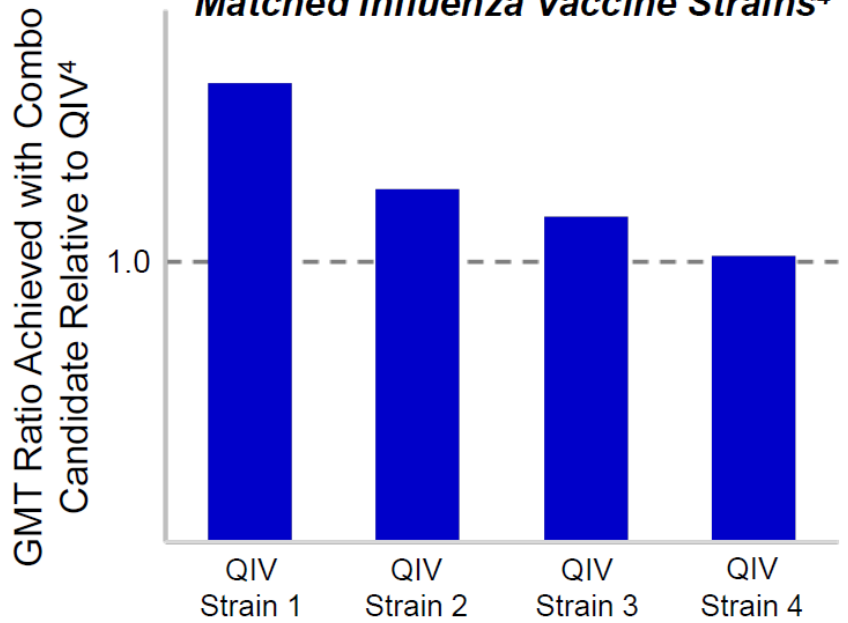
Licensed Influenza / COVID-19[2] Comparators
Administered Separately During the Same Visit

Topline Phase 1/2 Results on Next-Gen Reformulated mRNA Flu + COVID-19 Combination Candidates

GMT Ratios were Consistent with the Criteria Applied to Approved Vaccines Against the Respective **Influenza** and **SARS-CoV-2 Strains**[3]

Safety Profile Consistent with that of Pfizer-BioNTech COVID-19 Vaccine

GMT Ratios >1 Relative to QIV for All Matched Influenza Vaccine Strains[4]



Advancing Combo Program into Phase 3 Trial Expected to Begin in the Coming Months

1. Program being advanced in collaboration with BioNTech SE; 2. Pfizer-BioNTech Omicron BA.4/BA.5-adapted bivalent COVID-19 vaccine; 3. Phase 1/2 data on point estimates of GMT ratios achieved with lead combination candidates; 4. Point estimates of GMT ratios achieved with a lead combination candidate relative to QIV administered concomitantly with Pfizer-BioNTech Omicron BA.4/BA.5-adapted bivalent COVID-19 vaccine; Gen: Generation; GMT: Geometric mean titer; QIV: Quadrivalent influenza vaccine.

Moderna Shifts to a Large Loss in Q3 and Draws Down $1.8 Billion in Cash

Third quarter 2023 financial results

In $ millions, except per share amounts	3Q 2023	3Q 2022	Change (3Q'23 vs. 3Q'22)	
Net product sales	**$ 1,757**	**$ 3,120**	**$ (1,363)**	**(44)%**
Other revenue[1]	74	244	(170)	(70) %
Total revenue	**1,831**	**3,364**	**(1,533)**	**(46)%**
Cost of sales	2,241	1,100	1,141	104 %
Research and development	1,160	820	340	41 %
Selling, general and administrative	442	278	164	59 %
Total operating expenses	**3,843**	**2,198**	**1,645**	**75 %**
(Loss) income from operations	**(2,012)**	**1,166**	**(3,178)**	**(273)%**
Other income, net	54	51	3	6 %
Provision for income taxes	1,672	174	1,498	861 %
Net (loss) income	**$ (3,630)**	**$ 1,043**	**$ (4,673)**	**(448)%**
(Loss) earnings per share – Diluted	$ (9.53)	$ 2.53	$ (12.06)	(477) %
Weighted average shares – Diluted[2]	381	412	(31)	(8) %
Weighted average shares – Basic[2]	381	390	(9)	(2) %
Effective tax rate	(85) %	14 %		

[1]Includes grant revenue and collaboration revenue

[2]We generated a net loss in Q3 2023, therefore the basic and diluted weighted average shares calculation was the same

In $ billions	9/30/2023	6/30/2023	Change (9/30 vs. 6/30)	
Cash, cash equivalents and investments	$ 12.8	$ 14.6	$ (1.8)	(12)%

moderna

This is one of the largest quarterly losses seen in the history of the biotech sector.

We did a little checking on CapIQ and there have not been any companies in biopharma or life science tools that have reported a loss that big in the last seven quarters.

Source: https://investors.modernatx.com/events-and-presentations/events/default.aspx

Moderna Still Showing a Very Strong Pipeline

We will continue to deliver great impact with our mRNA medicines

Anticipating up to 15 launches in the next 5 years[1]

	Respiratory vaccines	Latent/other vaccines	Oncology	Rare disease
by 2025	**RSV** (older adults) mRNA-1345	**Seasonal Flu** mRNA-1010		
	Flu/COVID mRNA-1083	**NextGen COVID** mRNA-1283		
by 2028	**Flu/COVID/RSV** NextGen	**RSV/hMPV** (older adults) mRNA-1365	**CMV** mRNA-1647	**Norovirus** (older adults) mRNA-1403/-05
	RSV 2-18Y mRNA-1345	**Pandemic Flu** mRNA-1018	**EBV (IM)** mRNA-1189	**Lyme** mRNA-1975/-82
	NextGen Flu mRNA-1011/-1020	**Endemic hCOV** mRNA-1287	**VZV** mRNA-1468	**HSV** mRNA-1608

Subject to regulatory discussions[2]

Oncology	Rare disease	
INT (adjuvant melanoma) mRNA-4157	**MMA** mRNA-3705	**PA** mRNA-3927
INT (undisclosed indication) mRNA-4157	**PKU** mRNA-3210	**GSD1a** mRNA-3745
INT (adjuvant NSCLC) mRNA-4157		

1 Subject to positive clinical data and regulatory discussions/approvals
2 Subject to future regulatory discussions, there may be potential for accelerated or conditional approvals in some markets

moderna

Source: https://investors.modernatx.com/events-and-presentations/events/default.aspx

mRNA-1083 (flu + COVID-19 combination vaccine) Phase 3 trial is now dosing participants

mRNA-1083 has Fast Track designation from FDA

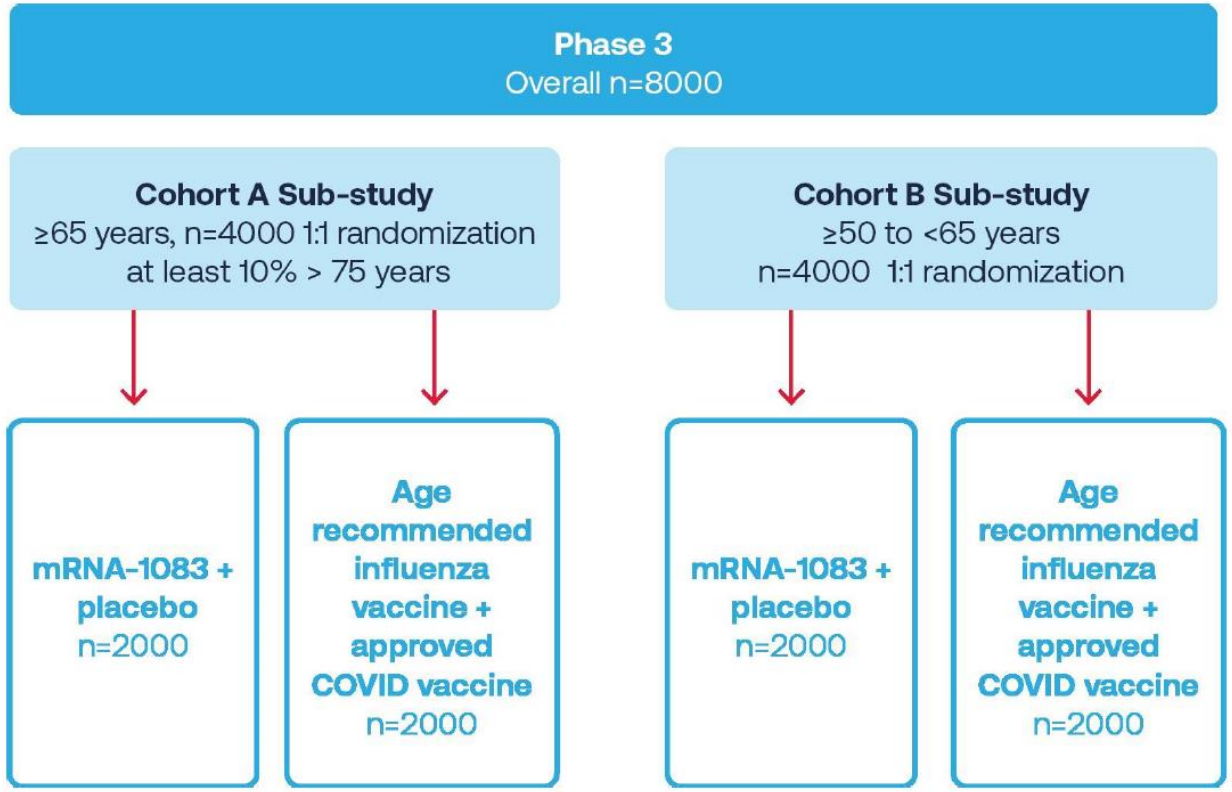
Design
Randomized, stratified, observer-blind, active-control study to evaluate the immunogenicity, safety and reactogenicity of mRNA-1083

Number of participants
8,000 healthy adults ≥ 50 years old

Vaccination schedule
mRNA-1083 and placebo or age recommend quadrivalent influenza vaccination and COVID-19 vaccine administered as two IM injections on day 1

Duration
Study participants will be followed for 6 months after study injection

Site location
Northern Hemisphere (United States and Canada)



Industry News

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

How The IRA Could Delay Pharmaceutical Launches, Reduce Indications, And Chill Evidence Generation

John Michael O'Brien, James Motyka, Julie Patterson

NOVEMBER 3, 2023 **Health Affairs** 10.1377/forefront.20231101.123865

Research beyond the trials required for initial FDA approval is a critical component of expanding accessible treatment options for patients. New indications, obtained by approximately a third of drugs, can reduce insurance-related barriers that patients face in accessing drugs for evidence-based off-label use. Furthermore, long-term outcomes data inform prescribing practices and clinical guidelines.

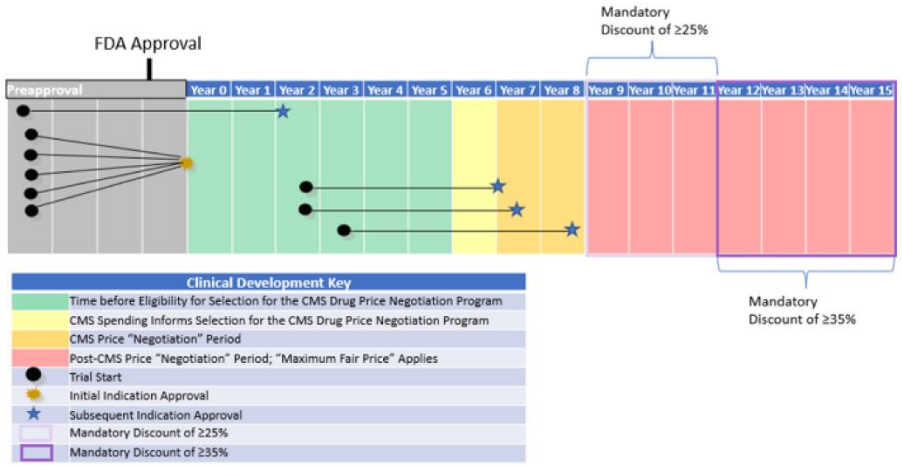
Drug manufacturers' decisions to take on the risks and costs of post-approval research about new indications and long-term health outcomes have historically aligned with the incentives offered by market exclusivity, which typically lasts for 13–17 years after FDA approval. The probability of launching a new indication peaks 7–8 years prior to generic entry and drops consistently and levels out to nearly zero in the years after a generic is introduced.

The Inflation Reduction Act (IRA) of 2022 significantly changes the economic incentives surrounding clinical development in the United States, affecting drug manufacturers' decisions about whether to pursue the types of post-approval research described above. The Medicare Drug Price Negotiation Program established by the IRA changes clinical development incentives by requiring the Centers for Medicare and Medicaid Services (CMS)—for the first time—to "negotiate" with drug manufacturers the "maximum fair price" of small-molecule drugs selected from among the 50 single-source drugs with the highest total Medicare Part B and D gross spending for which at least seven years have elapsed since their initial FDA approval or licensure date. Quotation marks around the word "negotiate" indicate that this is the term used by CMS in its publications. However, many manufacturers believe, and have alleged in lawsuits, that the process described by the agency does not provide a genuine opportunity to negotiate.

Case Study #2, Empagliflozin: Unintended Consequences On Long-Term Outcomes Studies

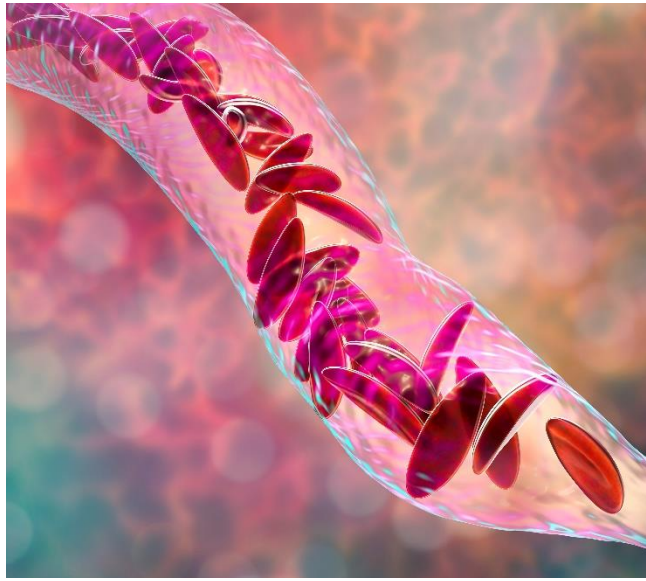
This case study discusses empagliflozin, a sodium-glucose cotransporter-2 inhibitor first approved in 2014 as a treatment for patients with type 2 diabetes mellitus (see exhibit below). The drug received an additional indication to reduce cardiovascular death in adults with type 2 diabetes mellitus approximately two years post-approval. Subsequently, the manufacturer started two new trials nearly three years post-initial approval to investigate the drug's safety and effectiveness in a new group of patients (those with heart failure with reduced and preserved ejection fraction). Because the primary outcomes of the trials risk of cardiovascular death and hospitalization for heart failure, the studies used extended time horizons of almost three and four years. Accordingly, the additional indications resulting from these clinical trials did not receive FDA approval until more than seven years after the drug was initially approved, when, under the IRA, a drug would already be eligible for selection for the Drug Price Negotiation Program.

This example highlights the way in which the IRA will disproportionately disincentivize long-term outcomes trials that demonstrate reductions in hard outcomes, evidence that is highly valued by practicing clinicians and guideline developers alike. Stakeholders have discussed potential ways to mitigate this impact, including: use of a transparent, value-based approach to "maximum fair price" determination, delaying the price negotiation period when new indications are approved, and allowing manufacturers to increase prices above inflation without incurring IRA-imposed inflation rebates when new evidence is generated.



Sources https://www.healthaffairs.org/content/forefront/ira-could-delay-pharmaceutical-launches-reduce-indications-and-chill-evidence, https://www.npcnow.org/resources/new-analysis-shows-ira-may-lead-delayed-launches-fewer-subsequent-indications-and-less

FDA Panel Says Vertex/CRISPR to Assess Safety Risks of Gene Therapy in Follow-up Study



Oct 31, 2023 (Reuters) - A panel of advisers to the U.S. health regulator said on Tuesday Vertex Pharmaceuticals and CRISPR Therapeutics could assess potential safety risks of their sickle cell disease gene therapy after approval.

If the therapy is approved, Vertex has proposed a 15-year follow up of patients to evaluate the safety outcomes of the therapy.

The inherited red-blood-cell disorder causes the cells to become sickle-shaped due to abnormal levels of hemoglobin in the body. A vaso-occlusive crisis occurs when sickled red blood cells block blood flow to the point that tissues become deprived of oxygen and causes pain.

The panel members said the 15-year follow up will help generate data from real-time monitoring of the therapy, which uses the new gene editing CRISPR technology.

Staff reviewers to the U.S. Food and Drug Administration said the new type of technology raised concerns about the "off target", or unintended genomic alterations that can potentially cause other side effects, but did not raise any concerns about the therapy's efficacy.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/fda-panel-says-vertexcrispr-assess-safety-risks-gene-therapy-follow-up-study-2023-10-31/

Vertex AdComm Panelists on Exa-Cel Saw Risks as Theoretical and Benefit as Unequivocal

Rob Stein, NPR, Oct 31, 2023

"In totality, the data support the remarkable clinical benefit of exa-cel in patients with sickle cell disease," Dr. William Hobbs, Vertex's vice president, clinical development, told the committee.

Because the FDA concurred in an analysis posted Friday, the agency did not ask the advisers to take the usual step of assessing exa-cel's benefits or whether the agency should approve the therapy.

Instead, because of the high stakes of approving an entirely new kind of technology to treat people for the first time, the FDA instead asked the advisers to focus on whether sufficient research had been done to spot "off-target" effects of the treatment — unintended editing errors that missed their mark in the DNA and that could potentially cause long-term health problems.

While agreeing additional research could be helpful, several committee members expressed enthusiasm for the treatment and few concerns that theoretical issues would outweigh the clear benefits.

"It's really exciting to see how many patients have been treated and how positive the results have been," said Scot Wolfe of the UMass Chan Medical School in Worcester, Mass. **"We want to be careful to not let the perfect be the enemy of the good."**

Source: https://www.npr.org/sections/health-shots/2023/10/31/1208041252/a-landmark-gene-editing-treatment-for-sickle-cell-disease-moves-closer-to-realit

BioMarin to Replace CEO Bienaimé with Genentech Veteran Alexander Hardy

Kristin Jensen, *Biopharma Dive*, Nov 2, 2023 (excerpt)

BioMarin is bringing on a new chief executive as the gene therapy company struggles with an initially disappointing launch for an important new product.

Alexander Hardy, 55, will take over the reins at BioMarin as of Dec. 1, having stepped down from his role as CEO of Roche's Genentech unit on Wednesday. He replaces Jean-Jacques Bienaimé, 70, who led the company for 18 years and will initially stay on as an adviser and board member.

"Serving as CEO of this industry-leading, innovative and impactful company over the past 18 years has been the highlight of my career," said Bienaimé on a call with investors Wednesday evening. "We have built an incredible organization with great potential to be further unlocked by Alexander and the team."

Hardy will be tasked with guiding BioMarin through a pivotal period in its development. After years of ups and downs, the company in June finally won U.S. approval for Roctavian, the first gene therapy to treat hemophilia A. But complicated negotiations with payers have made it difficult to move patients onto the therapy, which has a list price of $2.9 million in the U.S. and is also approved in Europe.

JJ Bienaimé
Long serving CEO of BioMarin is stepping down

Source: https://www.biopharmadive.com/news/biomarin-ceo-bienaime-hardy-roctavian-sales-launch/698615/

Alpine Immune Sciences Presents Initial Clinical Data on Povetacicept in Autoimmune Glomerulonephritis at ASN

Press Release, Nov 2, 2023

Povetacicept is a potent dual antagonist of the BAFF (B cell activating factor) and APRIL (a proliferation inducing ligand) cytokines, which play key roles in pathogenesis of multiple autoimmune diseases via their roles in the activation, differentiation and/or survival of B cells, particularly antibody-secreting cells, as well as T cells and innate immune cells. RUBY-3 is a multiple ascending dose, multi-cohort, open label, phase 1b/2a study of povetacicept in autoimmune glomerulonephritis, where povetacicept is administered subcutaneously (SC) once every four weeks for up to 48 weeks.

Key Highlights from the Late-Breaking ASN Poster Include:

- As of October 25th, 20 participants with IgA nephropathy (IgAN) have been enrolled, 12 at the 80 mg dose level, of whom 5 have UPCR data available at 24 weeks.
- In IgAN, treatment with low-dose povetacicept, 80 mg SC every four weeks was associated with clinically meaningful improvements in proteinuria, with a 53.5% reduction from baseline in urine protein to creatinine ratio (UPCR; n=5) at 24 weeks. In addition, at 24 weeks, 4/5 (80%) had achieved remission, as defined as UPCR < 0.5 g/g and ≥50% reduction in UPCR from baseline with stable renal function (≤ 25% reduction in eGFR from baseline). (Fig. 1)
- In IgAN, treatment with low-dose povetacicept was also associated with a >60% reduction in the key disease-related biomarker galactose-deficient IgA1 (Gd-IgA1), as well as stable renal function as assessed by estimated glomerular filtration rate (eGFR) (+7.1% from baseline at 24 weeks; n=5).
- The first participant with primary membranous nephropathy (pMN), also treated with povetacicept 80 mg SC every four weeks, achieved an immunological remission, defined as a reduction in the highly disease-relevant biomarker anti-PLA2R1 to an undetectable level, from a baseline of 209 to < 2 RU/mL by 22 weeks.
- Povetacicept has been well tolerated, with no reported administration-associated reactions, no instances of IgG < 3 g/L, and no severe infections.
- A higher dose of povetacicept, 240 mg SC every four weeks, continues to enroll.

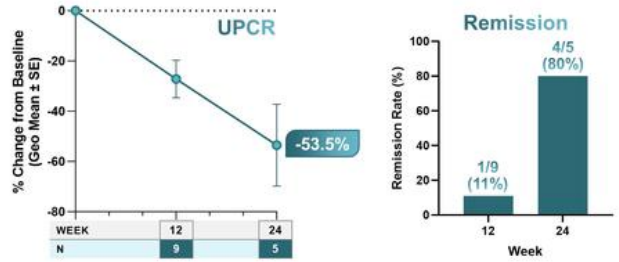


Figure 1. Clinically Meaningful Improvements in Proteinuria, Suggesting Remission

Source: https://ir.alpineimmunesciences.com/news/news-details/2023/

Reviva Announces Topline Results from Global Pivotal Phase 3 RECOVER Trial of Brilaroxazine in Schizophrenia

Press Release, October 30, 2023

Reviva Pharmaceuticals Holdings, Inc. (NASDAQ: RVPH) ("Reviva" or the "Company"), a late-stage pharmaceutical company developing therapies that seek to address unmet medical needs in the areas of central nervous system (CNS), inflammatory and cardiometabolic diseases, today announced positive topline results and successful completion of its pivotal Phase 3 RECOVER trial evaluating the efficacy, safety and tolerability of once-daily brilaroxazine, a serotonin-dopamine signaling modulator in adults with schizophrenia. The trial successfully met its primary endpoint, with brilaroxazine at the 50 mg dose achieving a statistically significant and clinically meaningful 10.1-point reduction in Positive and Negative Syndrome Scale (PANSS) total score compared to placebo (-23.9 brilaroxazine 50 mg vs. -13.8 placebo, $p<0.001$) at week 4. Brilaroxazine also achieved statistically significant and clinically meaningful reductions in all major symptom domains and secondary endpoints at week 4 with the 50 mg dose vs. placebo. The 15 mg dose of brilaroxazine was numerically superior to placebo on the primary endpoint and most secondary endpoints, and reached statistical significance on two key secondary endpoints.

"We are excited to report positive topline results for our Phase 3 RECOVER trial, further confirming the well-tolerated safety profile and improvements in all major symptom domains including PANSS total score, positive and negative symptoms, and Clinical Global Impression – Severity score (CGI-S) as previously observed in our Phase 2 REFRESH trial," said Laxminarayan Bhat, Ph.D., Founder, President, and CEO of Reviva. "Importantly, we believe the unique multifaceted mechanism of action of brilaroxazine, a serotonin-dopamine signaling modulator, has potential to improve additional key disease drivers like neuroinflammation. The RECOVER pivotal results highlight the potentially differentiated therapeutic profile of once-daily brilaroxazine and underscore the potential to address treatment limitations for the 24 million people living with schizophrenia around the world. We expect to report long-term data from our OLE trial in the fourth quarter of 2024 and initiate a registrational Phase 3 RECOVER-2 trial in the first quarter of 2024, which if successful will help support our planned New Drug Application (NDA) submission to the FDA expected in 2025."

Source: https://revivapharma.com/press-releases/

Reviva Data Table

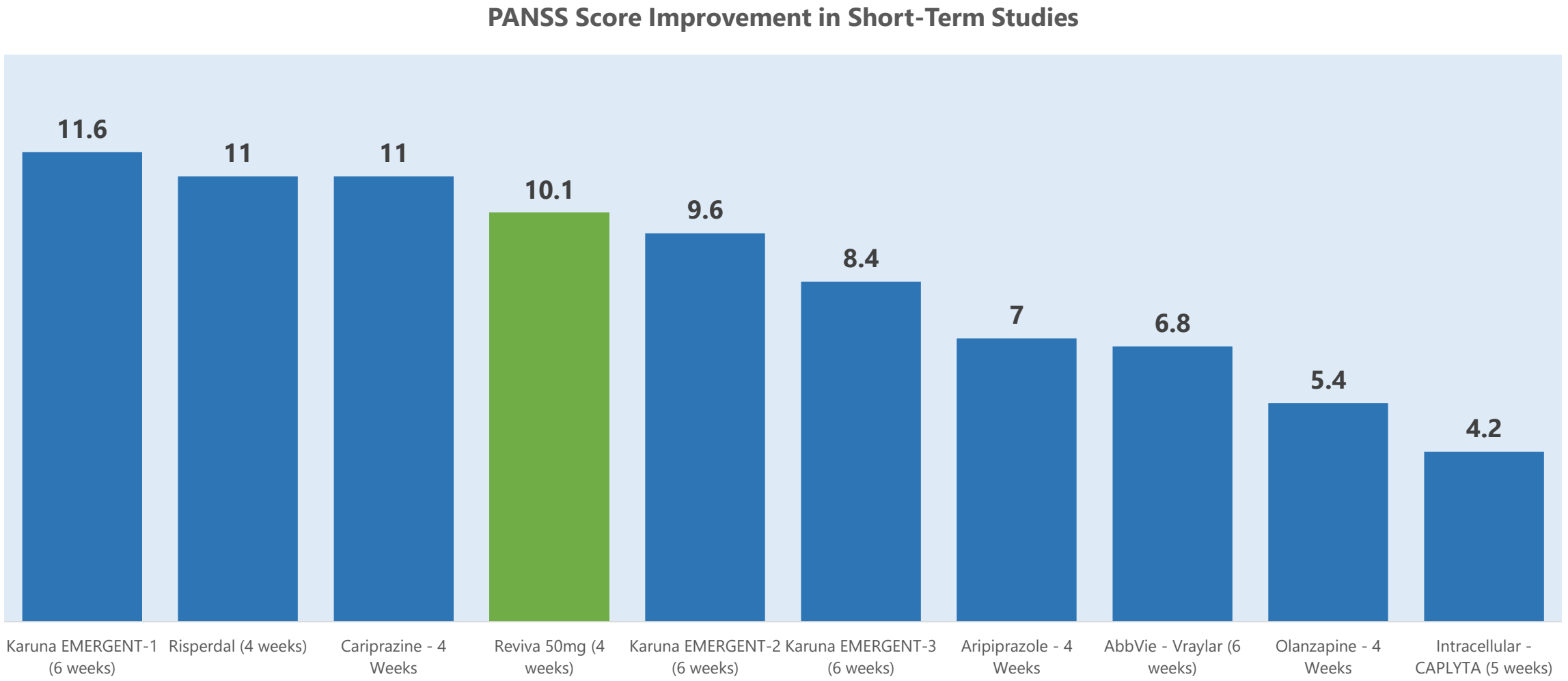
Key statistically significant and clinically meaningful improvements with brilaroxazine vs. placebo in patients with schizophrenia and a mean PANSS total score of 97-99 at baseline include:

Primary and Secondary Endpoints	Point Reduction/ Improvement for Brilaroxazine 50 mg vs. Placebo at Week 4	Cohen's d Effect Size	P Value
PANSS Total Score	10.1	*0.6*	*< 0.001*
Positive Symptoms	2.8	*0.5*	*< 0.001*
Negative Symptoms (NS)	2.0	*0.4*	*0.003*
NS Marder Factor	2.1	*0.4*	*0.002*
PANSS Social Cognition	1.6	*0.5*	*< 0.001*
PANSS Excitement/Agitation	2.1	*0.5*	*< 0.001*
Personal and Social Performance	6.3	*0.5*	*< 0.001*
CGI-S score	1	*0.5*	*< 0.001*

Source: https://revivapharma.com/press-releases/

Comparison of Reviva Data To Other Agents

Brilaroxazine is highly competitive with the best agents on the market. The molecule is very similar structurally to existing agents such as aripiprazole. Showed solid improvement in cognition. On the other hand, it has not shown direct evidence that it can address some of the unmet needs in schizophrenia care.



Sangamo to Focus on Neuroscience and Restructuring

Investing.com, Nov 3, 2023

Sangamo Therapeutics Inc. (NASDAQ:SGMO) has announced a strategic shift towards becoming a neurology-focused genomic medicine company during its recent earnings call. The company plans to prioritize resources and investments in neurology programs while deferring new investments in Fabry disease and CAR-Treg programs. These changes are expected to reduce annual operating expenses by approximately 50%, enabling the company to fund operations until Q3 2024 without additional capital.

Key takeaways from the call include:

1. Sangamo is undergoing a strategic transformation to focus on neurological diseases with limited treatment options.
2. The company will defer new investments in Fabry disease and CAR-Treg programs until securing collaboration partners or external investments.
3. To conserve cash resources, Sangamo will reduce its U.S. workforce, close its Brisbane facility, and transition to the Richmond facility.
4. The company's COO and Chief Scientist Officer will be leaving, and new leadership roles will be filled to support the neurology-focused pipeline.
5. Sangamo is actively seeking potential partners or financing to fund the Phase 3 trial for their Fabry disease program.
6. The company expects to fund its operations until the third quarter of 2024 without raising additional capital.
7. Sangamo is confident in the potential of its pipeline programs, including Nav1.7 for small fiber neuralgia and Prion disease. The company is also working on identifying a Blood-Brain Barrier Penetrant Capsid to expand its delivery capabilities. Sangamo anticipates sharing non-human primate data on new novel delivery capsids in early 2023 and expects to submit an IND for NAV1.7 in 2024.

The company is also seeking an ideal partner for their Fabry program who has a commitment to patients, capital resources, and the ability to complete the study and commercialize globally. Sangamo's CAR-Treg program is progressing well, and they plan to share data from multiple cohorts in 2023. They are also focusing on epigenetic regulation therapies for neurological diseases and are using Zinc Fingers technology for precise gene regulation.

Source: https://ng.investing.com/news/stock-market-news/earnings-call-sangamo-therapeutics-to-focus-on-neurology-streamline-operations-and-reduce-costs-93CH-1130154

British Biotech Races US's 'Buff Billionaires' For Secret of Eternal Youth

Julia Kollewe, *The Guardian*, Nov 5, 2023

About a decade ago, 125 amateur cyclists from all over the UK filed into the laboratories at King's College London. Aged between 55 and 79, they were there to participate in a long-term study examining how regular physical activity affects the ageing process.

The study is one of many projects undertaken at British universities in recent years, as the UK carves out a leading role in ageing research globally. While still in its infancy, the longevity science sector is set to become a multibillion-dollar industry, forecast to grow to $2bn (£1.6bn) by 2030, according to Insight Analytics.

A number of longevity biotech startups have sprung up, such as Senisca in Exeter, Genflow Biosciences in London, and Shift Bioscience and clock.bio in Cambridge. In the US, the pack is led by California firms such as Altos Labs, which also has a research institute in Cambridge, Calico, backed by Google's owner Alphabet, Unity Biotechnology and Retro Biosciences.

"We punch way above our weight in terms of the quality and the quantity of our scientific output in the ageing space," said Lorna Harries, professor of molecular genetics at the University of Exeter, who set up the spinout Senisca in 2020. "But while we're a scientific powerhouse, we need to develop our ability to turn our findings into things that are tangible outcomes in the real world."

"Potentially, you could live to 120 if you did all the right things and you were lucky enough to have the right genes," said Prof Lynne Cox at the University of Oxford, who specialises in cell senescence – the way cells that have been damaged or stressed change to a state that can damage surrounding tissues.

Ageing is generally regarded as the accumulation of damage to cells, or wear and tear, over time, that can lead to loss of function and common diseases such as diabetes, heart disease, dementia and cancer.

In 1993, Cynthia Kenyon at the University of California at San Francisco conducted a pioneering study which demonstrated that mutations in one gene in a species of worm could double their lifespan. But this could not be reproduced in humans. Today, there are various attempts at cellular reprogramming or other tweaks to halt or reverse ageing.

One area of research is inflammation, a main driver of biological ageing. Cox said: "The human genome is full of bits of viral DNA that crept in there over our evolution, and they're normally repressed. But as we get older, they jump out again and trigger inflammation, the body's response to an infection. The problem is the immune system is also old, and so it can't deal with it."

The anti-ageing industry in the US has attracted a flurry of interest from a clutch of health-obsessed tech entrepreneurs, some of whom are known as **"buff billionaires"** for their newfound fitness. Among those is Amazon founder Jeff Bezos, who backs Altos Labs.

Bezos and PayPal founder Peter Thiel are investors in San Francisco-based Unity Biotechnology, which focuses on eliminating or modulating senescent cells to restore damaged tissues, initially for neurological conditions and eye diseases. The artificial intelligence entrepreneur Sam Altman, chief executive of OpenAI, has invested in Retro Biosciences, which is betting on cellular reprogramming, as is NewLimit, backed by the cryptocurrency billionaire Brian Armstrong, chief executive of Coinbase.

A group at Oxford University is looking at ways of improving elderly immune systems by making cells more able to clear out their rubbish, in a process called autophagy.

Centenarians tend to pass on longevity genes, but having the right gut bacteria is also key, academics say. Researchers in Japan found that gut bacteria in centenarians are different from those of other older people; one bacterium even acts as an antibiotic and kills harmful bacteria in the gut.

Researchers talk about a paradigm shift – moving to treating the shared causes of ageing diseases rather than their consequences, which will relieve the pressure on the NHS and other health systems.

Some are confident that the UK can be among the leaders in the longevity industry. Miles Witham, a professor of clinical trials for older people at Newcastle University, says: "We are world leaders in terms of laboratory ageing research in the UK; we're also world leaders in the epidemiology of ageing in the UK. What is hard is to make sure that what we've learned comes through into clinical trials in humans and eventually into the clinic [to patients]. Nobody's really doing enough of this in any country in the world. We're trying to make sure that the UK is at the forefront of this."

Source: https://www.theguardian.com/business/2023/nov/05/british-biotech-races-uss-buff-billionaires-for-secret-of-eternal-youth

The 2023 Healthcare Power Ranking Of Tech Giants

All major tech companies want to build strongholds early in this lucrative segment. The road is bumpy, marked with expensive failures and exciting successes.

Andrea Koncz, *Medical Futurist*, Nov 2, 2023 (excerpt)

1 Google

No matter whether it's about population genomics, artificial intelligence, longevity, or activity tracking, Google is there. And what's more, they started to conquer the three most important fields: AI, ageing and, in a broader sense, life science research. It seems they are everywhere in healthcare.

A very recent – and exciting – announcement from Google Cloud is that they teamed up with CareCloud to help ambulatory practices and other small and medium healthcare providers make use of generative artificial intelligence to inform clinical decision-making and boost operational efficiencies using cloud services.

By using Google's offerings such as Vertex AI and Generative AI App Builder, the company is developing tools to bring physicians at all practices the same AI-enabled capabilities that are increasingly available at large hospitals and health systems – but which are out of reach for smaller practices.

2 Microsoft

Microsoft has a massive advantage: a huge user base in hospitals and health practices all around the world.

In September 2020, it launched Cloud for Healthcare, a new, healthcare-centric cloud. It integrates the company's existing services like Microsoft Teams, Azure IoT and its Healthcare Bot. Building on its traditional strength, Microsoft Cloud for Healthcare started offering a $95-a-month package that can help smaller practices manage health data at scale.

In April 2021, Microsoft acquired AI-powered speech-technology company, Nuance. The company's software can listen and transcribe doctor-patient conversations into organized medical notes. And of course, recent announcements come from the realm of generative AI. Like the cooperation with Epic, which also incorporates the use of Nuances DAX system. These new AI copilot capabilities aim to support healthcare professionals in areas like note summarization, ambient clinical documentation, improving administrative efficiency, or using real-time data to support diagnostics.

"Health systems using Epic's EHR system will be able to run generative AI solutions through Microsoft's OpenAI Azure Service. Microsoft uses OpenAI's language model GPT-4 capabilities in its Azure cloud solution." – the companies announced.

Source: https://medicalfuturist.com/the-healthcare-power-ranking-of-tech-giants/

The 2023 Healthcare Power Ranking Of Tech Giants

All major tech companies want to build strongholds early in this lucrative segment. The road is bumpy, marked with expensive failures and exciting successes.

continued...

3 Amazon

In the last couple of years, Amazon has shown exponential growth in interest in the pharma industry and healthcare. Looking at the company's profile, it is not surprising that it's aiming for the online pharmacy market.

In 2023 Amazon also entered the generative AI realm by launching genAI-based clinical documentation services. The Amazon Web Services tool, called HealthScribe, allows providers to build clinical applications that use speech recognition and generative AI to create transcripts of patient visits.

However, remote pharmaceutical services aren't the only remote component of health that Amazon is looking into. In 2021, the company's telehealth branch expanded into 21 more states in the U.S.

In 2022, the company coughed out $3.9 billion for One Medical, a chain of primary care clinics around the United States. This deal seems to have meant the end of Amazon Care, which was shot down at the end of 2022. Amazon Clinic, the successor of Amazon Care is moving forward with solid steps. It expanded its virtual care service across the United States, which lets patients connect with multiple telehealth provider groups. "Visits cost an average of $75 and Amazon will not accept insurance for the visits." – they announced in the summer of 2023.

4 Nvidia

"For over a decade, we have partnered with the medical devices ecosystem to bring innovative diagnostic imaging, robotic surgery and patient monitoring devices to the market," Kimberly Powell, Vice President of Healthcare of NVIDIA, told The Medical Futurist in an interview.

NVIDIA's technology is unique in that it is a single computing platform that is embedded in a medical device, at the edge of a workstation or server at the hospital, or available on every public cloud. That means they can serve applications that need to be done in real-time like emergency room triage, robotic surgery, or ICU patient monitoring to assist in the detection and understanding of disease all the way to studying patient populations to predicting patient outcomes.

The company announced a collaboration with Medtronic in 2023 to accelerate the development of AI in the healthcare system and bring new AI-based solutions into patient care.

NVIDIA gear was used in a fascinating study in 2023, where authors trained a large language model for medical language and fine-tuned it across a wide range of clinical and operational predictive tasks.

Source: https://medicalfuturist.com/the-healthcare-power-ranking-of-tech-giants/

McKinsey
Health Institute

Reframing employee health: Moving beyond burnout to holistic health

A new McKinsey Health Institute survey across 30 countries offers insights into how organizations can help create a workplace that prioritizes physical, mental, social, and spiritual health.

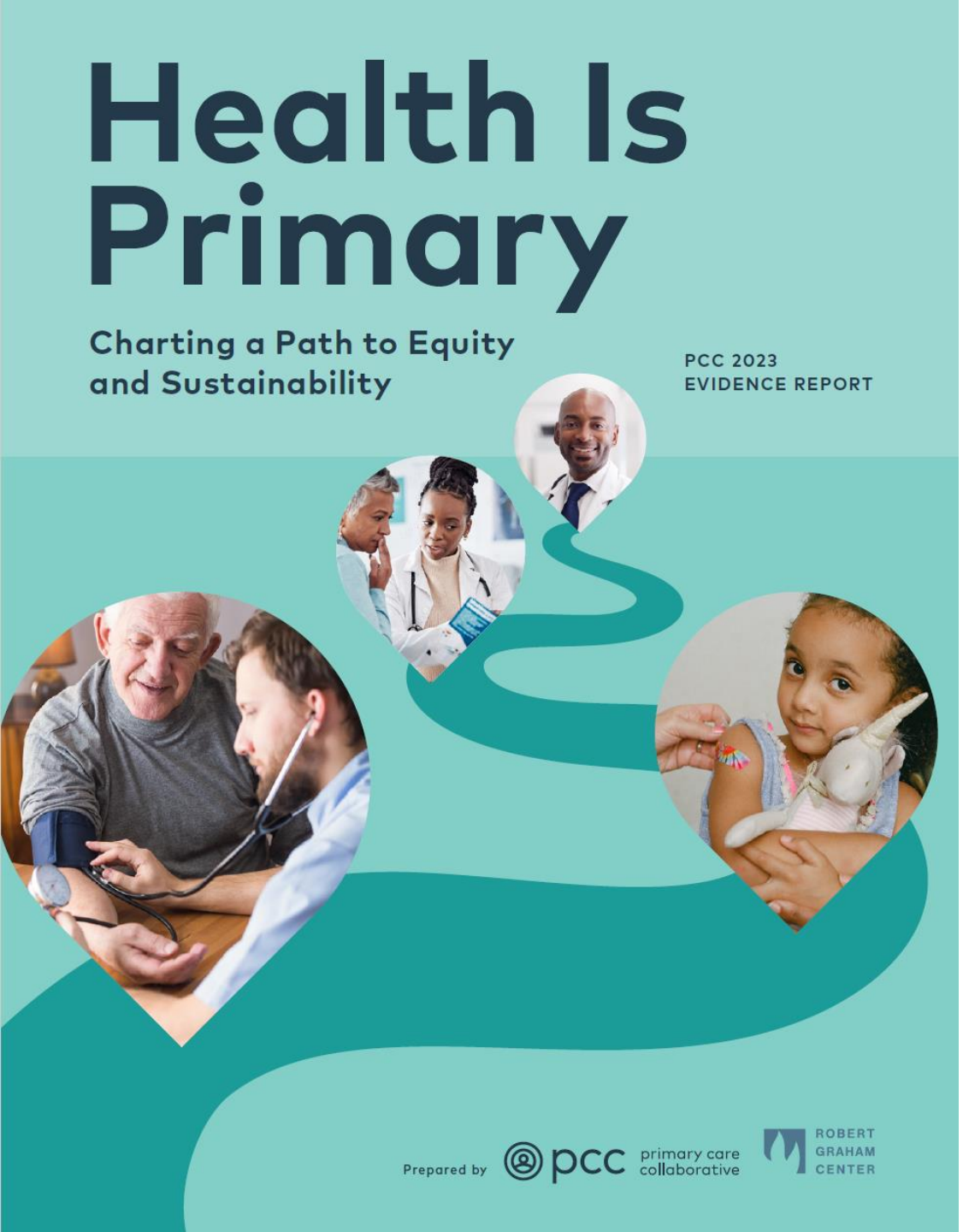
by Jacqueline Brassey, Brad Herbig, Barbara Jeffery, and Drew Ungerman

Holistic health encompasses physical, mental, social, and spiritual health. The McKinsey Health Institute's 2023 survey of more than 30,000 employees across 30 countries found that employees who had positive work experiences reported better holistic health, are more innovative at work, and have improved job performance.

For employees, good holistic health is most strongly predicted by workplace enablers, while burnout is strongly predicted by workplace demands. Providing enablers alone will not mitigate burnout, and addressing demands alone will not improve holistic health. A complementary approach is needed.

Organizational, team, job, and individual interventions that address demands and enablers can boost employee holistic health. These may include flexible working policies, leadership trainings, job crafting and redesign, and digital programs on workplace health.

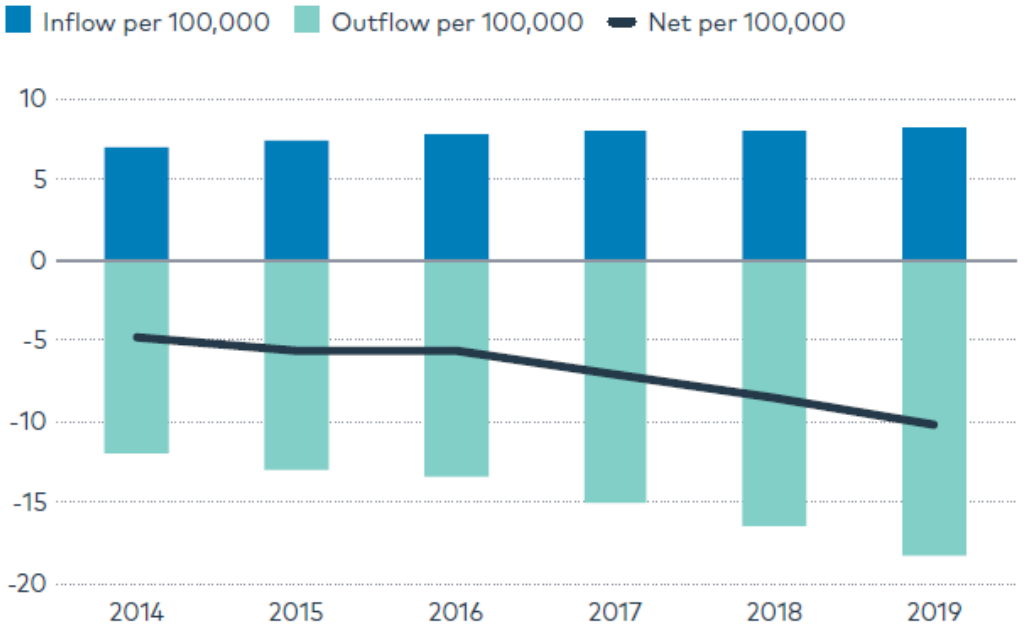
Source: https://www.mckinsey.com/mhi/our-insights/reframing-employee-health-moving-beyond-burnout-to-holistic-health#/



Primary Care Crisis in America Worsens

FIGURE 1

Inflow and Outflow, Primary Care Clinicians per 100,000 Population, 2014–2019 (with Physician Retirement at Age 65)



Annually since 2014, there has been a net decrease in the number of Primary Care Clinicians available per 100,000 individuals in the United States (Figure 1). Overall, there was a deficit of 4.91 PCCs per 100,000 in 2014, and that has more than doubled to a net decrease of 10.11 PCCs per 100,000 individuals in 2019.
The decrease for Primary Care Physicians is even steeper. More specifically, there was a net loss of 8.03 PCPs per 100,000 based on more retirements than entrances in 2012 as compared to a net loss of 14.22 PCPs per 100,000 in 2020.

Source: https://thepcc.org/sites/default/files/resources/pcc-evidence-report-2023.pdf

Substantial Medically Disenfranchised Population

Primary Care Collaborative

MEDICAL NEED IS SIGNIFICANT

The number of medically disenfranchised in this country is estimated to be 100 million, about 30 percent of the U.S. population, according to an analysis by the National Association of Community Health Centers (NACHC) and HealthLandscape.[6] Black, Hispanic, and Asian American/Pacific Islander individuals, as well as those living in rural and poor urban areas are more likely to be disenfranchised as a percentage of their population in comparison to White Americans. The definition of medically disenfranchised is derived by adding the populations in Health Professional Shortage Areas (HPSAs) and Medically Underserved Areas/Populations (MUA/Ps) against primary care professionals serving in these geographies and populations, and then subtracting those currently served by Community Health Centers (CHCs).[6,7]

TABLE 1

Medically Disenfranchised Populations by Race and Ethnicity

	U.S. Population	Medically Disenfranchised
White	75.8%	68.7%
Black	13.6%	15.7%
Asian American/ Pacific Islander	1.3%	3.5%
Hispanic	18.9%	21.9%

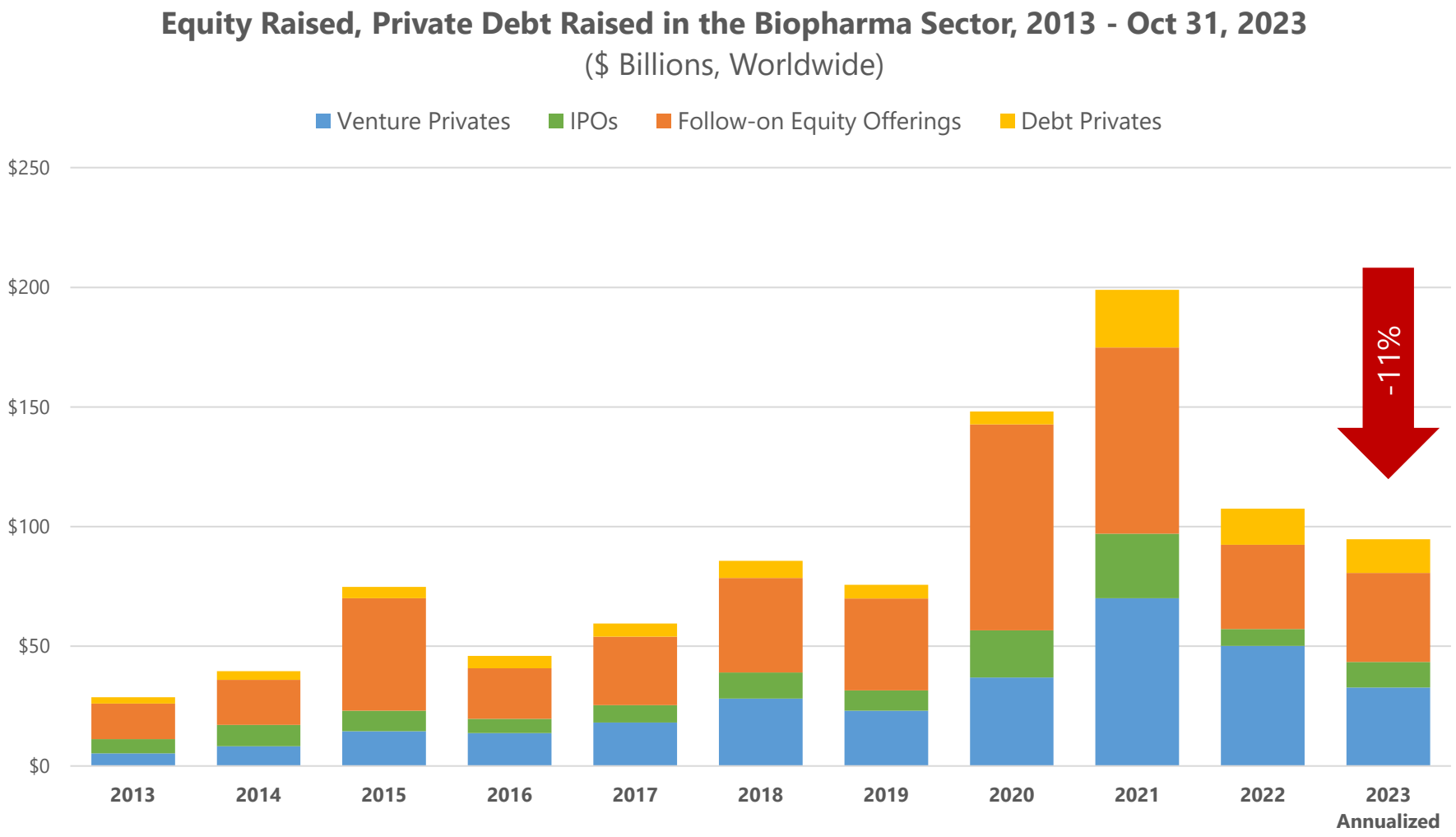
Source: "Closing the Primary Care Gap: How Community Health Centers Can Address the Nation's Primary Care Crisis," NACHC. Accessed August 15, 2023. https://www.nachc.org/resource/closing-the-primary-care-gap-how-community-health-centers-can-address-the-nations-primary-care-crisis/

Source: https://thepcc.org/sites/default/files/resources/pcc-evidence-report-2023.pdf

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

Capital Markets Environment

Overall Biopharma Capital Raised To Date In 2023 Is Down 11% Versus 2022 (On an Annualized Basis)



Venture private volumes and follow-on equity volumes this year have been down modestly compared to 2022.

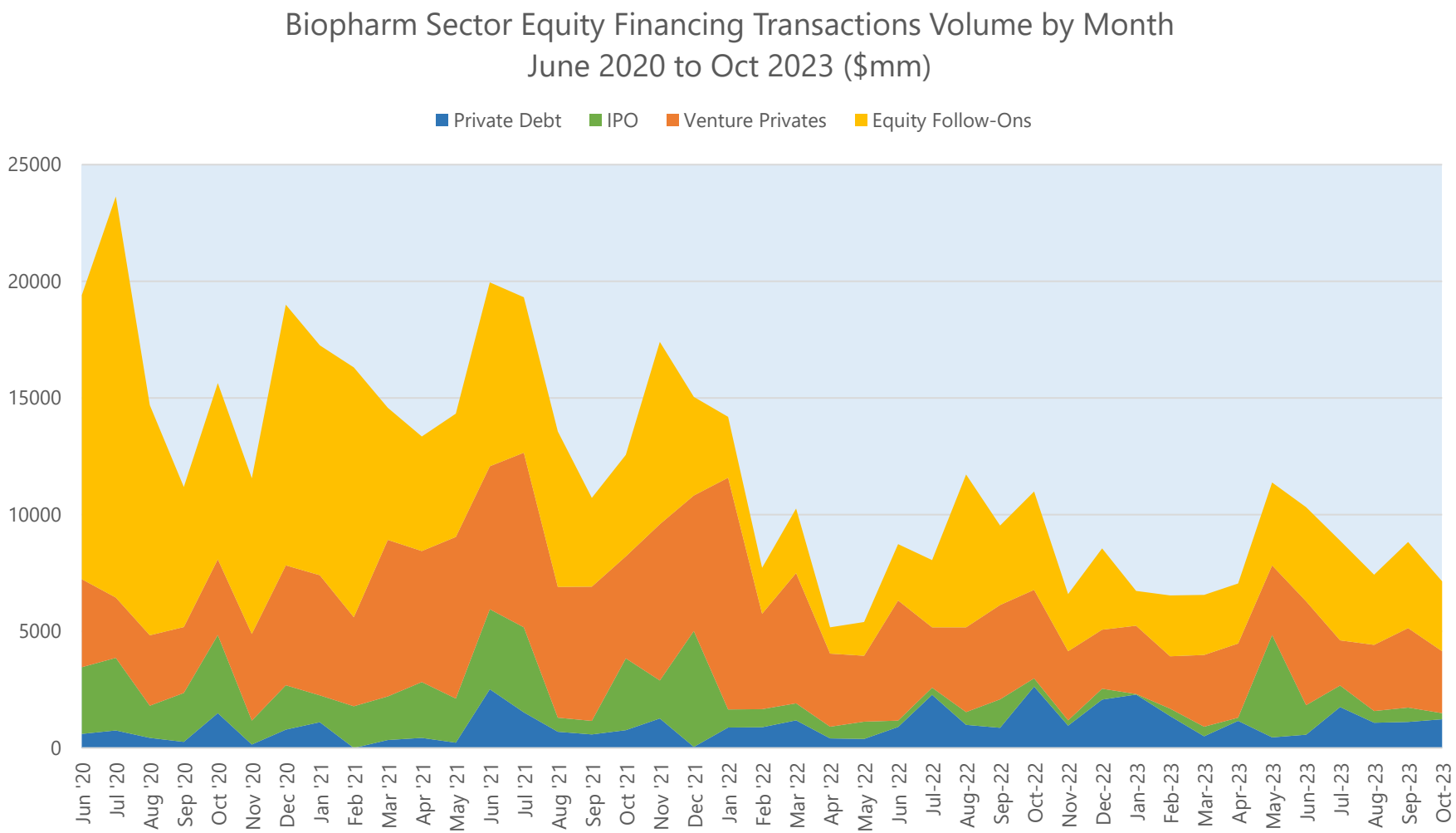
The markets have been materially weaker in 2023 than in 2021 and 2022.

The pace of capital raising in 2023 exceeds that of all years prior to 2020.

We have returned to a Pre-Pandemic type fundraising environment.

Source: CapitalIQ and Stifel research

Monthly Biopharma Market Capital Raise Data Shows Return to Q1 Activity Levels in October

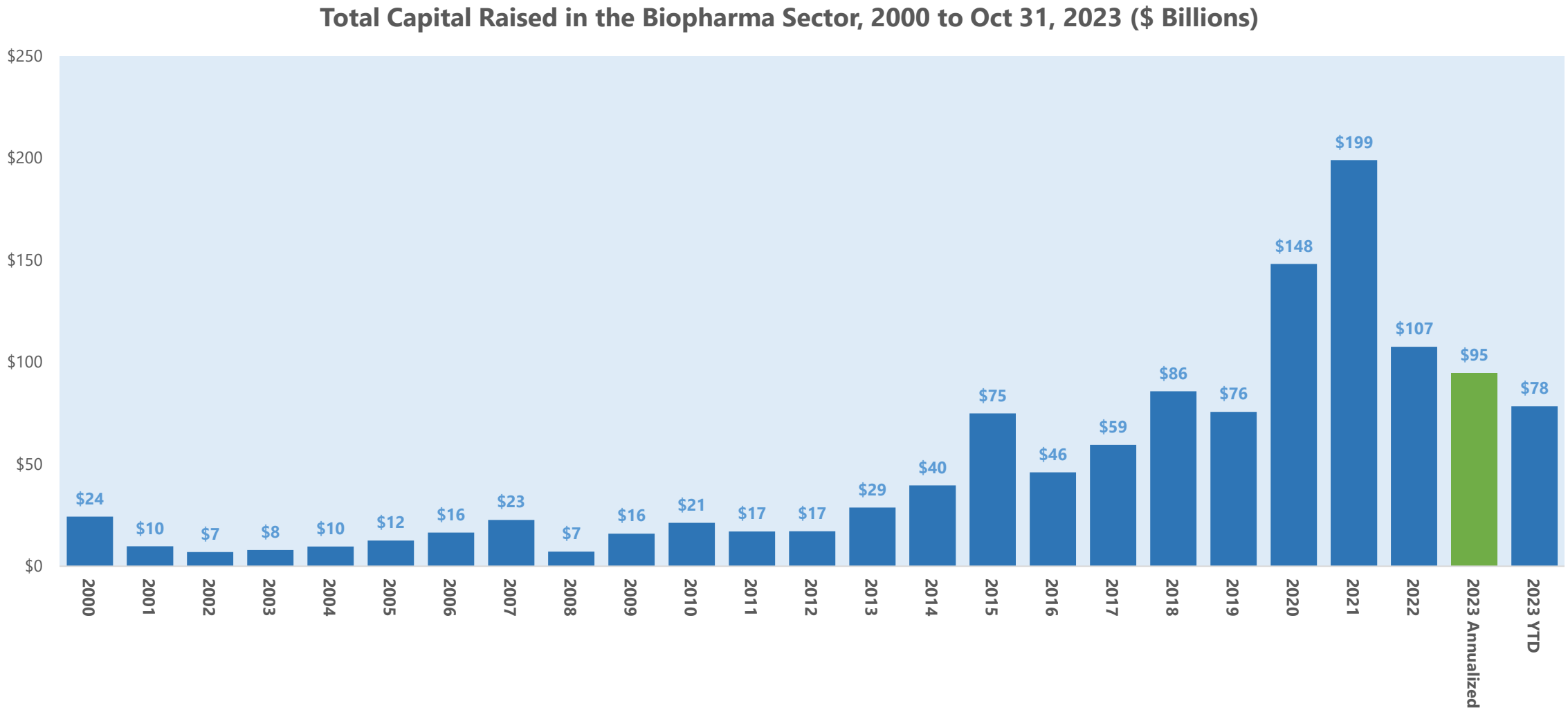


October was a challenging month for the capital markets overall as the full effect of the Fed's "higher for longer" mantra sunk in for the capital markets. The result is that issuance volumes sunk to 2023Q1 levels.

Recent issuance volumes remain well down from levels seen during the Pandemic.

Source: CapitalIQ and Stifel research

Total Capital Raised in Biopharma Above Levels of 2019 and Before

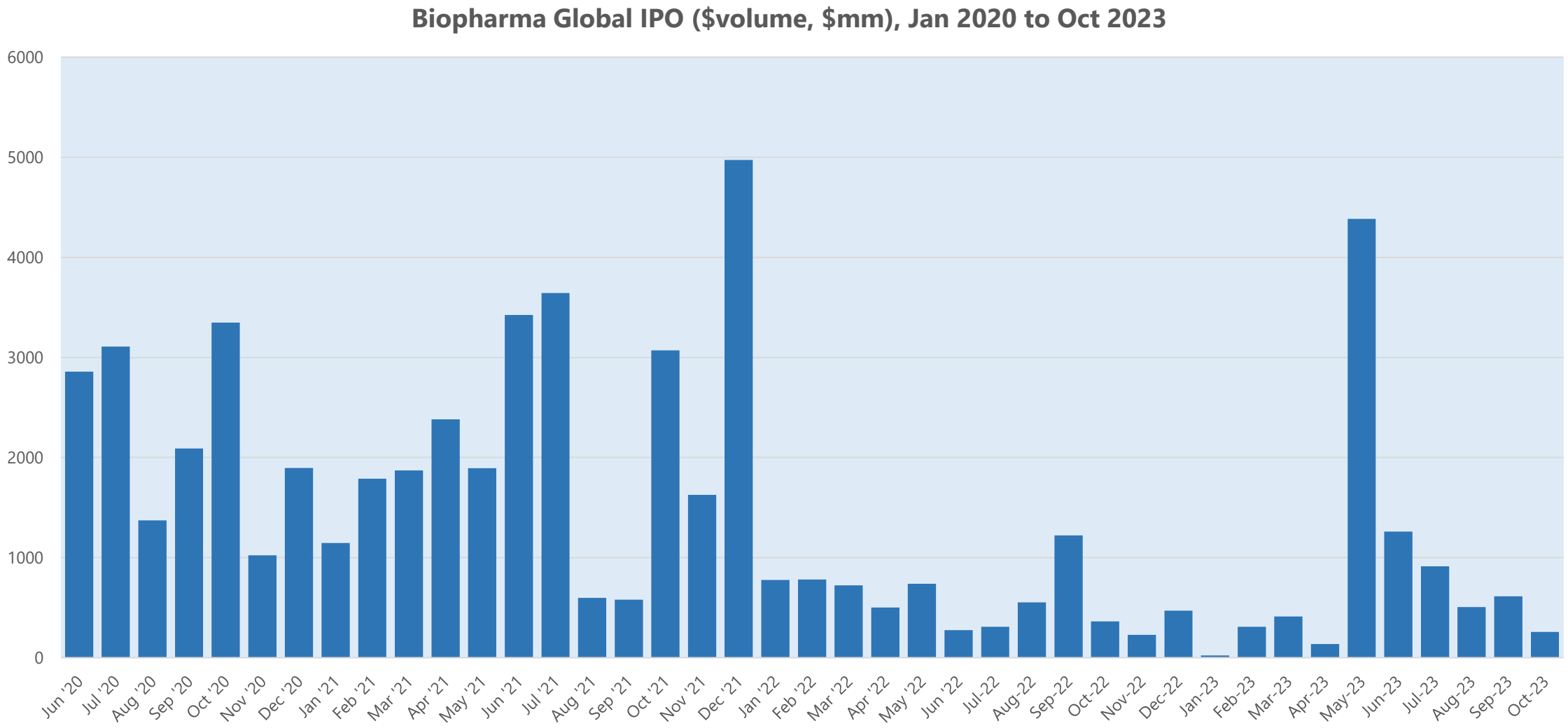


Source: CapitalIQ and Stifel research. Note that this chart includes IPOs, follow-ons and venture privates. The chart includes venture / private debt after 2012 but does not include public debt.

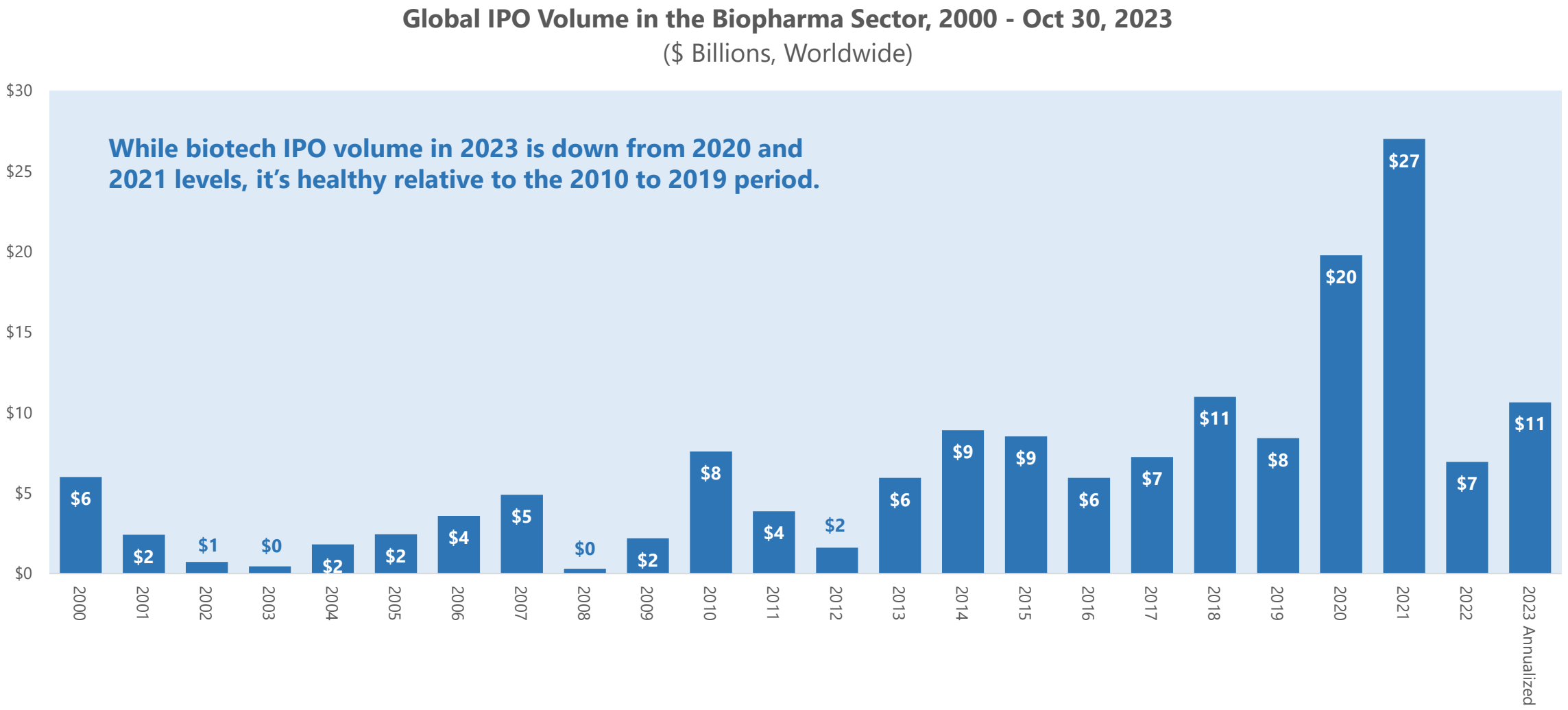
The Biopharma IPO Market

IPO Market Soft in October 2023

There was one IPO in the market last week.



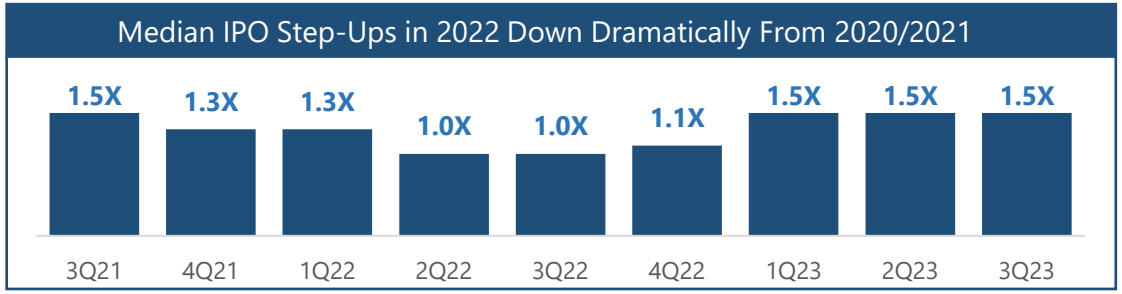
Annualized 2023 Global Biotech IPO Volume Up 57% From 2022 and Down 59% Versus 2021

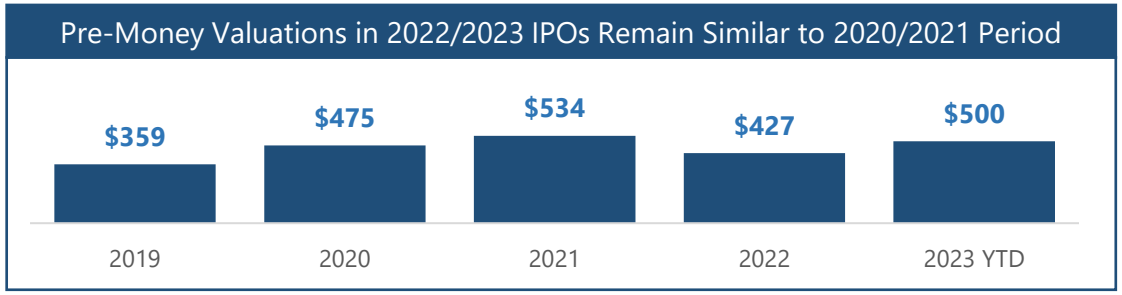


Source: CapitalIQ.

U.S. Biotech IPO Market Conditions

- Going into the second half of this year we saw only three IPOs. Since then, we have seen eight additional IPOs of $50mm or more in size.
- Unfortunately, this year's crop has struggled in a hostile capital market. At this point only two of the ten deals are trading above first day offer.
- The principal market challenge has been a hawkish Fed.
- These IPOs came at a median step-up to last round valuation of 1.5x. 2023 step-ups have been substantially higher than for companies that issued in 2022. Those step-ups were down dramatically from the Pandemic period.
- The market remains selectively open with a number of quality issuers on file.
- The tone of the market remains difficult but appeared to be starting to turn with last week's more dovish Fed commentary.





Source: Stifel Capital Markets. Pre-money values are fully diluted, accounting for options and warrants using the Treasury Stock Method.

30 Most Recent Biotech IPOs

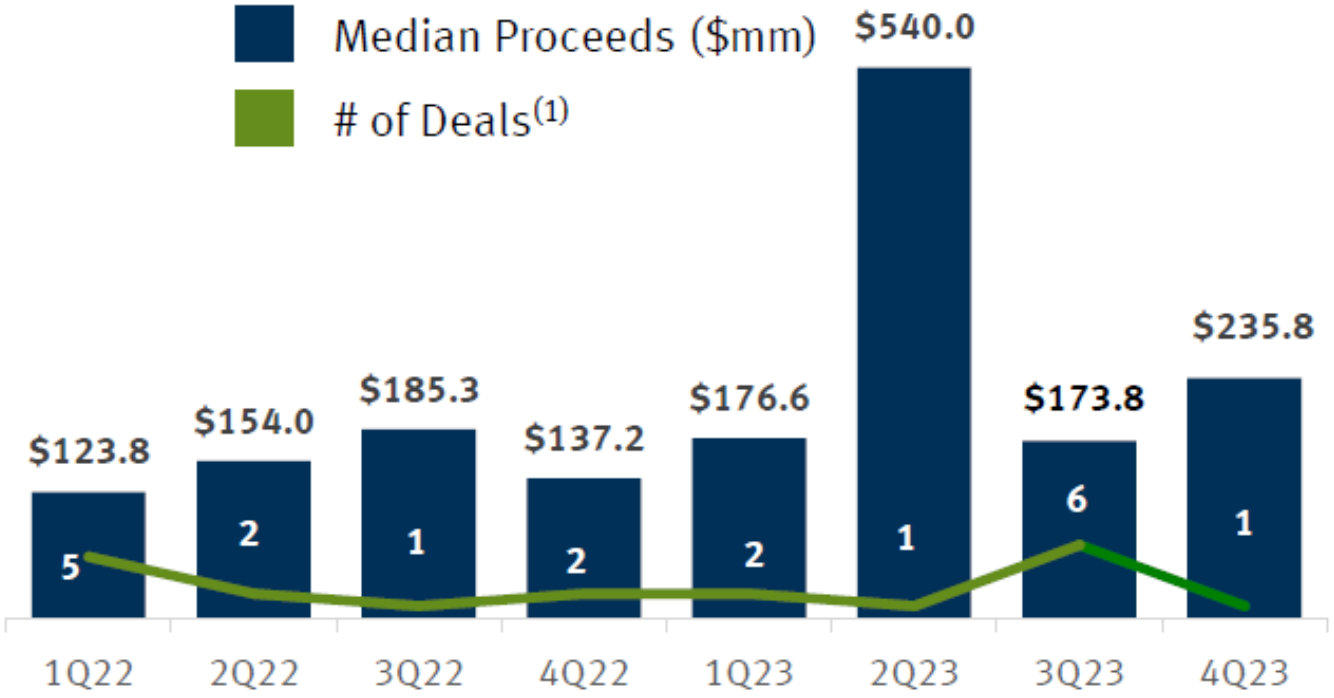
($ in millions)

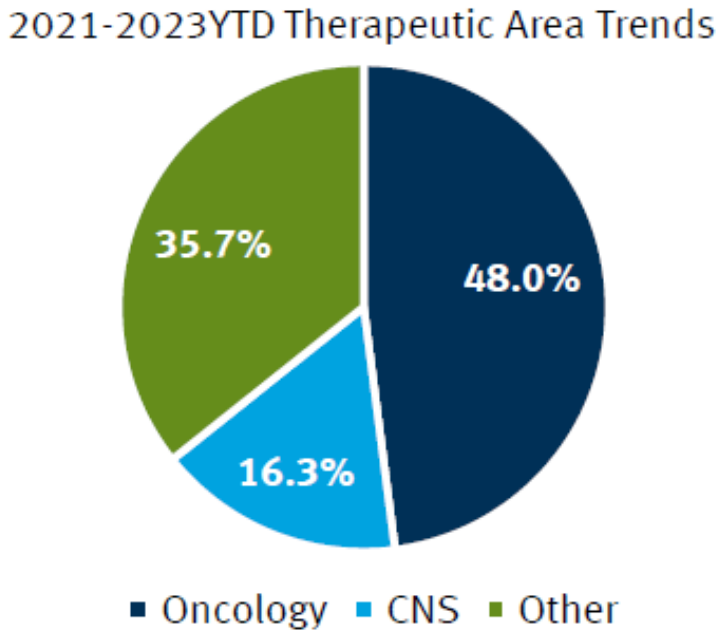
Issuer	Offer Date	Issuance Amount	Pre-Money Valuation	Pricing vs. Range	Step-Up	Price Change Offer to Day 1	Price Change Offer to Current
Abivax SA[3]	10/20/23	$235.8	$495.0	Low End	NA	(20.4%)	(20.0%)
Adlai Nortye Ltd[4]	09/29/23	97.5	769.3	Midpoint	1.2x	(34.8%)	(64.7%)
RayzeBio, Inc.	09/14/23	311.0	800.6	High End	1.4x	33.3%	2.3%
Neumora Therapeutics Inc.	09/14/23	250.1	2,509.6	Midpoint	1.5x	(4.4%)	(31.4%)
Turnstone Biologics Corp.	07/20/23	80.0	194.1	Low End	0.5x	(8.3%)	(83.4%)
Sagimet Biosciences Inc.	07/13/23	85.0	301.4	Midpoint	1.5x	(0.3%)	(76.8%)
Apogee Therapeutics, Inc.	07/13/23	300.1	505.8	High End	2.0x	24.9%	(7.3%)
ACELYRIN, Inc.	05/04/23	540.0	1,221.5	High End	1.5x	30.6%	(47.4%)
Mineralys Therapeutics, Inc.	02/09/23	192.0	452.8	High End	1.7x	15.3%	(52.5%)
Structure Therapeutics, Inc.	02/02/23	161.1	414.3	High End	1.2x	73.3%	354.5%
Acrivon Therapeutics, Inc.[5]	11/14/22	99.4	183.0	Below	0.9x	33.1%	(59.8%)
Prime Medicine, Inc.	10/20/22	175.0	1,501.9	Midpoint	1.2x	(9.6%)	(67.1%)
Third Harmonic Bio, Inc.	09/14/22	185.3	496.0	Midpoint	1.0x	15.8%	(59.4%)
PepGen, Inc.	05/05/22	108.0	169.1	Below	0.8x	7.4%	(54.7%)
HilleVax, Inc.	04/28/22	200.0	449.8	Midpoint	1.3x	12.3%	(35.6%)
AN2 Therapeutics, Inc.	03/25/22	69.0	230.7	Midpoint	1.0x	2.7%	(3.1%)
Arcellx, Inc.	02/04/22	123.8	436.7	Low End	1.3x	12.0%	111.7%
Vigil Neuroscience, Inc.	01/07/22	98.0	329.0	Below	1.4x	(9.6%)	(39.4%)
Amylyx Pharmaceuticals, Inc.	01/07/22	190.0	955.8	Midpoint	1.9x	(4.9%)	(17.2%)
CinCor Pharma, Inc.[6]	01/07/22	193.6	417.9	Midpoint	1.2x	0.0%	62.5%
Vaxxinity Inc	11/11/21	78.0	1,720.2	Below	1.0x	27.3%	(92.5%)
IO Biotech, Inc.[7]	11/04/21	100.1	300.6	Low End	1.0x	11.8%	(94.0%)
Evotec SE	11/03/21	435.0	3,411.2	Below	NA	1.1%	(61.6%)
LianBio	11/01/21	325.0	1,490.0	Midpoint	1.7x	(14.4%)	(75.6%)
Entrada Therapeutics, Inc	10/28/21	181.5	455.3	Midpoint	1.3x	19.8%	(27.5%)
Aura Biosciences Inc	10/28/21	75.6	349.3	Low End	1.3x	5.7%	(48.2%)
Xilio Therapeutics Inc	10/21/21	117.6	339.4	Low End	1.2x	0.0%	(87.1%)
Ventyx Biosciences, Inc.	10/20/21	151.6	690.2	Midpoint	1.3x	31.4%	(8.7%)
Pyxis Oncology, Inc.	10/07/21	168.0	394.5	High End	1.5x	(17.5%)	(90.2%)
Theseus Pharmaceuticals, Inc.	10/06/21	160.0	500.2	High End	1.1x	16.1%	(86.6%)
Last 30 IPO Summary Statistics:							
Mean		$182.9	$749.5		1.3x	8.3%	(28.7%)
Median		$164.6	$454.1		1.3x	6.6%	(50.4%)

Shows U.S. market listings and excludes companies that raised less than $50 million or more than $1bn. Price change to current is computed to Oct 27, 2023. IPO's highlighted in yellow are those where Stifel acted as an underwriter. Source: Stifel Capital Markets.

U.S. Biotech IPO Market Open to High Quality Issuers This Year

Biopharma IPOs: Fewer But Larger Transactions



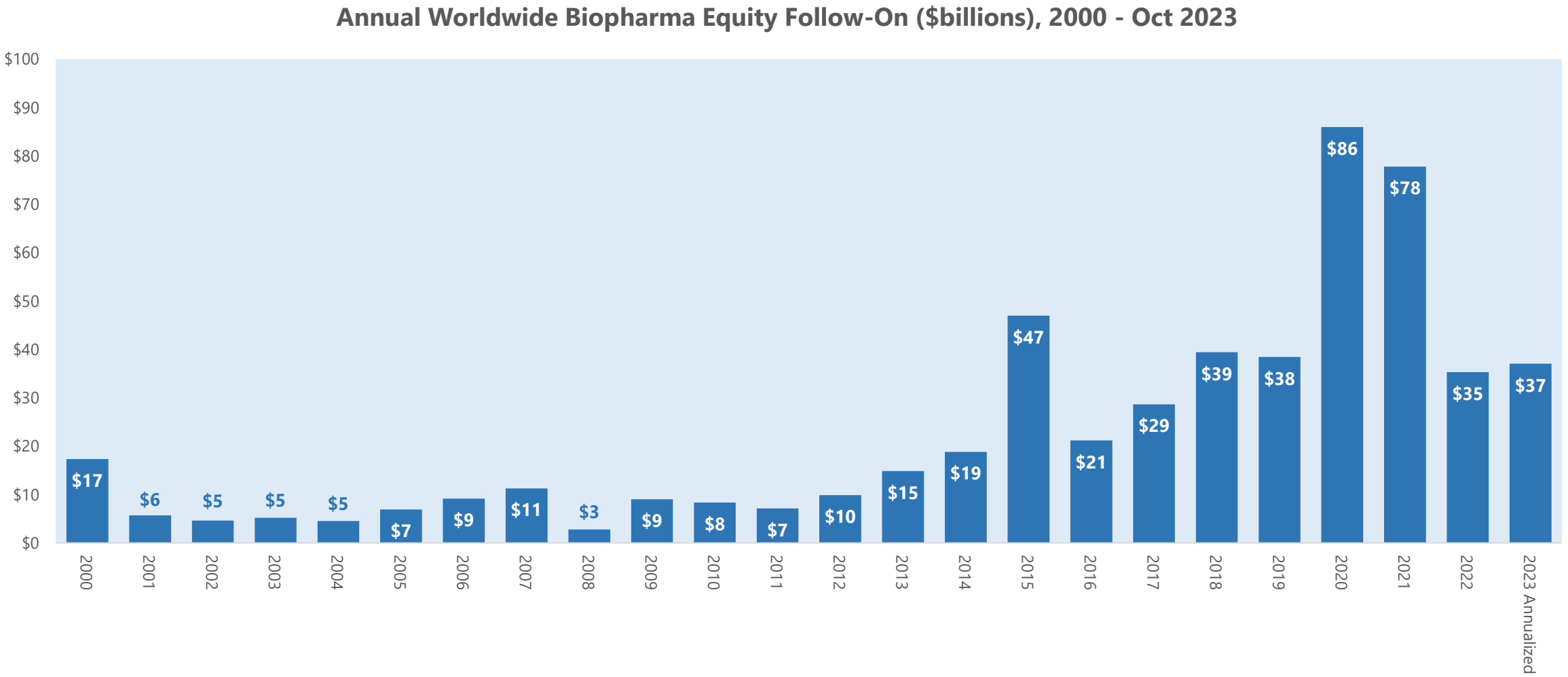


Source: Stifel Capital Markets.

The Biopharma Follow-on Equity / Secondary Market

Annualized 2023 Global Follow-On Equity Volume Up 5% From 2022 and Down 52% Versus 2021

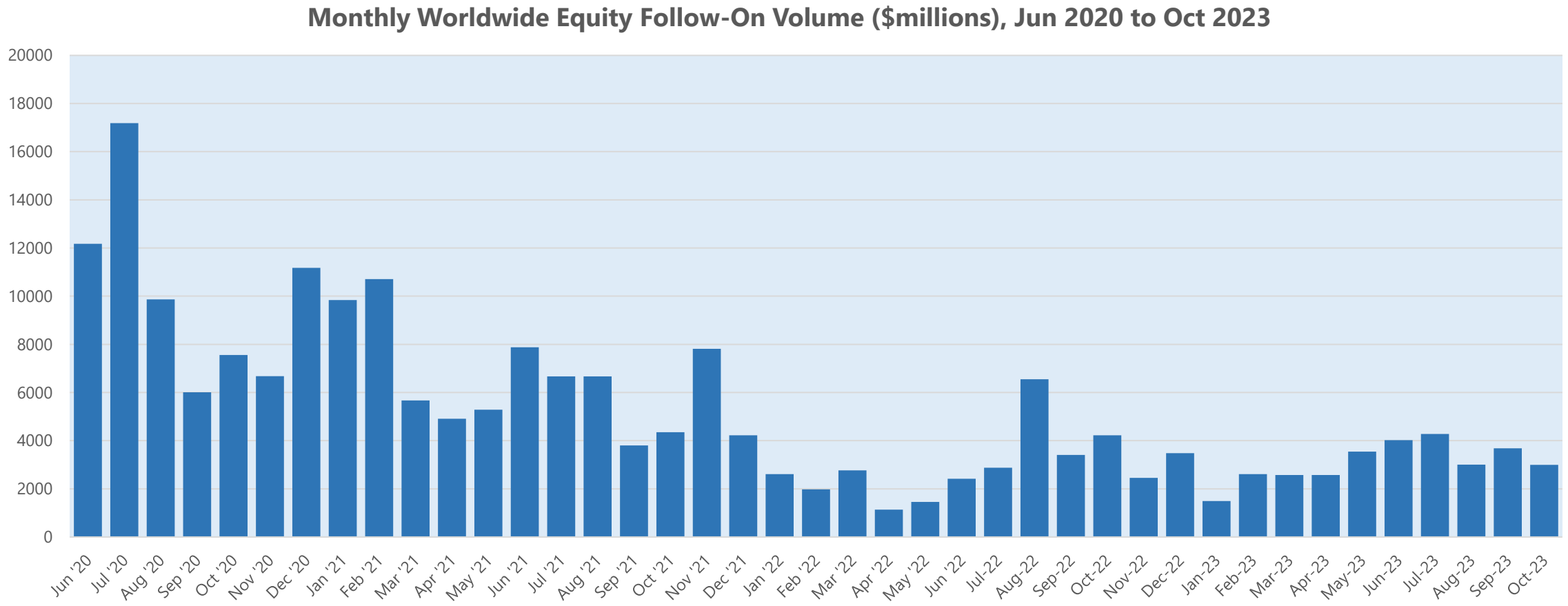
Looking back, the 2022 to 2023 follow-on equity market looks very similar volume-wise to the markets of 2018 and 2019.



Source: CapitalIQ and Stifel research

Monthly Global Biopharma Follow-On Volume Weak in October

The follow-on market weakened in October but remained well above levels seen at the trough in Q2 2022. Last week saw $448 million in issuance. The largest follow-ons last week included a $185 million PIPE by Viridian and an $88 million PIPE by Vyne Therapeutics.



Source: CapitalIQ.

Viridian Therapeutics Appoints New Chief Executive Officer, Unveils Next Generation FcRn Inhibitor Programs and Announces $185 Million Private Placement Financing

WALTHAM, Mass.--(BUSINESS WIRE)--Oct. 30, 2023-- Viridian Therapeutics, Inc. (NASDAQ: VRDN), a biotechnology company focused on discovering and developing potential best-in-class medicines for serious and rare diseases, today announced that Stephen Mahoney has been appointed the company's President and Chief Executive Officer, and a member of the Board of Directors, effective immediately. Viridian also disclosed a preclinical portfolio of FcRn inhibitors designed to deliver next generation treatments for patients suffering from antibody-mediated autoimmune diseases. To advance its expanded strategic priorities, the company also announced that it has entered into an agreement to sell shares of its common and Series B preferred stock to certain institutional investors in a private placement transaction and will receive aggregate gross proceeds of $185 million, before deducting estimated offering expenses.

VIRIDIAN

Stifel was pleased to act as lead placement agent on Viridian's latest offering.

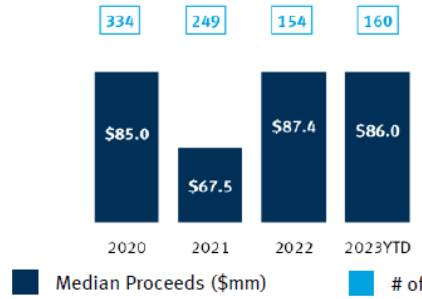
$185 Million Financing to Fund Expanded Pipeline and Extend Cash Runway

Viridian announced it has entered into agreements for a private placement financing that is expected to close by November 1, 2023, and result in anticipated gross proceeds of approximately $185 million, before deducting estimated offering expenses. The financing was led by Fairmount Funds with participation from both existing investors, including Braidwell LP, Commodore Capital, Deep Track Capital, Venrock, Paradigm BioCapital and Perceptive Advisors, as well as new investors, including entities managed by RTW Investments, LP and Surveyor Capital (a Citadel company). In the private placement, Viridian is selling an aggregate of 8,789,022 shares of its common stock at a price of $12.38 per share and an aggregate of 92,312 shares of its Series B preferred stock at a price of $825.3746 per share, which are convertible into approximately 6,154,441 shares of common stock, subject to beneficial ownership conversion limits. Proceeds will be used to fund pipeline programs, including the FcRn portfolio, and for general corporate purposes and working capital. The company also expects that the proceeds will extend its cash runway to fund its operating plan into 2026.

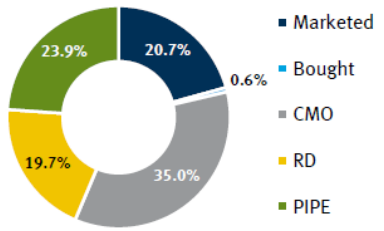
Source: https://investors.viridiantherapeutics.com/news-releases/news-release-details/viridian-therapeutics-appoints-new-chief-executive-officer

Follow-Ons Have Transitioned To A Catalyst Driven Market[1]

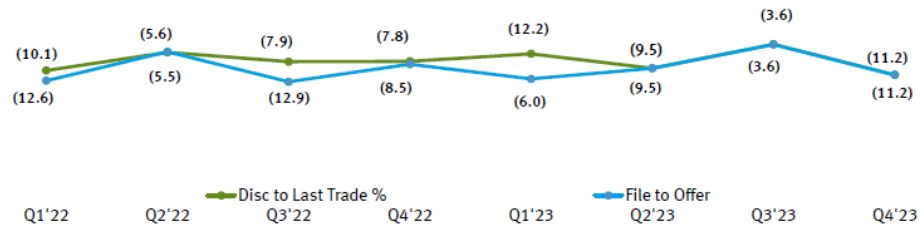
Historical biotech FOs



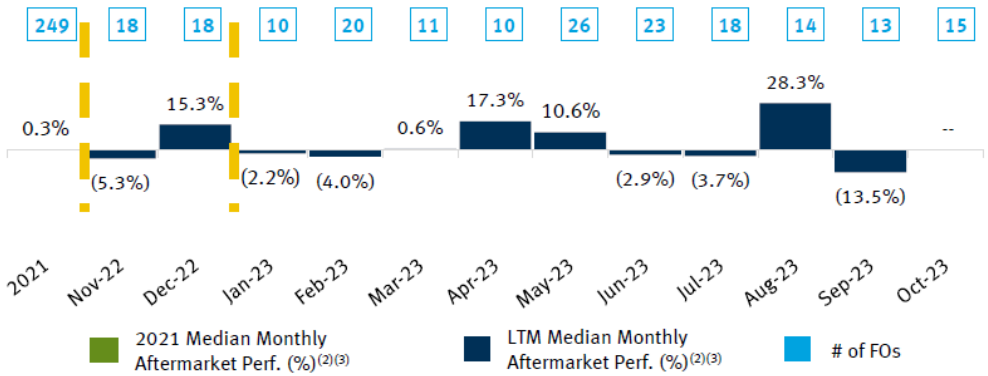
2022-2023YTD execution format



Discounts Have Remained in Line Despite Recent Volatility[2]



Aftermarket Performance Has Been Mixed[1]



Recent Biotech FOs By Market Cap[2]

Pricing Date	Issuer	Execution Format	Market Cap ($mm)	Total Proceeds ($mm)	File to Offer (%)	% Change: Offer to 1 Day (%)	% Change: Offer to Current (%)	Deal Catalyst	Warrants?
Recent FOs with Market Cap >$2.5bn									
10/18/23	Ultragenyx Pharmaceutical Inc	Marketed	$2,632.9	$300.0	(18.5%)	11.5%	9.4%	✓	✓
10/16/23	Nuvalent Inc	Marketed	3,305.2	300.0	(3.4%)	(5.1%)	(9.0%)	✓	✓
10/11/23	Cerevel Therapeutics Holdings, Inc.	CMO	3,592.3	450.0	--	1.7%	0.2%		
09/28/23	Madrigal Pharmaceuticals, Inc.	CMO	3,161.4	500.0	(0.0%)	(3.7%)	(20.6%)	✓	
09/27/23	Immunovant Inc	Marketed	5,221.6	450.1	(4.9%)	4.7%	(12.1%)	✓	
07/18/23	argenx SE	Marketed	26,972.1	1,100.0	1.1%	7.9%	(6.1%)	✓	
06/28/23	Axsome Therapeutics, Inc.	CMO	3,632.7	225.0	(10.0%)	(0.0%)	(17.2%)		
05/08/23	Legend Biotech Corporation	RD	11,330.6	350.0	(4.5%)	7.4%	(0.5%)		
05/04/23	ImmunoGen Inc	Marketed	2,771.6	325.0	2.0%	5.4%	20.0%	✓	
04/19/23	Vaxcyte Inc	Marketed	3,408.9	500.2	(3.2%)	11.7%	14.6%	✓	
	Average (n=10)		**$6,602.9**	**$450.0**	**(4.1%)**	**4.1%**	**(2.1%)**		
	Median (n=10)		**$3,500.6**	**$400.0**	**(3.3%)**	**5.0%**	**(3.3%)**		
Recent FOs with Market Cap $500mm - $2.5bn									
10/24/23	IDEAYA Biosciences, Inc.	CMO	$1,624.6	$125.0	(13.8%)	10.9%	8.8%	✓	
10/11/23	Scholar Rock Holding Corporation	CMO	559.2	85.0	--	17.7%	50.9%	✓	
10/02/23	Biohaven Ltd.	CMO	1,644.4	225.0	(8.6%)	5.5%	22.0%	✓	
09/19/23	HilleVax, Inc.	CMO	565.9	100.0	(13.4%)	16.6%	(12.4%)		
09/12/23	Crinetics Pharmaceuticals Inc	Marketed	1,426.2	350.0	17.3%	(6.7%)	(7.4%)	✓	
09/13/23	Rocket Pharmaceuticals, Inc.	CMO	1,231.2	175.0	4.6%	32.7%	10.9%	✓	
09/11/23	Cymabay Therapeutics Inc	Marketed	1,760.8	225.0	--	2.9%	(10.9%)	✓	
08/09/23	Mirati Therapeutics	CMO	1,840.6	300.0	--	33.1%	99.2%	✓	
08/09/23	Merus N.V.	CMO	1,141.3	150.0	(3.9%)	4.1%	(8.8%)		
08/01/23	Tarsus Pharmaceuticals Inc	Marketed	590.0	100.0	(20.5%)	(1.4%)	(21.4%)	✓	
	Average (n=10)		**$1,238.4**	**$183.5**	**(3.8%)**	**11.5%**	**13.1%**		
	Median (n=10)		**$1,328.7**	**$162.5**	**(1.9%)**	**8.2%**	**0.7%**		
Recent FOs with Market Cap <$500mm									
10/26/23	Monte Rosa Therapeutics, Inc.	RD	$124.1	$25.0	(0.0%)	11.2%	11.2%	✓	
10/26/23	Theratechnologies Inc.	CMO	31.0	25.0	(21.9%)	(7.9%)	(2.0%)	✓	
10/19/23	Arcutis Biotherapeutics, Inc.	CMO	186.8	100.0	(17.5%)	(1.4%)	(6.6%)	✓	
10/11/23	Astria Therapeutics, Inc.	RD	213.3	64.0	(19.6%)	(0.2%)	(25.4%)	✓	✓
10/05/23	ALX Oncology Holdings Inc.	CMO	262.5	55.0	--	2.7%	4.8%	✓	
10/02/23	VistaGen Therapeutics, Inc.	RD	62.9	100.0	(23.9%)	(21.9%)	(45.7%)	✓	✓
09/29/23	Synlogic Inc	Marketed	31.6	21.0	(58.8%)	(1.1%)	(34.5%)	✓	✓
09/29/23	Capricor Therapeutics, Inc.	RD	149.9	23.0	(46.9%)	(26.6%)	(41.6%)	✓	✓
09/28/23	Soleno Therapeutics, Inc.	CMO	233.0	120.0	(3.2%)	38.0%	12.6%	✓	
08/15/23	AN2 Therapeutics, Inc.	RD	189.5	70.0	4.2%	2.8%	61.4%		
	Average (n=10)		**$148.5**	**$60.3**	**(18.8%)**	**(0.4%)**	**(6.6%)**		
	Median (n=10)		**$168.4**	**$59.5**	**(18.5%)**	**(0.6%)**	**(4.3%)**		
	Average (n=30)		**$2,663.3**	**$231.3**	**(8.9%)**	**5.1%**	**1.5%**		
	Median (n=30)		**$1,328.7**	**$162.5**	**(3.6%)**	**3.5%**	**(4.1%)**		

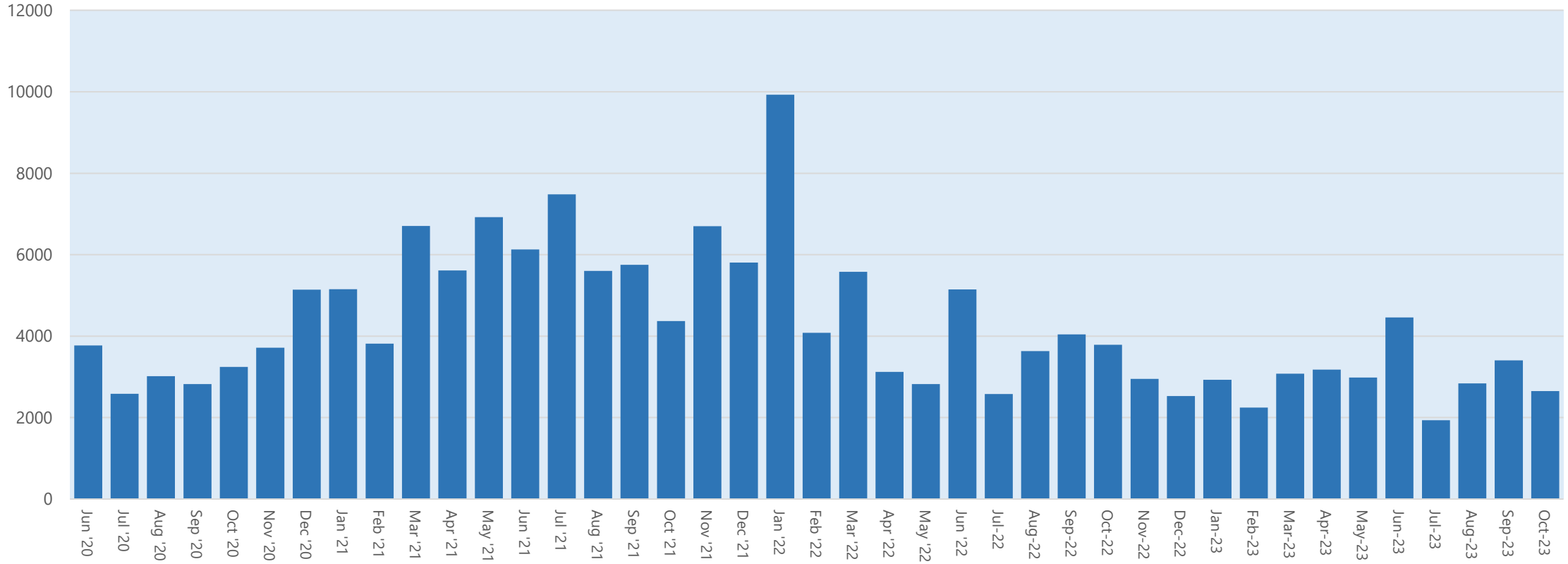
Source: Stifel Capital Markets, FactSet and Dealogic as of October 27, 2023. Notes: File to offer represents "all-in" discount for offerings with warrants. Footnotes: (1) Includes marketed, bought, confidentially marketed, registered direct and PIPE offerings with proceeds of $20.0 million and greater; (2) Only includes marketed, confidentially marketed and registered direct offerings with proceeds of $20.0 million and greater, excludes bought and PIPE offerings, (3) Median monthly aftermarket performance represents +30 day performance.

Venture Equity Environment

Monthly BioPharma Private Equity / Venture Placement Volume Held Steady in October 2023

Despite an extremely challenging capital market, the volume of venture placements held up reasonably well in October 2023. Volumes have been more or less flat since November 2022.

Monthly Private Equity Placement ($volume, $mm), Jan 2020 to October 2023

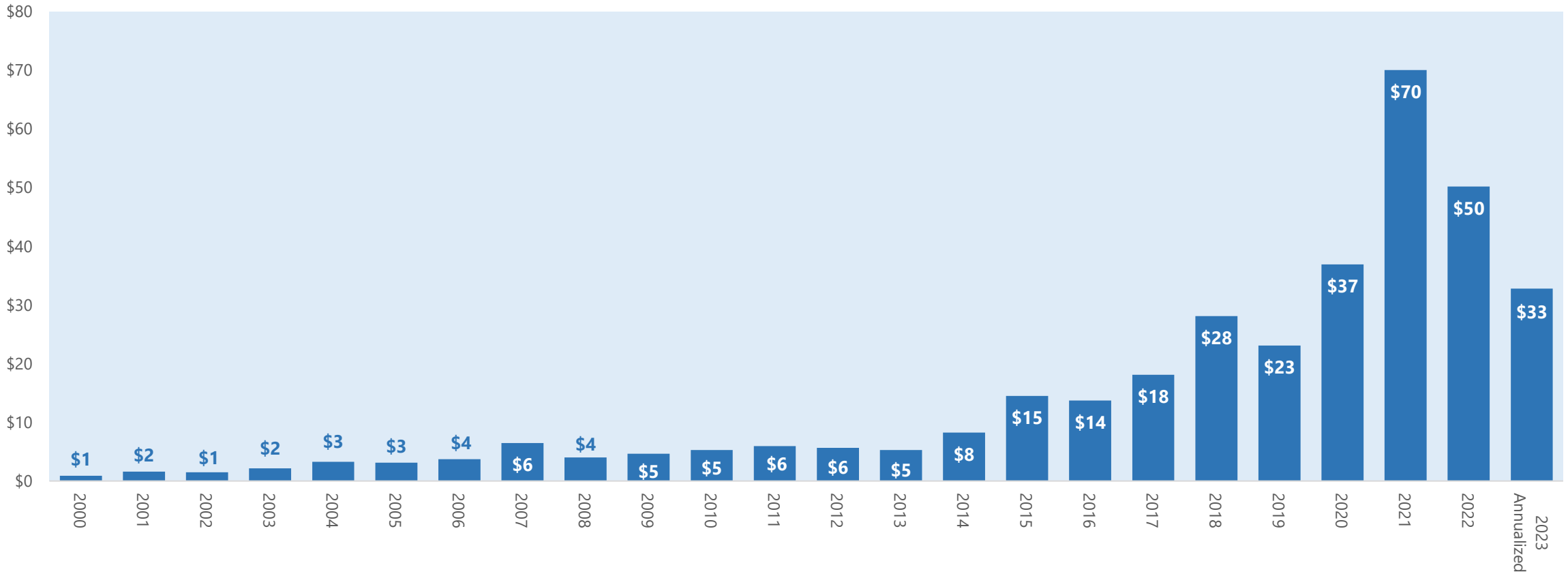


Source: Stifel internal database, CapIQ, Crunchbase

We Are On Track To Do $33 Billion in Venture Equity Deals in 2023; Volume Down Substantially From 2021/2022 Period

Venture Privates in the Biopharma Sector, 2000 - Oct 2023

($ Billions, Worldwide)



Source: Stifel internal database, CapIQ, Crunchbase

Top Biopharma Venture Equity Financings YTD 2023

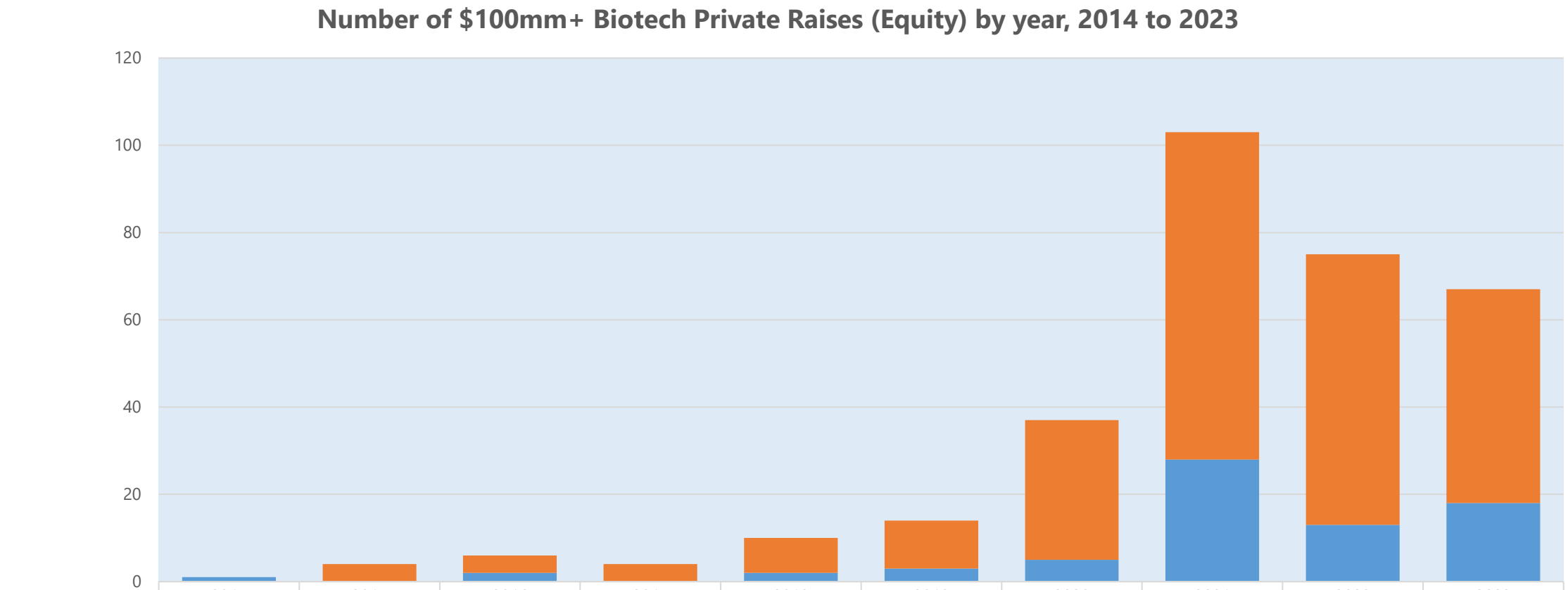
There have been 56 raises announced so far in 2023 for $100mm or more.

Company	Announcement Date	Amount Raised ($mm)	Round	Lead Investor	Stage at Funding	Primary TA	Company Focus	Modality / Technology	Post-Money Valuation ($mm)	HQ Country
Kriya	7/26/2023	$430	Series C	Patient Square	Preclinical	Rare Disease	Gene therapy for endocrine / CV	Gene Therapy	$600	United States
elevatebio	5/24/2023	$401	Series D	AyurMaya	Platform	Multiple	Cell and gene therapy holding company	Cell Therapy	$1246	United States
ReNAgade Therapeutics	5/23/2023	$300	Series A	MPM Capital	Platform	Multiple	RNA editing and delivery	RNA	$300	United States
Generate: Biomedicines A Flagship Pioneering Company	9/14/2023	$273	Series C	Flagship	Phase I	Cancer and others	AI for protein design	AI	$643	United States
Orbital Therapeutics	4/26/2023	$270	Series A	ARCH	Platform	Multiple	RNA medicines	RNA	$270	United States
ReCode Therapeutics	9/19/2023	$250	Series B	Pfizer Venture	Preclinical	Neurology	RNA for pulmonary diseases	RNA	$330	United States
Aiolos Bio	10/24/2023	$245	Series A	Atlas Venture	Phase II	Rare Disease	Pulmonary and immunology	Antibody	$245	United States
Apollo Therapeutics	9/06/2023	$227	Series C	Patient Square	Phase I	Cancer	Hub and spoke therapeutics	Diverse / Immunology	$371.5	United Kingdom
MapLight	10/30/2023	$225	Series C	Novo Holdings	Phase II	Neuro	Neurologic platform	Small Molecule	NA	United States
Genesis Therapeutics	8/21/2023	$224	Series B	Andreessen Horowitz	Platform	Cancer	AI platform for medicine	AI	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 10 years

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



	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
$100mm-200mm		4	4	4	8	11	32	75	62	49
$200mm+	1		2		2	3	5	28	13	18

Source: DealForma

MapLight Therapeutics Closes $225 Million Series C Funding

SAN FRANCISCO, Oct. 30, 2023 /PRNewswire/ -- MapLight Therapeutics, a clinical-stage biopharmaceutical company working to develop targeted, novel therapeutics to improve the lives of people with brain disorders, today announced the closing of an oversubscribed $225 million Series C financing to continue the advancement of MapLight's transformative treatments for neuropsychiatric and neurological conditions.

New investors Novo Holdings, 5AM Ventures, Cowen Healthcare Investments, and others joined MapLight's existing syndicate in the financing. This round of funding will advance ML-007C-MA, a novel M1/M4 muscarinic agonist agent combined with a precision matched peripheral muscarinic antagonist, into Phase 2 trials for schizophrenia and Alzheimer's disease psychosis in 2024 and enable continued progress on the company's other pipeline programs.

In addition to ML-007C-MA, MapLight currently has two other products in clinical development: ML-007 is under study for dyskinesia, and ML-004, a 5HT-1b agonist is currently in Phase 2 for social communication deficits in patients with autism spectrum disorder. MapLight's pipeline preclinical assets include ML-016, a GPR-6 antagonist under study for both Parkinson's disease and depression, and ML-009, in development to treat hyperactivity and impulsivity.

"MapLight is advancing what we believe will be the best-in-class muscarinic agent for difficult-to-treat disorders including schizophrenia and Alzheimer's disease psychosis. Schizophrenia alone affects around 3 million adults in the U.S. and 1 percent of the worldwide population," said Jim Trenkle, Ph.D., MBA, Partner in the Venture Investments group at Novo Holdings. "We are delighted to partner with a very strong group of existing and new investors to catalyze significant advancements in the fight against these important central nervous system disorders, and to support the talented, dedicated team at MapLight."

In connection with the financing, Jim Trenkle, Ph.D., MBA, Partner in the Venture Investments group at Novo Holdings will join the MapLight Therapeutics Board of Directors.

"MapLight has built a diverse pipeline of innovative neuroscience therapeutics targeting a spectrum of Central Nervous System (CNS) disorders where the challenges faced by patients and families are significant and the unmet need is high. This financing will fuel the important clinical development necessary to bring these innovative therapies to patients."

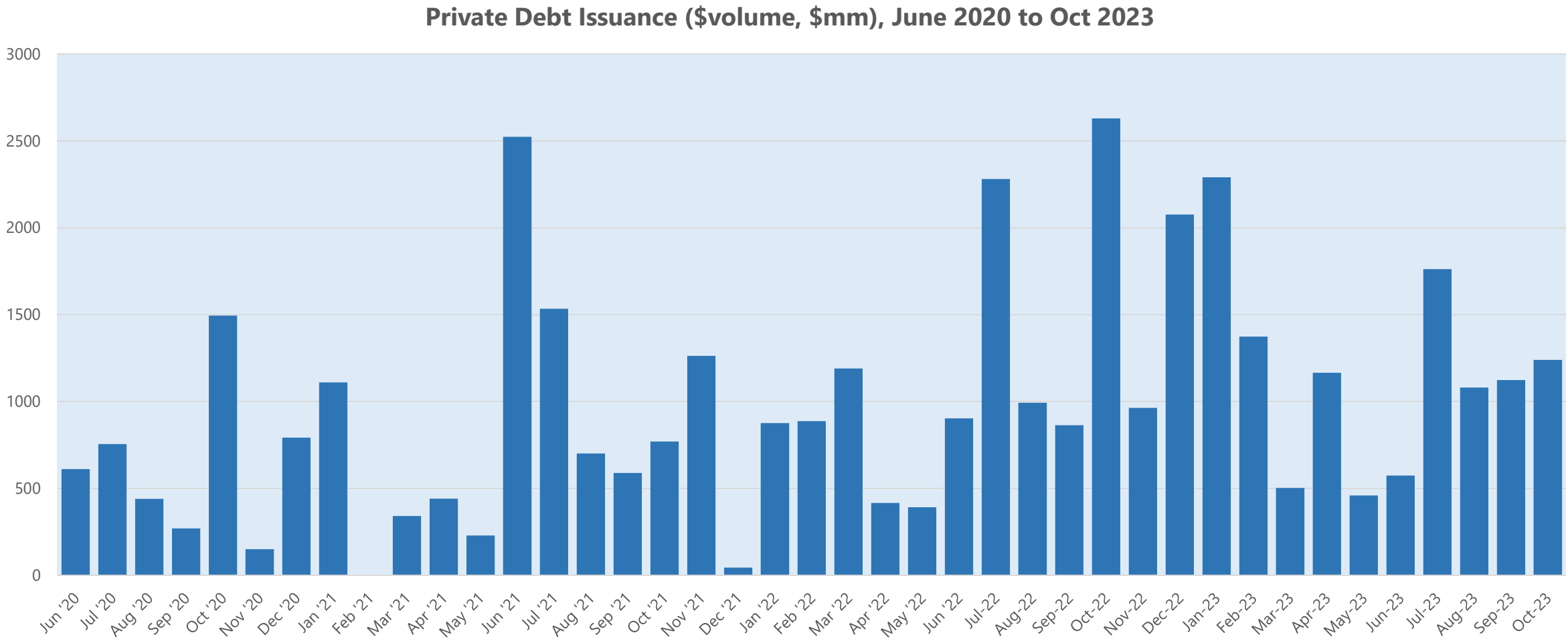
Chris Kroeger
Chief Executive Officer

Source: https://www.prnewswire.com/news-releases/maplight-therapeutics-closes-225-million-series-c-funding-round-to-advance-pipeline-of-central-nervous-system-therapeutics-301970884.html

Private Debt Environment

Biopharma Private Debt Volume Solid in October 2023

Last month saw over $1.2 billion in deal volume in the private debt market for biopharmas. This was the fourth strongest month of the year.

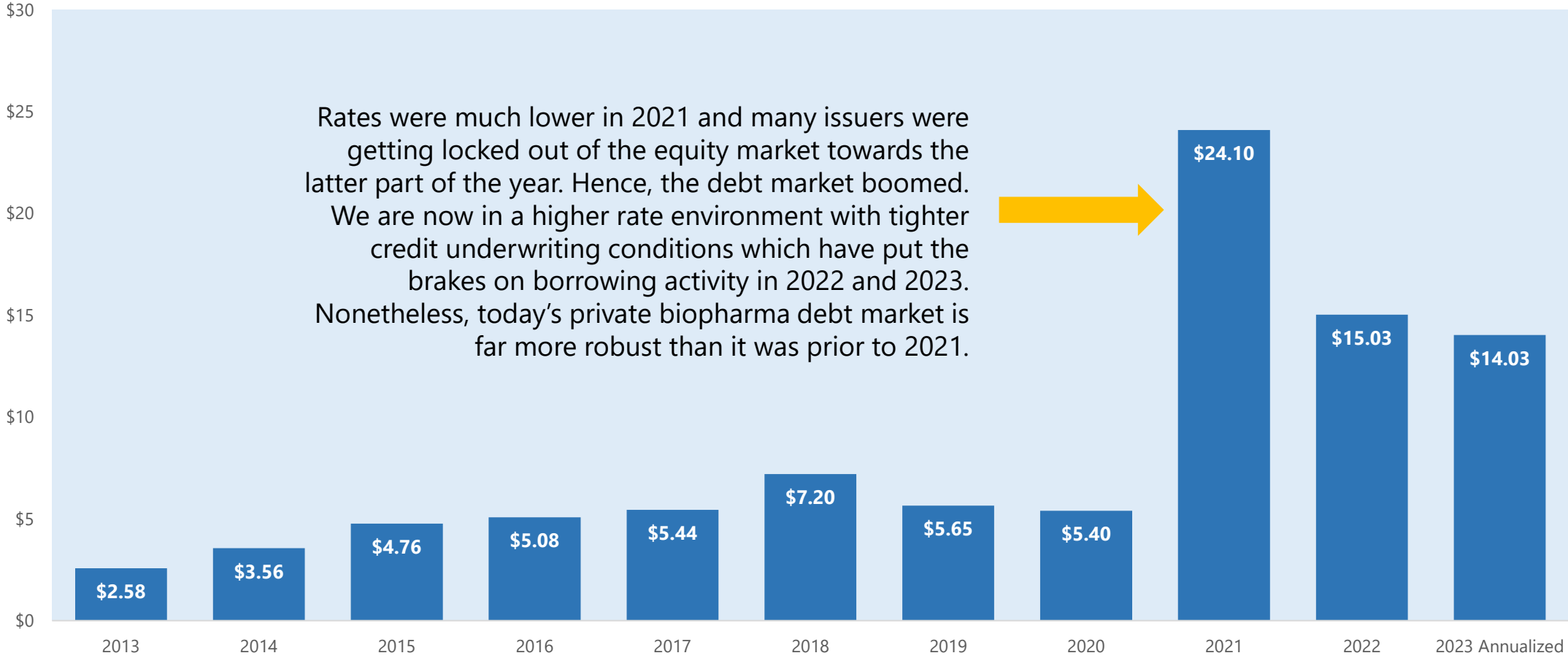


Source: Data from CapitalIQ, Crunchbase.

On An Annualized Basis, Debt Market Transaction Dollar Volume is Flat to 2022

Private Debt Market Volume in Life Sciences, 2013-2021 ($ millions)

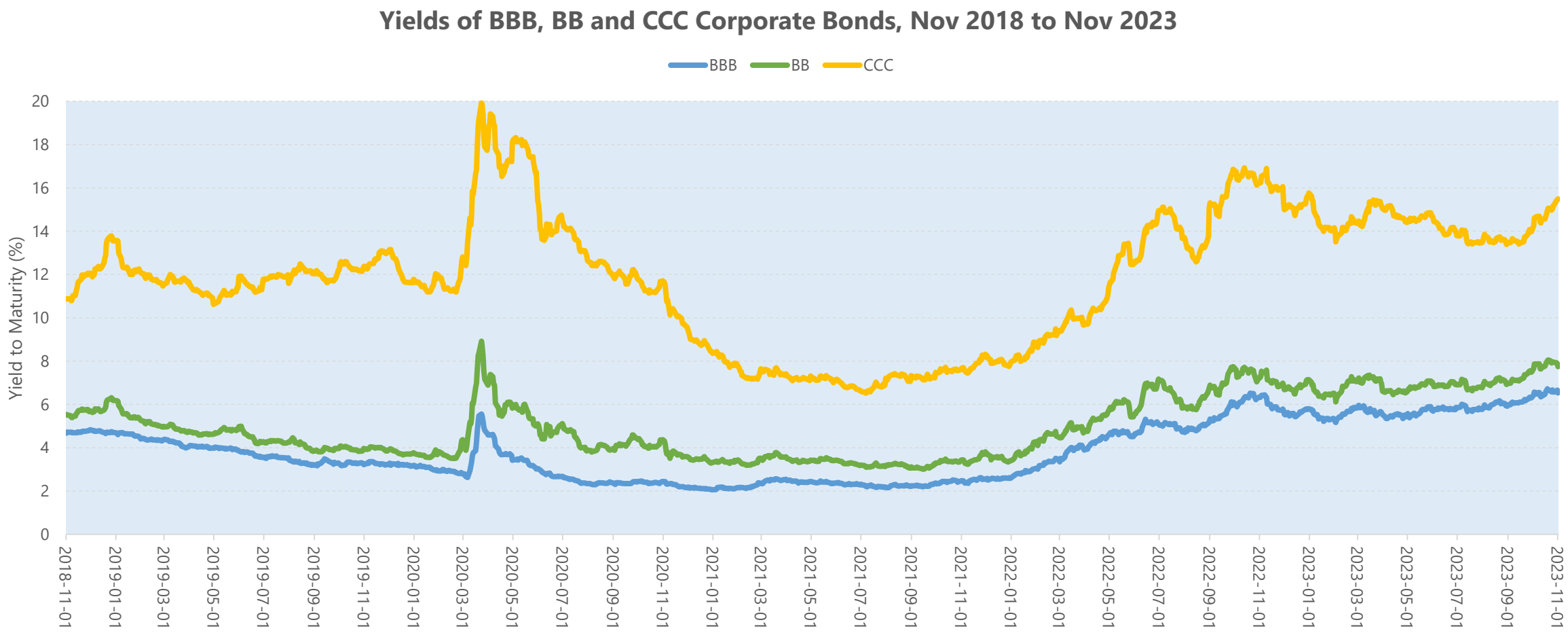
($ Billions, Worldwide)



Source: Stifel Debt Transaction Database

Credit Market Yields for CCC Bonds Today are Over 15% and Creeping Up

Conditions at the low end of the fixed income market have deteriorated in the last six weeks.



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

"We would expect to see quite frankly more cracks in credit. We're staying very liquid right now because we think the worst is ahead of us in terms of corporate credit."

Bloomberg, Nov 3, 2023

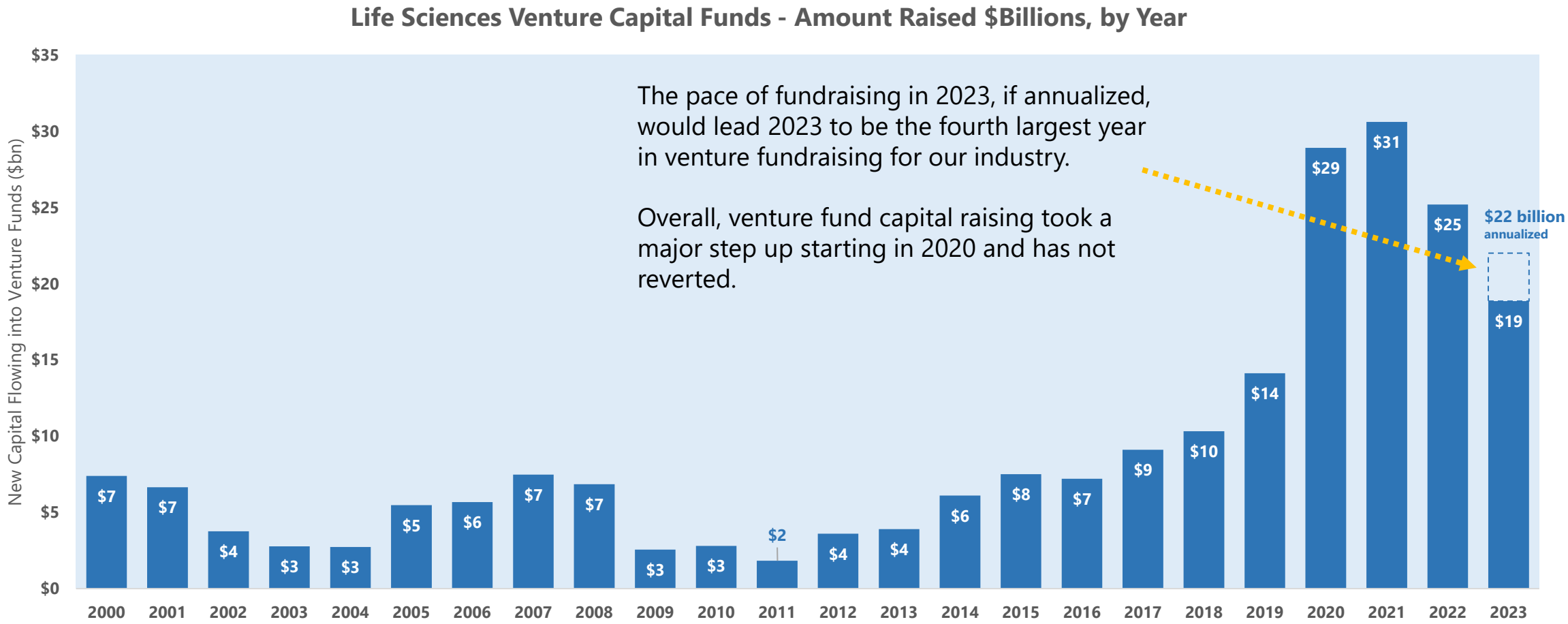
Bob Diamond
Atlas Merchant Capital
(former CEO Barclays)

Source: https://www.bloomberg.com/news/articles/2023-11-03/ex-barclays-ceo-diamond-says-worst-ahead-for-corporate-credit

Venture Funds Capital Raising

New Capital Flows Into Life Sciences Venture Funds Remains Solid

There has been more venture money raised in our sector in the last five years than the prior nineteen years combined. This is a *huge* positive. We like to refer to this as the "wave of private capital".



Source: Stifel internal database

A Big Month for Funding of Venture Funds

VC Firm Bioluminescence Ventures Launches with $477M in Assets • Biospace

Media Coverage | 1 November 2023

OrbiMed Raises $4.3 Billion Across Private Investment Funds

NEW YORK, October 24, 2023 – OrbiMed, a global healthcare investment firm, is pleased to announce it has raised more than $4.3 billion in commitments for its latest private investment funds, including OrbiMed Private Investments IX, OrbiMed Asia Partners V and OrbiMed Royalty & Credit Opportunities IV.

Revelation Partners

NEWS

Revelation Partners Closes $608 Million Fund, Surpassing $500 Million Target

Revelation Partners today announced the closing of its $608 million Fund IV, far surpassing...

READ MORE →

ABINGWORTH

30 Oct 2023

Abingworth raises $356 million for new Clinical Co-Development Co-Investment Fund (CCD-CIF)

Sofinnova News Sofinnova Digital Medicine 25 October, 2023

Sofinnova Partners raises $200M Digital Medicine Fund

We count six transactions in the last two weeks for $5.3 billion of capital flows into venture funds. To state the obvious, this has been highly unusual.

Blue Owl Capital Announces Agreement to Acquire Funds Managed by Cowen Healthcare Investments from Cowen Investment Management (CIM)

October 30, 2023

Top Ten Biopharma Fund Raises 2023

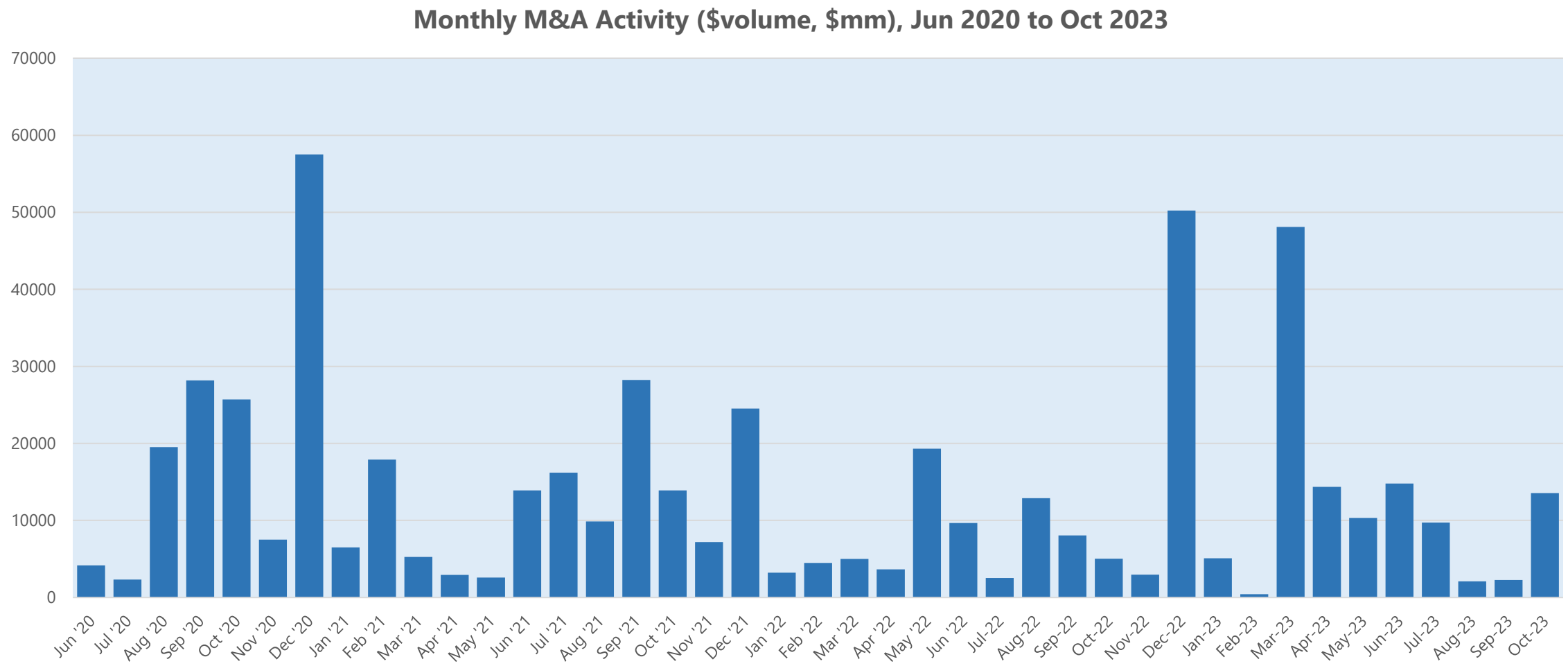
Month	Fund	Approach / Sweet Spot	Amount Raised ($ millions)	Home Country
Feb-23	Patient Square Capital	Life sciences platforms and strong management teams, mid-to-late stage with a long perspective and patient-centric approach.	$3,900	United States
Oct-23	Orbimed IX	Orbimed Private Investments IX is the latest installment of one of the world's largest and most successful venture groups. Focused on both early stage and late stage investments.	$1,860	United States
Apr-23	Lux	Lux Capital invests in life science companies with big ideas and the leaders to back them. Not afraid of early-stage investment.	$1,115	United States
Apr-23	Canaan	Canaan is an early-stage life science and tech venture capital firm that invests in visionaries with transformative ideas.	$850	United States
Apr-23	Forbion Ventures	Forbion Ventures Fund VI invests in Series A and B therapeutics companies with a focus on European companies.	$823	Netherlands
Oct-23	Orbimed Asia	Orbimed Asia invests in commercial and venture stage companies in China and India. Has a phenomenal track record.	$751	United States
Apr-23	Forbion Growth	Forbion Growth Opportunities Fund II invests in innovative European later-stage biopharma companies focused on major market needs.	$658	Netherlands
Apr-23	Gilde Healthcare	Gilde Healthcare Venture & Growth VI invests in growth companies with cost conscious good care solutions. Focus areas include digital, medtech and therapeutics.	$657	Netherlands
Oct-23	Revelation Partners	Revelation Partners provides flexible capital to the healthcare sector. Active in biopharma and willing to do secondary portfolio purchases.	$608	United States
Mar-23	SR One	SR One Fund II collaborates with entrepreneurs to build high quality biotechs in the US and Europe. Does privates and public deals.	$600	United States

Source: Company press releases, Stifel research.

Deals Environment Update

Last Month Saw $13.5 Billion in M&A Volume

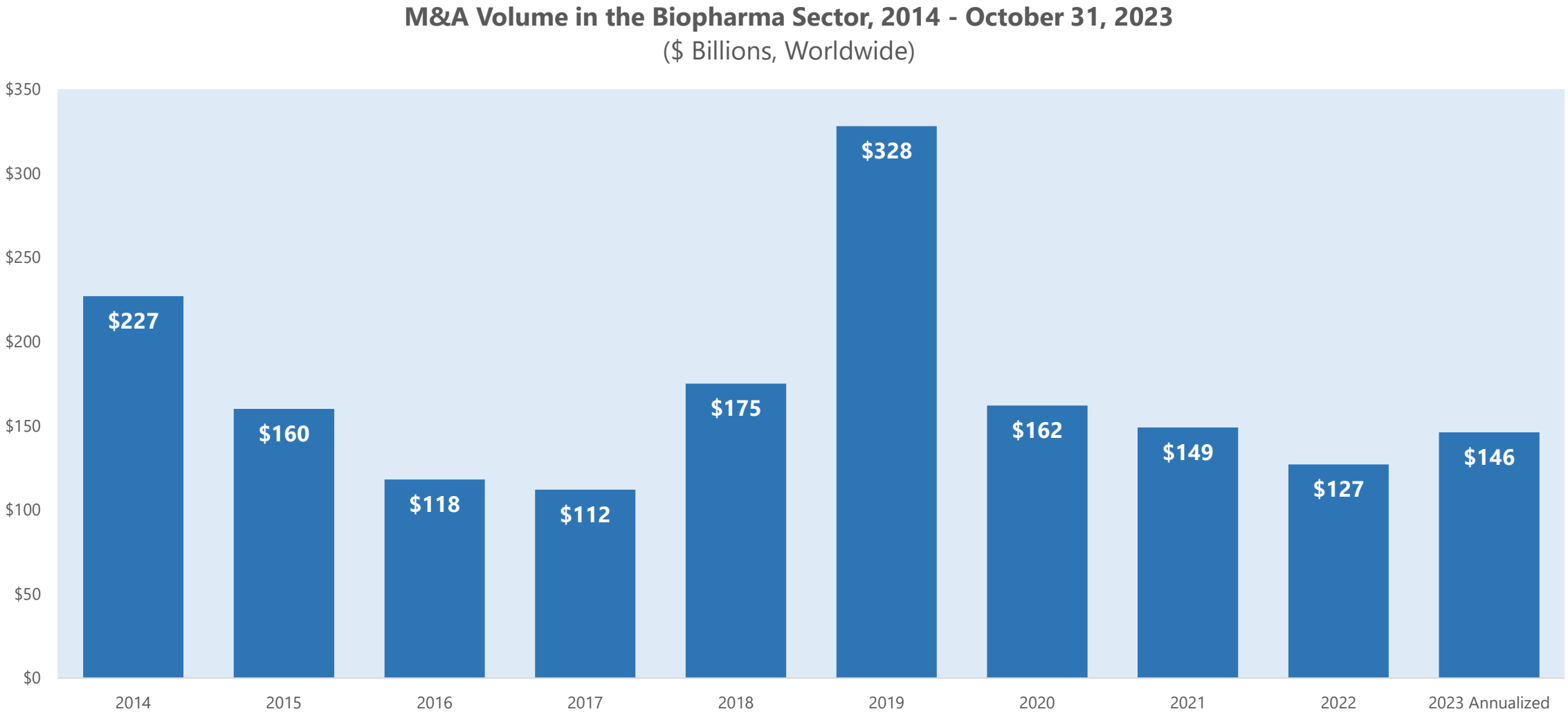
We opened the year with a very strong two quarters of M&A. Then Q3 was moribund as, among other things, we sorted through the FTC issues with the Amgen/Horizon merger. October was very different as it was the fourth busiest month of the year.



Source: S&P, CapitalIQ

So Far, We Have Seen $121 Billion in M&A in 2023

We have seen $121 billion in M&A volume (announced deals) so far this year. This puts us on pace for a $146 billion year.



Source: S&P, CapitalIQ, Stifel calculations.

Cellectis Announces Strategic Collaboration and Investment Agreements with AstraZeneca

November 1, 2023 -- Cellectis (Euronext Growth: ALCLS – NASDAQ: CLLS) today announced it has entered into (i) a Joint Research Collaboration Agreement (the "Collaboration Agreement", (ii) an investment agreement relating to an initial equity investment of $80M, and (iii) a memorandum of understanding (the "MOU") relating to an additional equity investment of $140M, with AstraZeneca (LSE/STO/Nasdaq: AZN). The Collaboration Agreement aims to accelerate the development of next generation therapeutics in areas of high unmet need, including oncology, immunology and rare diseases.

Under the terms of the Collaboration Agreement, AstraZeneca will leverage Cellectis' proprietary gene editing technologies and manufacturing capabilities to design novel cell and gene therapy candidate products. As part of the Collaboration Agreement, 25 genetic targets have been exclusively reserved for AstraZeneca, from which up to 10 candidate products could be explored for development. AstraZeneca will have an option for a worldwide exclusive license on the candidate products, to be exercised before IND filing.

Pursuant to the Collaboration Agreement, Cellectis' research costs under the collaboration will be funded by AstraZeneca and Cellectis will receive an upfront payment of $25M. Under the terms of the Collaboration Agreement, Cellectis is also eligible to receive an investigational new drug (IND) option fee and development, regulatory and sales-related milestone payments, ranging from $70M up to $220M, per each of the 10 candidate products, plus tiered royalties.

As a condition to the signing of the Collaboration Agreement, AstraZeneca has agreed to make an initial equity investment of $80M in Cellectis by subscribing for 16,000,000 ordinary shares, at a price of $5.00 per share (the "Initial Investment"). The new shares are issued to AstraZeneca by the board of directors of Cellectis pursuant to the 17th resolution of Cellectis' shareholders meeting held on June 27, 2023. Following settlement and delivery of the new shares (expected to be on November 6, 2023), AstraZeneca will own approximately 22% of the share capital, and 21% of the voting rights of the Company, will have the right to nominate a non-voting observer on the board of directors of Cellectis, and will have the right to participate pro rata in Cellectis's future share offerings.

Additionally, the MOU contemplates that AstraZeneca will make a potential further equity investment in Cellectis of $140M by subscribing for two newly created classes of convertible preferred shares of Cellectis: 10,000,000 "class A" convertible preferred shares and 18,000,000 "class B" convertible preferred shares, in each case at a price of $5.00 per share (the "Additional Investment").

Source: https://www.cellectis.com/en/press/cellectis-announces-strategic-collaboration-and-investment-agreements-with-astrazeneca/

Beam Announces Agreement for Lilly to Acquire Beam's Opt-In Rights to Verve Therapeutics' Base Editing Programs for Cardiovascular Disease

CAMBRIDGE, Mass., Oct. 31, 2023 (GLOBE NEWSWIRE) -- Beam Therapeutics Inc. (Nasdaq: BEAM), a biotechnology company developing precision genetic medicines through base editing, today announced that Eli Lilly and Company (Lilly) has agreed to acquire certain rights under Beam's amended collaboration and license agreement with Verve Therapeutics, Inc. (Verve), including Beam's opt-in rights to co-develop and co-commercialize Verve's base editing programs for cardiovascular disease, which includes programs targeting PCSK9, ANGPTL3 and an undisclosed liver-mediated, cardiovascular target.

Under the terms of the agreement, Beam will receive a $200 million upfront payment and $50 million equity investment. Beam is also eligible to receive up to $350 million in potential future development-stage payments upon the completion of certain clinical, regulatory and alliance events for a total of up to $600 million in potential total deal consideration.

"As the pioneers in base editing, we've had a long-standing vision of enabling a wide range of disease-modifying therapies based on precision genome editing. Our strategy to achieve this has been to advance a diversified portfolio of wholly owned programs, continue to innovate in our platform, and establish creative partnerships that expand the reach of base editing and drive both near- and long-term value creation. Our initial collaboration with Verve and this new transaction with Lilly are exemplary of our execution of that strategy," said John Evans, chief executive officer of Beam. "This deal provides meaningful upfront capital to advance our portfolio of clinical- and research-stage programs, with significant additional value achievable as the Verve programs advance through development. In parallel, it provides Verve with a world-class partner for the long term, given Lilly's deep expertise and resources in the cardiovascular space. We are excited to see the broad therapeutic potential of base editing fully realized through our pipeline and through the programs enabled by our past and future collaborations."

Source: https://investors.beamtx.com/news-releases/news-release-details/beam-announces-agreement-lilly-acquire-beams-opt-rights-verve

Galapagos to Transfer Jyseleca® (filgotinib) Business to Alfasigma for €50 Million Upfront and royalties

Mechelen, Belgium; 30 October 2023, 21:01 CET; regulated information – inside information – Galapagos NV (Euronext & NASDAQ: GLPG) and Alfasigma S.p.A. today announced that they have signed a letter of intent contemplating a transfer of the Jyseleca® business to Alfasigma, including the European and UK Marketing Authorizations, the commercial, medical and development activities for Jyseleca® and approximately 400 positions in 14 European countries.

In the contemplated transaction, Galapagos will receive a €50 million upfront, potential milestone payments totaling €120 million and mid-single to mid-double-digit royalties on European sales. Galapagos will pay up to €40 million by June 2025 to Alfasigma for Jyseleca® related development activities. In addition, Galapagos plans to streamline its remaining operations and further build efficiencies, with an envisaged reduction of approximately 100 positions across the organization. Galapagos estimates annualized savings ranging between €150 million and €200 million.

This repositioning of the company marks yet another significant milestone in Galapagos' ongoing transformation into an innovative biotechnology company with a patient-centric research and development pipeline focused on immunology and oncology. While Galapagos' commitment to transforming patient outcomes with life changing science and innovation remains unchanged, its ability to work efficiently across streamlined operations and portfolio are expected to accelerate these efforts.

Source: https://www.glpg.com/press-release/3914/galapagos-concludes-strategic-evaluation-and-signs-letter-of-intent-to-transfer-jyseleca-business-to-alfasigma

RTW Biotech Opportunities to acquire Arix Bioscience's $550 Million Portfolio

QuotedData (Nov 1, 2023): RTW Biotech Opportunities (RTW) has announced that it will acquire Arix Bioscience. The transaction is expected to deliver RTW with an expected pro-forma net asset value of approximately $550 million, an increase of 63% The deal will enhance RTW's profile, provide increased liquidity potential, a more efficient cost base, and a re-rating opportunity. Arix shareholders will receive new RTW shares at an implied premium of approximately 46 per cent to Arix's pre-strategic review share price. The deal is expected to be immediately accretive to RTW's NAV per share at completion.

The boards of RTW Bio and Arix believe the scheme has clear strategic rationale and offers compelling benefits to shareholders of both companies which are outlined in full below:

RTW is a best-in-class manager with superior capabilities: RTW is a leading, specialised life science investor with a record of over 14 years of success, including delivering an annualised net return of 21.6 per cent since inception from its leading private fund. RTW's capabilities are underpinned by a science-led investment approach and its full lifecycle strategy of investing and supporting growth companies across different stages of development, business inflection points and capital structures. A team of 43 investment professionals, the majority of whom have advanced scientific degrees, drive RTW's science-led approach, which is focused on solving the most challenging unmet patient needs by identifying, investing in, supporting, and building innovative life science companies. This long-term approach to investing enables RTW to maximise value capture from the opportunities it participates in. RTW's infrastructure and scale provide superior access to the most exciting life science companies and events. In 2022, RTW had access to more than 200 medical meetings and 200 deals from syndicate and partner investors alone. RTW intends to utilise its sophisticated infrastructure and science and research-led investment process to manage the assets of RTW Bio and Arix following completion of the scheme. Compared to Arix's focus on life science private and venture capital investing, RTW is able to offer a greatly enhanced investment offering with a scaled equity investing platform, company creation, royalty and structured financing as well as alternative vehicles that provides a wider opportunity for returns.

An enhanced return potential from deployment of new capital: RTW Bio has a track record of successfully deploying capital and generating returns. Through 2022 and year-to-date 2023, RTW Bio made 9 new investments and had 7 successful IPOs or exits of portfolio companies. The scheme enables RTW to access Arix's assets which comprise approximately $128 million of liquid assets, of which approximately $60 million is expected to be cash following completion of the scheme, costs of the share purchase and other transaction related costs.

Source: https://quoteddata.com/2023/11/rtw-biotech-opportunities-acquire-arix-bioscience/

Major Unmet Medical Needs

Top Causes of Death by Region: GBD Study

	1	2	3	4	5	6	7	8	9	10
Global	Ischaemic heart disease 0.81	Stroke 0.97	COPD 1.86	Alzheimer's disease 1.010	Lower respiratory infection 1.00	Lung cancer 1.12	Diabetes 0.82	Hypertensive heart disease 1.19	Chronic kidney disease 0.99	Colorectal cancer 0.83
Central Europe, Eastern Europe, and Central Asia	Ischaemic heart disease 2.11	Stroke 1.84	Alzheimer's disease 1.00	COPD 0.82	Colorectal cancer 1.02	Hypertensive heart disease 1.54	Lung cancer 0.86	Lower respiratory infection 0.48	Cardiomyopathy 2.37	Diabetes 0.61
Central Asia	Ischaemic heart disease 2.45	Stroke 1.64	COPD 1.40	Hypertensive heart disease 1.98	Alzheimer's disease 1.02	Cirrhosis 2.52	Diabetes 0.74	Lower respiratory infection 0.61	Lung cancer 0.85	Stomach cancer 1.29
Central Europe	Ischaemic heart disease 1.46	Stroke 1.59	Alzheimer's disease 1.04	Hypertensive heart disease 2.65	Lung cancer 1.12	Colorectal cancer 1.23	COPD 0.83	Cardiomyopathy 3.39	Lower respiratory infection 0.68	Diabetes 0.91
Eastern Europe	Ischaemic heart disease 2.49	Stroke 2.04	Alzheimer's disease 0.97	COPD 0.72	Colorectal cancer 0.90	Lung cancer 0.66	Stomach cancer 1.16	Hypertensive heart disease 0.73	Cardiomyopathy 1.79	Lower respiratory infection 0.32
High income	Ischaemic heart disease 0.63	Stroke 0.67	Alzheimer's disease 1.05	COPD 1.10	Lung cancer 0.97	Lower respiratory infection 1.01	Chronic kidney disease 1.30	Colorectal cancer 0.79	Diabetes 0.87	Hypertensive heart disease 1.10
Australasia	Ischaemic heart disease 0.63	Stroke 0.61	Alzheimer's disease 1.03	COPD 1.10	Lung cancer 0.83	Colorectal cancer 0.80	Chronic kidney disease 1.19	Lower respiratory infection 0.56	Prostate cancer 0.93	Diabetes 0.91
High income Asia Pacific	Alzheimer's disease 1.25	Stroke 0.70	Ischaemic heart disease 0.34	Lower respiratory infection 1.43	Lung cancer 0.87	Colorectal cancer 0.72	Stomach cancer 1.89	Chronic kidney disease 1.05	COPD 0.52	Liver cancer 2.88
High income North America	Ischaemic heart disease 0.89	Stroke 0.63	COPD 1.59	Alzheimer's disease 0.97	Lung cancer 1.18	Chronic kidney disease 1.63	Lower respiratory infection 0.72	Colorectal cancer 0.64	Diabetes 1.11	Prostate cancer 0.78
Southern Latin America	Ischaemic heart disease 0.49	Lower respiratory infection 2.61	Stroke 0.55	COPD 1.25	Alzheimer's disease 0.94	Chronic kidney disease 1.80	Colorectal cancer 1.35	Hypertensive heart disease 1.31	Diabetes 0.90	Lung cancer 1.00
Western Europe	Ischaemic heart disease 0.64	Stroke 0.70	Alzheimer's disease 0.99	COPD 1.08	Lung cancer 0.89	Lower respiratory infection 0.87	Colorectal cancer 0.89	Chronic kidney disease 1.18	Hypertensive heart disease 1.44	Prostate cancer 0.91
Latin America and Caribbean	Ischaemic heart disease 0.47	Stroke 0.43	Alzheimer's disease 1.04	Lower respiratory infection 1.31	COPD 1.12	Diabetes 1.15	Chronic kidney disease 1.40	Hypertensive heart disease 0.75	Prostate cancer 1.09	Cirrhosis 1.18
Andean Latin America	Ischaemic heart disease 0.37	Lower respiratory infection 2.26	Stroke 0.31	Chronic kidney disease 1.73	Alzheimer's disease 0.95	Diabetes 0.79	COPD 0.66	Stomach cancer 1.90	Cirrhosis 1.73	Prostate cancer 1.10
Caribbean	Ischaemic heart disease 0.71	Stroke 0.69	Lower respiratory infection 1.21	Diabetes 1.32	Alzheimer's disease 0.90	Prostate cancer 1.80	COPD 0.76	Chronic kidney disease 1.03	Hypertensive heart disease 1.11	Lung cancer 1.04
Central Latin America	Ischaemic heart disease 0.55	Stroke 0.34	Diabetes 1.37	Chronic kidney disease 1.89	COPD 1.20	Alzheimer's disease 1.03	Lower respiratory infection 0.75	Cirrhosis 1.49	Hypertensive heart disease 0.67	Prostate cancer 0.94
Tropical Latin America	Ischaemic heart disease 0.37	Stroke 0.50	Lower respiratory infection 1.69	Alzheimer's disease 1.09	COPD 1.24	Diabetes 0.98	Chronic kidney disease 0.90	Hypertensive heart disease 0.79	Prostate cancer 1.06	Lung cancer 0.87
North Africa and Middle East	Ischaemic heart disease 1.32	Stroke 0.91	Hypertensive heart disease 2.27	Alzheimer's disease 1.14	Chronic kidney disease 1.67	COPD 0.97	Cirrhosis 2.52	Diabetes 1.02	Lower respiratory infection 0.83	Lung cancer 0.77
North Africa and Middle East	Ischaemic heart disease 1.32	Stroke 0.91	Hypertensive heart disease 2.27	Alzheimer's disease 1.14	Chronic kidney disease 1.67	COPD 0.97	Cirrhosis 2.52	Diabetes 1.02	Lower respiratory infection 0.83	Lung cancer 0.77
South Asia	Ischaemic heart disease 0.76	COPD 2.84	Stroke 0.63	Diarrheal diseases 11.42	Lower respiratory infection 0.97	Diabetes 0.85	Tuberculosis 3.14	Falls 4.41	Alzheimer's disease 0.81	Asthma 2.23
South Asia	Ischaemic heart disease 0.76	COPD 2.84	Stroke 0.63	Diarrheal diseases 11.42	Lower respiratory infection 0.97	Diabetes 0.85	Tuberculosis 3.14	Falls 4.41	Alzheimer's disease 0.81	Asthma 2.23
South East Asia, East Asia, and Oceania	Stroke 1.39	Ischaemic heart disease 0.74	COPD 2.82	Lung cancer 1.85	Alzheimer's disease 1.01	Hypertensive heart disease 1.56	Lower respiratory infection 0.90	Stomach cancer 1.67	Diabetes 0.62	Chronic kidney disease 0.81
East Asia	Stroke 1.42	Ischaemic heart disease 0.77	COPD 3.17	Lung cancer 2.00	Alzheimer's disease 1.01	Hypertensive heart disease 1.65	Stomach cancer 1.95	Lower respiratory infection 0.66	Colorectal cancer 0.90	Esophageal cancer 5.18
Oceania	Ischaemic heart disease 1.08	Stroke 1.07	COPD 2.96	Diabetes 3.23	Asthma 4.24	Ischaemic heart disease 2.39	Lower respiratory infection 0.84	Hypertensive heart disease 1.10	Alzheimer's disease 0.92	Lung cancer 1.43
South East Asia	Stroke 1.27	Ischaemic heart disease 0.62	COPD 1.56	Lower respiratory infection 1.74	Diabetes 1.21	Alzheimer's disease 1.02	Chronic kidney disease 1.24	Hypertensive heart disease 1.26	Tuberculosis 7.68	Cirrhosis 1.88
Sub-Saharan Africa	Stroke 0.90	Ischaemic heart disease 0.71	Lower respiratory infection 1.58	Diarrheal diseases 1.72	Tuberculosis 1.84	Diabetes 1.28	Hypertensive heart disease 1.28	COPD 0.79	Alzheimer's disease 1.08	Chronic kidney disease 1.11
Central Sub-Saharan Africa	Stroke 0.99	Ischaemic heart disease 0.81	Lower respiratory infection 1.81	Tuberculosis 2.71	Hypertensive heart disease 2.07	COPD 1.15	Diarrheal diseases 1.73	Diabetes 1.10	Alzheimer's disease 1.11	Chronic kidney disease 0.97
Eastern Sub-Saharan Africa	Stroke 0.95	Ischaemic heart disease 0.66	Lower respiratory infection 1.42	Tuberculosis 1.69	Diarrheal diseases 1.41	Hypertensive heart disease 1.50	Diabetes 1.13	COPD 0.75	Cirrhosis 1.49	Alzheimer's disease 1.11
Southern Sub-Saharan Africa	Stroke 0.85	Ischaemic heart disease 0.55	Diabetes 2.50	Lower respiratory infection 2.51	COPD 1.37	Hypertensive heart disease 2.07	Chronic kidney disease 1.62	Alzheimer's disease 0.99	Diarrheal diseases 10.67	Tuberculosis 8.72
Western Sub-Saharan Africa	Ischaemic heart disease 0.79	Stroke 0.85	Lower respiratory infection 1.52	Diarrheal diseases 1.77	Malaria 17.64	Tuberculosis 1.54	Diabetes 1.11	Alzheimer's disease 1.08	Chronic kidney disease 1.10	COPD 0.62

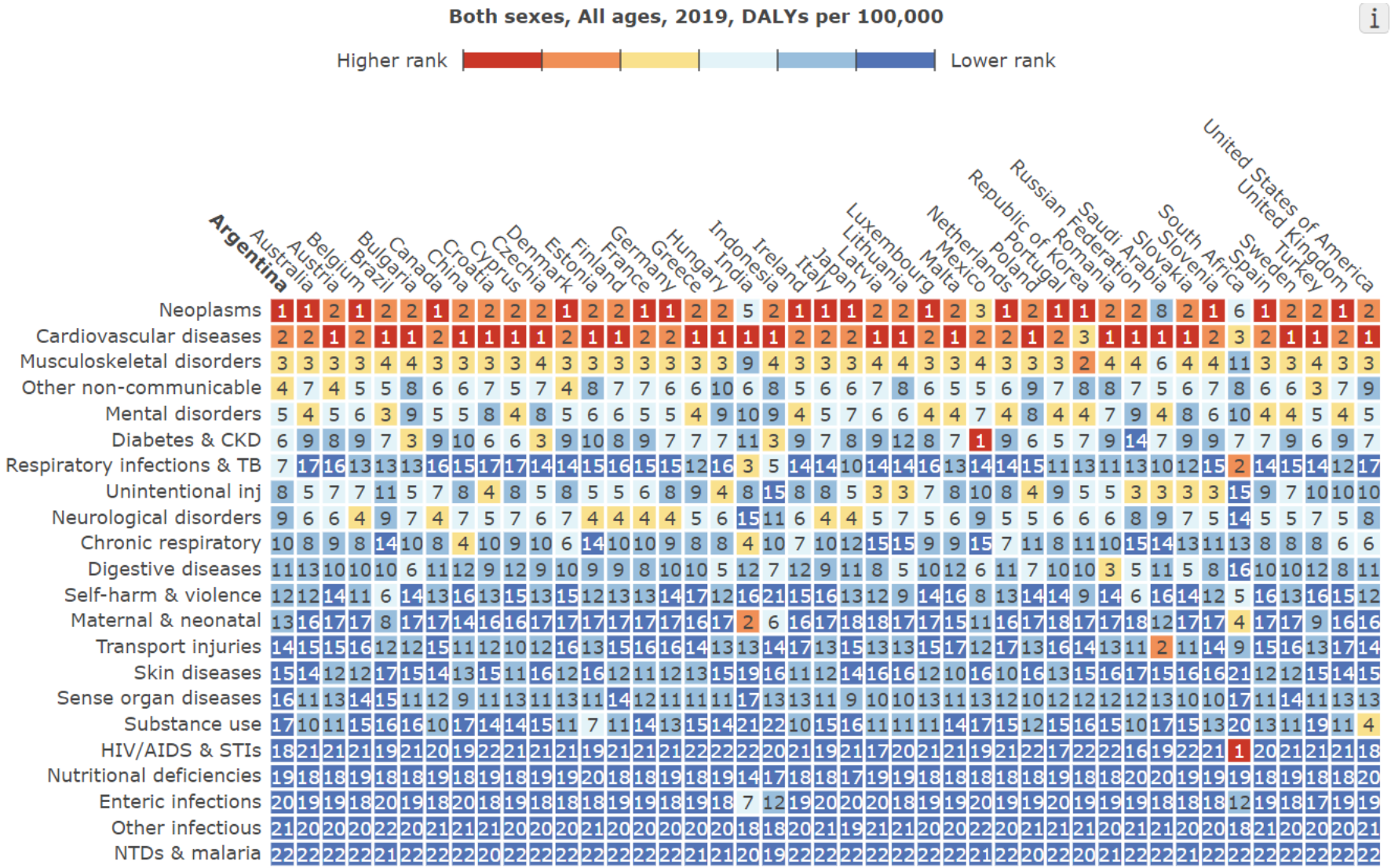
Values represent ratio of observed to estimated deaths based on sociodemographic index rounded to two decimal places. Colour ranges calculated to place a roughly equal number of cells in each column

Colour key:	(0.00 to 0.66)	(0.66 to 0.79)	(0.79 to 0.89)	(0.89 to 0.98)	(0.98 to 1.08)	(1.08 to 1.18)	(1.18 to 1.42)	(1.42 to 1.73)	(1.73 to 2.45)	(2.45 to ...)

Ten leading causes of total deaths with ratio of observed to expected deaths in 2019 by location for population aged ≥70, both sexes. Causes are ranked according to global estimates of deaths and colour coded based on ratio of observed to expected rates. Shades of blue represent lower observed deaths than expected rates based on sociodemographic index whereas red indicates observed deaths exceeded expected rates.

Sources: https://www.healthdata.org/results/data-visualizations, https://www.bmj.com/content/376/bmj-2021-068208

G20 Countries: Top Burden in Terms of DALY's (Years of Life Lost Due to Disability)



Source: https://vizhub.healthdata.org/gbd-compare/

Unaddressed Pathology: Mitochondrial Diseases

Morris G, Berk M. The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. *BMC Med*. 2015 Apr 1;13:68.

Syndromic or non-syndromic mitochondrial diseases, classified as cytopathies or encephalomyopathies, arise as a result of mutations in mitochondrial or nuclear DNA. However, mitochondrial dysfunction and impaired bioenergetics are implicated in the pathogenesis of many chronic illnesses, mainly neuroimmune or autoimmune in nature, despite these not being currently categorized as primary mitochondrial diseases. **Mitochondrial dysfunction with concomitant oxidative stress is evidenced in the brains and periphery of many patients with the diagnoses of multiple sclerosis (MS), chronic fatigue syndrome (CFS), Parkinson's disease (PD), and autism.**

Mitochondrial dysfunction in such individuals may well result from the presence of oxidative stress, as there is now ample evidence implicating oxidative stress as one of the major contributing factors in the development of mitochondrial dysfunction and compromised bioenergetic performance. In fact, the causative role of chronic oxidative stress in the development of mitochondrial damage and localized or systemic bioenergetic failure has now been established beyond reasonable doubt. Chronic oxidative stress develops in a cellular environment whenever production of reactive nitrogen species (RNS) and reactive oxygen species (ROS) exceeds the clearance ability of the cell's antioxidant defenses such as the glutathione (GSH) and thioredoxin systems. ROS and RNS are natural products of oxidative phosphorylation. These reactive species can also be generated by activated inflammatory cells, including macrophages and microglia. Oxidative stress and chronic inflammation are inextricably interconnected.

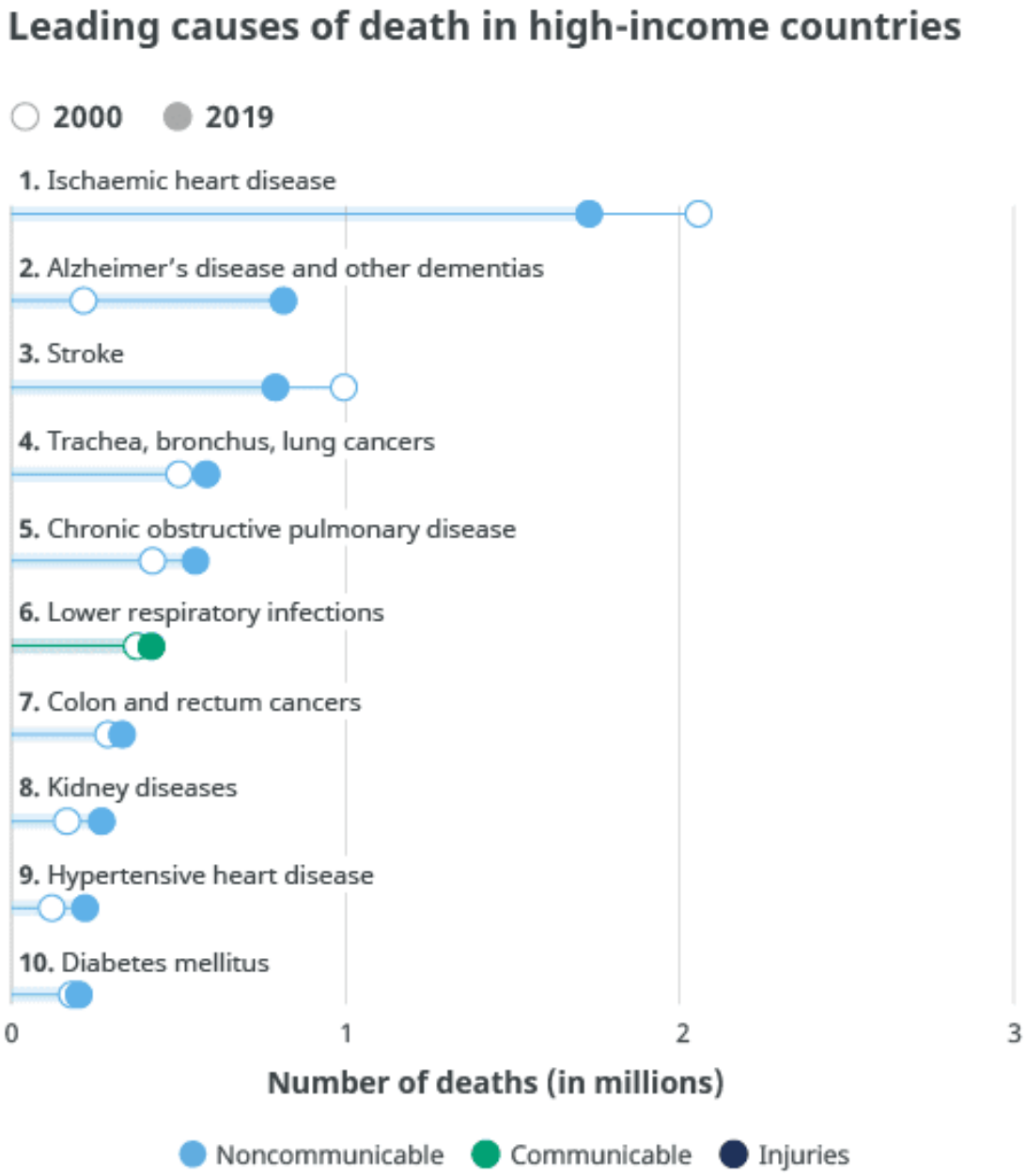
We have not seen any major breakthroughs in the last decade for how to address mitochondrial diseases. Because mitochondrial dysfunction is behind so many diseases, this is a substantial core cause of underlying pathologies.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4382850/

WHO: Top Causes of Death in High Income Countries

In upper-middle-income countries, there has been a notable rise in deaths from lung cancer, which have increased by 411 000; more than double the increase in deaths of all three other income groups combined. In addition, stomach cancer features highly in upper-middle-income countries compared to the other income groups, remaining the only group with this disease in the top 10 causes of death.

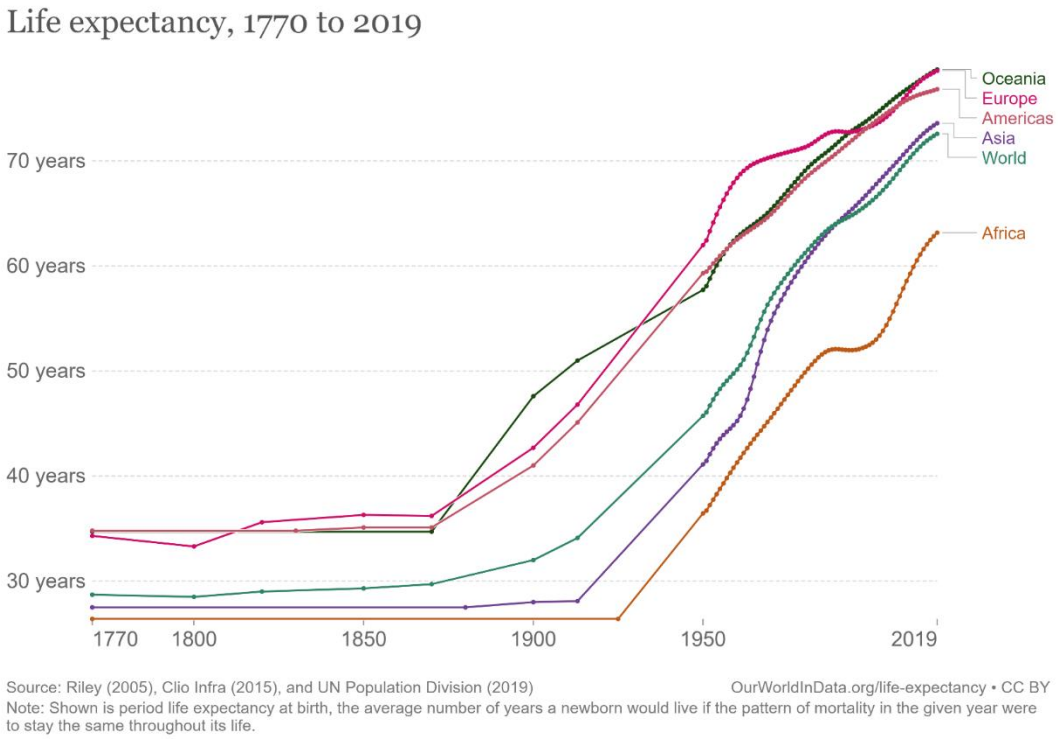
One of the biggest decreases in terms of absolute number of deaths is for chronic obstructive pulmonary disease, which has fallen by nearly 264 000 to 1.3 million deaths. However, deaths from ischaemic heart disease have increased by more than 1.2 million, the largest rise in any income group in terms of absolute number of deaths from this cause.

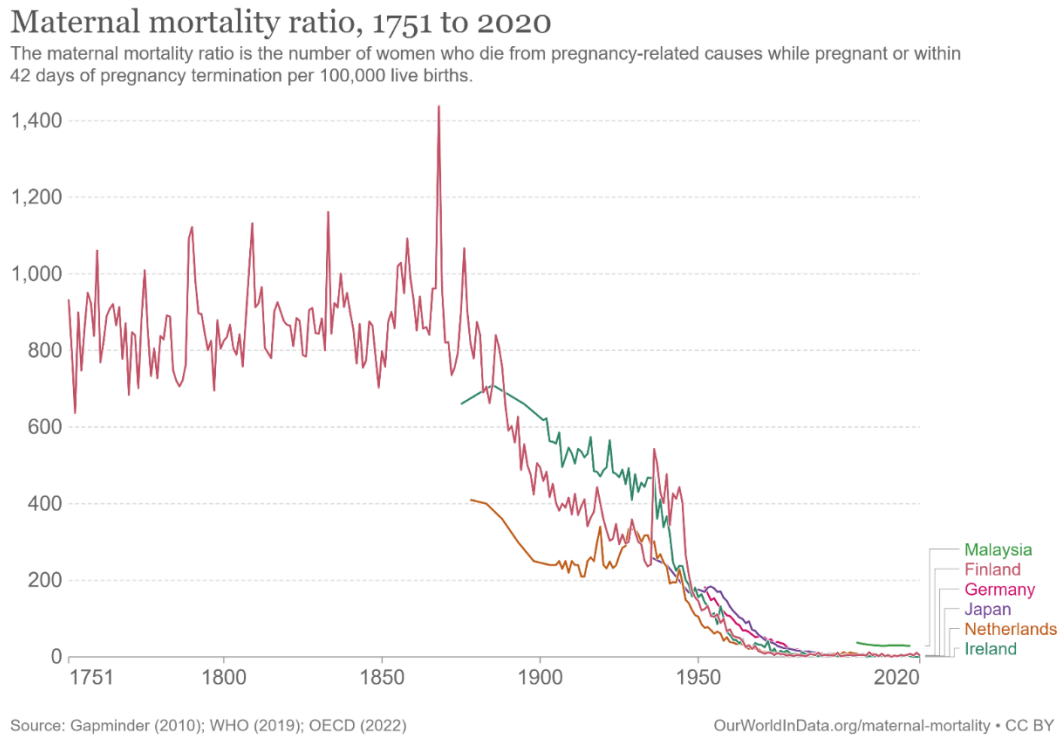


Source: WHO Global Health Estimates. Note: World Bank 2020 income classification.

Source: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

Life Expectancy Improvements Worldwide





Source: https://ourworldindata.org/life-expectancy

Vast Worldwide Improvements in Life Expectancy

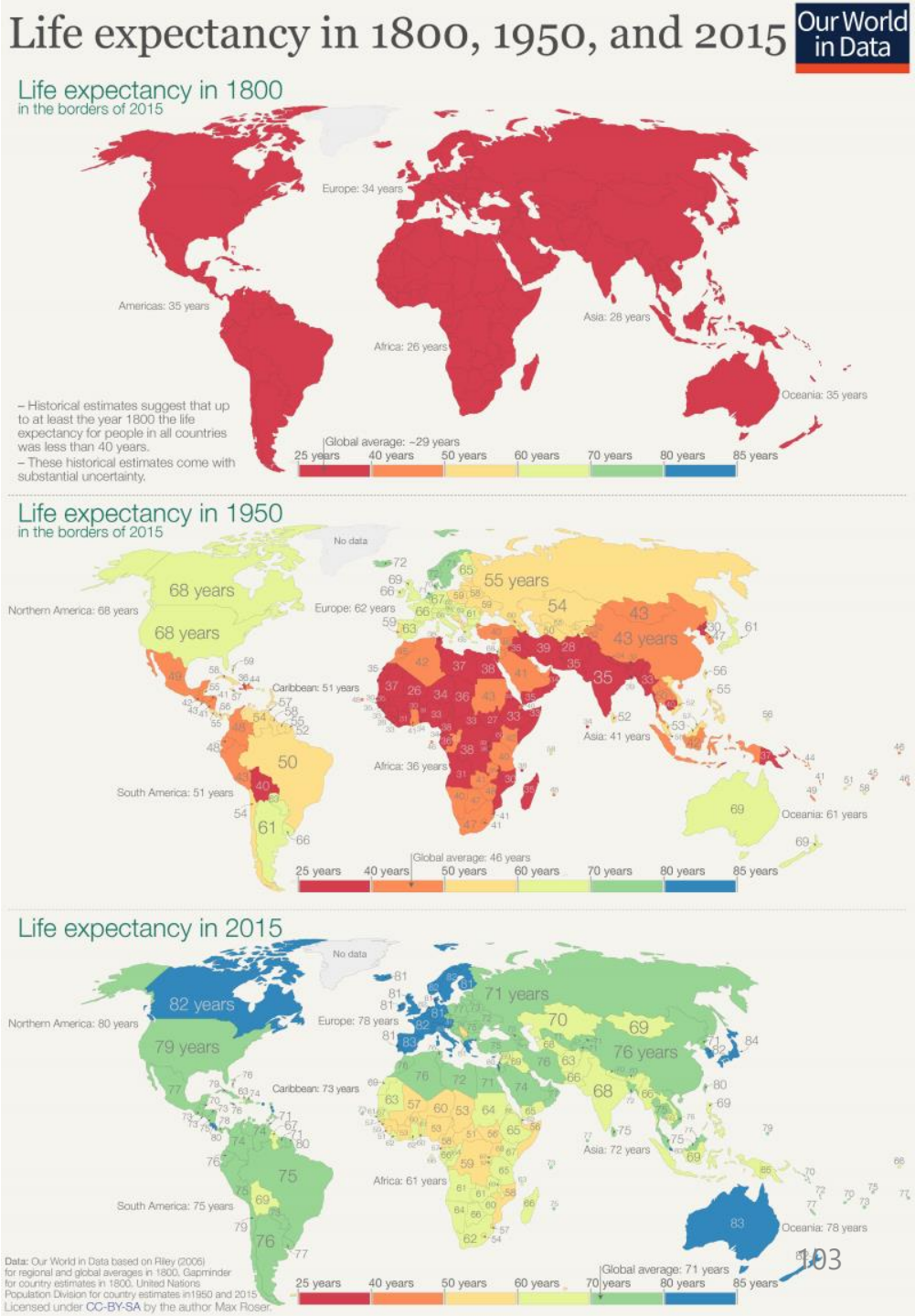
The three maps summarize the global history of life expectancy over the last two centuries: Back in 1800 a newborn baby could only expect a short life, no matter where in the world it was born. In 1950 newborns had the chance of a longer life if they were lucky enough to be born in the right place. In recent decades all regions of the world made very substantial progress, and it were those regions that were worst-off in 1950 that achieved the biggest progress since then. The divided world of 1950 has been narrowing.

Demographic research suggests that at the beginning of the 19th century no country in the world had a life expectancy longer than 40 years. Every country is shown in red. Almost everyone in the world lived in extreme poverty, we had very little medical knowledge, and in all countries our ancestors had to prepare for an early death.

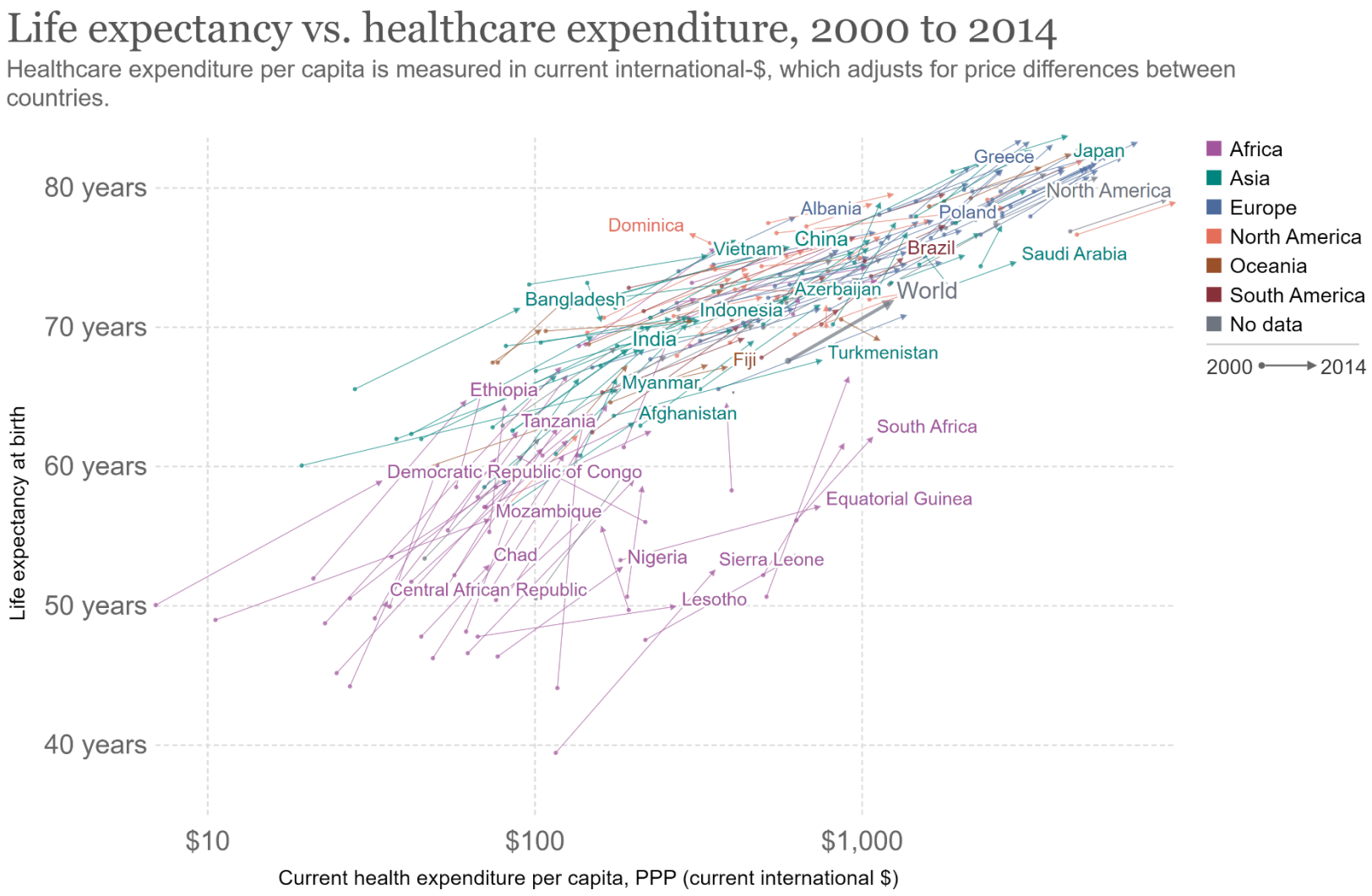
The decline of child mortality was important for the increase of life expectancy, but increasing life expectancy was certainly not only about falling child mortality – life expectancy increased at all ages.

Now, let's look at the change since 1950. Many of us have not updated our world view. We still tend to think of the world as divided as it was in 1950. But in health — and many other aspects — the world has made rapid progress. Today most people in the world can expect to live as long as those in the very richest countries in 1950. The United Nations estimate a global average life expectancy of 72.6 years for 2019 – the global average today is higher than in any country back in 1950. According to the UN estimates the country with the best health in 1950 was Norway with a life expectancy of 72.3 years.

Source: https://ourworldindata.org/life-expectancy



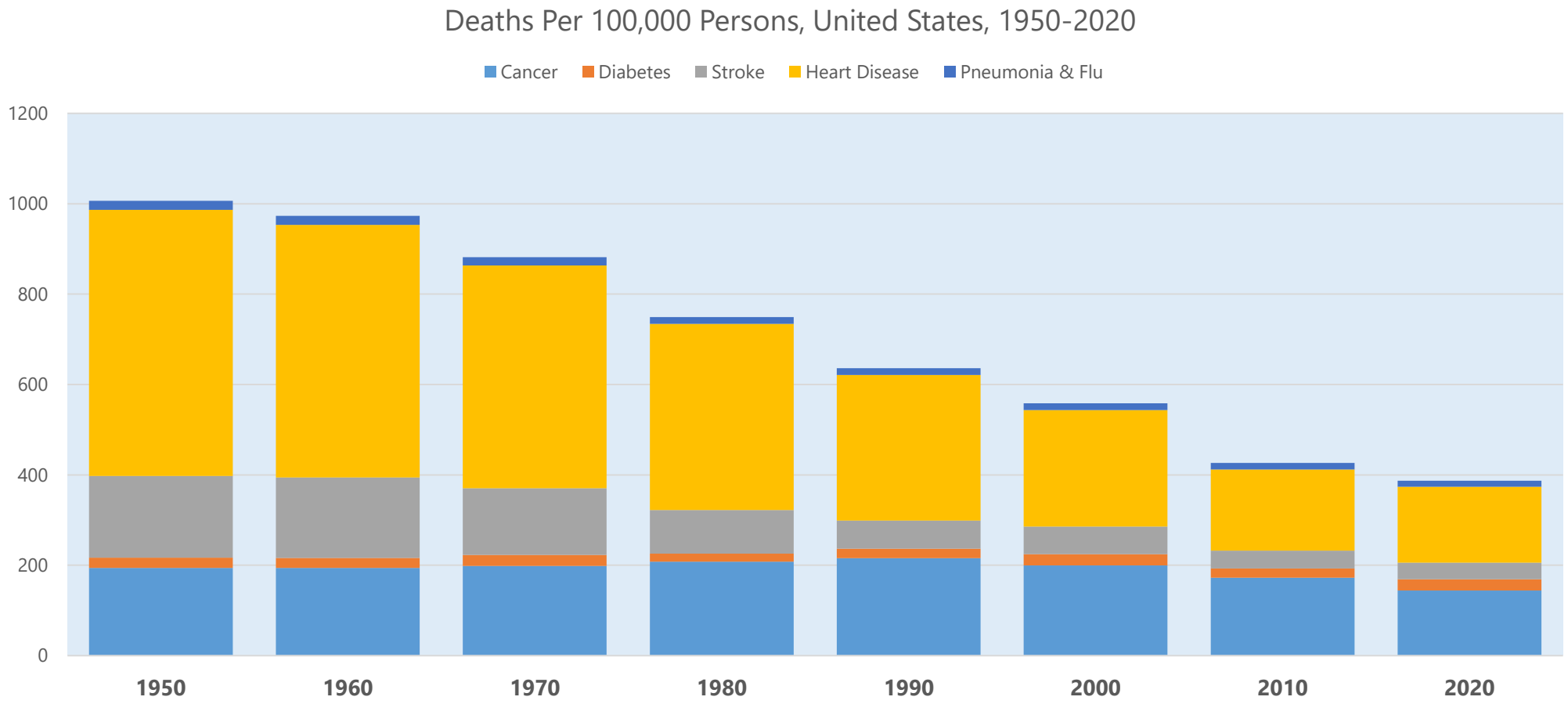
Healthcare Spend is Driving Life Expectancy Improvement



Source: Data compiled from multiple sources by World Bank

OurWorldInData.org/financing-healthcare • CC BY

Disease Mortality in the United States Improving

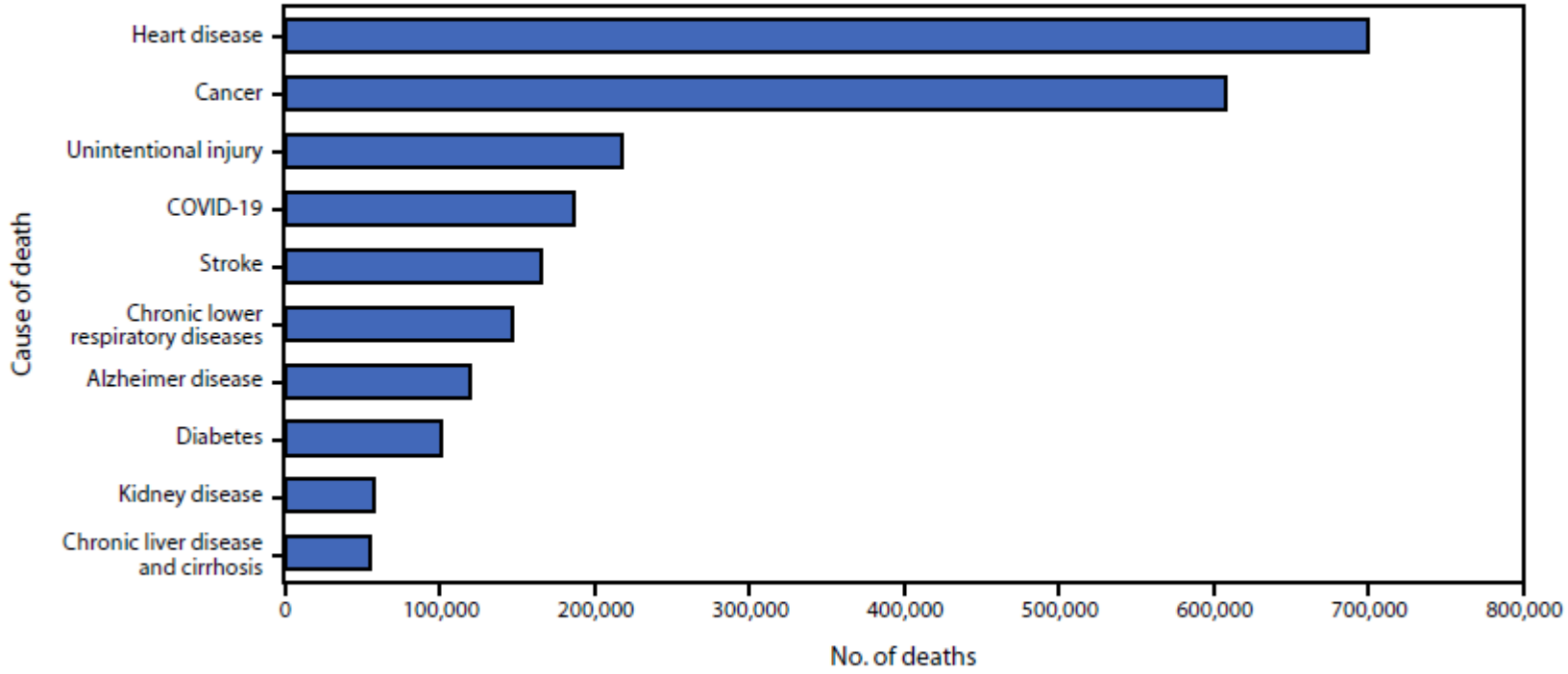


Source: CDC (https://www.cdc.gov/nchs/products/databriefs/db427.htm)

CDC Death Data for 2022 Out Last Week

Morbidity and Mortality Weekly Report

FIGURE 2. Leading underlying causes of death*,† — National Vital Statistics System, United States, 2022



* Data are provisional; National Vital Statistics System provisional data are incomplete, and data from December are less complete because of reporting lags. Deaths that occurred in the United States among residents of U.S. territories and foreign countries were excluded.
† Deaths are ranked by number of deaths per underlying cause of death.

Source: https://www.cdc.gov/mmwr/volumes/72/wr/pdfs/mm7218a3-H.pdf

CDC Data: Infant and Child Mortality *Rose* Last Year

TABLE. Provisional* number and rate of total deaths and COVID-19–associated deaths, by demographic characteristic — National Vital Statistics System, United States, 2021–2022

	No. of deaths (rate†)			
	2021		2022	
Characteristic	Total	COVID-19–associated§	Total	COVID-19–associated§
Total	**3,464,231 (879.7)**	**462,193 (115.6)**	**3,273,705 (832.8)**	**244,986 (61.3)**
Age group, yrs				
<1	**19,920 (558.8)**	167 (4.7)	**20,238 (567.8)**	231 (6.5)
1–4	**3,816 (25.0)**	66 (0.4)	**4,107 (26.9)**	152 (1.0)
5–14	**5,975 (14.3)**	185 (0.4)	**6,193 (14.8)**	203 (0.5)
15–24	**38,307 (88.9)**	1,652 (3.8)	**35,064 (81.4)**	641 (1.5)
25–34	**82,274 (180.8)**	7,033 (15.5)	**74,025 (162.7)**	2,376 (5.2)
35–44	**124,939 (287.9)**	17,412 (40.1)	**111,151 (256.1)**	5,183 (11.9)
45–54	**216,037 (531.0)**	39,360 (96.7)	**182,689 (449.0)**	12,169 (29.9)
55–64	**478,171 (1,117.1)**	79,199 (185.0)	**416,393 (972.8)**	30,526 (71.3)
65–74	**724,266 (2,151.3)**	111,412 (330.9)	**667,308 (1,982.1)**	53,228 (158.1)
75–84	**829,653 (5,119.4)**	110,536 (682.1)	**823,908 (5,083.9)**	67,116 (414.1)
≥85	**940,780 (15,743.3)**	95,168 (1,592.6)	**932,528 (15,605.2)**	73,157 (1,224.2)
Unknown	**93 (—)**	3 (—)	**101 (—)**	4 (—)
Sex				
Female	**1,626,123 (733.3)**	202,687 (91.8)	**1,558,144 (700.9)**	112,287 (49.8)
Male	**1,838,108 (1,048.0)**	259,506 (144.5)	**1,715,561 (984.8)**	132,699 (76.3)
Race and ethnicity				
AI/AN, NH	**26,972 (1,109.2)**	5,053 (201.8)	**23,440 (973.3)**	2,115 (86.8)
Asian, NH	**92,432 (461.7)**	13,707 (66.6)	**88,963 (447.2)**	6,786 (34.1)
Black or African American, NH	**449,764 (1,118.0)**	61,959 (151.4)	**410,126 (1,028.0)**	28,695 (72.9)
NH/OPI, NH	**5,223 (924.3)**	1,175 (200.9)	**4,590 (824.8)**	378 (67.8)
White, NH	**2,548,809 (893.9)**	304,586 (105.0)	**2,444,427 (855.4)**	180,212 (61.2)
Hispanic or Latino	**315,664 (724.7)**	72,910 (161.7)	**275,254 (643.4)**	25,076 (60.9)
Multiracial, NH	**17,316 (406.0)**	2,018 (50.7)	**16,819 (394.2)**	1,045 (26.7)
Unknown	**8,051 (—)**	785 (—)	**10,086 (—)**	679 (—)

Abbreviations: AI/AN = American Indian or Alaska Native; NH = non-Hispanic; NH/OPI = Native Hawaiian or other Pacific Islander.

* National Vital Statistics System provisional data for 2022 are incomplete. Data for 2021 are final. These data exclude deaths that occurred in the United States among residents of U.S. territories and foreign countries.

† Deaths per 100,000 standard population. Age-adjusted death rates are provided overall and by sex and race and ethnicity.

§ Deaths of persons coded to *International Classification of Diseases, Tenth Revision* (code U07.1), with COVID-19 as an underlying or contributing cause of death.

Source: https://www.cdc.gov/mmwr/volumes/72/wr/pdfs/mm7218a3-H.pdf

US Infant Mortality Rises For The First Time in 20 Years

***BMJ* 2023;383:p2569**

Infant mortality in the US rose by 3% in 2022, increasing for the first time in 20 years from 5.44 per 1000 live births in 2021 to 5.60, the Centers for Disease Control and Prevention has reported. This is in stark contrast to a decline of 22% in infant mortality between 2002 and 2021.

The increase is part of worsening US health in almost every area when compared with other prosperous industrial nations. US life expectancy fell to 76.4 in 2021, the lowest level since 1996.

Source: https://www.bmj.com/content/383/bmj.p2569

SSRI's Japanese Physician Survey of 442 Diseases: Biggest Unmet Needs for a New Drug (20,201 surveyed)

k	Condition	Number of Doctors Identifying Need	Percentage of physicians who desire new drugs	Percentage of physicians by point of dissatisfaction with existing treatments					
				Efficacy	Safety	Cost burden	Dosage and administration	Dosage form	Absence of treatments
1	Retinitis pigmentosa	n=158	78.5%	38.6%	4.4%	3.8%	2.5%	1.3%	48.1%
2	Leiomyosarcoma	n=107	68.2%	61.7%	15.9%	8.4%	0.9%	1.9%	19.6%
3	Abnormal very-long-chain fatty acid metabolism	n=6*	66.7%	33.3%	0.0%	0.0%	0.0%	0.0%	50.0%
4	Primary hyperoxaluria	n=3*	66.7%	33.3%	33.3%	0.0%	0.0%	33.3%	33.3%
5	Mesothelioma	n=154	66.2%	62.3%	16.2%	13.6%	1.3%	0.6%	9.1%
6	Sporadic inclusion body myositis	n=130	60.8%	29.2%	3.1%	3.8%	0.8%	1.5%	36.2%
7	Niemann-Pick disease type C	n=10*	60.0%	30.0%	0.0%	10.0%	0.0%	0.0%	20.0%
8	Biliary tract cancer	n=870	58.9%	51.8%	10.8%	6.8%	1.1%	1.0%	10.0%
9	Treatment-resistant schizophrenia	n=1,055	56.5%	48.2%	18.9%	3.6%	2.3%	3.4%	6.9%
10	Non-dystrophic myotonia	n=16*	56.3%	25.0%	6.3%	12.5%	6.3%	6.3%	25.0%
10	Cockayne syndrome	n=16*	56.3%	18.8%	6.3%	0.0%	0.0%	0.0%	43.8%

Source: https://www.ssri.com/e/news/press_release/2022/02/28/1406

Chinese Physicians Interest in New Drugs: Common Diseases (SSRI Survey of 11,106 Physicians in 2022)

Rank	TOTAL		
	Condition	Percent of Physicians Who See Diseases	% of all Chinese physicians who want new drugs for disease
1	Hypertension	69.4%	29.5%
2	Dyslipidemia	59.1%	25.0%
3	Diabetes	66.2%	22.7%
4	Type 2 Diabetes	64.9%	22.3%
5	COPD	41.0%	20.2%
6	Atrial fibrillation	43.8%	20.2%
7	Cerebral infarction	44.1%	19.3%
8	Hypertriglyceridemia	58.3%	17.9%
9	Constipation	42.8%	15.8%
10	Bronchial asthma	32.2%	15.7%

Source: https://www.ssri.com/e/news/press_release/2022/06/09/1570

Chinese Physicians Interest in New Drugs: Less Common Diseases (SSRI Survey of 11,106 Physicians in 2022)

Rank	Physician coverage of at least 1%			Physician coverage of at least 5%		
	Condition	Physician coverage	% of physicians who want new drugs	Condition	Physician coverage	% of physicians who want new drugs
1	Acute myeloid leukemia (AML)	3.9%	79.0%	Cholangiocellular carcinoma	5.2%	70.6%
2	Acute lymphoid leukemia (ALL)	3.9%	74.1%	Pancreatic cancer	7.9%	69.6%
3	Cholangiocellular carcinoma	5.2%	70.6%	Small cell lung cancer	13.2%	68.7%
4	Pancreatic cancer	7.9%	69.6%	Hepatocellular carcinoma	13.4%	68.5%
5	Small cell lung cancer	13.2%	68.7%	Biliary tract cancer	6.6%	67.1%

U.S. and Japan Physician Survey in 2014 of Biggest Unmet Needs

It's interesting to note that in 2014 three conditions that were highly ranked by U.S. physicians have seen significant medical progress. These are obesity, dementia and migraine.

Ranking	US n=6,175			JAPAN n=20,288		
	Medical condition	Feel a need for new products	% of respondents treating this condition (for reference)	Medical condition	Feel a need for new products	% of respondents treating this condition (for reference)
1	Obesity	27.4%	*52.1%*	Dementia	14.5%	*33.3%*
2	Depression/depressive state	23.7%	*51.1%*	Seasonal allergic rhinitis/ hay fever	10.1%	*43.0%*
3	Diabetes	22.1%	*51.6%*	Sepsis	9.5%	*22.6%*
4	Dementia	20.5%	*33.9%*	Perennial allergic rhinitis	8.8%	*33.2%*
5	Migraine	19.5%	*47.6%*	Diabetes	8.4%	*57.2%*
6	Anxiety disorder	18.8%	*46.5%*	Depression/depressive state	8.2%	*31.2%*
7	Hypertension	17.8%	*54.1%*	Hypoalbuminemia	7.7%	*23.8%*
8	COPD	16.0%	*38.5%*	Atopic dermatitis	7.6%	*23.7%*
9	Lower back pain	15.7%	*47.6%*	COPD	7.5%	*33.7%*
10	Dyslipidemia	15.6%	*44.0%*	Gastric cancer	7.1%	*18.3%*
11	Osteoarthritis	15.1%	*36.7%*	Hypertension	7.1%	*61.6%*
12	Fibromyalgia	14.8%	*31.0%*	Schizophrenia	6.6%	*15.0%*
13	Headache	14.8%	*49.8%*	Bronchial asthma	6.5%	*41.9%*
14	GERD/NERD	14.3%	*55.6%*	DIC	6.2%	*14.5%*
15	Diabetic neuropathy	13.9%	*34.8%*	Interstitial pneumonia	6.1%	*15.1%*

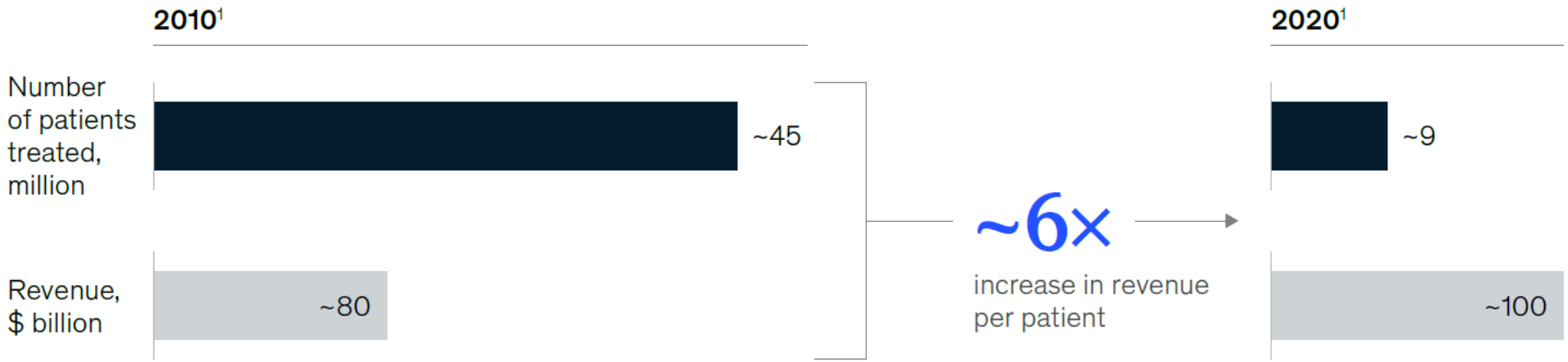
Source: https://www.ssri.com/e/pub/press_release_20160210.pdf

Pharma Revenue is Up Even Though Fewer Patients Getting Top 20 Drugs

McKinsey Helix Report, 2022

Exhibit 9

From 2010 to 2020, the number of US patients on top 20 blockbuster drugs fell by ~80%, but revenue increased by ~25%.



[1]Excluding vaccines (ie, Prevnar).
Source: McKinsey analysis of blockbuster drugs; IMS Health, National Sales Perspectives, 2010; CMS's ASP Drug Pricing; PHAST volume data; DailyMed dosage data, HCP interviews on treatment duration; EvaluatePharma® May 2022, Evaluate Ltd.

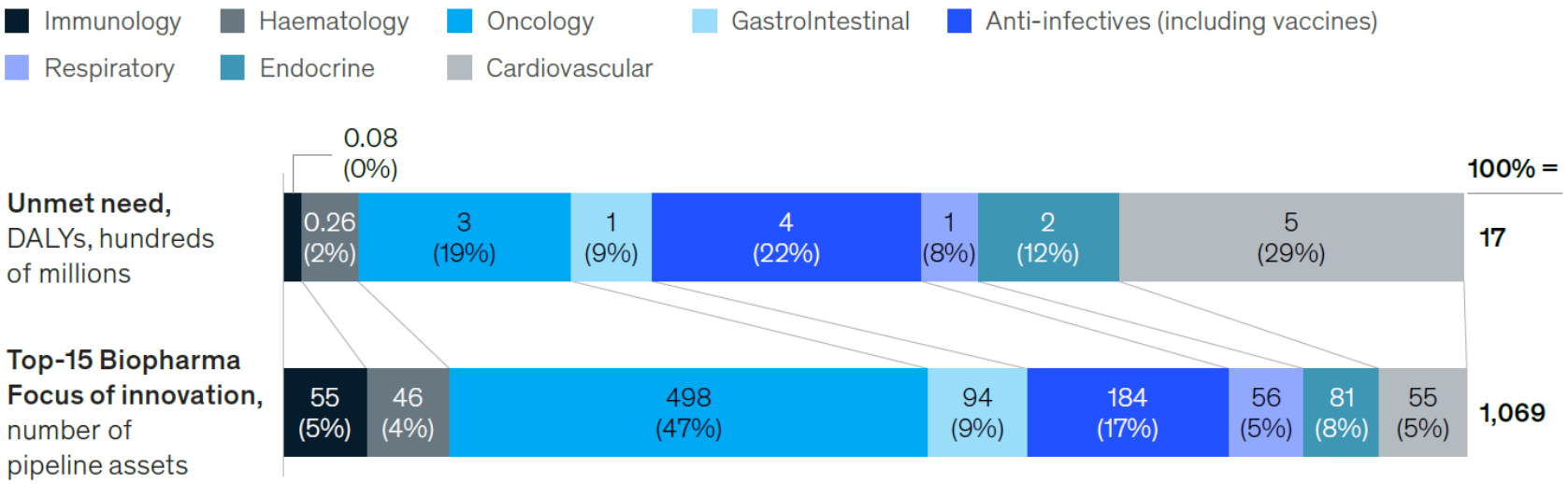
Source: https://www.mckinsey.com/industries/life-sciences/our-insights/the-helix-report-is-biopharma-wired-for-future-success#/

Pharma R&D Spend Not Well Aligned with Unmet Medical Needs

McKinsey Helix Report, 2022

Exhibit 11

Innovation efforts do not fully align with global patient needs.



Sources: WHO, EvaluatePharma, PharmaProjects

McKinsey: From the perspective of population health, there are substantial unmet needs in large disease areas, and few corresponding assets are in the pipeline (Exhibit 11). One extreme example is next-generation anti-infectives, where demand increases every year as drug resistance grows. By 2050, antibiotic-resistant bacteria may cause over 10 million deaths, 40% more than cancer, most in developing regions where access is already inequitable. The industry has created no novel antibiotic class since the 1980s and has not focused major research efforts in this critical arena.

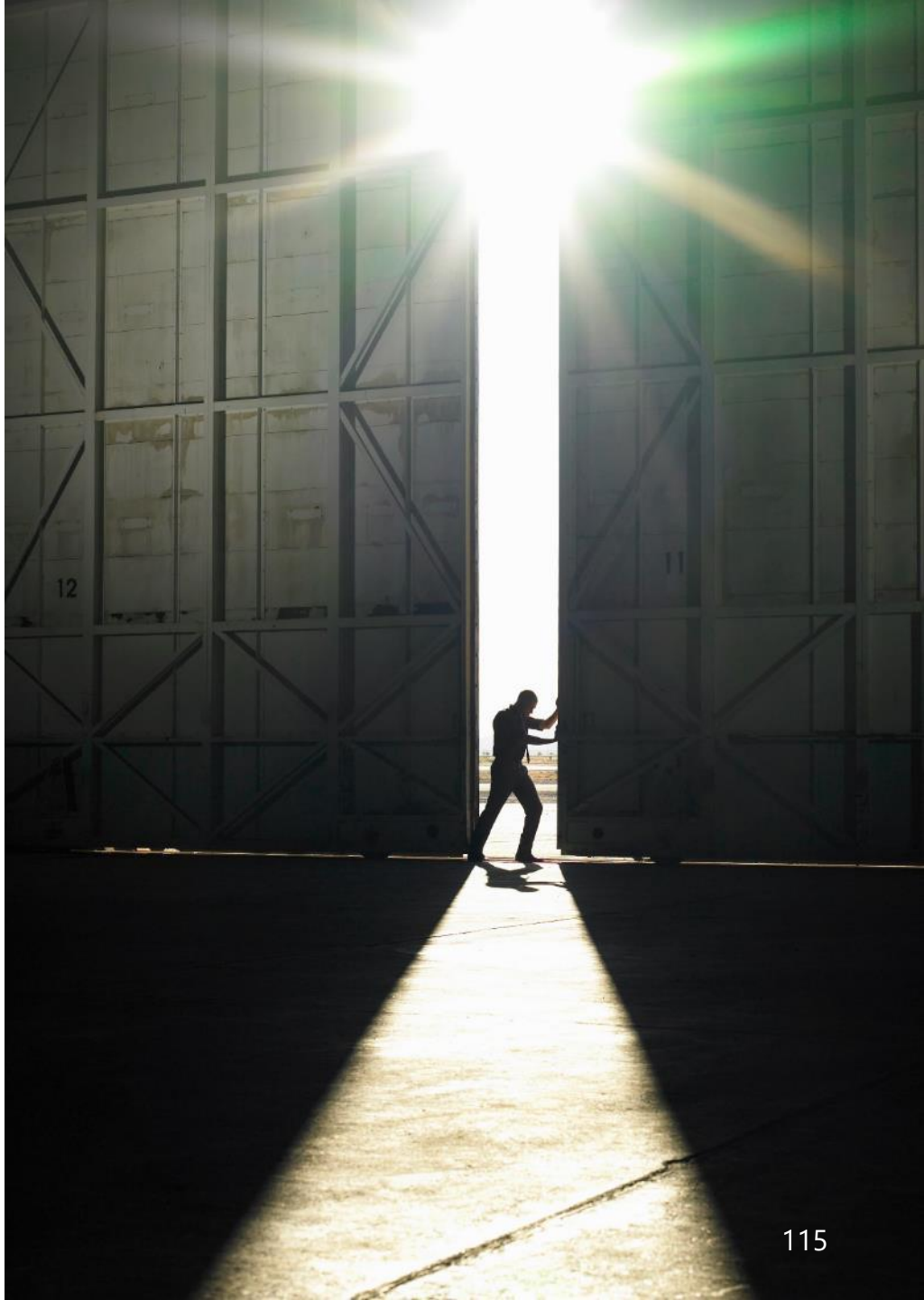
Source: https://www.mckinsey.com/industries/life-sciences/our-insights/the-helix-report-is-biopharma-wired-for-future-success#/

Our View: Where Are the Next Big Opportunities for Pharma?

One might bucket the search for the next generation of transformational treatments into two major categories:

Payor Centric Solutions: Opportunities to deliver solutions to payors. If payors face very high costs from dealing with a disease, they should be willing to pay handsomely for a solution to such disease. This is not to discount the patient's role in any way, but someone must be willing to pay for a new drug and introducing a product with high cost-saving potential or brilliant life saving properties is essential in today's brutal pricing environment.

Consumer Centric Solutions: The excitement for obesity drugs to date is more patient driven than payor driven. Many people are willing to spend a lot of money to get thin. There are obviously many things that consumers want other than to lose weight. One need not look far into our society's many travails to identify what opportunities might exist. Historically, almost all large drugs have been payor-driven rather than consumer-driven but this can change. It's a critical point in a post-IRA world where payor behavior is shifting.



Illustrative Payor Centric Needs

1. **Cancer**: The largest market in cancer is in front-line treatments for the big five tumor types. A giant opportunity is to develop a pan-cancer treatment approach with efficacy that extends beyond today's chemotherapies and checkpoint inhibitors.

2. **COPD**: Current treatments treat the inflammatory aspects of COPD but do not impact the underlying causes of lung disease which involve cellular damage and fibrosis. The literature suggest that this disease is a highly heterogenous phenotype that could be treated with a range of targeted approaches.* With an economic cost in the U.S. alone of at least $50bn per annum, there is obviously large commercial potential for a transformative drug.**

3. **Heart Failure**: Despite several approved pharmaceutical agents, heart failure remains one the largest costs in Medicare as patients experience frequent and expensive visits to hospitals as their heart muscle weakens. A number of researchers are working on novel, promising approaches to this disease.

4. **Insulin Insensitivity**: Type 2 diabetes accounts for roughly 25% of all healthcare expense in the United States. Over two thirds of Type 2 diabetics suffer from insulin insensitivity which is a well-defined biological failure to transport glucose into a cell. The societal and patient consequences are extreme. Current insulin sensitizers such as pioglitazone are far from ideal. We note a number of promising approaches to this problem in the literature. A good drug in this area would easily cross $50bn in sales.

5. **Kidney Failure**: Chronic kidney disease remains a fatal and costly disease. Today's RAS inhibitors and SGLT2 inhibitors help but do not reverse the disease in any way. There is an acute need for new treatments in this area and a number of promising scientific developments involving the underlying fibrotic process. A good drug here could easily hit $50bn in sales.

*See, for example: https://www.atsjournals.org/doi/full/10.1513/AnnalsATS.201303-055AW
**See, for example: https://www.lung.org/research/trends-in-lung-disease/copd-trends-brief/copd-burden

Illustrative Patient Centric Pharma Opportunities

Lifestyle Oriented Patient Needs

Patients are interested in drugs that:

1. Would cause them to be less fatigued
2. Enable them to age more slowly
3. Enable them to look better
4. Avoid allergies
5. Improve their recall and cognition
6. Improve their mood
7. Avoid the common cold
8. Reduce their anxiety
9. Avoid hair loss
10. Require them to sleep less
11. Reduce skin problems such as acne

Serious Symptomatic Diseases of High Concern

Patients are interested in drugs that address:

1. Addiction to cigarettes and drugs
2. Asthma
3. Autism spectrum disorder
4. Chronic fatigue syndrome
5. Dementia and Alzheimer's
6. Dry eye
7. Endometriosis
8. Fibromyalgia
9. Hashimoto's disease
10. Lower back pain
11. Osteoarthritis

Disclosure

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