Biopharmaceutical Sector

Weekly Update – December 18, 2023

STIFEL | Healthcare

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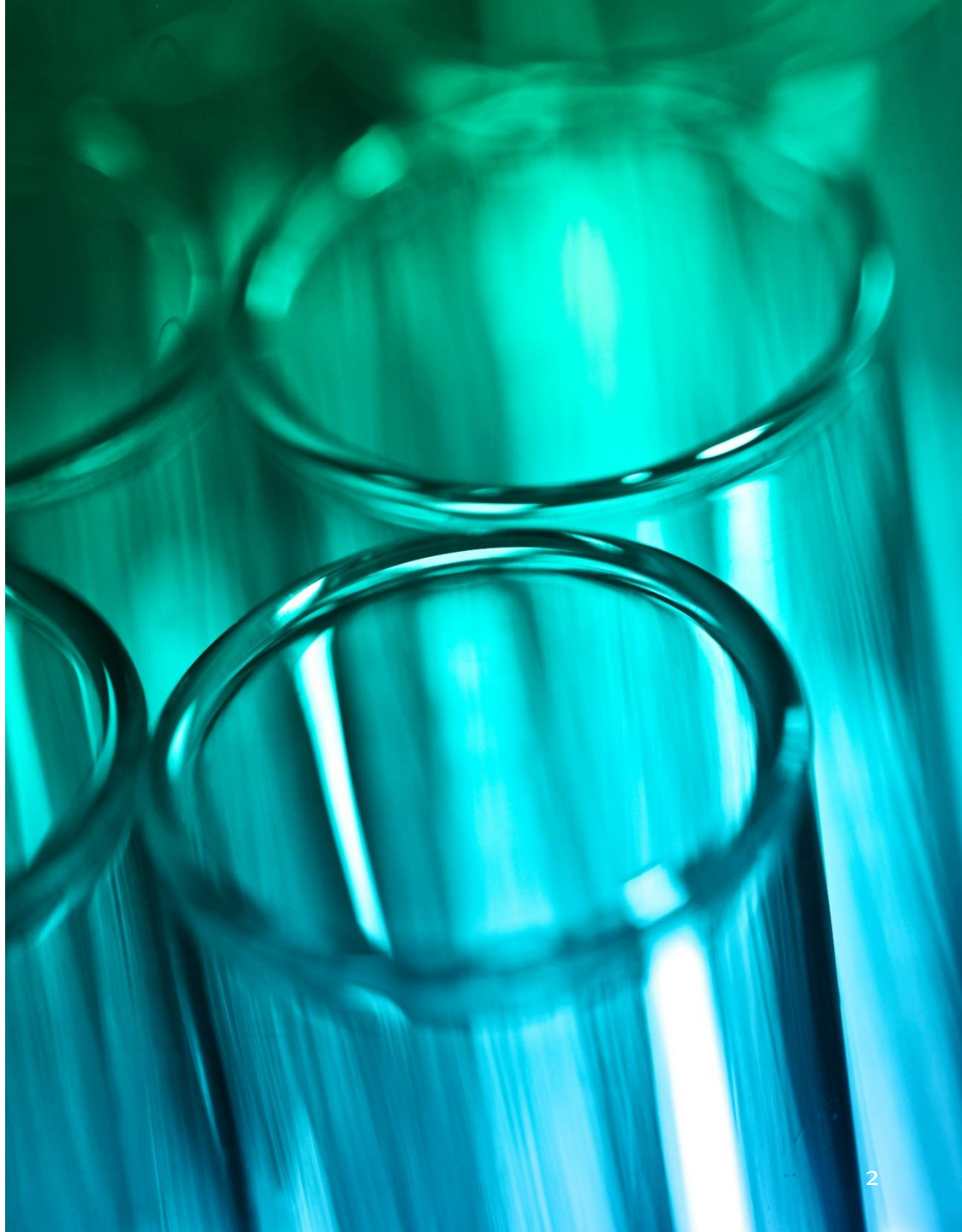
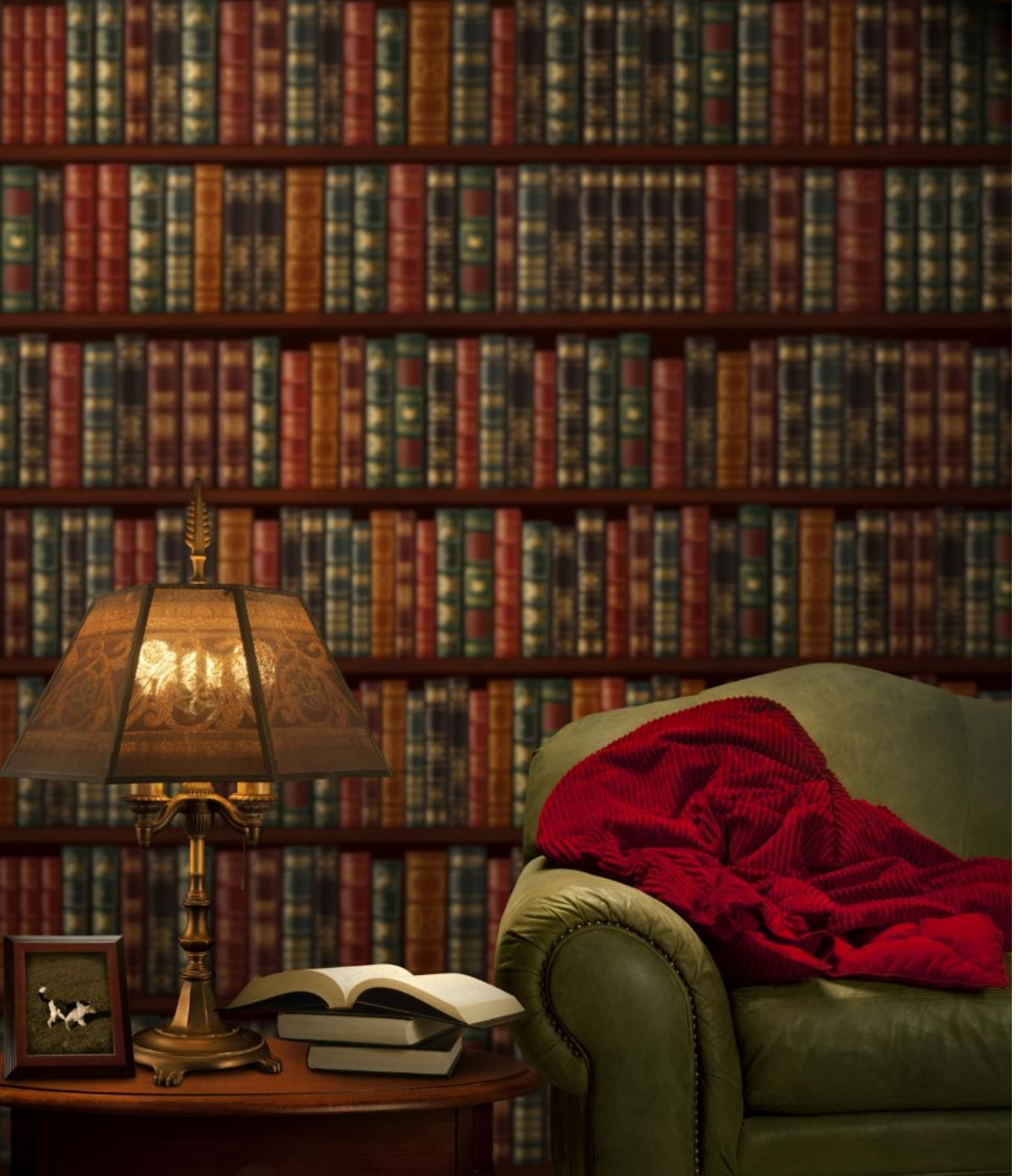


Publishing Schedule Update

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

We will not be publishing on the week of Dec 25th. We will publish a year in review issue prior to the JPM conference.

Wishing you a Happy New Year in advance!



Accessing Past Issues

Recent issues in case you missed and want to read:

Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 22, 2023 (Bullish on Biotech)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (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 December 15, 2023.

Please join us.

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

The week of Jan 7, 2024 will feature over 30,000 biopharma professionals in SF for JPM, Biotech Showcase and many other events.

To meet with Stifel
yeungn@stifel.com

Headed to JPM? Make the Most of It

Tyler Patchen, *Biospace*, Dec 13, 2023

December usually signals the start of the holiday season and all the joys associated with gift-giving and family gatherings. But for those in the biotech world, it also means there is only a month until the JP Morgan Healthcare Conference in San Francisco.

Plan Ahead

Decide on your goals and objectives are beforehand. Are you there to raise money, in-license assets or just hear talks and meet people? Having your objectives ironed out early will make your experience much smoother, Jakob Dupont, an executive partner at Sofinnova Investments, told BioSpace.

Additionally, companies should make meeting arrangements now as people's schedules can get very full, said Shaun Bagai, CEO of RenovoRx. Wyatt McDonnell, CEO of Infinimmune, added that if you are banking on meeting somebody in particular, connect with that person ahead of time to be sure they are attending.

Prepare for small talk

Bresge said the conference has no environment that creates deep conversations, but it is an excellent environment to get face time with numerous players in the industry. "It's a really good opportunity to meet anybody and everybody that you want to and need to meet across the industry whether that's investors, bankers, pharma companies, vendors," Bresge said.

Play the field

Neil McFarlane, CEO of Zevra Therapeutics, suggested attending as many company presentations as possible. "This can be extremely helpful to new attendees looking to gain exposure to best practices to introduce their companies," he told BioSpace. "Additionally, I would advise attendees to attend as many networking events as possible."

Practice your elevator pitch

With significant networking events being a part of every JPM, Lishan Aklog, Lucid Diagnostics CEO, said that having your company's story prepared is critical. You may run into people who are interested, but you will only have a few minutes to tell your company story, he said.

Find a good meeting spot

Bagai mentioned that getting meeting spaces can be complex depending on where the meeting is, and meeting outside a pre-booked room can be challenging. But Dupont said that while JPM's home is billed as the Westin St. Francis Hotel off of Union Square, meetings do not have to be there.

Manage your expectations

Brent Vaughan, CEO of Cognito Therapeutics, told BioSpace that it's vital to know that you may not speak to everyone you hope to, or dive into the depth you'd planned on.

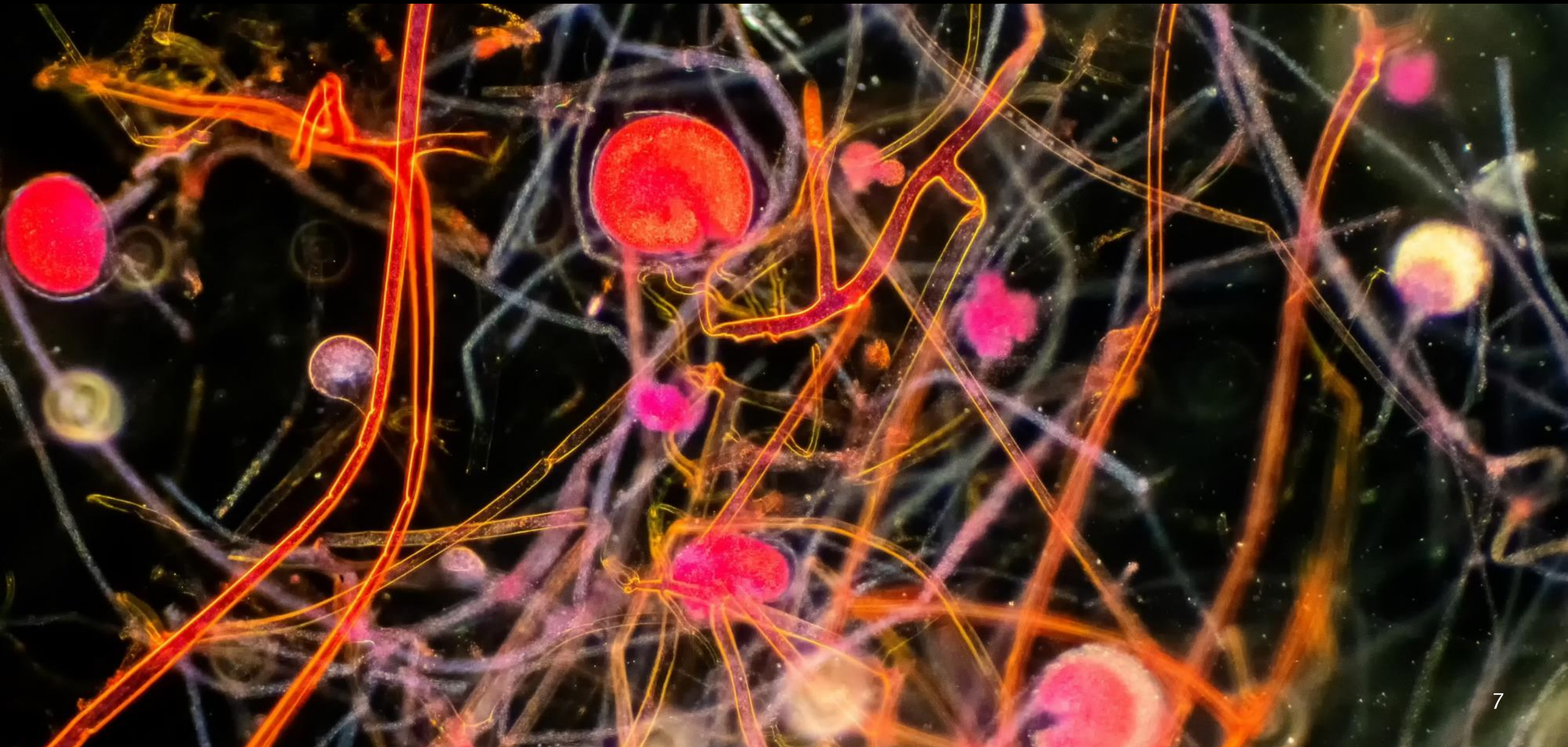
"If you're lucky enough to have meetings with some of them, I think you should think about what your goals are. Your goal is to decide if there's enough mutual interest for a more material meeting," Vaughan said. "If you find a group that wants to give you an hour and have people sit down and listen to it, I think you're pretty fortunate."

Bring an umbrella and comfortable shoes

According to Ray Therapeutics's CEO Paul Bresge, it often rains during the conference. And nestled in the heart of hilly San Francisco, wearing the right footwear will help make the extensive walking more enjoyable, experts told BioSpace.

Source: https://www.biospace.com/article/headed-to-jpm-here-are-some-tips-to-make-the-most-of-it/

Macroeconomics Update



CPI Inflation Controlled in November

BUREAU OF LABOR STATISTICS, DECEMBER 12, 2023

CONSUMER PRICE INDEX FOR MONTH OF NOVEMBER 2023

The Consumer Price Index for All Urban Consumers (CPI-U) increased 0.1 percent in November on a seasonally adjusted basis, after being unchanged in October, the U.S. Bureau of Labor Statistics reported today. Over the last 12 months, the all items index increased 3.1 percent before seasonal adjustment.

The energy index fell 2.3 percent over the month as a 6.0-percent decline in the gasoline index more than offset increases in other energy component indexes. The food index increased 0.2 percent in November, after rising 0.3 percent in October. The index for food at home increased 0.1 percent over the month and the index for food away from home rose 0.4 percent.

The index for all items less food and energy rose 0.3 percent in November, after rising 0.2 percent in October. Indexes which increased in November include rent, owners' equivalent rent, medical care, and motor vehicle insurance. The indexes for apparel, household furnishings and operations, communication, and recreation were among those that decreased over the month.

The all items index rose 3.1 percent for the 12 months ending November, a smaller increase than the 3.2-percent increase for the 12 months ending October. The all items less food and energy index rose 4.0 percent over the last 12 months, as it did for the 12 months ending October. The energy index decreased 5.4 percent for the 12 months ending November, while the food index increased 2.9 percent over the last year.

Source: https://www.bls.gov/news.release/cpi.nr0.htm

U.S. prices rose only 0.1% in November.

Good news!

If one excludes energy there was 0.3% inflation, still good news.

The main source of price inflation was rental costs but this is an imputed index that is not necessarily reflective of market realities.

Markets rose on last week's inflation update.

Fed Comments Positive After Last Week's FOMC Meeting

USA Today, Dec 13, 2023 (excerpt)

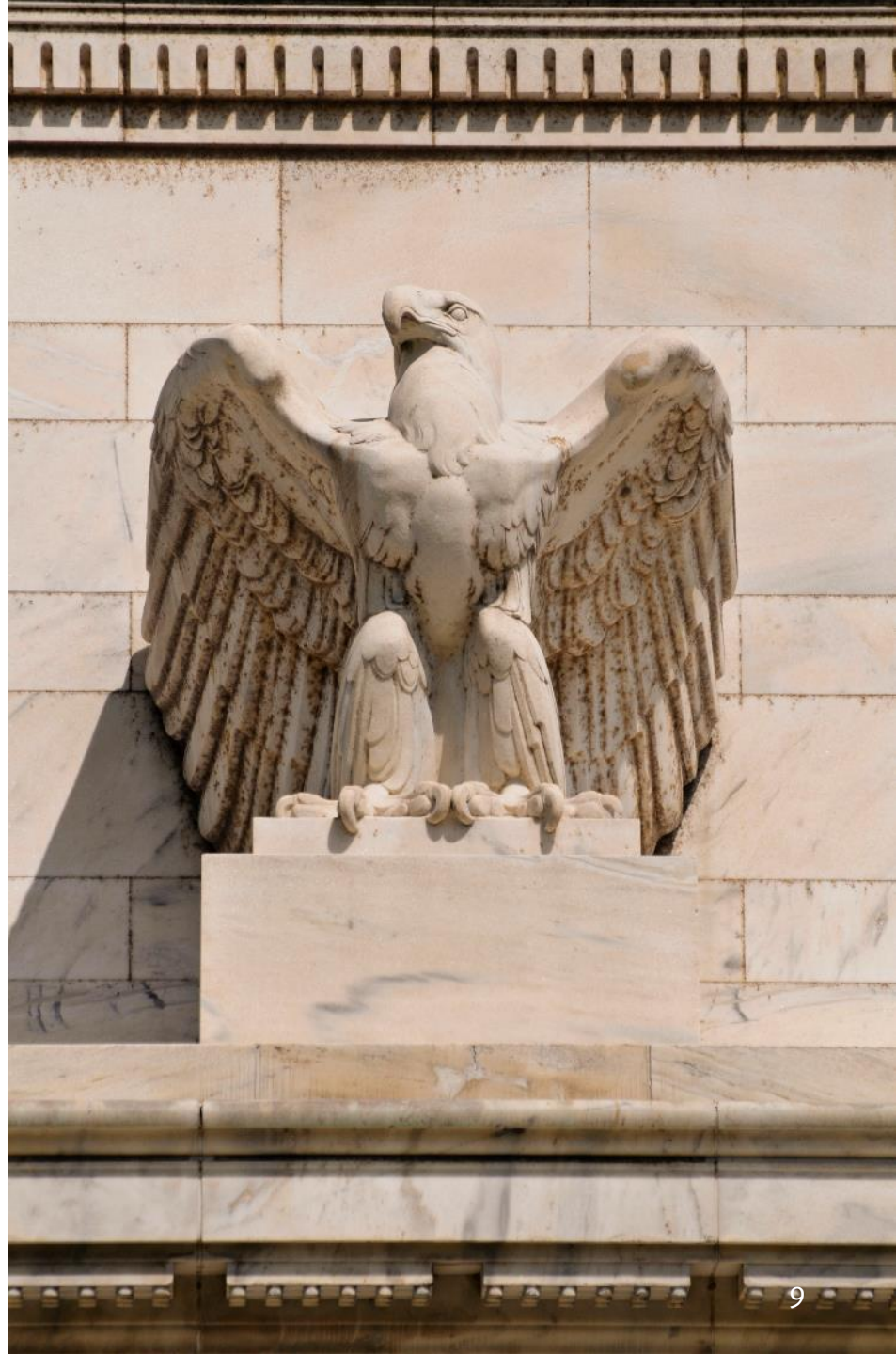
WASHINGTON – The Federal Reserve left its key short-term interest rate unchanged again Wednesday, hinted that rate hikes are likely over and forecast three cuts next year amid falling inflation and a cooling economy.

That's more rate cuts than many economists expected.

The decision leaves the Fed's benchmark short-term rate at a 22-year high of 5.25% to 5.5% following a flurry of rate increases aimed at subduing the nation's sharpest inflation spike in four decades. The central bank has now held its key rate steady for three straight meetings since July.

That provides another reprieve for consumers who have faced higher borrowing costs for credit cards, adjustable-rate mortgages and other loans as a result of the Fed's moves. Yet Americans, especially seniors, are finally reaping healthy bank savings yields after years of paltry returns.

Source: https://www.usatoday.com/story/money/2023/12/13/fed-interest-rate-hike-live-updates/71896343007/



Fed’s John Williams Says the Central Bank isn’t ‘Really Talking About Rate Cuts Right Now’

Yun Li, CNBC, Dec 15, 2023 (excerpt)

New York Federal Reserve President John Williams said Friday rate cuts are not a topic of discussion at the moment for the central bank.

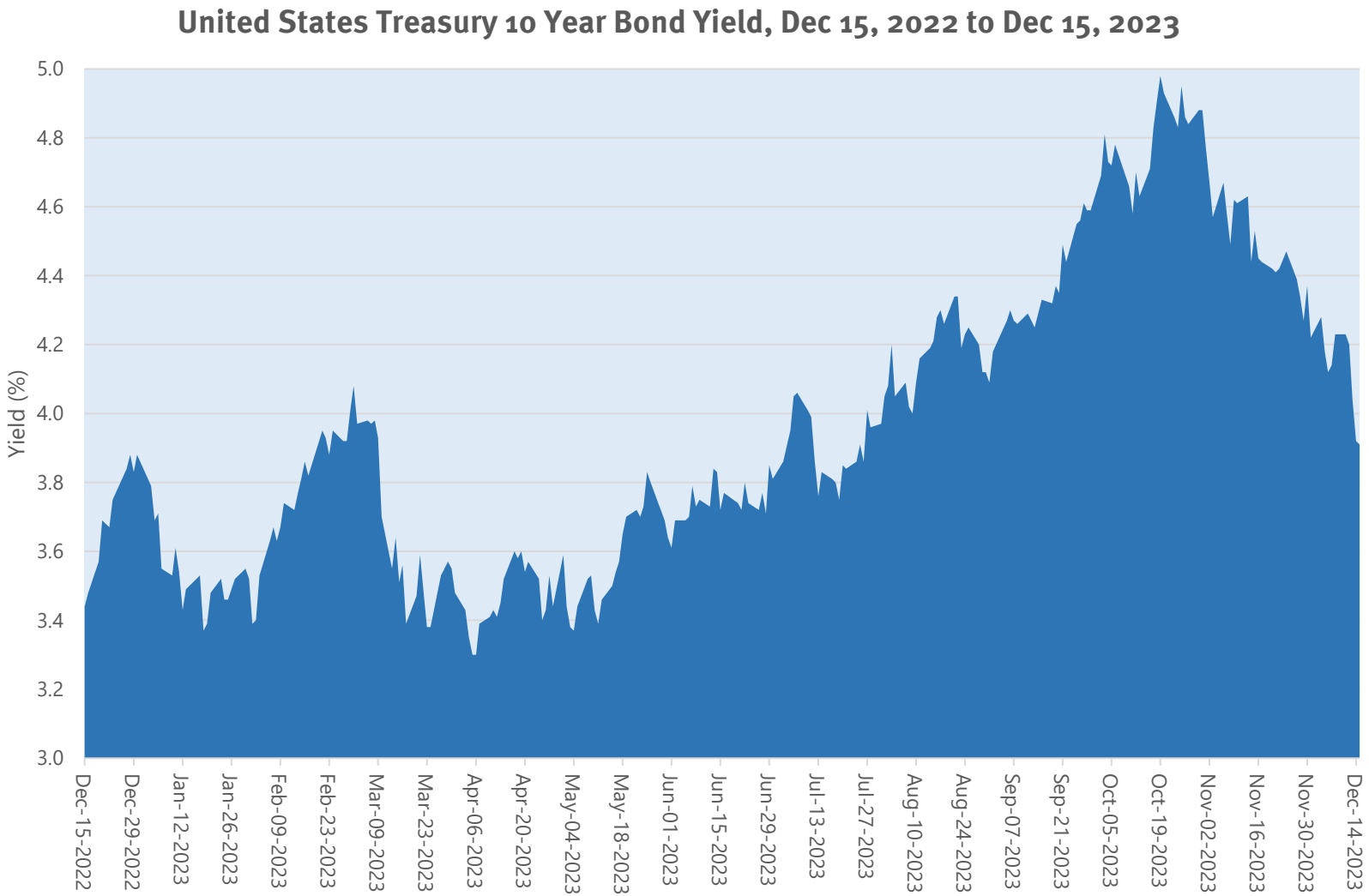
"We aren't really talking about rate cuts right now," he said on CNBC's "Squawk Box." "We're very focused on the question in front of us, which as chair Powell said… is, have we gotten monetary policy to sufficiently restrictive stance in order to ensure the inflation comes back down to 2%? That's the question in front of us."

The Dow Jones Industrial average shot to a record and the 10-year Treasury yield fell below 4.3% this week as traders took the Fed's Wednesday forecast for three rate cuts next year as a sign the central bank was changing its tough stance and would start cutting rates sooner than expected next year.

Traders are betting that the central bank would cut rates deeper than three times, according to fed funds futures. Futures markets also indicate that the Fed could start cutting rates as soon as March.

Source: https://www.cnbc.com/2023/12/15/feds-john-williams-says-the-central-bank-isnt-really-talking-about-rate-cuts-right-now.html

Treasury Wow Factor



Ten-Year US Treasury Bond Yields have dropped by over 100 basis points since peaking in October.

Never before have we been so excited by something so boring as the U.S. Treasury yield.

This move is a giant positive for biotech.

Source: S&P CapitalIQ.

Wall Street Caught Off Guard by “Risk On” Trade

Denitsa Tsekova and Emily Graffeo, *Bloomberg*, Dec 15, 2023 (excerpt)

Wall Street investors and analysts spent months strategizing how to position for 2024. Federal Reserve Chair Jerome Powell shredded their best-laid plans in a matter of minutes this week.

Even the most ardent stock and bond bulls were caught off guard by the central bank’s decision to signal the end of its historic monetary-tightening campaign with a dovish 2024 pivot. In the aftermath, the Dow Jones Industrial Average and Nasdaq 100 surged to records, while bonds soared, credit boomed and risky assets around the world rallied.

The dramatic moves upended countless outlooks. JPMorgan Asset Management’s Philip Camporeale increased the equity allocation in his stock-bond portfolio to the highest in nearly two years after Powell’s speech. John Roe at $1.4 trillion Legal & General said he’s unwinding long duration bets on inflation-protected Treasuries and reconsidering his underweight exposure to stocks. And Spencer Hakimian of Tolou Capital Management said signs the Fed will start cutting rates as soon as the first quarter prompted him to wager on a steeper yield curve.

This story mirrors the conversation taking place among life science investors at present. Numerous funds went to heavy cash positions or remained net short as evidence of a rally hit in early November.

The strength of the rally fundamentals became ever more evident last week as Powell’s Fedspeak melted away to reveal an dovish stance on rates. While the Treasury market has responded quickly, biotech stocks appear to us to have probably not responded nearly enough to the positive news. Funds are scrambling to get more positively positioned and to take off shorts as it becomes clear that the biotech stock market is going to be in “risk on” mode for many months to come.

Source: https://www.bloomberg.com/news/articles/2023-12-15/wall-street-s-wild-week-upends-2024-trading-plans-in-big-fed-bet

Biden Goes Into 2024 With the Economy Getting Stronger, but Voters Feel Horrible About It

Josh Boak, Associated Press, Dec 11, 2023 (excerpt)

President Joe Biden goes into next year's election with a vexing challenge: Just as the U.S. economy is getting stronger, people are still feeling horrible about it.

Pollsters and economists say there has never been as wide a gap between the underlying health of the economy and public perception. The divergence could be a decisive factor in whether the Democrat secures a second term next year. Republicans are seizing on the dissatisfaction to skewer Biden, while the White House is finding less success as it tries to highlight economic progress.

"Things are getting better and people think things are going to get worse — and that's the most dangerous piece of this," said Democratic pollster Celinda Lake, who has worked with Biden. Lake said voters no longer want to just see inflation rates fall — rather, they want an outright decline in prices, something that last happened on a large scale during the Great Depression.

By many measures, the U.S. economy is rock solid. Friday's employment report showed that employers added 199,000 jobs in November and the unemployment rate dropped to 3.7%. Inflation has plummeted in little over a year from a troubling 9.1% to 3.2% without causing a recession — a phenomenon that some once skeptical economists have dubbed "immaculate."

In a possible warning sign for Biden, people surveyed for the index brought up the 2024 election. Sentiment rose dramatically more among Republicans than Democrats, potentially suggesting that GOP voters became more optimistic about winning back the White House.

Source: https://apnews.com/article/biden-economy-jobs-inflation-sentiment-53db7f95d14db2557b00424254208272

China Has Another Massive Headache Now: It Can't Stem Deflation

Laura He, CNN, Dec 11, 2023

While many central banks around the world are still trying to cool inflation, China is grappling with falling prices.

The Consumer Price Index (CPI) dropped 0.5% in November on an annual basis, the biggest fall since the depths of the pandemic three years ago, according to data released by China's National Bureau of Statistics on Saturday.

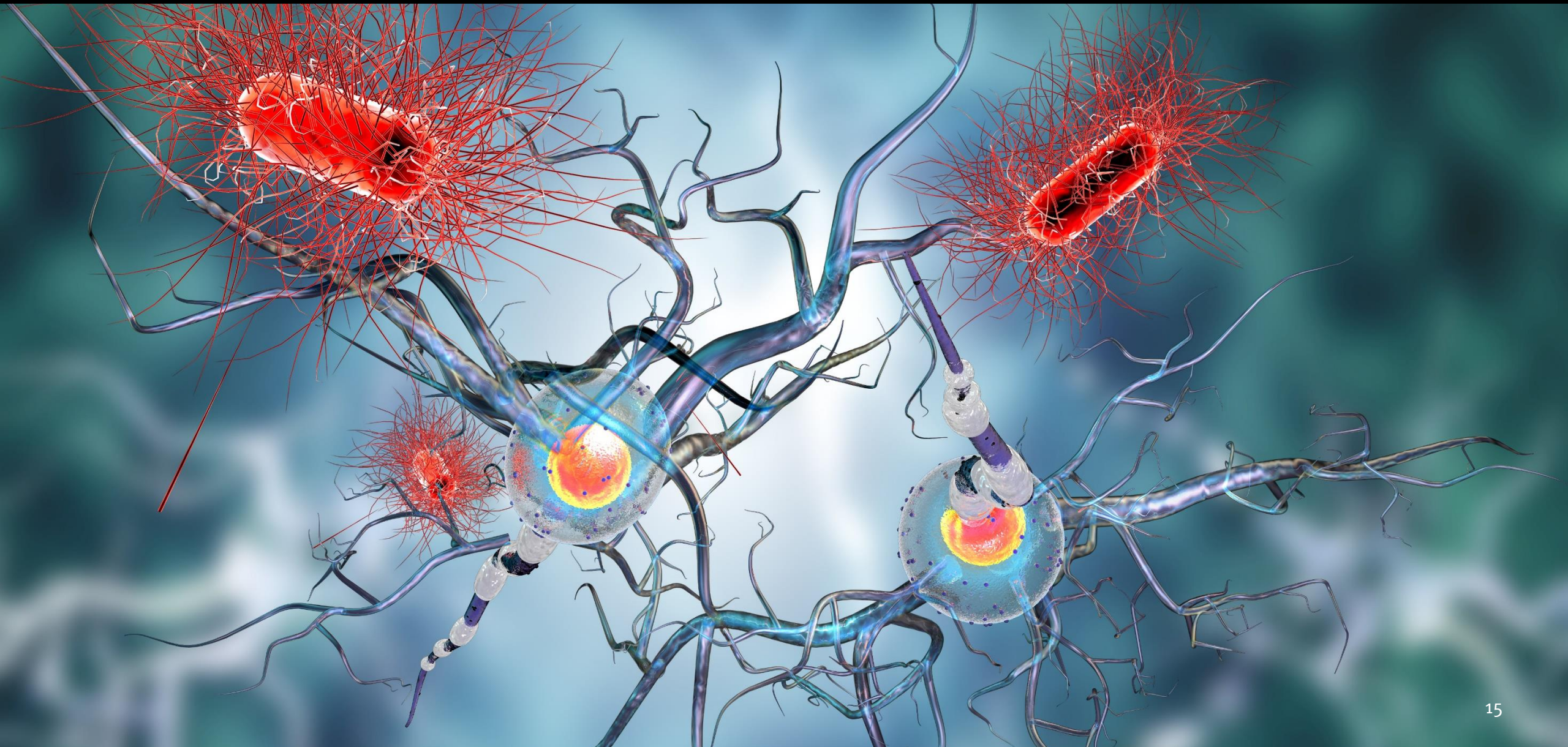
The drop marked an acceleration in the rate of deflation from October, when the CPI fell 0.2% from a year earlier, and prompted calls for urgent action from Beijing to boost demand and prevent a downward spiral of prices.

The data come days after Chinese policymakers vowed to strengthen fiscal and monetary support to boost the world's second biggest economy, which is struggling with a real-estate crisis, high youth unemployment and subdued consumer confidence.

China has been fighting weak prices for most of this year due to the property market slump and weak spending. Deflation is bad for the economy because consumers and companies may put off purchases or investments in anticipation of prices falling further. That in turn could further slow the economy, and create a vicious cycle.

Source: https://www.cnn.com/2023/12/11/economy/china-cpi-deflation-worsens-intl-hnk/index.html

Biopharma Market Update



The XBI Closed at 85.7 Last Week (Up 8.1%)

The XBI headed up last week for the sixth time in seven. At the FOMC meeting last week, the Fed struck a dovish tone, suggesting that increases in rates had peaked. The XBI continued its upward rise and is now up 33% since its trough on Oct 27th. The XBI is finally *up* YTD.

Biotech Stocks Up Last Week

Return: Dec 9 to Dec 15, 2023

Nasdaq Biotech Index: +6.0%
Arca XBI ETF: +8.1%
Stifel Global Biotech EV (adjusted): 8.6%*
S&P 500: +2.5%

Return: Jan 1 to Dec 15, 2023

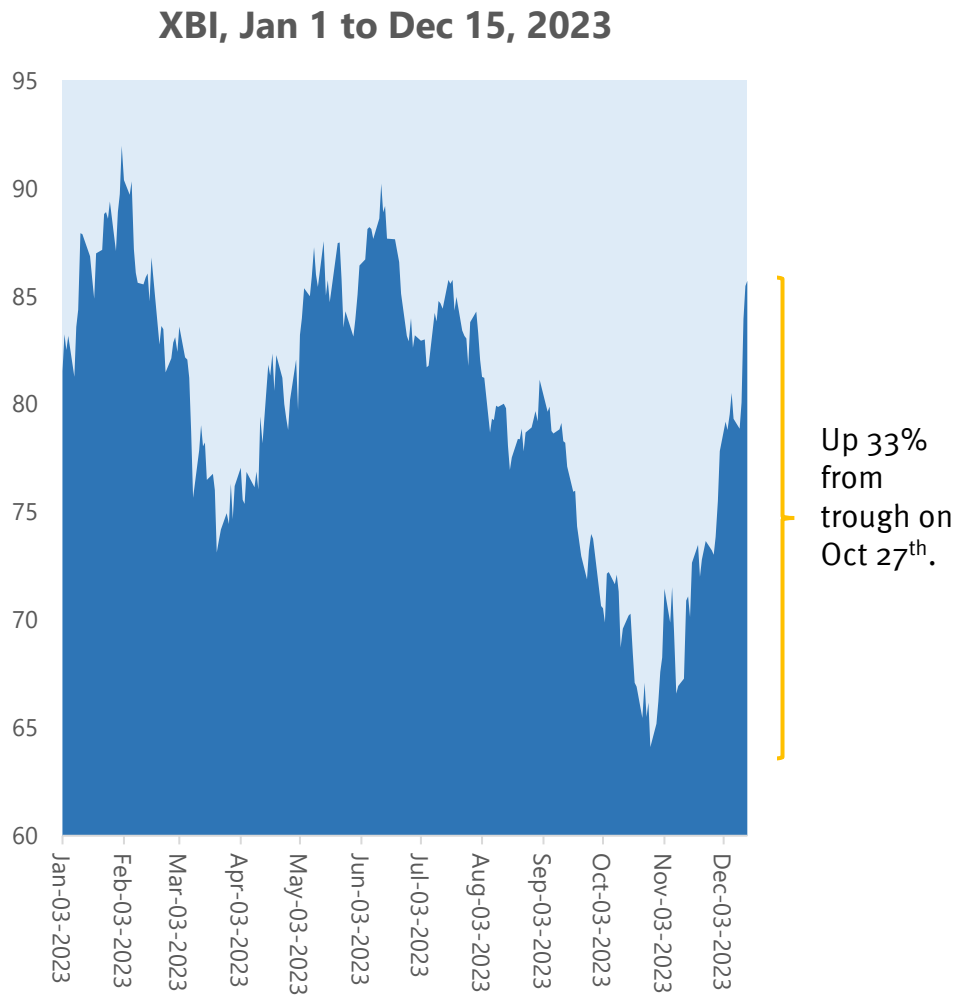
Nasdaq Biotech Index: +0.3%
Arca XBI ETF: +3.2%
Stifel Global Biotech EV (adjusted): 13.6%*
S&P 500: +22.9%

VIX Flat

Oct 21: 29.7%
Jan 20: 19.9%
May 26: 18.0%
July 21: 13.6%
Sep 29: 17.3%
Oct 27: 21.2%
Dec 1: 12.6%
Dec 8: 12.35%
Dec 15: 12.28%

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 27: 4.86%
Dec 1: 4.24%
Dec 8: 4.23%
Dec 15: 3.91%



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

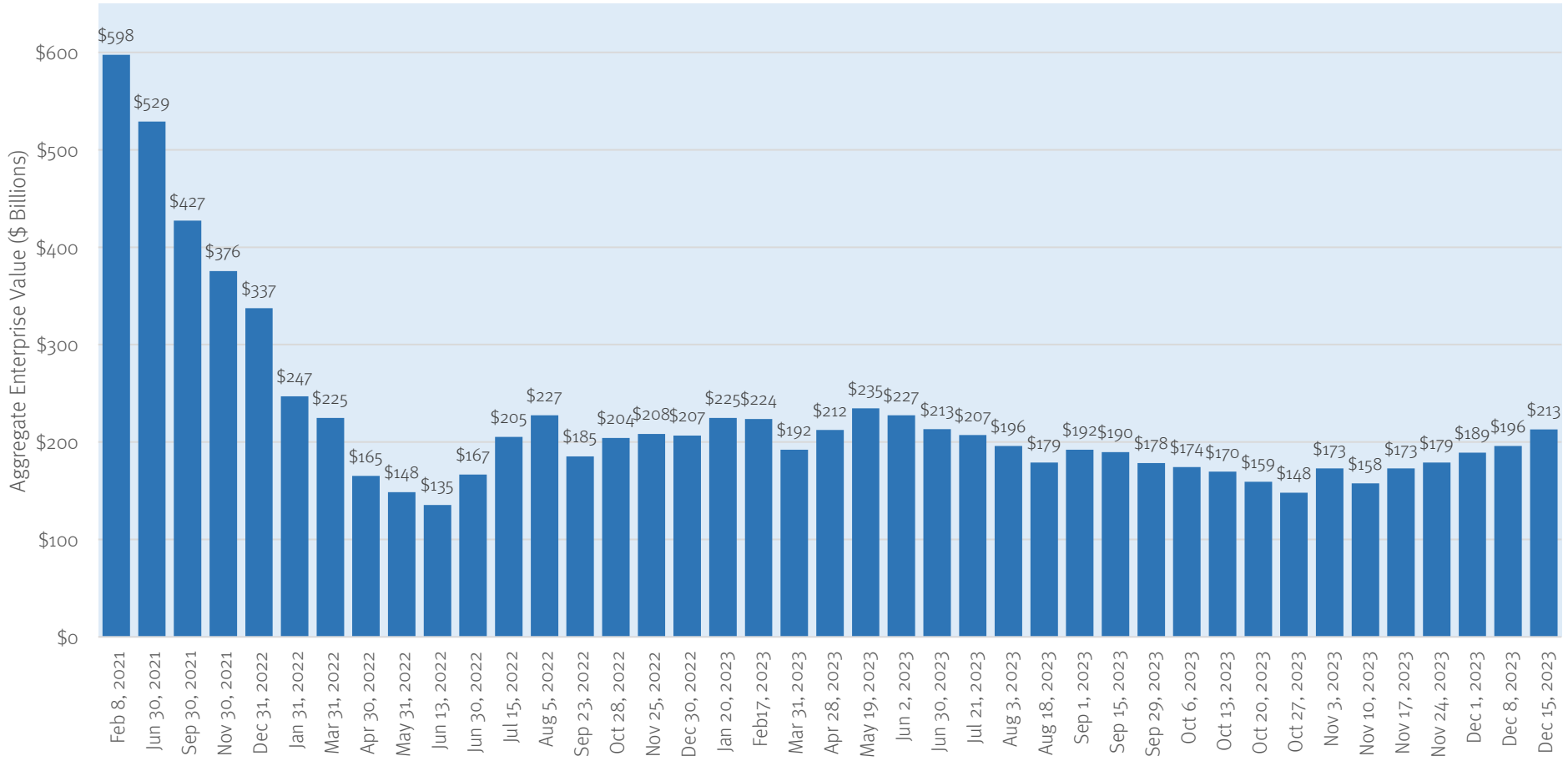
Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector is Now Up 44% in Recent Rally

The total enterprise value of the global biotech sector rose by 8.6% last week and is now up 13.6% for the year after adjusting for exits and entries. Biotech values are up 44% since their recent trough on October 27, 2023.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Dec 16, 2023

($ Billions)



While biotech is up 44% since trough, this rally is still in its early days.

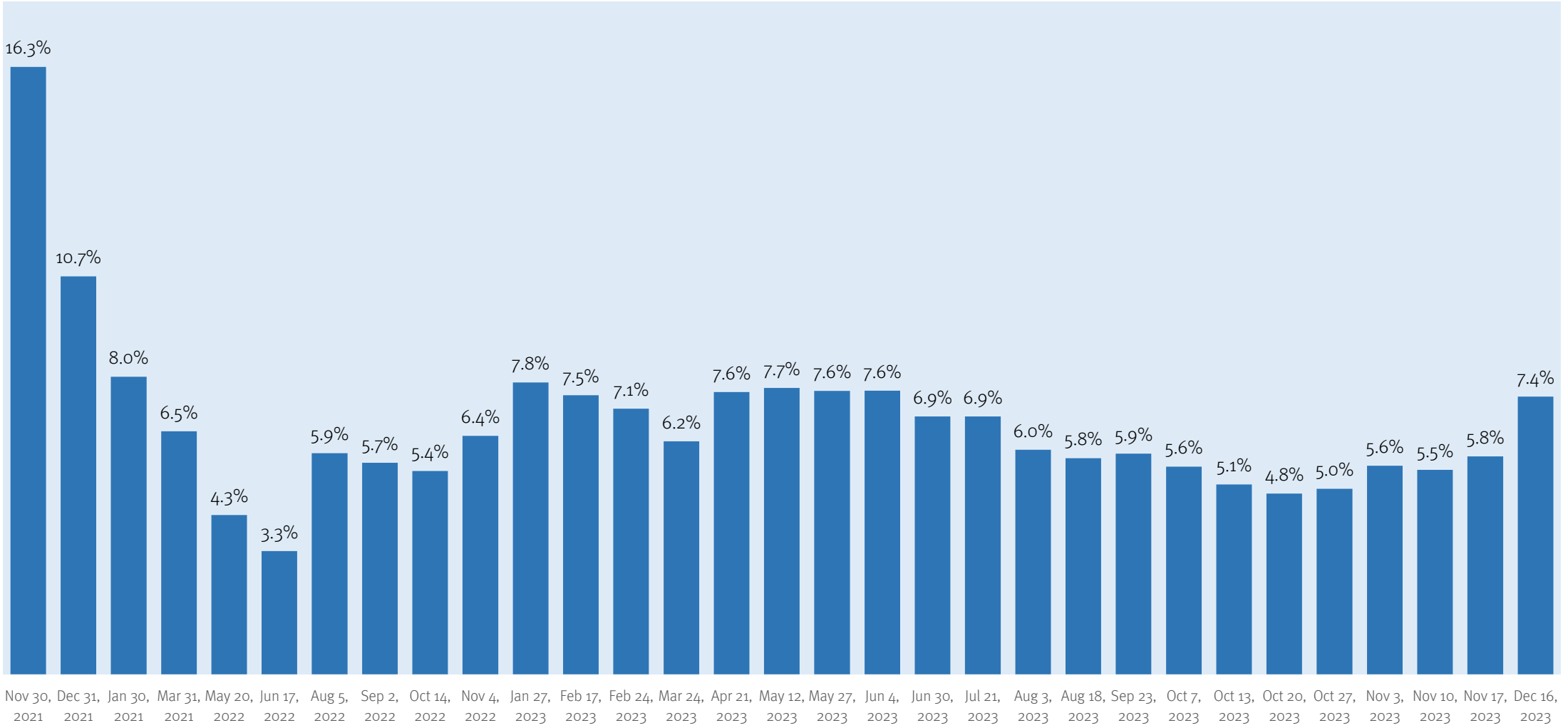
It's clear from this chart that the market would need to rally much more from here to get anywhere near where it was at the end of 2022.

We say, it's still very much "buy-o-tech" time.

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

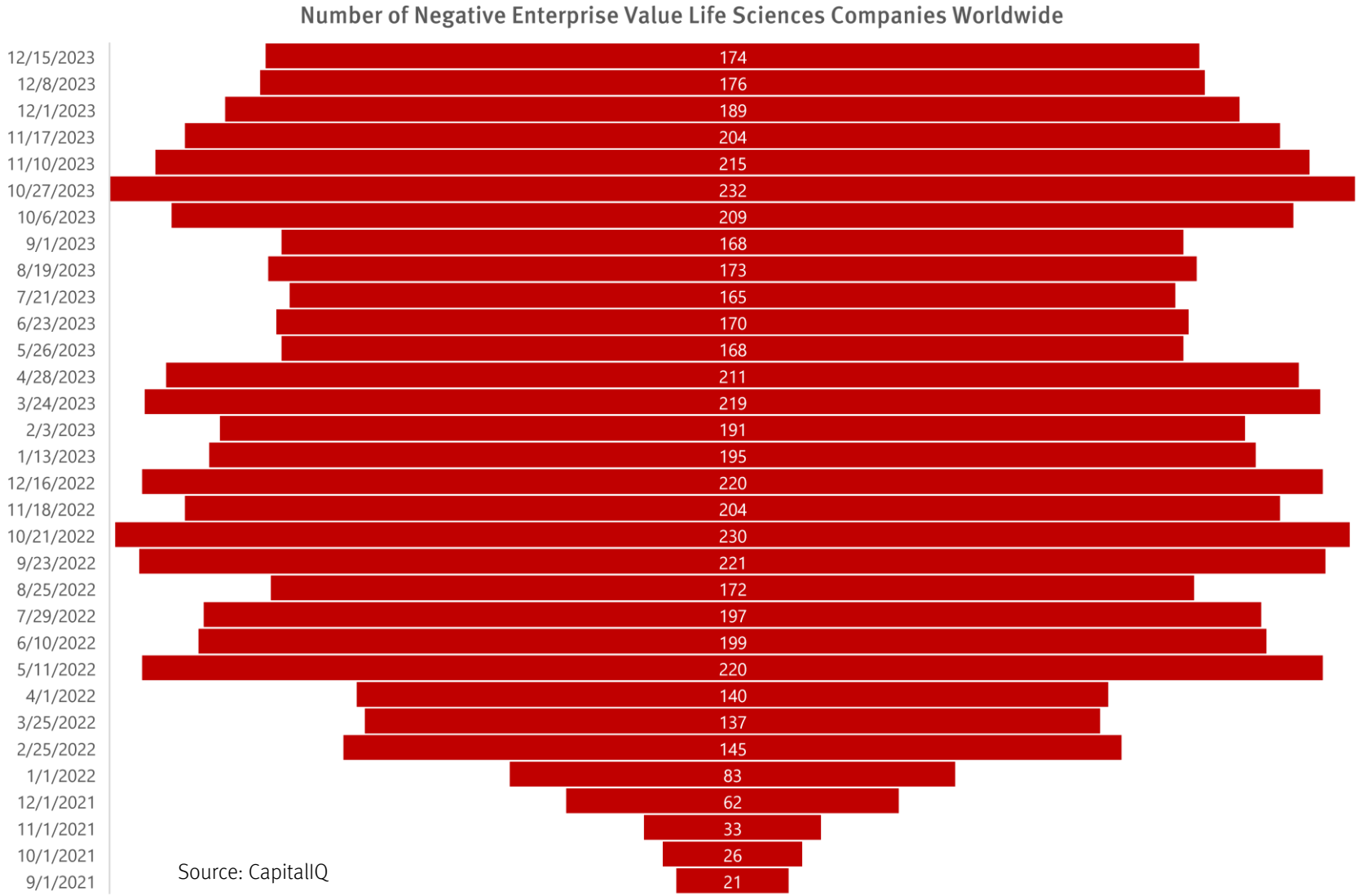
Billion Dollar Biotechs Are Coming Back

Percent of Global Biotechs with an Enterprise Value of $1bn or More, Nov 2021 to Dec 2023



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

Number of Negative Enterprise Value Life Sciences Companies Fell to 174 in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide fell from 176 last week to 174 last Friday.

The negative EV life science company population has shrunk by 25% since peaking on Oct 27, 2023.

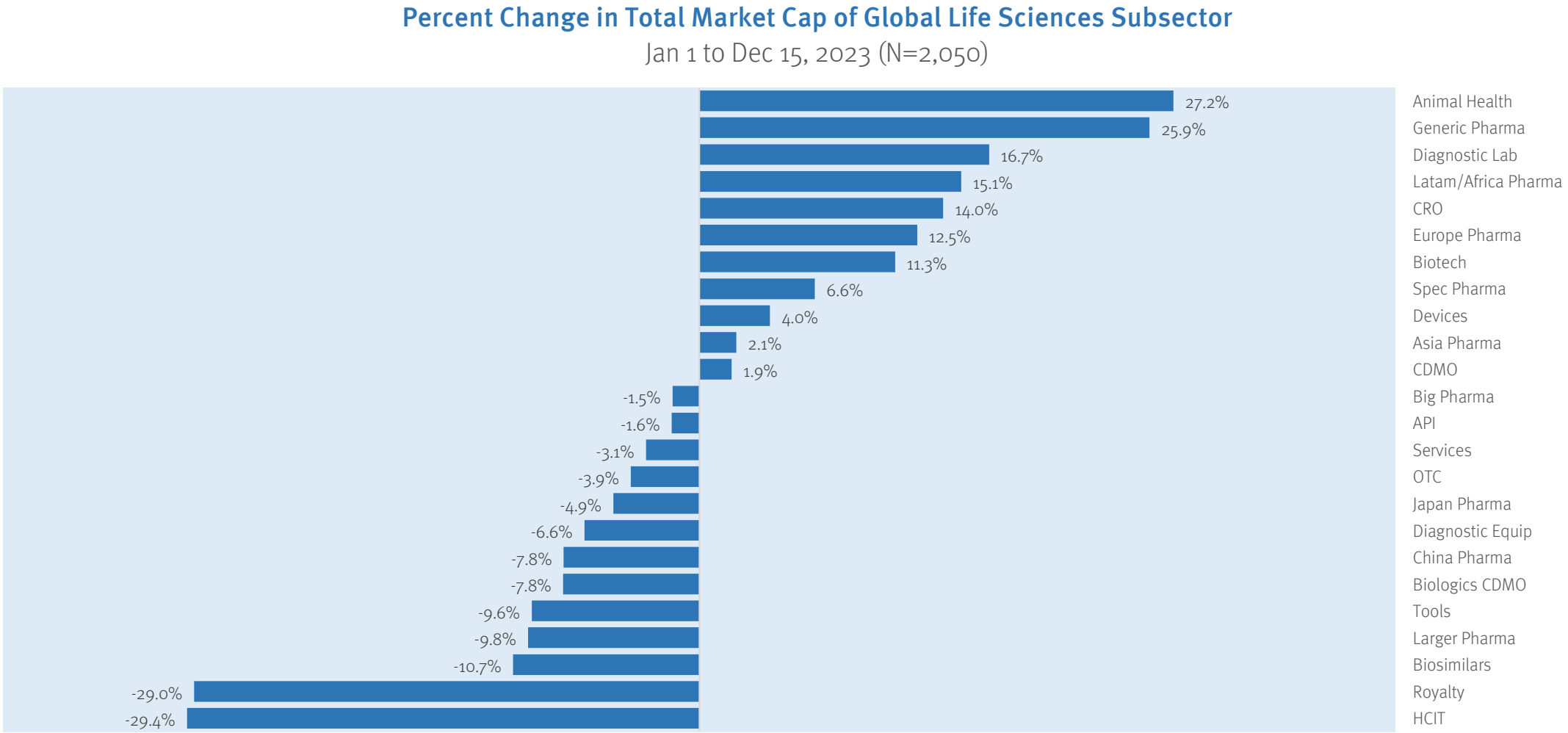
Life Sciences Sector Up 2.1% Last Week

Last week saw a 2.1% rise in life sciences stocks worldwide. The sector's value rose by $184 billion. Biotech was up the most followed by life science tools, HCIT, medical devices and diagnostics.

Sector	Firm Count	Enterprise Value (Dec 8, 2023, $mm)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$84,579	-0.3%	2.5%	-0.6%
Biotech	808	$213,471	8.6%	26.1%	-5.1%
CDMO	40	$139,155	2.4%	-9.3%	-20.9%
Diagnostics	83	$272,153	3.3%	11.2%	7.1%
OTC	30	$27,312	-0.9%	-0.7%	-4.0%
Pharma	725	$5,766,800	0.9%	3.1%	-1.0%
Pharma Services	39	$203,685	2.8%	0.9%	7.4%
LS Tools	52	$668,536	6.1%	10.9%	-10.0%
Medical Devices	181	$1,601,339	4.0%	6.6%	3.5%
HCIT	11	$22,049	5.8%	0.2%	-30.0%
Total	**2050**	**$8,999,080**	**2.1%**	**4.7%**	**-0.7%**

Source: CapitalIQ and Stifel analysis.

Animal Health, Generics and Diagnostics Players Have Done Best in 2023. HCIT and Royalty Players Have Fared Least Well



Source: CapitalIQ and Stifel analysis.

Will Calendar Change Bring an End to Run of Volatility in Biotech?

Barbara Ryan, *Pharmaceutical Executive*, Dec 12, 2023 (excerpt)

The XBI, as of late last month, was trading about 15% off of its lows back in October and continues to be volatile. The biotech index continues to trade in an inverse correlation with rates, with the pendulum swinging between whether investors latch on to the peak Fed narrative or shift back to the higher-for-longer one—each based upon economic data. The bull/bear debate on the economy remains in play, with the bulls betting on a soft landing, while the bears point to corporate commentary and earnings, which are suggestive of a recession.

The biotech financing market continues to be challenging with over 200 trading below enterprise value (EV), and depressed valuations are driving painful dilution for the companies that actually can finance.

Despite the underperformance of biotech, fundamentals for the sector as a whole remain quite positive.

The innovation renaissance is alive and well, with record numbers of FDA new drug approvals in each of the past several years. M&A continues to be another bright spot. Beginning in 2025, large pharma will be losing exclusivity for products currently representing over $350 billion in revenue, leaving a huge growth gap that needs to be filled through M&As, licensing, and partnering. Dealmaking has always been a key pillar of the industry's growth strategies.

More good news: according to EY's Annual Fire Power Report, large pharma has a record $1.4 trillion to fund deals. There have been a total of 30 public biotech acquisitions this year, and 15 of these were above $1 billion each, which surpasses the number in any year for the past 10.

As we wind down 2023, the hope will be for rate relief in the year ahead—and substantially improved biotech performance.

Barbara Ryan
Pharma Analyst & Consultant

Source: https://www.pharmexec.com/view/calendar-change-bring-end-run-volatility-biotech

It’s Biotech Stocks’ Time to Shine

Bets on interest-rate cuts plus a surge in pharma deals mean the worst is likely over for the biotech sector

David Wainer, *Wall Street Journal*, Dec 13, 2023 (excerpt)

These are hard times for the biotech sector. Barely a day goes by without layoffs being announced somewhere in Boston or California, and there are still more than 100 biotech stocks worth less than the cash they have in the bank.

Yet there are also very clear signs that the worst might be over for the sector. For investors with a long-term horizon, a recent rally leaves plenty of room for further gains.

The most important reason to bet that biotech has bottomed has nothing to do with the industry itself, but with the direction of borrowing costs.

To an even greater degree than high-growth tech companies, biotech firms struggle in a rising interest-rate environment because many of them don’t expect to have a product in the market for years.

With Wall Street gearing up for rate cuts and Federal Reserve officials increasingly confident that they don’t need to keep raising interest rates to defeat inflation, that all-important metric is looking more promising for the industry. To top it off, not only do falling rates lower the cost of capital for these companies—they also solidify their exit path by increasing pharma’s appetite for acquisitions.

Tim Opler, a managing director at Stifel, says this turbulent period is reminiscent of 2002 and 2003—a time of high rates, massive pressure on pharma earnings and patent challenges. “Sentiment was dark and the thought was that the pharma industry would never recover,” he writes, noting that pessimism was greatest in 2003. The Nasdaq Biotech Index subsequently tripled in value over the next decade.

Predicting near-term moves for the biotech industry is a fool’s errand, but the industry looks like it may be turning a corner, suggesting the moment for long-term investors is now.

Source: https://www.wsj.com/finance/investing/its-biotech-stocks-time-to-shine-7eb26f83

Biotech Stocks Undergo Recovery After Year of 'Wreckage'

Sector benefits from shifts in interest rate expectations after 50% fall

Nicholas Megaw and Anna Mutoh, *Financial Times*, Dec 14, 2023 (excerpt)

A rally in biotech stocks has raised hopes of a turnaround from the sector's worst run this century, as drug developers suffered from rising interest rates and a backlash to pandemic-era euphoria.

Even as the wider US stock market approaches a record high, the S&P biotechnology index remains more than 50 per cent below its early 2021 peak.

However, the sector has been one of the biggest beneficiaries of a recent shift in interest rate expectations, bouncing more than 25 per cent since the start of November. A 5 per cent gain on Wednesday pushed it into positive territory for the year after declines of more than 20 per cent in 2021 and 2022."In late 2020 and early 2021, many early-stage companies hit valuations that didn't make any sense," said Andy Acker, a healthcare portfolio manager at Janus Henderson. "Now we have the opposite situation . . . [so] we're combing through the wreckage to try to identify companies that have been left for dead."

Rising interest rates have weighed on valuations across industries, but the effect tends to be particularly damaging in sectors such as biotech where most companies focus on growth far in the future. The Federal Reserve on Wednesday left benchmark US interest rates at 5.25-5.5 per cent, up from near zero two years ago, but signalled cuts will begin next year.

The impact of rates has been exacerbated by an influx of high-risk companies that went public in 2020 and 2021.Traditionally, start-ups working on new drugs would raise funding privately until they had clinical data to reassure investors about their chances of success.

When markets were surging at the height of the coronavirus pandemic, however, many companies listed their stock with little data."

There were companies that, if we were all honest with ourselves, probably weren't ready to be public," said Rahul Chaudhary, head of healthcare equity capital markets at Leerink Partners.More than 250 healthcare companies listed in the US between 2020 and 2021, according to Dealogic. Their poor performance has made it harder for others to follow them, with just 24 deals in 2023.

Some companies specialising in areas such as anti-obesity drugs have managed to attract investors despite the tough environment. "Innovation is still happening in the sector, the problem is some innovation has not been valued highly," said Lorence Kim, managing partner at Ascenta Capital and a former chief financial officer at Moderna.

Kim said that should create opportunities for investors, with "a half-off sale in everything" before the macro picture changes.

Source: https://www.ft.com/content/f2c97f94-3c88-446b-a05b-2eed14843435

Life Sciences Funds Generate Healthy November Gains

Stephen Taub, *Institutional Investor*, Dec 12, 2023 (excerpt)

Most hedge funds that specialize in life sciences and biopharma stocks posted strong gains in November, enabling several to move into the black with one month remaining in the year.

In fact, at least five funds generated double-digit returns last month, exceeding the broad market averages, which enjoyed their best month in well over a year. For its part, the iShares Biotechnology ETF (IBB) gained 6.4 percent in November but is down 7.7 percent for the year.

Indeed, this year the number of publicly traded small and midcap companies acquired by pharma as well as the total dollars deployed via M&A are outpacing 2022, according to a document put together by RA Capital that was obtained by Institutional Investor. “The pool of companies that pharma is sorting through is heavily beaten down relative to the amount of cash that pharma has to deploy,” the hedge fund firm notes. Given that biotech stocks have been weak for several years now, RA Capital is confident that big pharma will be shopping aggressively. “Biotech has recovered from its extreme lows of October but is still down on the year and remains in a comparative slump,” the firm says. “Eventually, biotech will recover sustainably and start to lift all boats.”

Sure enough, in November, RA Capital surged 10.7 percent and is now up 1.2 percent in 2023. The fund was helped last month by the acquisition of Immunogen, its third-largest long, by AbbVie, for a 95 percent premium. Elsewhere, Soleus Capital Management gained 10.5 percent last month and is up 3.7 percent for the year. Soleus was one of the few biopharma hedge funds to be in the black in 2022. United Therapeutics, its largest common stock long, gained nearly 8 percent last month, and No. 2 long Teva Pharmaceuticals jumped 14.5 percent.

Perceptive Advisors gained nearly 11 percent, enabling it to eke out a 20 basis points rise for the year. Its strong performance last month does not include the huge gain made earlier this month by No. 2 long Cerevel Therapeutics after AbbVie agreed to acquire the biopharma, known for its neuroscience pipeline.

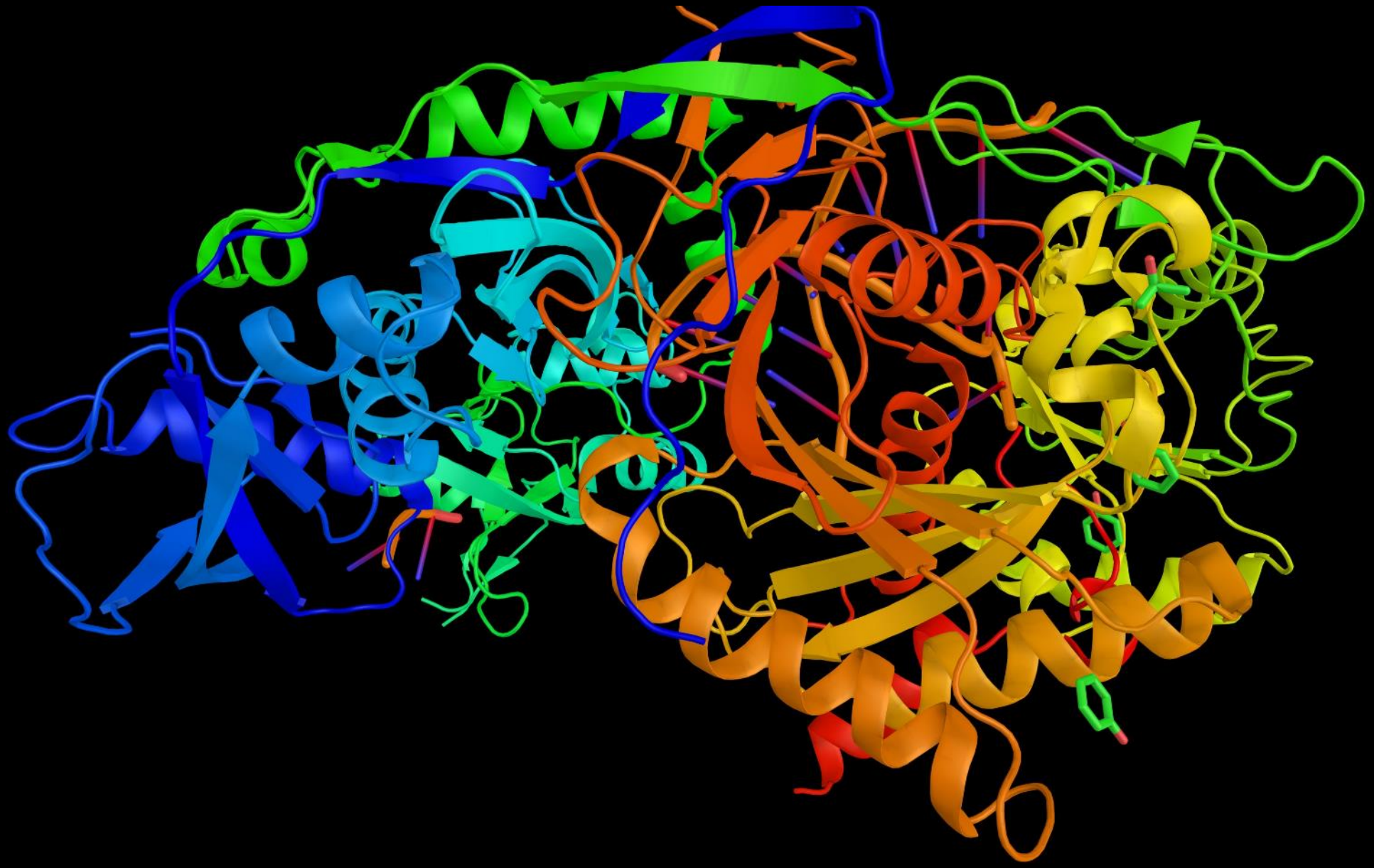
Deerfield Capital, meanwhile, was up 6.5 percent in November and 1.2 percent for the year. Armistice Capital also moved into the black by posting an 8.3 percent jump. It is now up 1.9 percent for 2023.

One of the top performers in the group remains Cormorant Asset Management. It rose just 1.2 percent last month but is up 22.4 percent for 2023.

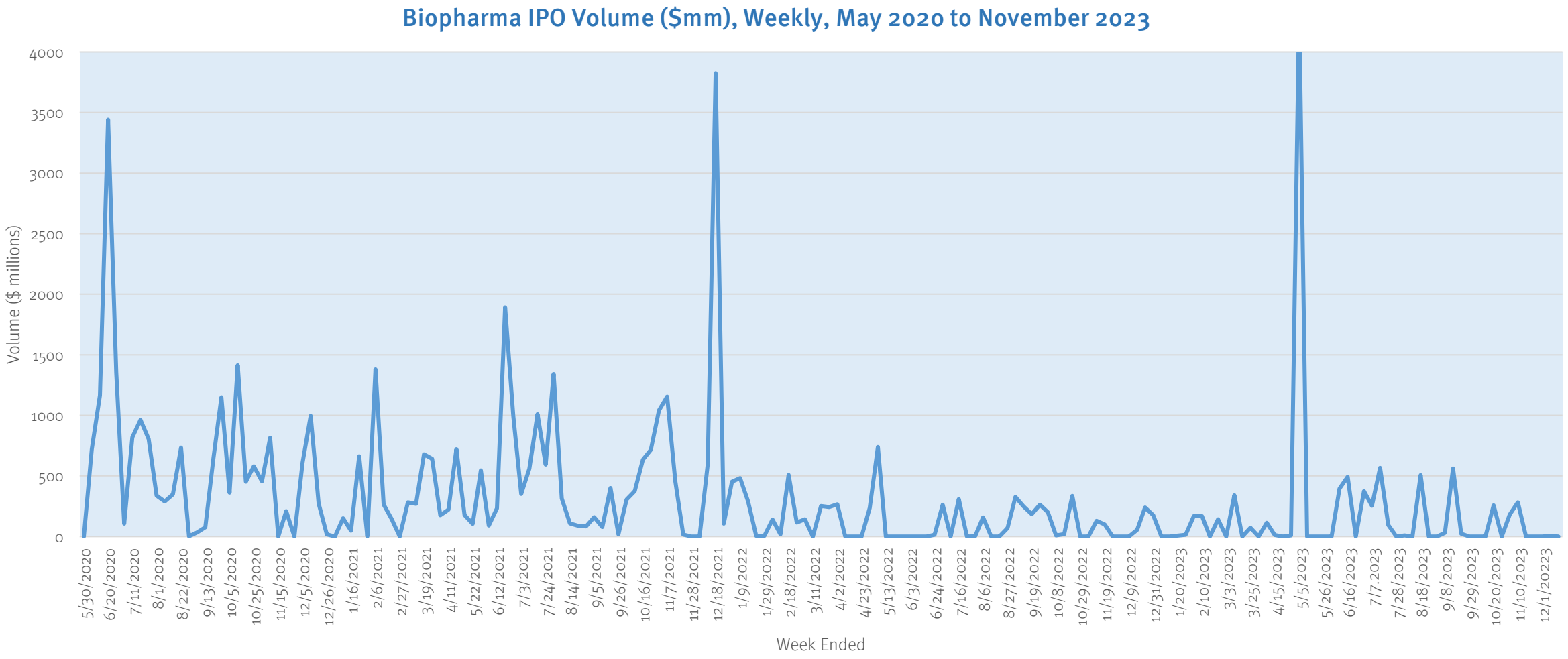
Although Averill Partners lost 4.5 percent in November, it remains up 10 percent for the year. The fund is known for its shorting prowess and often performs opposite the group from month to month.

Source: https://www.institutionalinvestor.com/article/2ckmg8y51u1zgu3817t34/premium/life-sciences-funds-generate-healthy-november-gains

Capital Markets Update



No IPOs Last Week



Source: Data from CapitalIQ and Stifel research.

PWC: IPO Window to Gradually Reopen in 2024

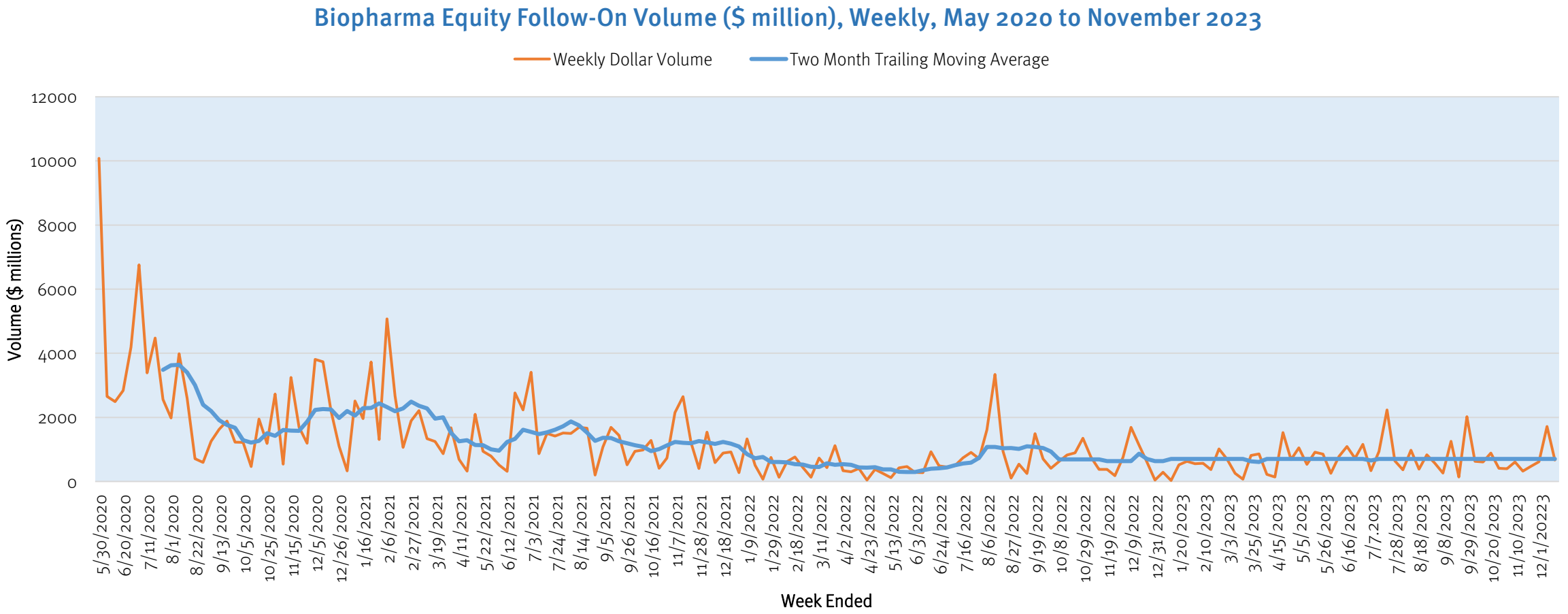
PWC Pharmaceutical and Life Sciences: U.S. 2024 Deals Outlook (excerpt), December 2023

"IPO markets are critical for biopharma and we expect the window to gradually reopen in 2024, likely skewing toward companies with strong clinical data. Looking beyond traditional M&A, the sector will also seek out increasingly creative structures that allow for greater R&D funding while still maintaining control over the development of critical compounds, leaving the door open for an increased role for private equity and structured solutions such as private credit. Along with asset swaps, profit-sharing arrangements, innovative joint ventures (JVs) or collaborations and divestitures, creativity will be essential to executing on strategic priorities in 2024, including delivering top quartile returns to shareholders while limiting capital exposure."

Source: https://www.pwc.com/us/en/industries/health-industries/library/pharma-life-sciences-deals-outlook.html

Last Week Average for Follow-On Offerings

Last week saw $670 million in follow-on biopharma volume. This was much less active than the week before. The largest offering was a $200 million follow-on by Syndax on the back of positive data at ASH.

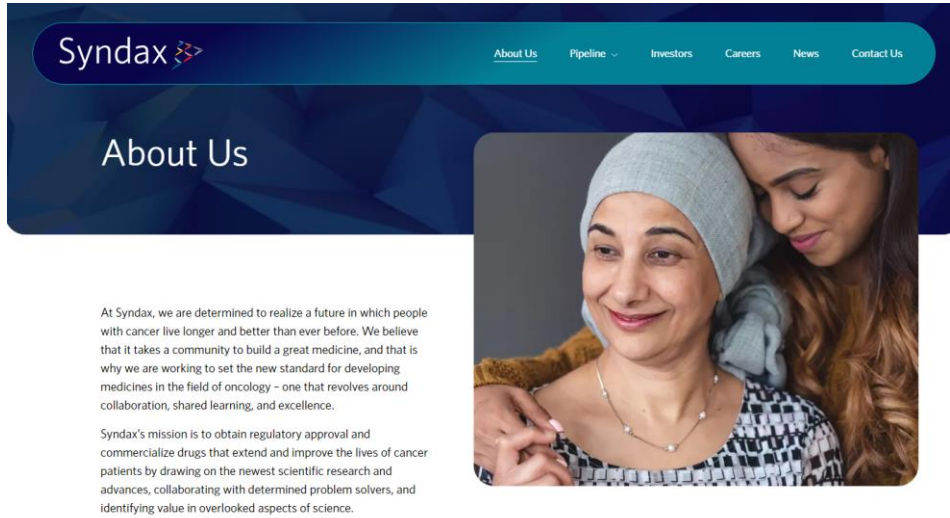


Source: Data from CapitalIQ and Stifel research.

Syndax Raises $200 Million Follow-On

WALTHAM, Mass., Dec. 14, 2023 /PRNewswire/ -- Syndax Pharmaceuticals, Inc. ("Syndax" or the "Company") (Nasdaq: SNDX), a clinical-stage biopharmaceutical company developing an innovative pipeline of cancer therapies, today announced the pricing of an underwritten public offering of 10,810,810 shares of its common stock. The public offering price of each share of common stock is $18.50. The aggregate gross proceeds from this offering are expected to be approximately $200.0 million, before deducting underwriting discounts and commissions and other offering expenses payable by Syndax. In addition, Syndax granted the underwriters a 30-day option to purchase up to an additional 1,621,621 shares of common stock. All of the shares of common stock are being sold by Syndax. The offering is expected to close on December 19, 2023, subject to customary closing conditions.

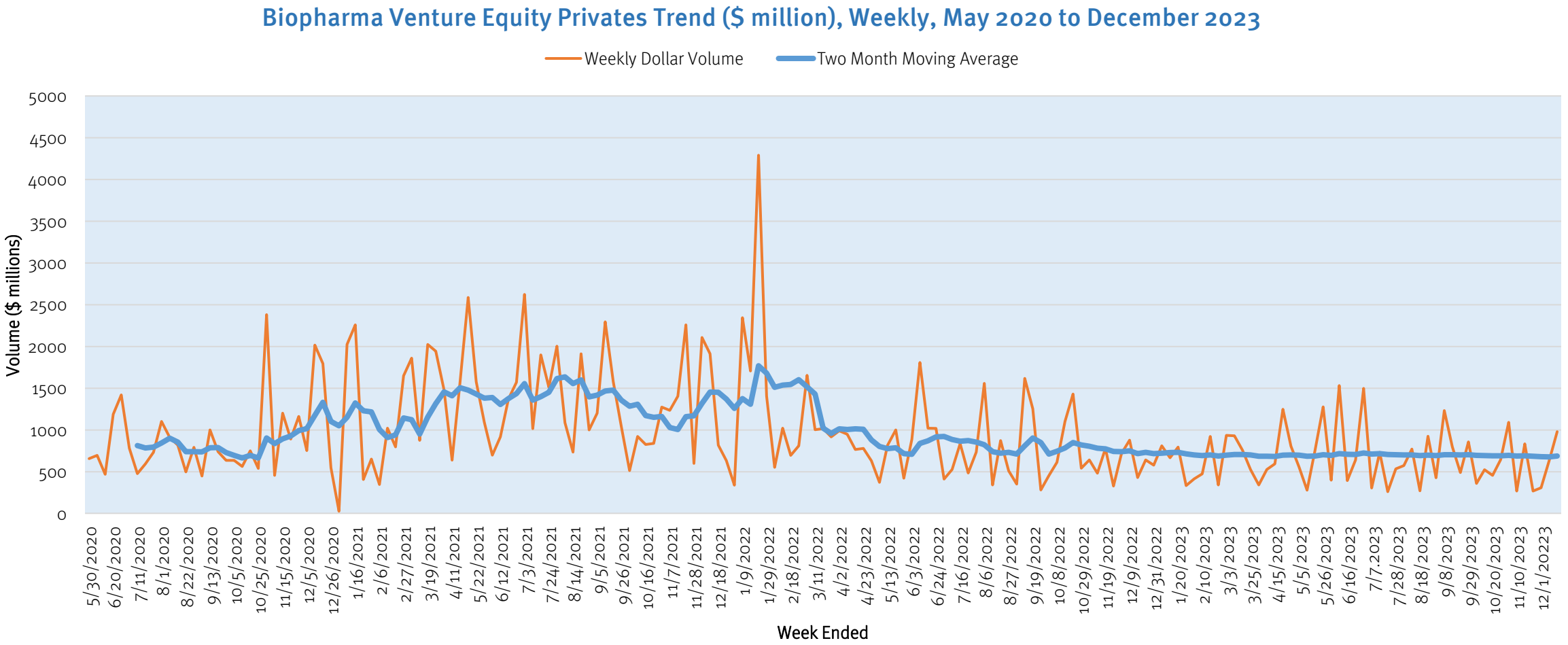
Goldman Sachs & Co. LLC, J.P. Morgan, TD Cowen and Stifel are acting as joint book-running managers for the offering. B. Riley Securities is acting as manager for the offering.



Source: https://ir.syndax.com/news-releases/news-release-details/syndax-announces-pricing-200-million-public-offering-common

Last Week Saw $980 Million in Venture Privates

The market picked up substantially from the prior two weeks. Tome Bio was the largest offeror, raising $231 million in the private market.



Source: Data from CapitalIQ, Crunchbase.

Tome Biosciences Raises $231 Million

WATERTOWN, Mass., Dec. 12, 2023 (GLOBE NEWSWIRE) Tome Biosciences, Inc., the programmable genomic integration company, has launched to usher in a new era of genomic medicines based on programmable genomic integration (PGI). PGI enables the insertion of any DNA sequence, of any size, into any programmed genomic location. The Company has raised $213 million in Series A and B funding from investors: Andreessen Horowitz (a16z) Bio + Health, ARCH Venture Partners, GV, Longwood Fund, Polaris Partners, Bruker Corporation, FUJIFILM Corporation, Alexandria Venture Investments and others.

PGI combines the site-specificity of CRISPR/Cas9 with enzymes capable of inserting or writing sequences of DNA, including entire genes, without the need for double-strand DNA breaks. Tome's most advanced PGI technology, called integrase-mediated PGI (I-PGI), utilizes proprietary integrases and is based on groundbreaking PASTE technology first discovered by Tome's Co-Founders, Omar Abudayyeh, PhD, and Jonathan Gootenberg, PhD, while at MIT as investigators.

Just as a word processor is capable of pasting text anywhere in a document, I-PGI can insert large DNA sequences anywhere in the genome with unprecedented precision. Thus far, I-PGI has demonstrated insertions of more than 30kb of genetic code with site-specificity in multiple different dividing and non-dividing cell types, and can be multiplexed to enable complex cell engineering that will underpin the future development of cell therapies. The Company initially plans to develop integrative gene therapies for monogenic liver diseases and cell therapies for autoimmune diseases.

Source: https://www.globenewswire.com/news-release/2023/12/12/2794660/0/en/Tome-Biosciences-Launches-with-Over-200-Million-in-Funding-to-Advance-Programmable-Genomic-Integration-Platform.html

"PGI represents the maturation of editing technologies, breaking current barriers in genomic medicines discovery. PGI is revolutionary in that we can finally reprogram the human genome with an elegance and efficiency previously unimaginable. For patients with rare monogenic diseases, PGI allows for potentially curative treatments with a single drug per disease regardless of genetic heterogeneity, and for patients with more common disorders, PGI allows for the creation of cell therapies at the speed of biologics discovery."

Rahul Kakkar
Chief Executive Officer
Tome Biosciences

Paper on Tome's Technology

nature biotechnology

Article

https://doi.org/10.1038/s41587-022-01527-4

Drag-and-drop genome insertion of large sequences without double-strand DNA cleavage using CRISPR-directed integrases

Received: 30 April 2022

Accepted: 23 September 2022

Published online: 24 November 2022

Check for updates

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Programmable genome integration of large, diverse DNA cargo without DNA repair of exposed DNA double-strand breaks remains an unsolved challenge in genome editing. We present programmable addition via site-specific targeting elements (PASTE), which uses a CRISPR–Cas9 nickase fused to both a reverse transcriptase and serine integrase for targeted genomic recruitment and integration of desired payloads. We demonstrate integration of sequences as large as ~36 kilobases at multiple genomic loci across three human cell lines, primary T cells and non-dividing primary human hepatocytes. To augment PASTE, we discovered 25,614 serine integrases and cognate attachment sites from metagenomes and engineered orthologs with higher activity and shorter recognition sequences for efficient programmable integration. PASTE has editing efficiencies similar to or exceeding those of homology-directed repair and non-homologous end joining-based methods, with activity in non-dividing cells and in vivo with fewer detectable off-target events. PASTE expands the capabilities of genome editing by allowing large, multiplexed gene insertion without reliance on DNA repair pathways.

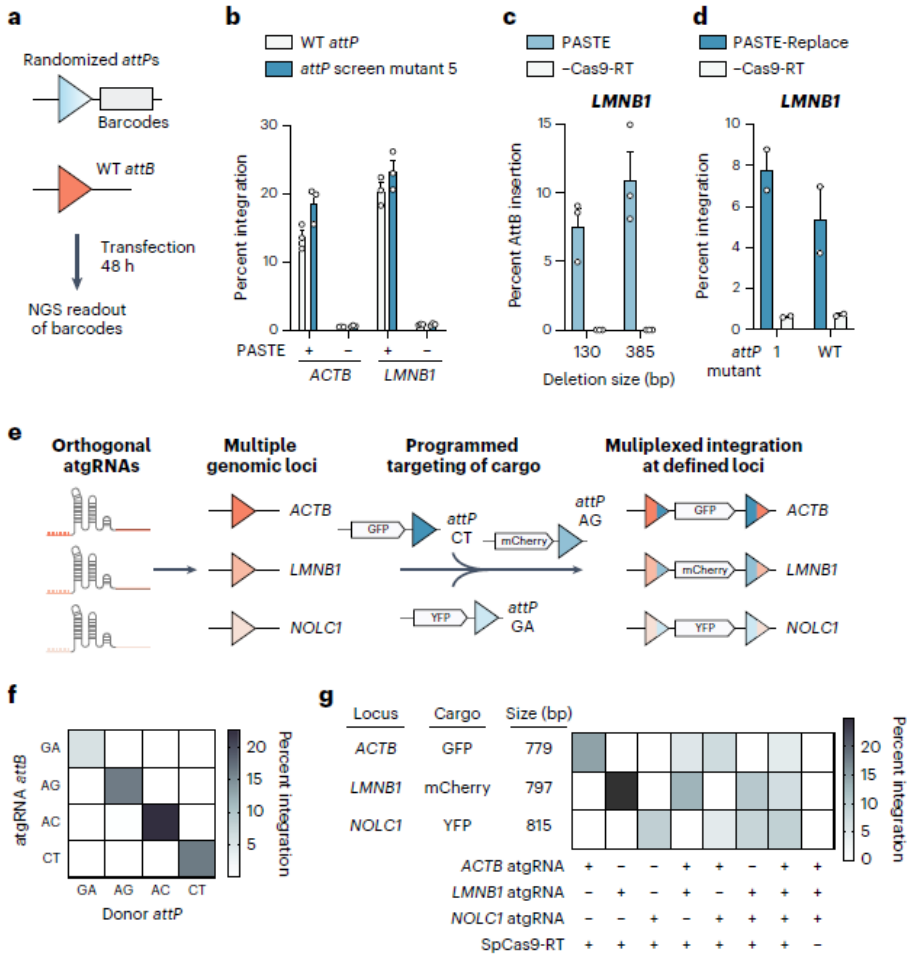
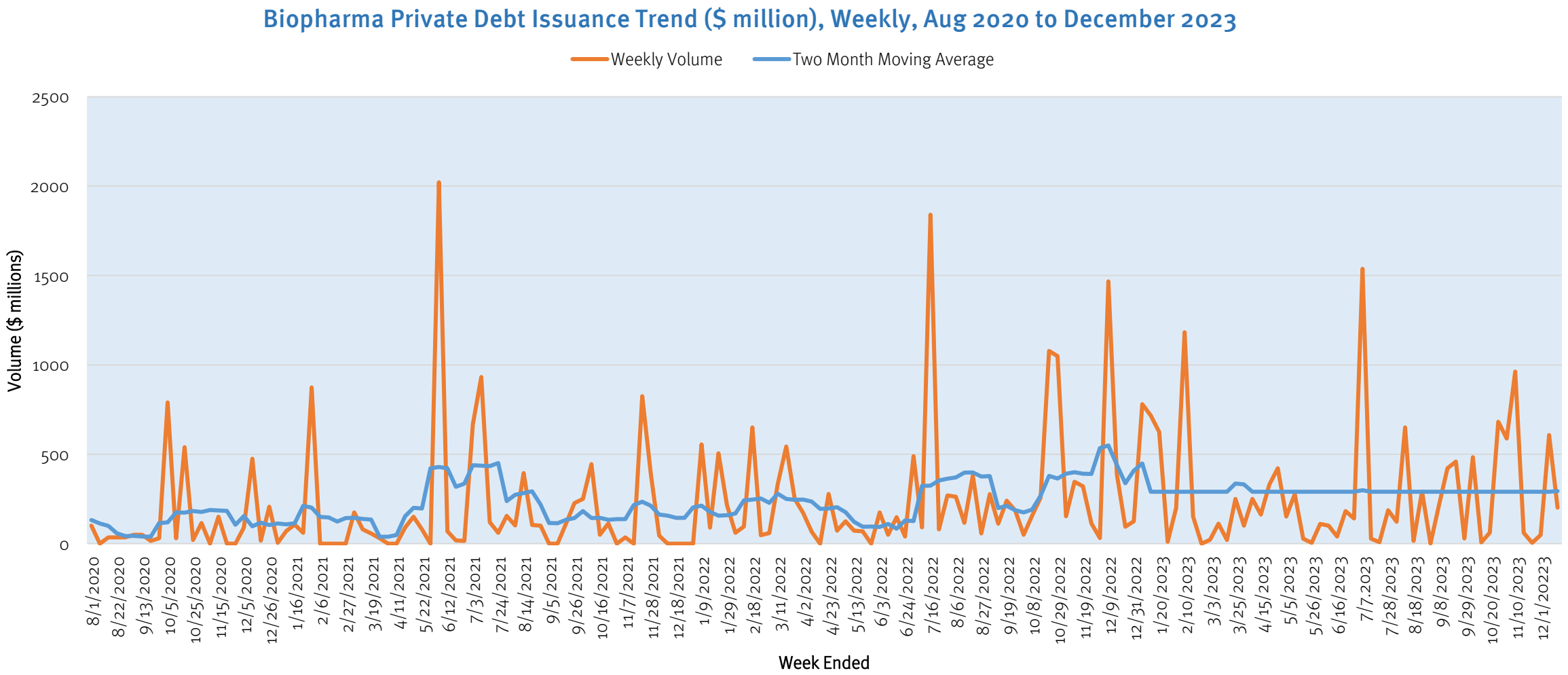


Fig. 4 | Multiplexed and orthogonal gene insertion with PASTE. a, Schematic for *attP* mutagenesis screen for identifying *attP* mutants that promote higher integration efficiencies with PASTE. **b**, Evaluation of two *attP* variants from the pooled screen for PASTE integration activity at the *ACTB* and *LMNB1* loci. **c**, *attB* site replacement efficiency with the PASTE-Replace system at the *LMNB1* locus. **d**, EGFP gene replacement efficiency with the PASTE-Replace system at the *LMNB1* locus using payloads with either *attP* mutant 1 or WT *attP*. **e**, Schematic of multiplexed integration of different cargo sets at specific genomic loci. Three fluorescent cargos (GFP, mCherry and YFP) are inserted orthogonally at three different loci (*ACTB*, *LMNB1* and *NOLC1*) for in-frame gene tagging. **f**, Orthogonality of the top four *attB*/*attP* dinucleotide pairs evaluated for GFP integration with PASTE at the *ACTB* locus. **g**, Efficiency of multiplexed PASTE insertion of combinations of fluorophores at *ACTB*, *LMNB1* and *NOLC1* loci. Data are shown as mean ± s.e.m.; $n = 3$.

Source: https://www.nature.com/articles/s41587-022-01527-4

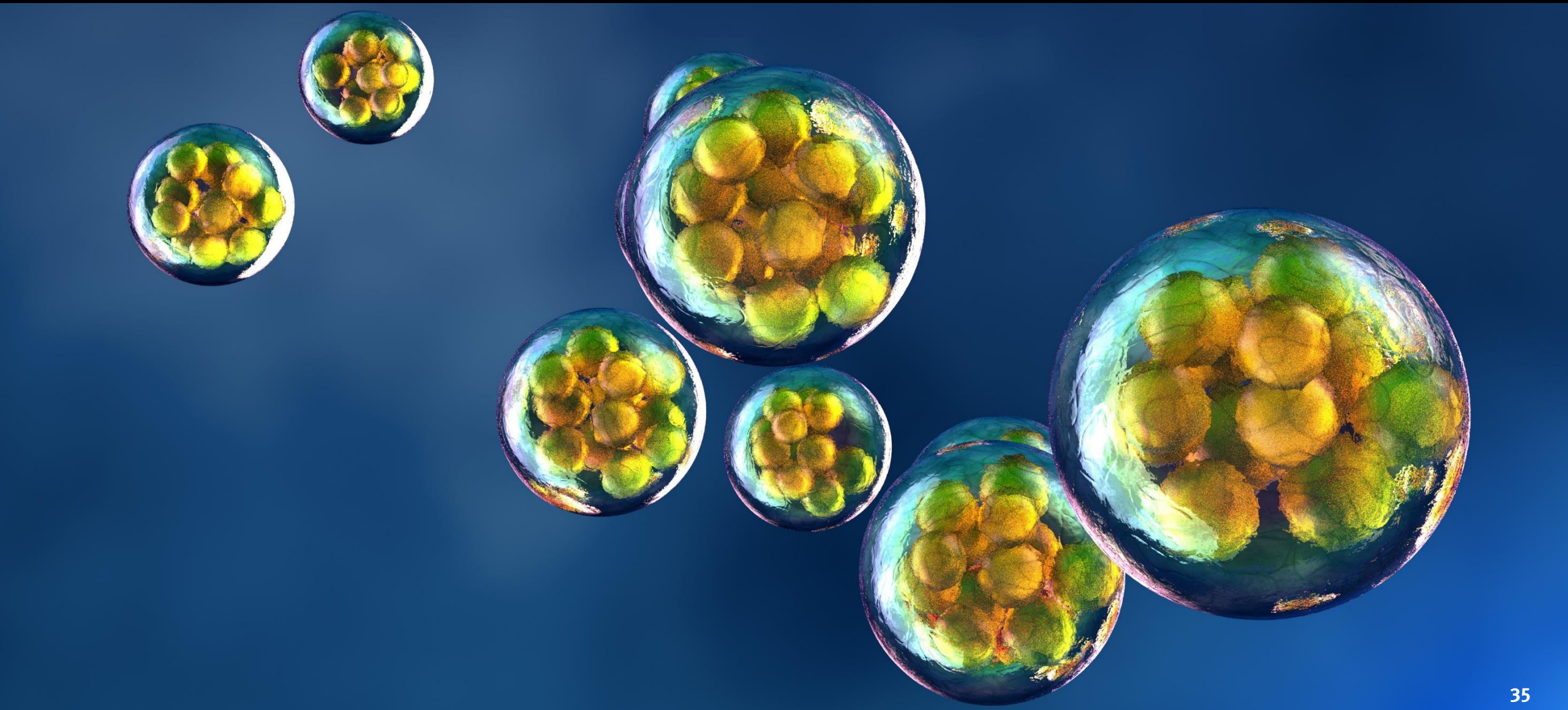
Weekly Global Biopharma Private Debt Placement Market Open in December

We saw $200 million in private debt deals get done last week. The market was open and active.



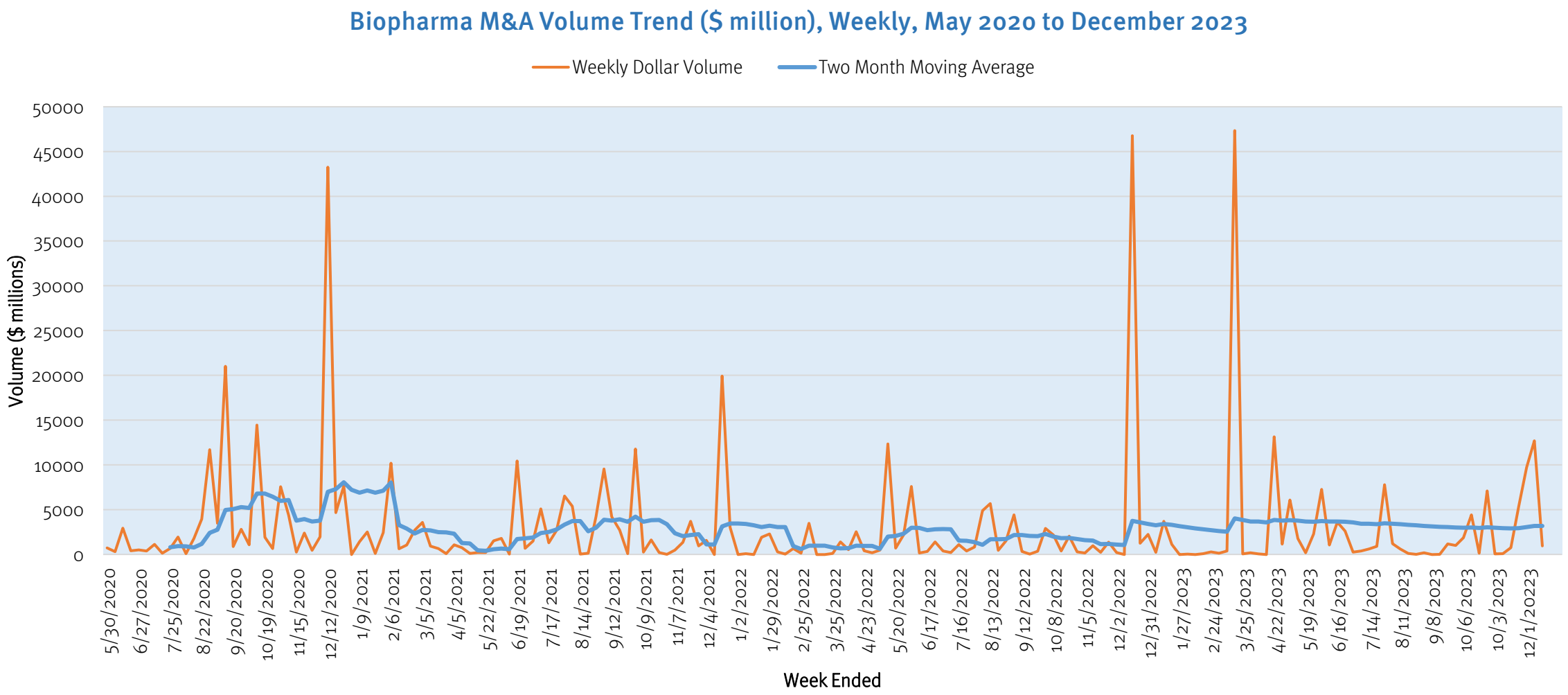
Source: Data from CapitalIQ, Crunchbase.

Deals Update



M&A Market Active

Last week saw AstraZeneca acquire Icosavax for $800 million upfront.



Source: S&P, CapitalIQ

AstraZeneca to Acquire Icosavax for $800 Million Upfront Plus Contingent Payment

Press Release, Dec 12, 2023

AstraZeneca has entered into a definitive agreement to acquire Icosavax, Inc. (NASDAQ: ICVX), a US-based clinical-stage biopharmaceutical company focused on developing differentiated, high-potential vaccines.

The proposed acquisition will build on AstraZeneca's expertise in respiratory syncytial virus (RSV), strengthening AstraZeneca's Vaccines & Immune Therapies late-stage pipeline with Icosavax's lead investigational vaccine candidate, IVX-A12. IVX-A12 is a potential first-in- class, Phase III-ready, combination protein VLP vaccine which targets both RSV and human metapneumovirus (hMPV), two leading causes of severe respiratory infection and hospitalisation in adults 60 years of age and older and those with chronic conditions such as cardiovascular, renal and respiratory disease.1-3 There are currently no treatments or preventative therapies for hMPV and no combination vaccines for RSV.4

As VLP vaccines mimic how naturally occurring viruses appear to the body's immune system, they may offer potential benefits over non-VLP vaccines, including a stronger immune response, greater breadth of protection, greater durability requiring fewer boosters and, compared to the current adjuvanted RSV vaccine, a lower incidence of side effects.6

Under the terms of the agreement, AstraZeneca, through a subsidiary, will initiate a tender offer to acquire all of Icosavax's outstanding shares for a price of $15.00 per share in cash at closing, plus a non-tradable contingent value right for up to $5.00 per share in cash payable upon achievement of a specified regulatory milestone and a sales milestone. **The upfront cash portion of the consideration represents a transaction value of approximately $0.8bn, a 43% premium to Icosavax's closing market price on 11th December 2023 and a 73% premium to the 60-day volume-weighted average price (VWAP) of $8.68 before this announcement.** Combined, the upfront and maximum potential contingent value payments represent, if achieved, a transaction value of approximately $1.1bn, a 91% premium to Icosavax's closing market price on 11th December 2023 and a 130% premium to the 60-day VWAP. As part of the transaction, AstraZeneca will acquire the cash and marketable securities on Icosavax's balance sheet, which totaled $229m as of 30th September 2023.

Source: https://www.astrazeneca.com/media-centre/press-releases/2023/astrazeneca-to-acquire-icosavax-including-potential-first-in-class-rsv-and-hmpv-combination-vaccine-with-positive-phase-ii-data.html

Icosavax Technology Developed at University of Washington by Neil King and David Baker

Charlotte Schubert, *Geekwire*, October 6, 2021

We are now in the "digital era" of vaccine development, University of Washington researcher Neil King said at the GeekWire Summit in Seattle on Tuesday.

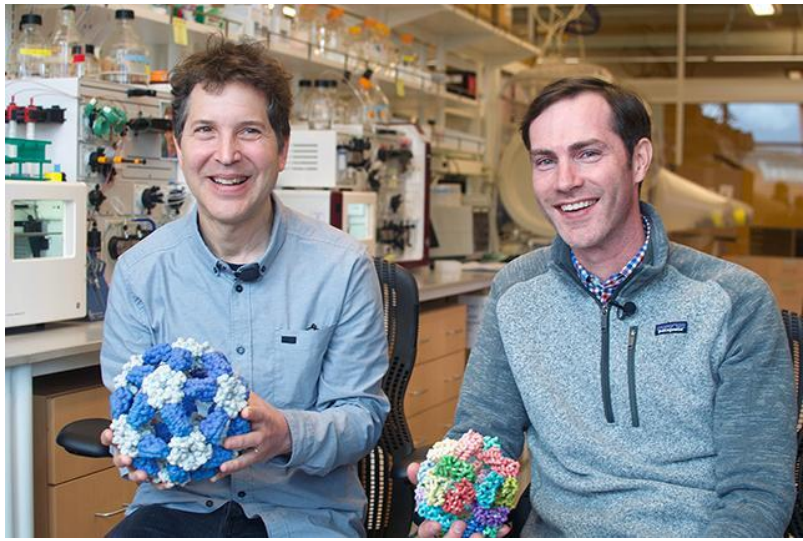
King talked about how to prevent the next pandemic and also discussed the development of experimental vaccines for COVID-19, flu and other viruses based on research from the UW's Institute for Protein Design, where he is an assistant professor.

"Ultimately I think computational protein design, in combination with technologies both old and new, is going to allow us to make vaccines that are safer and more effective against targets that have historically been really difficult," said King, who co-founded the vaccine company Icosavax, which went public this summer. Icosavax is moving forward with clinical trials for a COVID-19 shot based on IPD research, and a shot against respiratory syncytial virus, a cause of pneumonia.

King's lab deploys computational methods to predict how proteins behave and fold into specific shapes.

The experimental flu vaccine contains proteins from four flu viruses on a single particle. It's designed to prompt an exceptionally strong immune response to potentially "protect not only against this year's flu virus, but next year, too, and the years after that," said King. Developing such a "universal" flu vaccine has long been a goal of vaccine developers, and has the potential to supplant the annual cycle of flu shot manufacture to the strains that arise each year. The shot is now moving forward into clinical trials at the National Institutes of Health.

King talked about how far vaccine development has come. For much of the 20th century, vaccines were made from whole viruses or bacteria, typically highly weakened versions of microbes that did not cause infection but protected from disease. In the 1980's, researchers began to make vaccines with single viral or bacterial proteins or parts of proteins, such as improved vaccines for whooping cough and hepatitis C.



Icosavax cofounders David Baker (left), director of the UW Institute for Protein Design, and Neil King (right)

Source: https://www.geekwire.com/2021/icosavax-co-founder-uw-researcher-neil-king-talks-vaccine-development-digital-era/ and https://comotion.uw.edu/our-impact/success-stories/icosavax/

Pfizer to Close Seagen Deal + New Organization Announced

Press Release, Dec 12, 2023 (excerpt)

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announces that the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, expired December 11, 2023, with respect to Pfizer's pending acquisition of Seagen Inc. (NASDAQ: SGEN). Pfizer and Seagen have now received all required regulatory approvals to complete the acquisition. Pfizer expects to close the acquisition of Seagen on December 14, 2023, subject to the satisfaction of other customary closing conditions.

To address U.S. Federal Trade Commission concerns, Pfizer has chosen to irrevocably donate the rights of royalties from sales of Bavencio® (avelumab) in the U.S. to the American Association for Cancer Research (AACR).

Changes in Commercial Organization

Pfizer also announces changes in its commercial organization to incorporate Seagen and improve focus, speed and quality of execution. Specifically, Pfizer will create an end-to-end business organization called the Pfizer Oncology Division, which will integrate certain oncology commercial and R&D operations from both companies and will be led by Dr. Chris Boshoff, who will become Chief Oncology Officer, Executive Vice President, and continue reporting to Dr. Albert Bourla, Chairman and Chief Executive Officer. Pfizer will split its non-oncology commercial organization into two more focused business divisions: the Pfizer U.S. Commercial Division, which will be led by Aamir Malik, who will become Chief U.S. Commercial Officer, Executive Vice President, and continue reporting to Dr. Bourla; and the Pfizer International Commercial Division, which will be led by Alexandre de Germay, who will join Pfizer as Chief International Commercial Officer, Executive Vice President, and will report to Dr. Bourla. Biographical information for Alexandre de Germay can be found here.

After a stellar nearly 27-year career at Pfizer, Angela Hwang, Chief Commercial Officer, and President, Global Biopharmaceuticals Business will be leaving Pfizer. Angela has agreed to stay on as an advisor to help transition the organization into the new model. Under Angela's leadership, Pfizer introduced an unprecedented number of new medicines and vaccines to patients across the globe.

Source: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-receives-all-required-regulatory-approvals-complete

Aditxt, Inc. Enters into Definitive Agreement to Acquire Evofem Biosciences, Inc

RICHMOND, Va. & SAN DIEGO--(BUSINESS WIRE).—Dec 12, 2023-- Aditxt, Inc. (“Aditxt” or the “Company”) (NASDAQ: ADTX), a company dedicated to discovering, developing, and deploying promising health innovations, and Evofem Biosciences, Inc. (“Evofem”) (OTCQB: EVFM), a pioneer in women’s health, today announced the signing of a definitive agreement (the “Agreement”) under which Aditxt is to acquire Evofem in consideration of the issuance of a combination of common stock and preferred stock, and the assumption of certain senior indebtedness, having an aggregate amount of approximately $100 million (the “Transaction”). Pending a successful Transaction, it will also mark the establishment of a women's health mission within Aditxt's platform, aligning with global healthcare needs. Aditxt has assumed Evofem’s senior secured debt that was issued to the investor under the Securities Purchase and Security Agreement dated April 2020, as amended, and shall pay $5.0 million to Evofem’s senior secured debtholder by year-end 2023, $8.0 million by September 2024, and up to an additional $5 million thereafter.

Aditxt has also agreed to provide a $3.0 million loan to Evofem between the date of signing of the Agreement and closing and to cover Evofem’s legal costs related to the Transaction. At closing, the holders of Evofem’s common stock will exchange their shares for an aggregate of 610,000 shares of Aditxt common stock. In addition, Aditxt has agreed to issue up to an aggregate of 89,126 shares of preferred stock to the holders of Evofem’s currently outstanding unsecured notes, purchase rights, certain warrants, and preferred stock. Upon closing of the Transaction, which is currently anticipated to occur in the first half of 2024, Evofem will be a wholly owned subsidiary of Aditxt, with the Evofem management team to receive equity grants in the subsidiary of up to ten percent on a fully diluted basis after closing, and will continue to be led by Saundra Pelletier, Chief Executive Officer of Evofem, and the current management team.

Evofem’s Phexxi® is potentially a game changing option in contraception.

Evofem’s CEO Saundra Pelletier has courageously led the company but faced daunting financial headwinds.

This transaction deals with the company’s debt and allows Evofem to continue operating under Pelletier’s leadership.

Source: https://www.businesswire.com/news/home/20231212529968/en/Aditxt-Inc.-Enters-into-Definitive-Agreement-to-Acquire-Evofem-Biosciences-Inc.-Creator-of-Phexxi%C2%AE-the-First-and-Only-FDA-Approved-Hormone-Free-Contraceptive-Gel-to-Address-Diverse-Reproductive-Health-Needs-of-Women-Globally

Rain Oncology Enters into Agreement to be Acquired by Pathos AI for $1.16 in Cash per Share Plus Contingent Value Rights

NEWARK, Calif., Dec. 13, 2023 (GLOBE NEWSWIRE) - Rain Oncology Inc. (Nasdaq: RAIN) ("Rain"), today announced it has entered into a definitive merger agreement whereby Pathos AI, Inc. ("Pathos") will acquire Rain for $1.16 in cash per share plus a non-tradeable contingent value right (a "CVR") for potential cash payments of up to approximately $0.17 per share.

The Rain Board of Directors voted unanimously to approve the proposed Offer, Merger and related transactions contemplated by the Merger Agreement (collectively, the "Transaction"). The upfront cash consideration represents a 17% premium over Rain's unaffected stock price as of October 13, 2023. The Rain Board reached this determination following a comprehensive review of the proposal, along with the outcome of an extensive process to review strategic alternatives with the assistance of its independent financial and legal advisors.

"After a thorough assessment, the Rain Board determined that this Transaction is in the best interests of our stockholders, as it leverages Rain's strong cash position to provide a confirmed cash takeout for our stockholders and retains some future potential upside due to Pathos' continued interest in further developing milademetan for cancer patients using their proprietary PathOS Platform," said Avanish Vellanki, co-founder and chief executive officer of Rain.

Pursuant and subject to the terms of the merger agreement, a subsidiary of Pathos will commence a tender offer to acquire all outstanding shares of Rain for $1.16 in cash per share plus a CVR representing a contractual right to receive two potential contingent aggregate cash payments based on pipeline progress and the outcome of a D&O lawsuite.

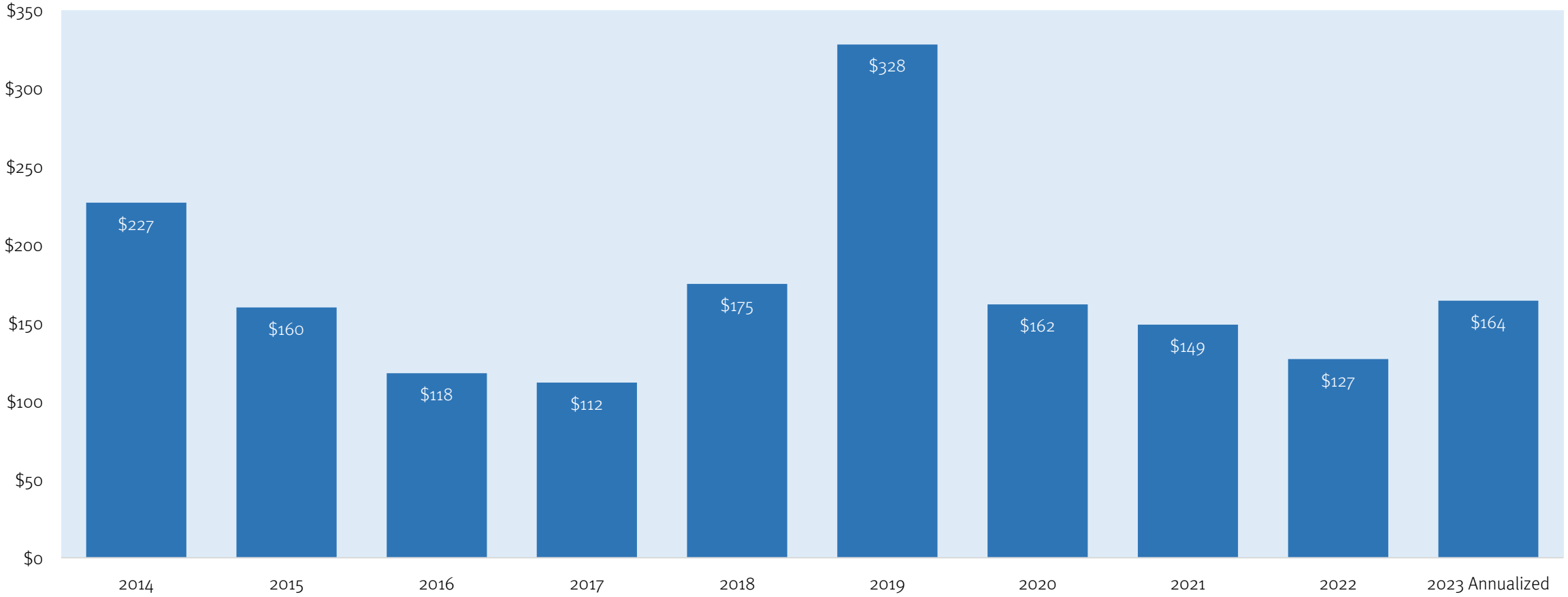
This strikes us an odd transaction because as of its last quarterly filing, Rain Oncology had close to $2 a share in cash.

Rain shareholders are not getting an ownership stake in PathosAI and instead are getting cashed out for what must be around 60% of cash going into the quarter.

Source: https://www.globenewswire.com/news-release/2023/12/13/2795922/0/en/Rain-Oncology-Enters-into-Agreement-to-be-Acquired-by-Pathos-AI-for-1-16-in-Cash-per-Share-Plus-Contingent-Value-Rights.html

Robust Year for Biopharma M&A Shaping Up

M&A Volume in the Biopharma Sector, 2014 - Dec 15, 2023
($ Billions, Worldwide)



Source: CapitalIQ and Stifel Analysis

SystImmune and Bristol-Myers Squibb Announce a Global Strategic Collaboration for BL-B01D1

December 11, 2023. REDMOND, Wash. & PRINCETON, N.J.--(BUSINESS WIRE)-- SystImmune, a clinical-stage biopharmaceutical company, and Bristol Myers Squibb (NYSE: BMY) today announced an exclusive license and collaboration agreement for SystImmune's BL-B01D1, a potentially first-in-class EGFRxHER3 bispecific antibody-drug conjugate (ADC). Under the terms of the agreement, the companies will jointly develop and commercialize BL-B01D1 in the United States. Through its affiliates, SystImmune will be solely responsible for development, commercialization, and manufacturing in Mainland China and will be responsible for manufacturing certain drug supplies for use outside of Mainland China. Bristol Myers Squibb will assume sole responsibility for development and commercialization in the rest of the world.

BL-B01D1, a bispecific topoisomerase inhibitor-based ADC which targets both epidermal growth factor receptor and human epidermal growth factor receptor 3 (EGFRxHER3), is currently being evaluated in a global multi-center Phase 1 study (BL-B01D1-LUNG101) for safety and efficacy in individuals with metastatic or unresectable non-small cell lung cancer (NSCLC).

Financial Highlights

Bristol Myers Squibb will pay SystImmune $800 million in an upfront payment and up to $500 million in contingent near-term payments. SystImmune is eligible to receive additional payments of up to $7.1 billion contingent upon the achievement of certain development, regulatory and sales performance milestones for a total potential consideration of up to $8.4 billion. The companies will share certain global development expenses and profits and losses in the United States. Through its affiliates, SystImmune will retain exclusive development and commercialization rights in Mainland China, where Bristol Myers Squibb will receive a royalty on net sales. Outside the United States and Mainland China, SystImmune will receive a tiered royalty on net sales. The agreement is subject to customary clearance by antitrust regulators.

A payment of $800 million upfront is not an everyday event for a molecule developed in China (or anywhere else).

The value paid is understandable.

We had previously noted how strong Systimmune's data looked in our ESMO review. Systimmune showed a 40% ORR in metastatic NSCLC with EGFR mutations. If Tagrisso is any guide this drug could generate large revenue for BMS.

Source: https://news.bms.com/news/details/2023/SystImmune-and-Bristol-Myers-Squibb-Announce-a-Global-Strategic-Collaboration-Agreement-for-the-Development-and-Commercialization-of-BL-B01D1/default.aspx

Largest Oncology License Deals in 2023 (By Upfront $ Millions)

Announced	Licensor	In-Licensee	Upfront (cash & equity)	Total Milestones	Licensor Country	Primary Tech	Stage Signed
10/19/2023	Daiichi Sankyo	Merck & Co. Inc.	$4,000	$18000	Japan	Antibody Conjugate	04 Phase II
12/11/2023	SystImmune	Bristol Myers Squibb Co.	$800	$7600	China	Antibody	03 Phase I
01/23/2023	HUTCHMED	Takeda Pharmaceutical	$400	$730	China	Small Molecule	06 Approved
05/02/2023	AbelZeta Pharma	Johnson & Johnson	$245	NA	China	Cell Therapy	03 Phase I
03/20/2023	OncoC4 Inc.	BioNTech SE	$200	NA	US	Antibody	04 Phase II
10/30/2023	Hengrui Pharmaceuticals	Merck KGaA	$170	$1221	China	Small Molecule	03 Phase I
04/03/2023	Duality Biologics	BioNTech SE	$170	$1500	China	Antibody Conjugate	04 Phase II
09/11/2023	Immatics N.V.	Moderna Inc.	$120	$1700	Germany	Antibody	02 Preclinical / IND
11/10/2023	Legend Biotech Corp.	Novartis AG	$100	1010	China	Cell Therapy	03 Phase I
10/20/2023	Hansoh Pharmaceutical	GSK	$85	1485	China	Antibody Conjugate	03 Phase I
09/12/2023	Insilico Medicine Inc.	Exelixis Inc.	$80	NA	China	AI/ML	03 Phase I
10/13/2023	Medilink Therapeutics Ltd.	BioNTech SE	$70	1000	China	Antibody Conjugate	03 Phase I
05/09/2023	Zion Pharma Ltd.	Roche	$70	610	China	Small Molecule	03 Phase I
02/23/2023	KYM Biosciences	AstraZeneca	$63	1100	China	Antibody Conjugate	03 Phase I
07/10/2023	Nanobiotix S.A.	Johnson & Johnson	$60	2670	France	Small Molecule	04 Phase II
11/06/2023	Biotheus Inc.	BioNTech SE	$55	1000	China	Antibody	04 Phase II
05/12/2023	Lanova Medicines	AstraZeneca plc	$55	545	China	Antibody Conjugate	02 Preclinical / IND
08/07/2023	Poseida Therapeutics	Astellas Pharma Inc.	$50	NA	U.S.	Cell Therapy	03 Phase I
10/27/2023	Henlius / Fosun Pharma	Intas Pharmaceuticals Ltd.	$45	152	China	Immunotherapy	06 Approved
10/30/2023	AnHeart Therapeutics	Nippon Kayaku Co. Ltd.	$40	NA	China	Small Molecule	04 Phase II

Source: DealForma

The Systimmune deal is the second largest oncology license deal of 2023.

The upfront and milestone package are very much inline with the high values set in the Daiichi / Merck transaction.

Importantly, the quality of Systimmune's data and novelty of their molecular approach is also competitive with Daiichi Sankyo's asset package.

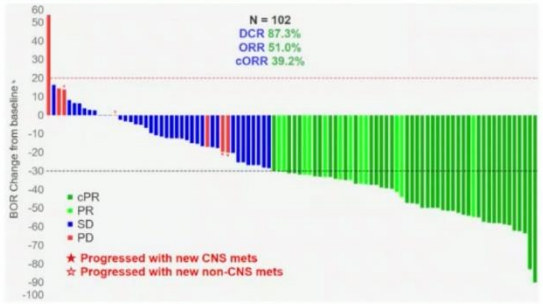
Remarkably, 15 of the 20 largest oncology license deals this year were for assets that originated in China.

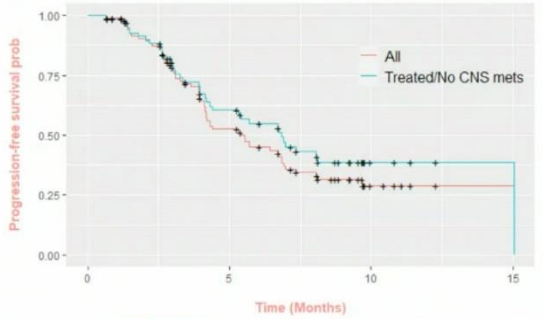
Impressive ESMO Data for BL-B01D1, a first-in-class EGFR×HER3 Bispecific ADC from Systimmune

08:30 - 10:00 Mini oral session 1 - NSCLC, metastatic

CHAIRS : LIZZA HENDRIKS, JORDI REMON MASIP, DANIEL SHAO WENG TAN, YI-LONG WU

Overall efficacy of NSCLC patients





The impact of baseline CNS metastasis

	All NSCLC	All NSCLC with treated/no CNS mets	All NSCLC with untreated CNS mets
Enrolled[1]	N = 102	N = 75	N = 27
Median Prior line	3 (1-8)	3 (1-8)	3 (1-7)
Prior TKI or ICI[2]	92% (94/102)	93% (70/75)	89% (24/27)
Prior PBC	89% (91/102)	91% (68/75)	85% (23/27)
DCR (95%CI), %	87.3 (79.2, 93.0)	86.7 (76.8, 93.4)	88.9 (70.8, 97.6)
ORR (95%CI), %	51.0 (40.9, 61.0)	52.0 (40.2, 63.7)	48.1 (28.7, 68.1)
cORR (95%CI), %	39.2 (29.7, 49.4)	41.3 (30.1, 53.3)	33.3 (16.5, 54.0)
mDOR (95%CI), mo	8.5 (5.4, NR)	12.3 (5.4, NR)	4.2 (2.2, NR)
mPFS (95%CI), mo[3]	5.6 (4.1, 6.8)	6.8 (4.3, NR)	4.1 (3.1, 5.6)

[1] Two patients (01061, 05003) were censored at their last tumor assessment before COVID-19 related delays exceeding 28 days. [2] TKI for patients with NSCLC EGFRmt, ICI for patients with NSCLC EGFRwt. [3] The mPFS, mDOR and CI were calculated based on Kaplan–Meier method and log-log transformation.

MADRID 2023 ESMO congress

Li Zhang

Li Zhang

BL-B01D1, a first-in-class EGFRxHER3 bispecific antibody-drug conjugate, in patients with non-small cell lung cancer: Updated results from first-in-human phase I study

MADRID 2023 ESMO congress **Granada Auditorium - Hall 3** **MADRID SPAIN 20-24 OCTOBER 2023**

GSK on Hunt for Drug Deals in China

Hannah Kuchler, *Financial Times*, Dec 17, 2023 (excerpt)

GSK is on the hunt for deals in China after the UK drugmaker rebuilt a “very strong” relationship with the government and local companies since a corruption scandal a decade ago.

Chief commercial officer Luke Miels told the Financial Times that the company was working on further deals with Chinese companies after it signed a licensing agreement in October worth up to $1.5bn for a cancer drug developed by Hansoh Pharma.

Miels said that the country’s high standards of chemistry made it a good hunting ground. “You can find molecules in China and [often] the Chinese companies just want the [domestic] rights so you can negotiate . . . [to] take it globally.”

Miels said the company intends to do as much global M&A in 2024 as it did this year. GSK reached five deals in 2023, including acquiring Bellus Health for $2bn, three licensing agreements and the vaccine partnership with Zhifei.

It is looking in particular for smaller bolt-on deals in its specialist areas such as respiratory and infectious diseases. These could be found for “an attractive price”, said Miels.

But he ruled out bidding for companies with potential obesity treatments, despite surging sales of weight loss and diabetes drugs sold by Novo Nordisk and Eli Lilly. He said GSK did not have the “internal capabilities” to invest in the new generation of drugs, called GLP-1s.

Source: https://www.ft.com/content/fbeb83e5-1880-4a9a-92fe-f57032760338

Sanofi Scraps Maze Deal After FTC Throws up Antitrust Obstacles

Press Release, Dec 12, 2023 (excerpt)

The Federal Trade Commission (FTC) has scuttled Sanofi's licensing deal with Maze Therapeutics. With the FTC moving to block the deal, the Big Pharma is pulling out rather than working through the antitrust maze that has sprung up between it and the asset.

In May, Maze and Sanofi revealed a deal for the Pompe disease program MZE001. Sanofi agreed to pay $130 million in upfront cash, plus up to $605 million in milestones, for worldwide rights to a drug candidate that could treat Pompe by stopping the buildup of glycogen. The asset would have slotted into a Pompe portfolio that features the enzyme replacement therapy Nexviazyme.

The FTC sees that as a problem. In a statement to disclose its plans to block the deal, the agency said the agreement would "eliminate a nascent competitor poised to challenge Sanofi's monopoly in the Pompe disease therapy market." The FTC expanded on the point in a heavily redacted complaint.

Source: https://www.fiercebiotech.com/biotech/sanofi-scraps-maze-deal-after-ftc-throws-antitrust-obstacles

Cracking the Obesity Code at Carmot Therapeutics

Scientists Can Make a Big Difference in the World

It can be hard to write about scientists. By definition, they tend to be retiring types who would rather spend a few more hours in the laboratory than on the PR circuit.

But a common thread is the instinct that a particular problem in medicine might be solved in a certain way or with a certain technology.

By definition, scientific discoveries involve an *insight*. A way of seeing an old problem in a new way. Or perhaps a problem that others didn't see at all.

Proust once said that "The real voyage of discovery consists not in seeking new landscapes, but in having new eyes."

Last week was Nobel Week in Oslo and Stockholm. We saw Professors Katalin Karikó and Drew Weissman receive the Nobel Prize for work on mRNA that was instrumental in leading to the mRNA vaccine for Covid19.

By now, the travails and focus of Katalin Karikó have been well chronicled. She saw the possibility that mRNA could be applied as a drug and went to work on overcoming technical barriers that would make this possible.

A similar story can be told about the importance of thought, insight and perspiration rather than well-equipped laboratories.

The Indian physicist CV Raman, best known for discovering the Raman effect (light scattering when light passes through materials) once said "the essence of science is independent thought, hard work and not equipment."

Importantly, scientists can also be entrepreneurs.

Most care little about the financial rewards of their work but cherish the opportunity to pursue a medicine that might be relevant for solving the problems of patients.

Hence the reason so many scientists turn to entrepreneurship.

Today, we wish to highlight the story of a key scientist that you may have never heard of:

Stig Hansen
Founder of Carmot Therapeutics
& CEO, Kimia Therapeutics

Stig Hansen Founds Carmot Therapeutics

At the moment, interest in designing new therapeutics for obesity and related illnesses is at an all time high. We are tracking more than fifty efforts to develop novel drugs for obesity.

The situation was very different when Dr. Stig Hansen decided to found Carmot Therapeutics in 2008 together with the fellow scientist Dr. Dan Erlanson.

Those with long memories might remember that 2008 was when the last real pharma hope in obesity therapeutics, rimonabant, from Sanofi was pulled from the market. At the time, the GLP-1's were known for potential in treating diabetes.

In 2008, the idea of going into obesity research at the time would about as popular with VCs as starting a company today using electroshock therapy to cure sepsis. The record shows that Carmot received its first financing from The Column Group via Tim Kutzey in 2010.

The Column Group left Dr. Hansen and his co-founders with a meaningful equity stake such that he is making more than $200mm from Roche's M&A deal.[1]

The funding history of Carmot is indeed remarkable: $2mm Series A in 2010, $13mm B in 2017, and $47mm C in 2020. Put that in context of initiation of Phase 1 with CT-868 in 2018, and CT-868 Phase 2 plus CT-388 Phase 1 in 2021. Carmot was able to build significant value with minimal dilution, benefiting early employees and investors.

Stig Hansen, Founder Carmot Tx

[1] See: https://medwatch.com/News/Pharma___Biotech/article16663331.ece

Stig Hansen's Background

Fresh off a scientific role at Sunesis Pharmaceuticals, Dr. Hansen was interested in coupling structure-based drug design with a custom library synthesis and screening platform called Chemotype Evolution.

Dr Hansen had previously invented an obesity drug candidate while at Sunesis and had filed a patent for this product in 2007.[2]

In this patent he and co-inventor Dan Erlanson wrote words which sound like they are from today:

> "Obesity has reached epidemic proportions globally, with more than 1 billion adults overweight—at least 300 million of them clinically obese—and is a major contributor to the global burden of chronic disease and disability. Obesity and being overweight pose a major risk for serious diet-related chronic diseases, including type 2 diabetes, cardiovascular disease, hypertension and stroke, and certain forms of cancer."

After his stint at Sunesis, Hansen took the arguably foolish step of starting his own biotech, Carmot Therapeutics.

Not an obvious move given that he had only been at the director level at Sunesis and had no business track record to speak of. Stig's idea at Carmot was to industrialize the creation of screening libraries with the objective of creating chemically better drugs for major problems in drug discovery.

His vision was not for the faint of heart. Dr. Hansen was looking at some of the toughest problems in drug discovery including how to target:

- Class B GPCRs
- Protein-Protein interactions
- De-ubiquinating enzymes

Under Dr. Hansen's leadership, Carmot advanced the Chemotype Evolution platform as well as the development of a pipeline comprising preclinical and clinical novel dual incretin modulators for the treatment of metabolic diseases. Notably, in collaboration with Amgen, Carmot used Chemotype Evolution to create the break-through discoveries that lead to LUMAKRAS, the first KRAS inhibitor approved by the FDA in 2021.[3,4]

[2]See https://patents.google.com/patent/US20080293777A1

[3]See, for example, Shin Y, Jeong JW, Wurz RP, Achanta P, Arvedson T, Bartberger MD, Campuzano IDG, Fucini R, Hansen SK, Ingersoll J, Iwig JS, Lipford JR, Ma V, Kopecky DJ, McCarter J, San Miguel T, Mohr C, Sabet S, Saiki AY, Sawayama A, Sethofer S, Tegley CM, Volak LP, Yang K, Lanman BA, Erlanson DA, Cee VJ. Discovery of *N*-(1-Acryloylazetidin-3-yl)-2-(1*H*-indol-1-yl)acetamides as Covalent Inhibitors of $KRAS^{G12C}$. ACS Med Chem Lett. 2019 Aug 20;10(9):1302-1308.

[4]See https://www.businesswire.com/news/home/20210629005271/en/Carmot-to-Receive-Royalty-Payments-Upon-Sales-of-Amgen%E2%80%99s-FDA-Approved-First-in-class-KRAS-G12C-Inhibitor-LUMAKRAS%E2%84%A2-sotorasib-Further-Demonstrates-the-Value-of-Carmot%E2%80%99s-Therapeutic-Platform

Carmot Cracks the Obesity Drug Category

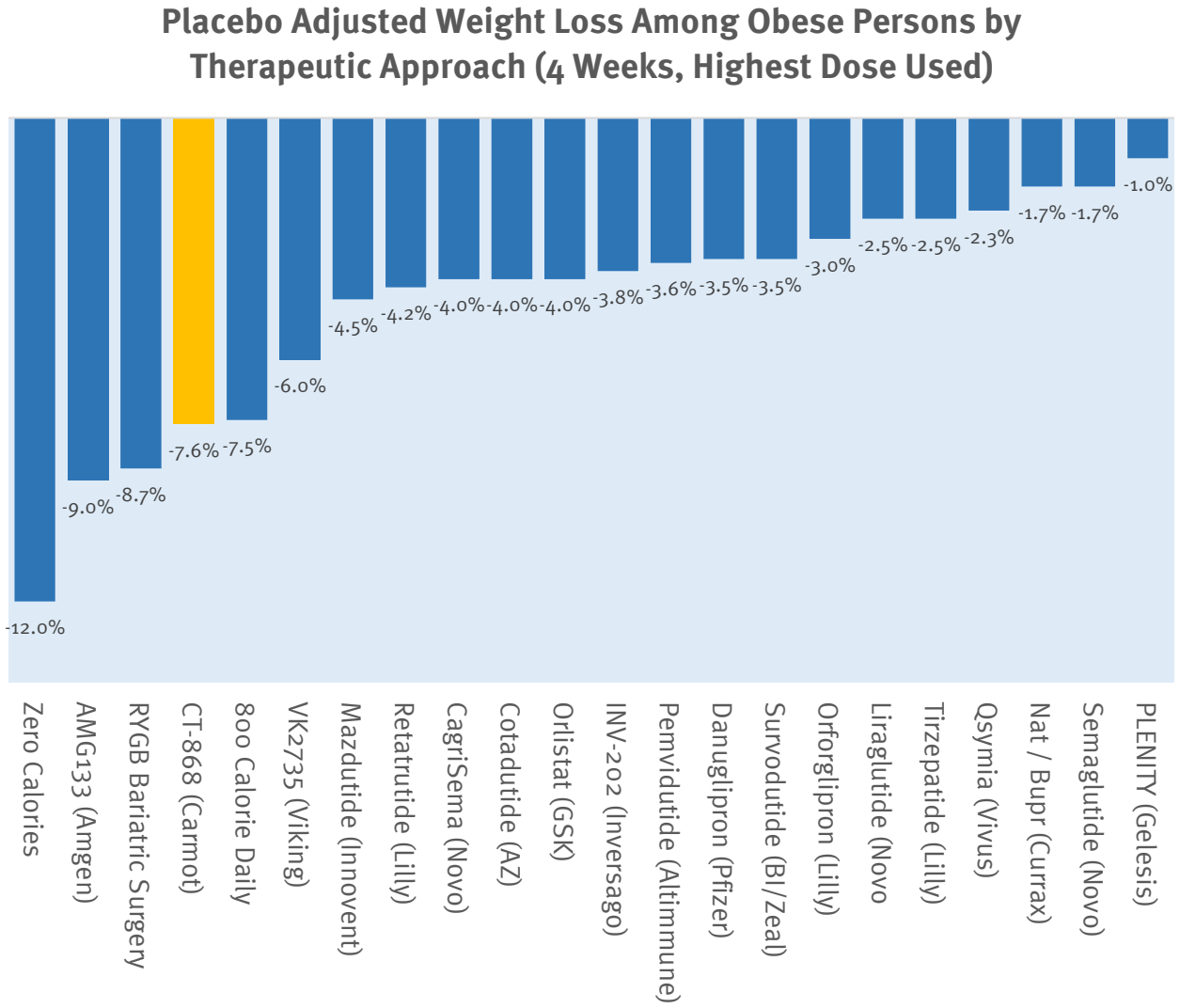
Coming into this, Stig was indeed well trained. Dr. Hansen had earned his PhD in molecular and cell biology from the University of Copenhagen, Denmark. He conducted his Ph.D. studies in the laboratory of Dr. Robert Tjian at UC Berkeley.

We cannot say that we were anywhere near Carmot at the time, but we are able to read patent filings that were made and can spot what, in retrospect, was more than a little brilliance.

To start on this, let's compare Carmot's lead drug, CT-868, to the competition. So, the first time that today's leading obesity drug seller, semaglutide was discovered was in 2006. At four weeks, semaglutide use is associated with 1.7% loss in body weight.

In contrast, Carmot's drug CT-868, a dual GLP-1 / GIP agonist has shown an impressive 7.6% weight loss at four weeks in its highest dosage form. Crazy really.

What's important is that the drug candidate has also has a good side effect profile. The Phase 1 trial had no discontinuations on drug.



Source: Stifel July 2023 Obesity Drug Report

How Carmot Cracked the Obesity Code

Compare this with Mounjaro (tirzepatide) with 2.5% weight loss. To be fair to tirzepatide and semaglutide, these drugs are typically started with dose escalation protocols so, at four weeks, may not shine as brightly as they might in later comparisons. But, nonetheless, the performance of CT-868 stands out. One might say that it is only #4 in our ranking. But, a closer examination shows that the #1 performer is a zero calorie diet (think Burmese prison confinement without food) and #3 is bariatric surgery. The only drug, so far, that has done better is Amgen's AMG-133. But, Amgen has yet to show us their side effect data and their spectacular weight loss result was seen with only one very high dose in a small number of patients.

It's well known that a liability of incretin mimetics that they can induce receptor internalization which means that the potential benefit of drugging a target can be lost.

So, we hinted at a little brilliance on the part of Mr Hansen and his team, which among others, included co-founder, Dan Erlanson, his original collaborator from Sunesis days. Perhaps the best way to explain is that the patent for Lilly's tirzepatide was filed in January 2016. It would not have appeared on the USPTO website (if one even knew to look) until mid 2017 at the earliest.

In March 2018, Carmot, led by Stig Hansen, filed a patent entitled "Modulators of G-Protein Coupled Receptors".[4] This patent described a molecule that was like tirzepatide, a GLP-1 / GIPR agonist. This team was remarkably prescient and hot on the heels of the scientists at Eli Lilly. However, the patent reveals a key insight: "Therapeutic agents that modulate G-protein coupled receptors (e.g., GLP-1R and/or GIPR) can produce a variety of effects depending on the degree of cAMP activation versus β-arrestin-based signaling. It has been shown that β-arrestin coupling is a key step in receptor internalization and subsequent de-sensitization and attenuation of signaling. Both GLP-1 (and the liraglutide analog) and GIP have been shown to produce rapid receptor internalization. Thus, compounds that activate GLP-1R and/or GIPR cAMP signaling but do not substantially couple to β-arrestin have the potential to prolong receptor signaling and extend pharmacological benefits. In some embodiments, the

[4] See https://patents.google.com/patent/US20230357347A1/en

How Carmot Cracked the Obesity Code (continued)

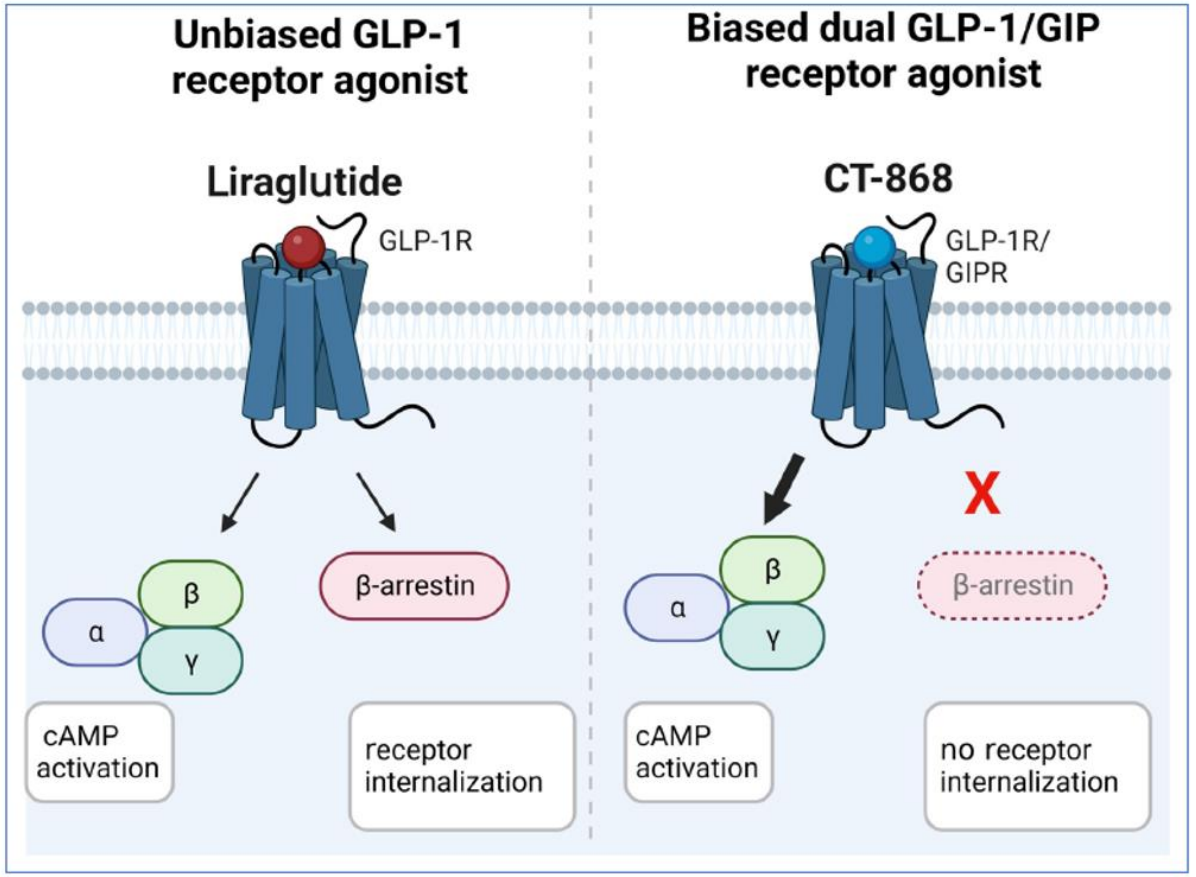
chemical entities described herein exhibit relatively strong GLP-1R and/or GIPR mediated cAMP activation with minimal or no detectable β-arrestin coupling."

The work on biased GLP-1 receptor agonists preceded Lilly's Tirzepatide patent for some time. For example, an NIH grant was awarded to Drs Hansen and Enquist in 2012 with the title: "Discovery of biased small molecule agonists of the GLP-1 receptor for treatment of metabolic disease".[5]

It would obviously be unfair to boil Carmot's accomplishments down to just one paragraph, but basically, the company's scientists, led by Stig Hansen, cracked the code to the incretin class by creating a molecule that avoided receptor internalization (see chart at right).

Carmot figured out that one could outengineer incumbent molecules to avoid receptor internalization and to bias signalling in favor of GLP-1. The rest is now history.

We anticipate that Roche, equipped with Carmot's science, is now going to be able to give both Lilly and Novo Nordisk a serious run for their money.



[5] See https://www.sbir.gov/node/400252

Industry News

House Passes Health Package With PBM Reforms, Site-Neutral Policy

Modern Healthcare, December 11, 2023

The House of Representatives passed a wide-ranging package of healthcare legislation Monday night that among other things would institute new transparency and pricing rules on pharmacy benefit managers and hospitals, and spares hospitals from some cuts while likely imposing others.

The Lower Costs More Transparency Act of 2023, approved on a bipartisan 320-71 vote, would require extensive new disclosures of prices and costs by hospitals, insurers, imaging services, diagnostic laboratories and PBMs. It also bans PBMs from the practice of spread pricing in Medicaid, requiring them to pass on savings they negotiate with drug companies and instead get paid a set administrative fee.

For hospitals, the bill helps those that treat a disproportionate share of uninsured patients by delaying for two years Disproportionate Share Hospital, or DSH, cuts. The cuts were written into law in the Affordable Care Act on the assumption that with more people insured, hospitals would deliver less uncompensated care, but that has not happened. The bill pushes off $8 billion in DSH cuts for each of the next two years.

Hospitals came out in opposition to the bill because it also includes so-called site neutrality provisions that bar hospitals in the Medicare program from receiving higher payments for administering drugs in hospital-owned doctors' offices than an independent doctor would receive.

The AHA has argued that when its doctors administer drugs in offsite clinics, it is not the same as when a free-standing physician's office does it because hospitals have greater requirements and costs. If hospitals can't charge more, it would limit access, the AHA has argued in letters to Congress.

This is potentially foundational legislation for the pharma industry given the games played with pricing by PBMs.

The Senate previously passed its own bill which, like this bill, includes a ban on spread pricing in Medicaid.

The site neutral policy is controversial with hospitals which mark up drugs significantly.

Source: https://www.modernhealthcare.com/politics-policy/house-passes-bill-covering-pbms-dsh-cuts-site-neutral-payments

As the 2024 Election Looms, Will We See a Health Policy Pause?

Lecia Bushak, *Medical Marketing and Media*, Dec 12, 2023

On the health policy front, 2023 was considerably quieter than 2022. As the pandemic receded, most of the activity centered around a single question: "What's next?"

That's not to say the year was devoid of memorable policy-related moments. President Joe Biden officially declared the pandemic's end in May. The Centers for Medicare and Medicaid Services chose the first 10 drugs for which Medicare would negotiate prices. Pharmacy benefit managers sat in the hot seat during multiple Congressional hearings about drug prices. And, after a long lag, Monica Bertagnolli was confirmed as the new National Institutes of Health director.

With the presidential election looming, we're unlikely to see more action in 2024. It's unlikely that any significant legislation, such as 2022's Inflation Reduction Act, will make its way into law.

"Attempts to seriously change policy from both sides don't have a chance of getting through in a Congress that is so closely divided," notes Terry Haines, founder of healthcare consultancy Pangaea Policy. "What you end up with is a standstill on anything consequential."

But some new contenders could seize the spotlight in 2024. They include health misinformation, AI and the next steps of the Medicare negotiation program.

Source: https://www.mmm-online.com/home/channel/features/2024-election-health-policy/

Matthew Fiedler, senior fellow at the Brookings Institution, shares Haines' sentiment that major legislation isn't likely to pass in 2024. His one possible exception: the ongoing implementation of the Medicare drug negotiation program.

"The negotiation process is going to continue to crank forward because there are statutory timelines that need to be met," he explains. "That is probably something that the current administration is perfectly happy to be talking about in an election year."

Some of the legal fights launched by pharma companies contesting the validity of the program will continue, but most experts believe the IRA is here to stay. "It is not going away," says Avalere Health president Sarah Alwardt. "Now that we've gotten past the shock phase of it, we'll see what happens when this becomes part of life."

As for cascading effects of the legislation, Alwardt believes companies might choose to abandon early pipeline assets set to enter a category that includes a negotiated drug. Similarly, she points to uncertainty on the payer front: "We don't know how payers are going to respond to including the drugs that are negotiated, versus ones that are similar that could be rebated.

Still, experts don't believe any PBM- or drug-pricing-related legislation will make it through Congress anytime soon. "I don't know if there would be enough support to do something in the next year, especially with the distraction of the election," Alwardt says.

Finally, there's the ongoing concern of stemming the tide of health-related misinformation, in the context of future pandemics or otherwise.

Generalized Cost Effectiveness (GCEA) Approach Makes A Big Difference in Assessing Hep C Drugs

Chou et.al., *AJMC,* Dec 5, 2023

Long employed by health technology assessment (HTA) agencies and regulators, cost-effectiveness analyses (CEAs) have been increasingly used by health care decision makers in the United States to assess the comparative economic value of new and existing technologies. CEAs monetize health benefits and typically produce incremental cost-effectiveness ratios (ICERs) to estimate the costs required to gain an additional quality-adjusted life-year (QALY) under a new technology. There remains some debate regarding the validity of QALYs as a decision-making tool in health. Additionally, questions remain around the ability of standard CEA approaches to adequately capture relevant drivers of value for a given treatment.

In 2018, The Professional Society for Health Economics and Outcomes Research (ISPOR) cautioned that traditional CEAs fail to account for key drivers of treatment value beyond posttreatment QALY gains.4 The report introduced a value flower, categorizing potential elements of treatment value into core, common, and potential/novel considerations for expanded CEA. Core elements include health gains (eg, increases in QALYs) and net costs of therapy (eg, difference between wholesale acquisition costs and rebates). More broadly used novel value elements include productivity gains (eg, increased work performance and prolonged working ages) and impact on informal caregivers (eg, reduced time away from work, lower levels of physical and emotional distress). Lastly, less commonly incorporated value elements include reduced uncertainty, improved future treatment options, and reductions in health inequity. At the heart of the value flower is the criticism that traditional CEAs employ a narrow definition of value…

Source: https://www.ajmc.com/view/generalized-cost-effectiveness-analysis-to-assess-treatment-value-in-hepatitis-c

This study aims to show that accounting for a broader definition of value through a generalized CEA (GCEA) more accurately reflects the true value that novel therapies can offer to society. To illustrate this argument, we conducted a class-level GCEA of direct-acting antiviral drugs (DAAs) for the treatment of chronic hepatitis C virus (HCV) genotype 1. We selected DAAs for the treatment of HCV because they are a uniquely well-suited technology to be evaluated in a GCEA due to (1) the vast public health impact of this viral disease, supporting the need for a societal perspective and (2) the duration of DAAs on the market, providing evidence of market dynamics for an innovative drug class.

Based on the results of this analysis, DAAs are cost-effective therapies for the treatment of HCV across a range of scenarios and inputs. **Compared with baseline CEA model outcomes, mirroring the traditional CEA approaches used by most HTA organizations, incorporating dynamic transmission and market pricing leads to the largest improvements in cost-effectiveness (decrease in ICER values of ~90%).** This substantial decrease in ICER values emphasizes the significant amount of value missed if disease transmission is not incorporated when evaluating treatments of viral disease that not only treat infected individuals but also limit their ability to transmit the disease to others. Additionally, the importance of considering the impact of price competition between both multiple branded and generic pharmaceutical agents is evident in our model results. Therefore, incentivizing continued innovation in all treatment spaces to establish differentiating factors between therapies is critical. Between the baseline analysis and subsequent model graduations, productivity and caregiver burden had little impact on ICER value compared with transmission dynamics and dynamic price/efficacy. In consequence, future models examining the broader societal perspective of viral diseases ought to prioritize inclusion of market dynamics and other aspects of value to more accurately capture the comprehensive value a treatment offers.

Jay Bradner Takes on Head R&D Job at Amgen

THOUSAND OAKS, Calif., Dec. 14, 2023 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced two changes to its senior leadership team in the areas of research and development (R&D) and technology, underscoring the advancement of the company's robust pipeline and its commitment to ongoing scientific and technological innovation. James Bradner, M.D., has joined Amgen as executive vice president of Research and Development, and chief scientific officer. Bradner is succeeding David M. Reese, M.D., who has been appointed executive vice president and chief technology officer. Both Bradner and Reese will report to Robert A. Bradway, chairman and chief executive officer at Amgen.

"For more than 40 years, Amgen's focus on innovation has enabled us to deliver life-changing medicines to patients suffering from serious diseases around the world," said Robert A. Bradway, chairman and chief executive officer at Amgen. "The steps we are announcing today reflect our conviction that the rapid convergence of 'biotech' and 'tech' will unlock the next frontier of innovation in biotechnology."

Bradner is a seasoned R&D leader who will be responsible for advancing Amgen's pipeline, which includes potential first-in-class medicines in all stages of development and across the company's four therapeutic areas of focus: oncology, inflammation, general medicine and rare disease, in addition to biosimilars. He will also be responsible for Amgen's worldwide research efforts.

Reese joined Amgen in 2005 and has led the R&D organization since 2018. During his tenure, Amgen has received approvals around the world for numerous innovative medicines and biosimilars. Building on Amgen's commitment to leveraging human data in drug discovery and development, Reese has led the development of a robust pipeline. Recently he has also been the key architect of Amgen's artificial intelligence (AI) and advanced technology initiatives with a focus on R&D. He will now be responsible for accelerating the use of technology and AI across all facets of the organization.

Jay Bradner
CSO, Amgen

Source: https://www.amgen.com/newsroom/press-releases/2023/12/amgen-announces-executive-appointments-to-accelerate-innovation

FDA Approves Enfortumab Vedotin-ejfv (Padcev) with Pembrolizumab for Urothelial Cancer

On December 15, 2023, the Food and Drug Administration (FDA) approved enfortumab vedotin-ejfv (Padcev, Astellas Pharma) in combination with pembrolizumab (Keytruda, Merck) for patients with locally advanced or metastatic urothelial cancer (la/mUC). FDA previously granted accelerated approval to this combination for patients with la/mUC who are ineligible for cisplatin-containing chemotherapy.

Efficacy was evaluated in EV-302/KN-A39 (NCT04223856), an open-label, randomized trial of 886 patients with la/mUC and no prior systemic therapy for advanced disease. Patients were randomized 1:1 to receive either enfortumab vedotin-ejfv with pembrolizumab or platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin). Randomization was stratified by cisplatin eligibility, PD-L1 expression, and presence of liver metastases.

The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS) as assessed by blinded independent central review.

Statistically significant improvements in both OS and PFS were demonstrated for enfortumab vedotin-ejfv with pembrolizumab compared with platinum-based chemotherapy. Median OS was 31.5 months (95% CI: 25.4, not estimable) for patients who received enfortumab vedotin-ejfv with pembrolizumab and 16.1 months (95% CI: 13.9, 18.3) for those who received platinum-based chemotherapy (Hazard ratio [HR] 0.47 [95% CI: 0.38, 0.58]; p-value<0.0001). Median PFS was 12.5 months (95% CI: 10.4, 16.6) for patients who received enfortumab vedotin-ejfv with pembrolizumab and 6.3 months (95% CI: 6.2, 6.5) for those who received platinum-based chemotherapy (HR 0.45 [95% CI: 0.38, 0.54]; p-value<0.0001).

Highly gratifying to see PADCEV go from a standing ovation at ESMO for remarkable urothelial cancer data to an FDA approval in just a few months.

Source: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enfortumab-vedotin-ejfv-pembrolizumab-locally-advanced-or-metastatic-urothelial-cancer

Pfizer Provides 2024 Guidance: Shares Down 7%

Pfizer Presentation Dec 12, 2023

2024 Financial Guidance[1]

	2023 Guidance[2]	2024 Legacy Pfizer Guidance[1]	Royalty Reclass[3]	2024 Seagen Impact	2024 Financial Guidance[1]
Reported Revenues	$58.0 – $61.0B[4]	$54.5 – $57.5B[4]	~$1.0B*	~$3.1B	$58.5 – $61.5B
Adjusted[1] SI&A Expenses	$13.3 – $14.3B				$13.8 – $14.8B
Adjusted[1] R&D Expenses	$11.9 – $12.9B				$11.0 – $12.0B
Effective Tax Rate on Adjusted[1] Income	~12.0%				~15.0%
Adjusted[1] Diluted EPS	$1.45 – $1.65	$2.45 – $2.65		~($0.40)[5]	$2.05 – $2.25

1. See Slide 14 for definitions and additional information regarding Pfizer's 2024 financial guidance. 2. As of October 31, 2023. 3. Beginning in Q1 2024, Pfizer's royalty income will be reclassified from Other (Income)/Deductions into the Revenue line. 4. Reported revenues range for 2023 Guidance and 2024 Legacy Pfizer Guidance does not include royalty income. 5. Predominantly driven by costs to finance the transaction.

* The calculation for both operational revenue growth rate ranges referenced on slide 11 assumes that the impact of the royalty income reclassification is applied to both 2023 standalone Pfizer Guidance and 2024 Financial Guidance for Revenue to ensure a like-for-like comparison. Consequently, there is no operational revenue growth attributable to the reclassification of royalty income.

Pfizer

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Pfizer is guiding to organic growth from 2023 to 2024 of 3 to 5%, excluding Covid products.

This guidance assumes sales next year of Covid products of around $8 billion.

Pfizer shares were hit hard and are down big for the year. Investors are quite pessimistic on the company and a series of negative articles on the company hit last week.

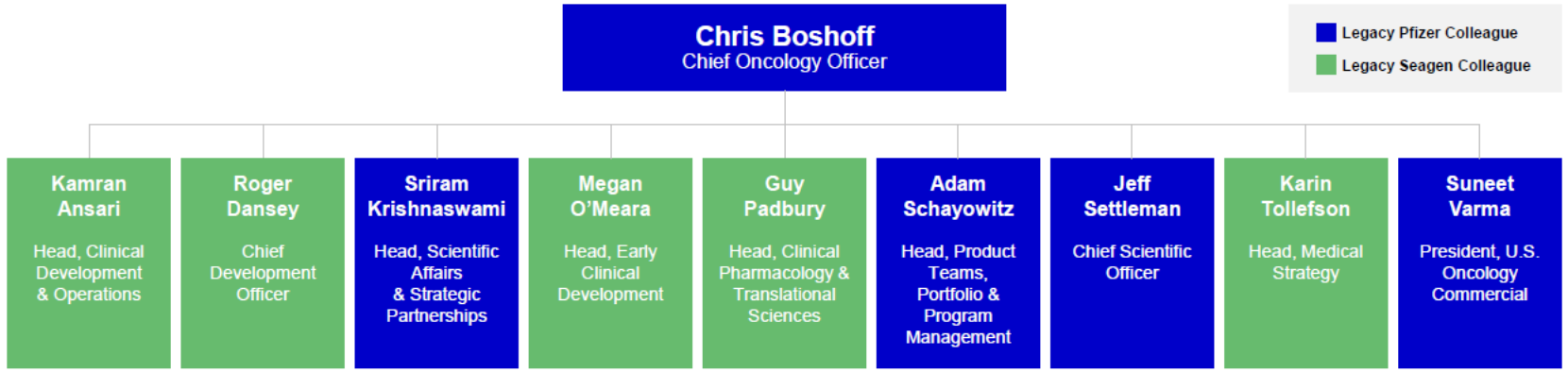
Our own view, for what it's worth, is that Pfizer is going to be improving commercial execution and has an underappreciated pipeline (e.g., ponsegromab highlighted previously). Further, the situation with the Pandemic has been essentially unknowable. Pfizer got its forecast there wrong, but it could have just as easily gone the other way.

Pfizer also pulled off a giant pharma M&A deal with minimal problems in a year when the FTC is downright difficult.

To paraphrase Joe Paterno, we'd like to think that most companies are never quite as good as people think when they are doing well and also, likely, much better than the critics say, when they appear down on their luck.

Source: https://investors.pfizer.com/Investors/Overview/default.aspx

Pfizer Oncology Organization Includes Mix of Seagen and Pfizer Professionals



Starting January 1, 2024, will establish a **new end-to-end business organization: Pfizer Oncology Division**

- Combination of several oncology operations currently residing in Biopharma and Oncology Research & Development (ORD)
- Integration of certain Oncology commercial and R&D operations from both companies
- Led by **Chris Boshoff**, who has been named **Chief Oncology Officer**

The personnel in Pfizer's oncology division are world class.

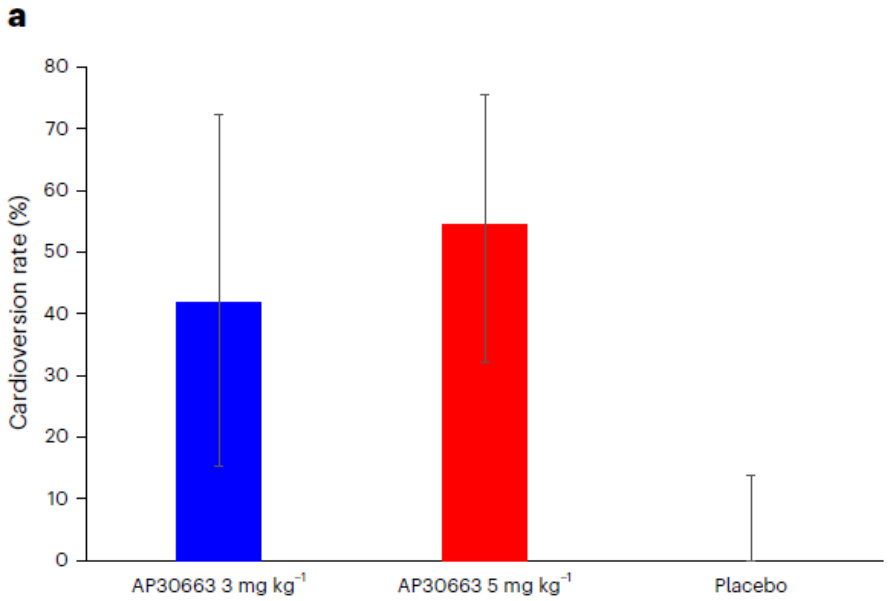
This organization should be able to deliver consistent and strong growth over years to come.

Source: https://investors.pfizer.com/Investors/Overview/default.aspx

Strong Benefit to Using Acesion's Atrial Fibrillation Therapy

Holst, A.G., Tomcsányi, J., Vestbjerg, B. et al. Inhibition of the KCa2 potassium channel in atrial fibrillation: a randomized phase 2 trial. Nat Med (2023).

Existing antiarrhythmic drugs to treat atrial fibrillation (AF) have incomplete efficacy, contraindications and adverse effects, including proarrhythmia. AP30663, an inhibitor of the $K_{Ca}2$ channel, has demonstrated AF efficacy in animals; however, its efficacy in humans with AF is unknown. Here we conducted a phase 2 trial in which patients with a current episode of AF lasting for 7 days or less were randomized to receive an intravenous infusion of 3 or 5 mg kg^{-1} AP30663 or placebo. The trial was prematurely discontinued because of slow enrollment during the coronavirus disease 2019 pandemic. The primary endpoint of the trial was cardioversion from AF to sinus rhythm within 90 min from the start of the infusion, analyzed with Bayesian statistics. Among 59 patients randomized and included in the efficacy analyses, the primary endpoint occurred in 42% (5 of 12), 55% (12 of 22) and 0% (0 of 25) of patients treated with 3 mg kg^{-1} AP30663, 5 mg kg^{-1} AP30663 or placebo, respectively. Both doses demonstrated more than 99.9% probability of superiority over placebo, surpassing the prespecified 95% threshold. The mean time to cardioversion, a secondary endpoint, was 47 (s.d. = 23) and 41 (s.d. = 24) minutes for 3 mg kg^{-1} and 5 mg kg^{-1} AP30663, respectively. AP30663 caused a transient increase in the QTcF interval, with a maximum mean effect of 37.7 ms for the 5 mg kg^{-1} dose. For both dose groups, no ventricular arrhythmias occurred and adverse event rates were comparable to the placebo group. AP30663 demonstrated AF cardioversion efficacy in patients with recent-onset AF episodes. $K_{Ca}2$ channel inhibition may be an attractive mechanism for rhythm control of AF that should be studied further in randomized trials.



Primary endpoint of cardioversion. a, Cardioversion rates in the full analysis set. The bar heights show the percentage of patients with cardioversion; the error bars show the 95% confidence intervals (CIs). AP30663 3 mg kg–1, n = 12 patients; AP30663 5 mg kg–1, n = 22 patients; placebo, n = 25 patients.

Source: https://www.nature.com/articles/s41591-023-02679-9#citeas

Impressive Performance of Aldosterone Synthase Inhibitor in CKD

Tuttle et.al.. Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial, Lancet, Dec 15, 2023

This was a multinational, randomised, controlled, phase 2 trial. People aged 18 years or older with an estimated glomerular filtration rate (eGFR) of 30 to less than 90 mL/min/1·73 m2, a urine albumin to creatinine ratio (UACR) of 200 to less than 5000 mg/g, and serum potassium of 4·8 mmol/L or less, taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, were enrolled. Participants were randomly assigned (1:1) to 8 weeks of empagliflozin or placebo run-in, followed by a second randomisation (1:1:1:1) to 14 weeks of treatment with once per day BI 690517 at doses of 3 mg, 10 mg, or 20 mg, or placebo. Study participants, research coordinators, investigators, and the data coordinating centre were masked to treatment assignment. The primary endpoint was the change in UACR measured in first morning void urine from baseline (second randomisation) to the end of treatment. This study is registered with ClinicalTrials.gov (NCT05182840) and is completed.

Findings

Between Feb 18 and Dec 30, 2022, of the 714 run-in participants, 586 were randomly assigned to receive BI 690517 or placebo. At baseline, 33% (n=196) were women, 67% (n=390) were men, 42% (n=244) had a racial identity other than White, and mean participant age was 63·8 years (SD 11·3). Mean baseline eGFR was 51·9 mL/min/1·73 m2 (17·7) and median UACR was 426 mg/g (IQR 205 to 889). Percentage change in first morning void UACR from baseline to the end of treatment at week 14 was −3% (95% CI −19 to 17) with placebo, −22% (−36 to −7) with BI 690517 3 mg, −39% (−50 to −26) with BI 690517 10 mg, and −37% (−49 to −22) with BI 690517 20 mg monotherapy. BI 690517 produced similar UACR reductions when added to empagliflozin. Investigator-reported hyperkalaemia occurred in 10% (14/146) of those in the BI 690517 3 mg group, 15% (22/144) in the BI 690517 10 mg group, and 18% (26/146) in the BI 690517 20 mg group, and in 6% (nine of 147) of those receiving placebo, with or without empagliflozin. Most participants with hyperkalaemia did not require intervention (86% [72/84]). Adrenal insufficiency was an adverse event of special interest reported in seven of 436 study participants (2%) receiving BI 690517 and one of 147 participants (1%) receiving matched placebo. No treatment-related deaths occurred during the study.

Interpretation

BI 690517 dose-dependently reduced albuminuria with concurrent renin–angiotensin system inhibition and empagliflozin, suggesting an additive efficacy for chronic kidney disease treatment without unexpected safety signals.

Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)02408-X/

Regeneron ASH Slides: Dupixent+BCMAxCD3 Combination in Severe Allergy Interesting

Novel Treatment Approach for Severe Allergy: Linvoseltamab plus Dupixent

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ALLERGY

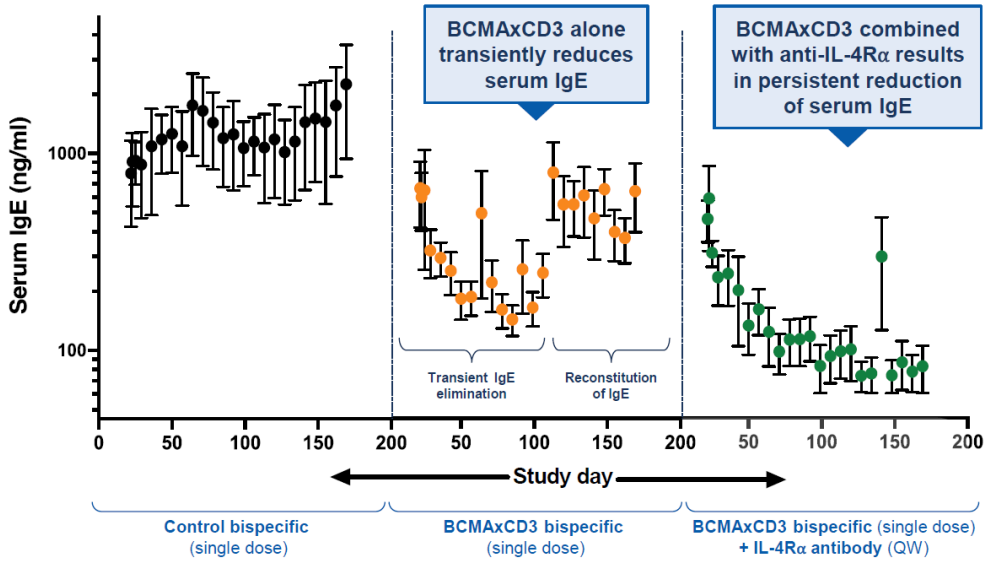
A therapeutic strategy to target distinct sources of IgE and durably reverse allergy

Andre Limnander, Navneet Kaur, Seblewongel Asrat, Carley Tasker, Anita Boyapati, Li-Hong Ben, John Janczy, Paulina Pedraza, Pablo Abreu, Wen-Chi Chen, Stephen Godin, Benjamin J. Daniel, Harvey Chin, Michelle DeVeaux, Karen Rodriguez Lorenc, Andres Sirulnik, Olivier Harari, Neil Stahl, Matthew A. Sleeman, Andrew J. Murphy, George D. Yancopoulos, Jamie M. Orengo*

Combination of linvoseltamab and Dupixent could eliminate IgE: potential groundbreaking approach for controlling severe allergy

- **Immunoglobulin E (IgE)** is the key driver of allergic reactions, such as food allergies:
  - Source: Long-lived plasma cells that produce IgE[2]
- **Linvoseltamab** (investigational BCMAxCD3 bispecific) effectively eliminates long-lived plasma cells, transiently eliminating IgE[1]
  - Unfortunately, these IgE-producing plasma cells are reconstituted from IgG memory B-cells that rapidly "switch" to IgE due to high levels of IL-4
- **Dupixent** blocks all IL-4Rα signaling, thus preventing reconstitution of IgE plasma cells, and resulting in permanent reduction of IgE[1,3]
- In atopic patients, **transient linvoseltamab** treatment with **Dupixent maintenance** has the potential of permanently eliminating IgE and durably reversing severe allergies, while allowing the restoration of other immunoglobulins

Transient plasma cell depletion with BCMAxCD3 plus sustained IL-4Rα blockade durably eliminates IgE production in cynomolgus monkeys[1]



Clinical program to explore combination in patients with severe food allergies to commence in 2024

7 [1]Limnander et al, Sci. Transl. Med. 2023.[2]Asrat et al, Sci. Immunol. 2020. [3]Le Floc'h et al, Allergy, 2020.

REGENERON

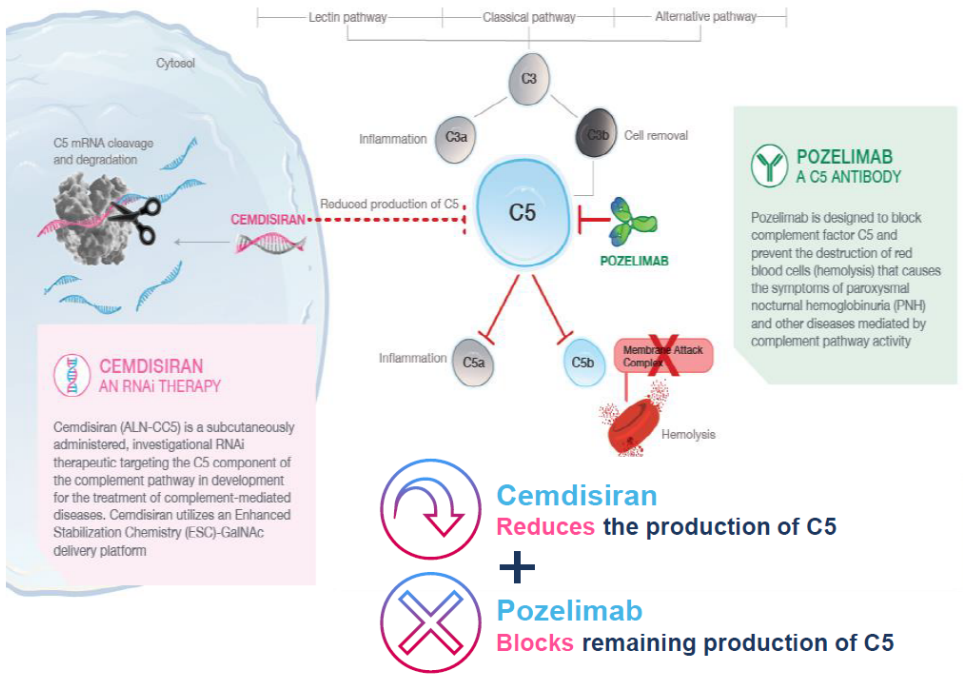
This slide contains investigational drug candidates that have not been approved by any regulatory authority.

Source: https://investor.regeneron.com/static-files/cb093452-9e37-41b0-9d52-c53b9275e99e

Regeneron ASH Slides: Complement mAb + siRNA for PNH, MG & GA

Regeneron pioneers Antibody + siRNA combination

Phase 3 Paroxysmal Nocturnal Hemoglobinuria (PNH) and Myasthenia Gravis (MG) programs advancing; Geographic Atrophy (GA) initiating shortly



Cemdisiran
Reduces the production of C5

+

Pozelimab
Blocks remaining production of C5

	Overview	Status
PNH	**Phase 3 ACCESS-1** Complement inhibitor-naïve patients	• Cohort A: ***New Data Presented Today*** • Cohort B: enrolling, data expected in 2026+
MG	**Phase 3 NIMBLE** Patients with symptomatic generalized myasthenia gravis	• Study enrolling • Data expected in 2025
GA	Patients with geographic atrophy secondary to age-related macular degeneration Systemic administration - *Single subcutaneous injection to treat both eyes*	• Phase 3 pivotal program initiating in 1H24

Our antibody + siRNA combination has the potential to improve on current standards of care across many diseases including complement mediated disorders:

- Complete and sustained C5 inhibition at a lower dose
- Reduced dosing frequency
- Convenient subcutaneous formulation

Regeneron is solely responsible for the development and commercialization of the c5 siRNA + monoclonal antibody combination. The C5 siRNA License Agreement contains a flat low double-digit royalty payable to Alnylam on our potential future net sales of the combination product and commercial milestones.

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REGENERON

This slide contains investigational drug candidates that have not been approved by any regulatory authority.

Source: https://investor.regeneron.com/static-files/cb093452-9e37-41b0-9d52-c53b9275e99e

Regeneron ASH Slides: GA Approach Could be Highly Differentiated

Geographic atrophy – combining our scientific capabilities in hematology with our leadership in ophthalmology

Pivotal Phase 3 program: plan to initiate in 1H 2024[1]

Program Overview

(Trials to initiate in 1H24)*

Two Phase 3 pivotal trials (multi-center, randomized, double-masked) in geographic atrophy secondary to age-related macular degeneration

- *Trial details coming soon*

	Current Geographic Atrophy Landscape	Regeneron Opportunity (Pozelimab + Cemdisiran Combo)
Market Opportunity	• ~1M diagnosed in U.S. • Increasing diagnosis and drug-treatment rates • 2 approved agents, many more in development	• Leadership in ophthalmology • Differentiated MOA
Route of Administration	• Q4W/Q8W intravitreal injections (IVT) • Bilateral disease requires injections in each eye	• Less invasive treatment option • Systemic administration enables treatment of bilateral disease • Q4W systemic treatment
Ocular Safety	• Reported cases of occlusive retinal vasculitis along with other ocular safety events	• Systemic administration potentially reduces risk of ocular safety events
Efficacy	• Approved agents lack evidence of maintenance of visual function	• Opportunity to demonstrate greater reduction in lesion growth rate along with preservation of visual function
Office Visits	• Administered in office by retinal specialist	• Potential for self-administration (subcutaneous coformulation)

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* Pending regulatory feedback

REGENERON

This slide contains investigational drug candidates that have not been approved by any regulatory authority.

Source: https://investor.regeneron.com/static-files/cb093452-9e37-41b0-9d52-c53b9275e99e

Regeneron ASH Slides: Formidable in Hematology

- **Linvoseltamab** demonstrated potential best-in-class efficacy in the primary analysis and is highly differentiated from competition, with U.S. filing planned by year-end 2023
- **Odronextamab** continues to show durable responses and a competitive profile ahead of a March 31, 2024 PDUFA date for FL & DLBCL, with studies ongoing in earlier lines of therapy
- **Pozelimab + cemdisiran** showed robust knockdown and clearing of C5 in an investigational cohort of patients from a pivotal study in PNH; this proof-of-concept paves the way for a potentially pivotal study in geographic atrophy to begin in Q1 2024
- Two **Factor XI** antibodies present opportunity to improve on current standard of care, with initial data to be shared in 2024 and plans for rapid advancement to pivotal studies
- **TMPRSS6** has the potential to be a first-in-class antibody treatment for iron overload disorders
- Leveraging next-generation CRISPR platform with Intellia: **NTLA-2001** pivotal Phase 3 study in ATTR-CM recently initiated; IND / CTA submission for **Factor 9** in Hemophilia B expected by year-end 2023

Making significant progress in hematology, with near-term approvals in heme-onc, multiple ongoing or near-term pivotal studies, and an emerging early-stage pipeline

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REGENERON

This slide contains investigational drug candidates that have not been approved by any regulatory authority.

Source: https://investor.regeneron.com/static-files/cb093452-9e37-41b0-9d52-c53b9275e99e

Tirzepatide Benefit Goes Away if Users Cease Therapy

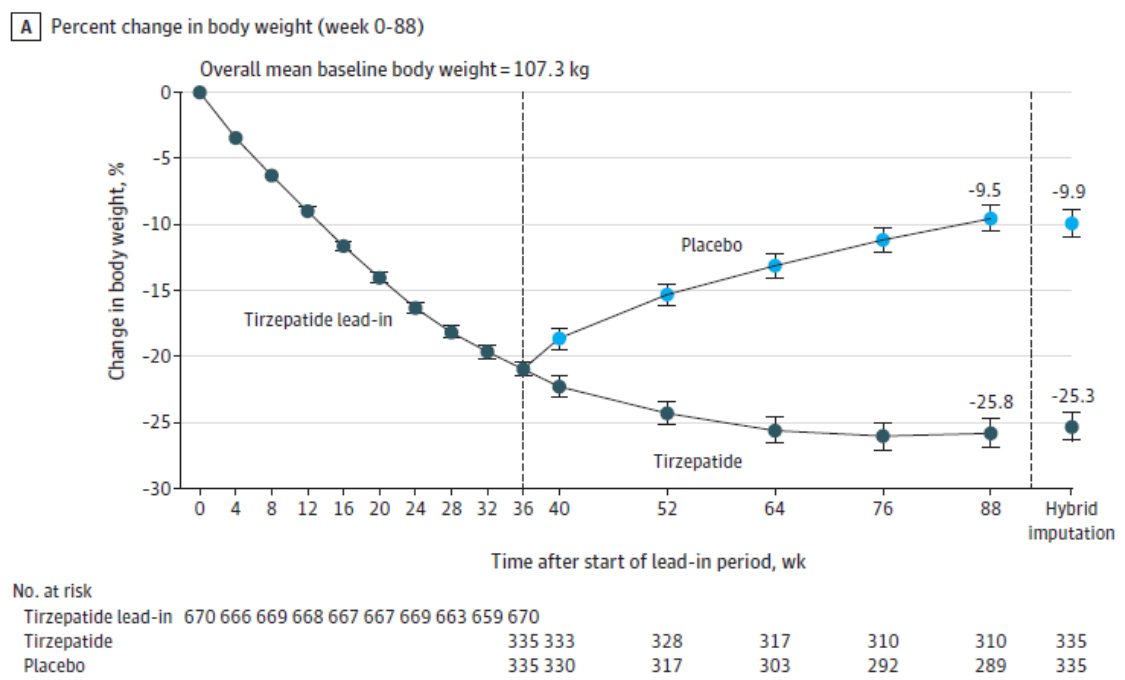
Louis Aronne et.al., "Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity The SURMOUNT-4 Randomized Clinical Trial," *JAMA*, Dec 11, 2023

Question: Does once-weekly subcutaneous tirzepatide with diet and physical activity affect maintenance of body weight reduction in individuals with obesity or overweight?

Findings: After 36 weeks of open-label maximum tolerated dose of tirzepatide (10 or 15 mg), adults (n = 670) with obesity or overweight (without diabetes) experienced a mean weight reduction of 20.9%. From randomization (at week 36), those switched to placebo experienced a 14% weight regain and those continuing tirzepatide experienced an additional 5.5% weight reduction during the 52-week double-blind period.

Meaning: In participants with obesity/overweight, withdrawing tirzepatide led to substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight reduction.

Figure 2. Effect of Tirzepatide vs Placebo on Body Weight and Waist Circumference

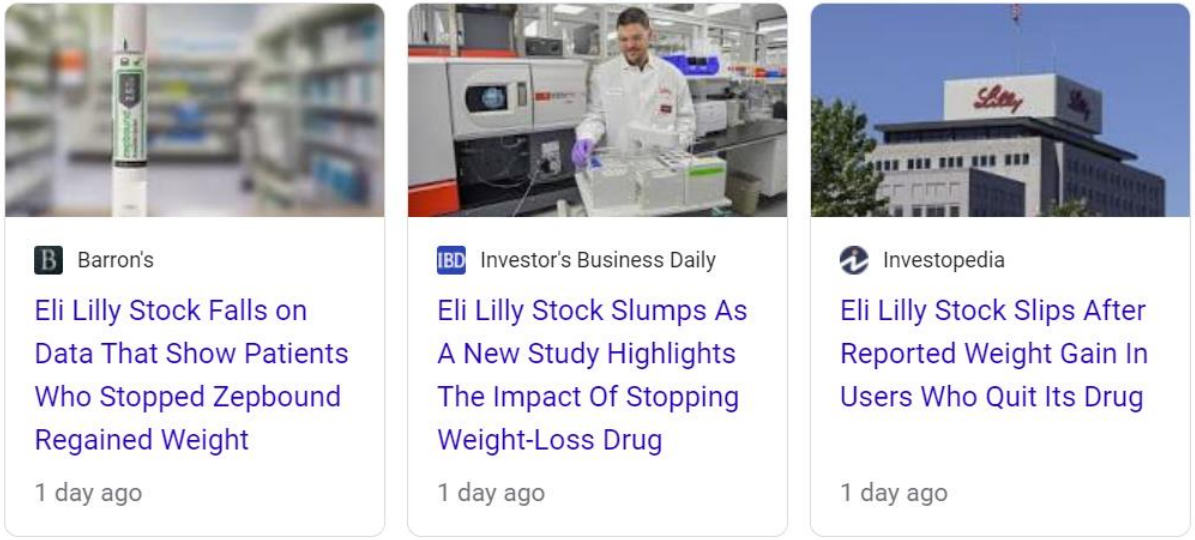


Source: https://jamanetwork.com/journals/jama/fullarticle/2812936

Sell Lilly. Really?

The recent study that users of tirzepatide regain lost weight after going off drug somehow caused Lilly shares to drop on Monday. To us, the question is whether this is a “bug or a feature”. In general, if one goes off any medicine for a chronic disease, one should expect the effect of the medicine go away. Lilly has never claimed otherwise. It’s a well understood truth in the pharma industry that drugs for chronic diseases are attractive because they need to be used for a long period of time.

News about Lilly, weight



Metaflammation In Obesity And Its Therapeutic Targeting

Schleh MW, Caslin HL, Garcia JN, Mashayekhi M, Srivastava G, Bradley AB, Hasty AH. Metaflammation in obesity and its therapeutic targeting. *Sci Transl Med*. Nov 22, 2023.

"Obesity-associated inflammation is a systemic process that affects all metabolic organs. Prominent among these is adipose tissue, where cells of the innate and adaptive immune system are markedly changed in obesity, implicating these cells in a range of processes linking immune memory to metabolic regulation. Furthermore, weight loss and weight cycling have unexpected effects on adipose tissue immune populations. Here, we review the current literature on the roles of various immune cells in lean and obese adipose tissue. Within this context, we discuss pharmacological and nonpharmacological approaches to obesity treatment and their impact on systemic inflammation.

Obesity is accompanied by chronic low-grade inflammation in metabolically impactful tissues such as adipose tissue (AT), liver, skeletal muscle, pancreatic islets, and the brain (Fig. 1). Inflammatory cytokine signaling can interfere with insulin signaling pathways leading to impaired glucose uptake and uncontrolled lipolysis, ultimately resulting in ectopic lipid storage and propagating insulin resistance in a vicious cycle. Although this Review will focus on AT, immune contributions to other organs are summarized in these excellent articles. AT immune cells serve a wide range of homeostatic functions that are modified upon obesity. In addition to the loss of their regulatory functions, heightened inflammatory phenotypes of immune cells in AT are typically met with systemic complications such as insulin resistance, hyperglycemia, and dyslipidemia—contributing to greater cardiometabolic disease risk. In addition, excessive pro-inflammatory cytokine release into the circulation is often present in obesity and metabolic syndrome, suggesting the induction of inflammatory processes as a clinical biomarker for metabolic disease risk."

Source: https://pubmed.ncbi.nlm.nih.gov/37992150/

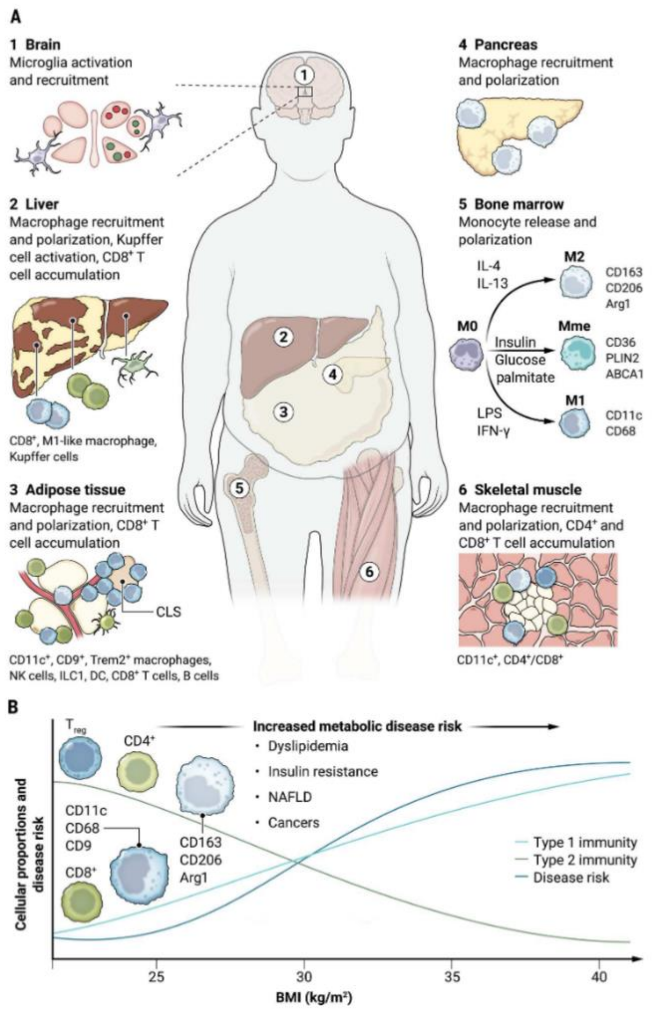


Fig. 1. Organ-specific inflammatory responses in obesity.(A) Inflammation is a coordinated immune response aimed to alleviate stresses induced by obesity and occurs in tissues such as liver, pancreas, adipose tissue, skeletal muscle, and the brain. Ectopic lipid accumulation in these tissues can initiate monocyte recruitment, macrophage polarization toward pro-inflammatory states, CD8+T cell accumulation, and excess accumulation of pro-inflammatory mediators. (B) Immune response to positive energy balance within the stromal compartments of these tissues increases type 1 immunity(light blue line) includingM1-like innate immune cells and CD8+Tcells. Conversely, obesity attenuates type 2 immunity(green line) phenotype, resulting in reduced M2-like innate immune cells as well as Treg and CD4+adaptive immune cells. This reciprocal relationship between type 1 and type 2 immunity in obesity is proposed to underlie tissue homeostasis and insulin resistance (dark blue line). CLS, crown-like structure; NAFLD, nonalcoholic fatty liver disease.

Promising Data from Vertex Pain Program

PNP program goals

- Develop a new class of medicines with a superior profile to existing therapies in PNP
- Secure broad PNP label

DPN Phase 2 study goals

- Establish proof-of-concept of the safety and efficacy of VX-548 over 12 weeks of treatment in DPN
- Further establish proof-of-concept of the safety and efficacy of the NaV1.8 inhibitor class in the chronic setting

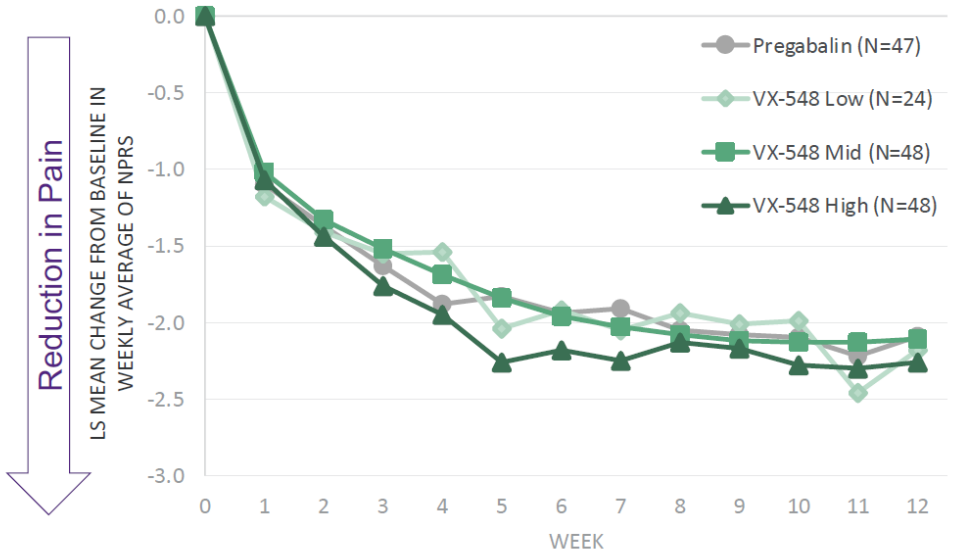
DPN Phase 2 results

- **Primary endpoint**: statistically significant and clinically meaningful reduction from baseline in weekly average pain scores across all VX-548 doses tested
- Favorable **safety and tolerability** profile for 12 weeks
- VX-548 exposure in three dose groups overlapping, and at the high end of the therapeutic range

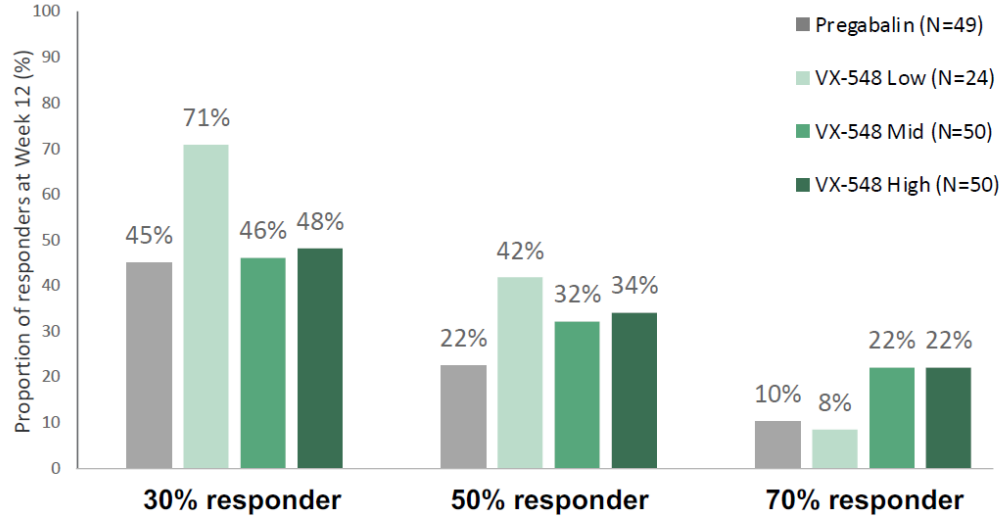
Source: https://investors.vrtx.com/events/event-details/vertex-pharmaceuticals-vx-548-phase-2-results-diabetic-peripheral-neuropathy

VX-548 Matched Efficacy of Pregabalin in Diabetic Peripheral Neuropathy

PRE-SPECIFIED ADDITIONAL ENDPOINTS INDICATE IMPROVED PAIN SCORES FOR PATIENTS TREATED WITH VX-548



Sustained reductions in pain throughout the treatment period for all VX-548 arms



With VX-548, more than 30% of patients achieved ≥50% reduction, more than 20% of patients in the mid- and high-dose groups achieved ≥70% reduction in pain scores

The pregabalin arm serves as a reference. Study was not designed or powered for comparisons between the VX-548 arms or between VX-548 and pregabalin.

Source: https://investors.vrtx.com/events/event-details/vertex-pharmaceuticals-vx-548-phase-2-results-diabetic-peripheral-neuropathy

Vertex Developed a CRISPR Cure. It's Already on The Hunt For Something Better.

Antonio Regalado, *MIT Technology Review*, December 15, 2023 (excerpt)

The company that just got approval to sell the first gene-editing treatment in history, for sickle-cell disease, is already looking for an ordinary drug that could take its place.

Vertex Pharmaceuticals has a 50-person team working "to make a pill that doesn't do gene editing at all," says David Altshuler, head of research at the Boston drug company.

"We're trying to out-innovate ourselves," he says.

Vertex won approval in the US to sell the world's first treatment using CRISPR, the gene-editing technique, on December 8. It took eight years to develop, and at huge expense. Regulatory documents filed with the government during the approval process exceeded a million pages.

Yet now that medicine's CRISPR era has begun, some of the technique's limitations are already visible.

The treatment, called Casgevy, is both tough on patients and hugely expensive. Patients must spend several weeks in a hospital as doctors remove, genetically edit, and then reintroduce their bone-marrow stem cells, which make blood. The treatment will cost $2.2 million, not including hospital costs, according to Vertex.

But it's unclear how many Americans will opt for gene editing. In an opinion column for MIT Technology Review, one patient who got the treatment, Jimi Olaghere, said the bone-marrow replacement an "intense months-long journey" that will create barriers to access.

"It's simultaneously a miracle and has a drawback that prevents wide use," says Geoffrey von Maltzahn, a partner at Flagship Pioneering, who leads biotech ventures but was not involved in the sickle-cell treatment. "That is a common duality."

In an interview with MIT Technology Review, Altshuler outlined three ideas Vertex is exploring to improve on its breakthrough CRISPR treatment.

One is to come up with a substitute for the intense chemotherapy that's used to kill a person's bone marrow and make space for the edited cells to take over. Vertex and other gene-editing companies, like Beam Therapeutics, say they are looking into gentler methods that could make the procedure easier for patients.

A second strategy Vertex and other companies are exploring is called "in vivo" editing. That's when gene-editing molecules are dripped directly into a person's veins, or even injected like a vaccine, no transplant needed.

To achieve in vivo editing for blood diseases, research groups are trying to develop homing systems—viruses or special nanoparticles—that would convey CRISPR directly to a person's blood-making stem cells. Such "single shot" editing concepts have won substantial support from the Bill & Melinda Gates Foundation, which thinks it could help solve sickle-cell and HIV in Africa. But it remains at an experimental stage, and some question if it will ever be possible.

The final idea is a conventional drug, the kind you swallow. That would be the easiest to distribute where it's needed. Angela Koehler, a biochemist at MIT, says "broadly accessible" drugs with a "low barrier to access" would have the greatest impact on sickle-cell disease globally.

"This does not diminish my excitement about the CRISPR-based approaches, but it partially explains the motivations of folks trying to develop 'traditional' drugs," says Koehler.

Source: https://www.technologyreview.com/2023/12/15/1085380/vertex-sickle-cell-pill-treatment/

Strong Rationale for HPV Screening in Women

Simms, K.T., Keane, A., Nguyen, D.T.N. et al. Benefits, harms and cost-effectiveness of cervical screening, triage and treatment strategies for women in the general population. *Nat Med* 29, 3050–3058 (2023).

In 2020, the World Health Organization (WHO) launched a strategy to eliminate cervical cancer as a public health problem. To support the strategy, the WHO published updated cervical screening guidelines in 2021. To inform this update, we used an established modeling platform, Policy1-Cervix, to evaluate the impact of seven primary screening scenarios across 78 low- and lower-middle-income countries (LMICs) for the general population of women. Assuming 70% coverage, we found that primary human papillomavirus (HPV) screening approaches were the most effective and cost-effective, reducing cervical cancer age-standardized mortality rates by 63–67% when offered every 5 years. Strategies involving triaging women before treatment (with 16/18 genotyping, cytology, visual inspection with acetic acid (VIA) or colposcopy) had close-to-similar effectiveness to HPV screening without triage and fewer pre-cancer treatments. Screening with VIA or cytology every 3 years was less effective and less cost-effective than HPV screening every 5 years. Furthermore, VIA generated more than double the number of pre-cancer treatments compared to HPV. In conclusion, primary HPV screening is the most effective, cost-effective and efficient cervical screening option in LMICs. These findings have directly informed WHO's updated cervical screening guidelines for the general population of women, which recommend primary HPV screening in a screen-and-treat or screen-triage-and-treat approach, starting from age 30 years with screening every 5 years or 10 years.

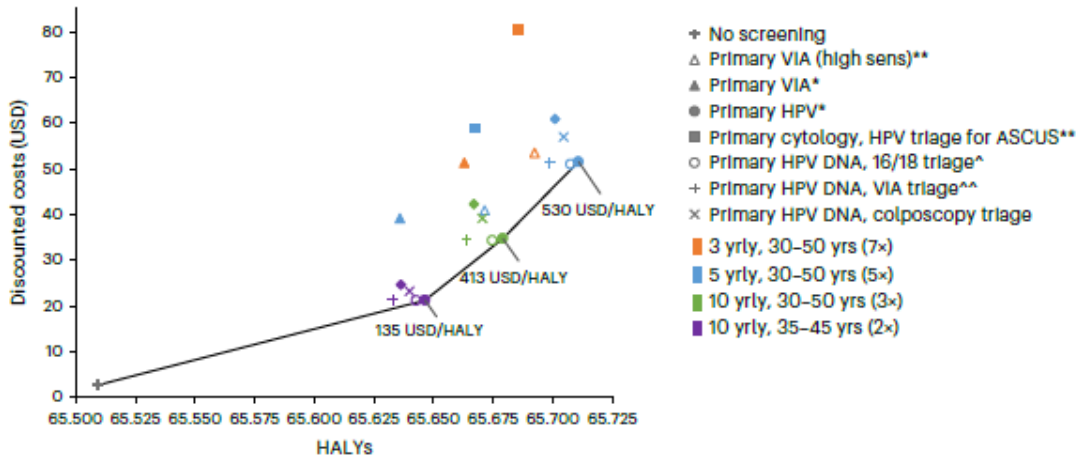


Fig. 4 | Cost-effectiveness plane depicting relationship between cost and HALYs for each screening strategy. The results are shown for alternative primary screening and triaging options and for different relevant screening intervals and age ranges. For those strategies appearing on the cost-effectiveness frontier, the incremental cost-effectiveness ratio is noted (cost per HALY). ASCUS, atypical squamous cells of undetermined significance; USD, US dollar ($); yrly, yearly; yrs, years. *All positive women treated after assessment of eligibility for ablative treatment. **Triage positive referred to colposcopy. ^^VIA triage positive women treated after assessment of eligibility for ablative treatment. ^HPV 16/18 positive women treated after assessment of eligibility for ablative treatment. Women positive for HPV types other than HPV 16/18 ('OHR') are triaged with VIA. +0% discount rate for effect, 3% discount rate for cost. As a reference point for a potential WTP threshold across 78 LMICs, the population-weighted average GDP per capita (pc) for 2019 across the 78 LMIC is US$2,093, and 69 of 78 (89%) of LMICs had a GDP pc equal to or above US$530 and 77/78 (99%) of LMICs had a GDP pc equal to or above US$136.

Source: https://www.nature.com/articles/s41591-023-02600-4

Underestimating AI in Healthcare

Daisy Wolf, Adela Tomsejova, Jay Rughani, and Vijay Pande, Andreesen Horowitz, Dec 13, 2023

Over the past half century, Wall Street was completely revolutionized by computers.

Not so long ago, human brokers on the stock exchange floor haggled to buy and sell every stock, writing their agreements on pieces of paper.

But in 1971, the NASDAQ, the world's first electronic stock exchange, was introduced. Electronic trading platforms followed in the 1980s, and the rise of the internet in the 1990s brought online brokerages like E*TRADE.

In the 2000s, technology radically changed not just how stocks were traded, but the decision behind which stocks to trade. Firms like Citadel, DE Shaw, and Two Sigma started to employ High Frequency Trading, computer algorithms capable of executing thousands of trades per second.

Quants, the algorithm writers, overtook master traders, who manually studied companies. Algorithms overtook hunches. The quant funds who led the pack raked in hundreds of billions of dollars.

100% of stock trades used to be made by humans. Today, 80% are made by computer algorithms.

AI is about to bring a similar revolution to healthcare.

Over the next few decades, at least half of the $4.3 trillion dollar American healthcare industry will be AI-driven.

AI will drive drug discovery, proposing medicines not yet dreamed up by man. AI will play a key role in diagnosis, helping humans know what's wrong sooner so they can get access to life-saving treatments. AI will change how care is delivered, as every human will have a world-class AI doctor in their pocket. And AI will eliminate a lot of the infuriating back office minutia in healthcare.

The markets are significantly undervaluing this opportunity.

This is partially because the market only knows non-AI healthcare companies today. In the digital health public markets, there are (1) tech-enabled service companies that have excelled in speedy go-to-markets, but have been low margin due to human labor, and (2) healthcare SaaS companies that are high-margin, but have struggled in go-to-market because of the difficulties of selling SaaS to human-loving healthcare entities.

AI health companies will not have these limitations. Margins will be way better than human services. Go-to-market will be far easier because AI companies can sell "AI humans," as opposed to fighting the uphill battle of selling software on which healthcare companies must train their overworked employees. Just like the internet completely transformed go-to-market for software companies, AI will transform go-to-market for healthtech companies.

To demonstrate the scale of the AI opportunity in healthcare, consider that publicly traded, profitable healthcare companies today (excluding pharma) generate $2.6 trillion in revenue and yet turn only $170 billion (~6.5%) of that revenue into profit. Imagine if these were able to achieve even a 15% increase in efficiency for having infinite access to low-cost AI "workers." That alone would drive $314 billion more in operating profit and ultimately $5.6 trillion in incremental enterprise value, even

Source: https://a16z.com/ai-healthcare-economics/

Underestimating AI in Healthcare (continued)

assuming no improvement in valuation multiples or growth in topline revenue. That would nearly triple the enterprise value of profitable public healthcare companies, and we believe that number is conservative!

So will this happen? What kinds of companies will capture this AI opportunity?

We can look to the introduction of the internet in the 1990s to see what happened in the last technological revolution. Pre-internet—in 1990—the biggest companies at the time were largely in non-tech industries like oil and gas (Exxon Mobil), pharma (Merck), CPG (Coca-Cola), auto (GM), and telecom (AT&T). While some small public companies in the 1990s like Apple and Microsoft embraced the internet and 500x-ed to become the biggest companies in the world, the vast majority of value accrued to startups founded as the internet was taking off. Today these startups—Alphabet, Meta, Amazon—have knocked all of the aforementioned biggest companies of 1990 off the top 10 list.

The same will likely happen with AI in healthcare. While some public healthcare companies will transform their strategies with AI and excel because of it, the vast majority of the value will accrue to AI health companies being started now.

Today resembles the early days of the internet. Will there be an AI bubble that bursts just like the dot com one did? Probably. But the best companies will rise from the ashes and transform human health.

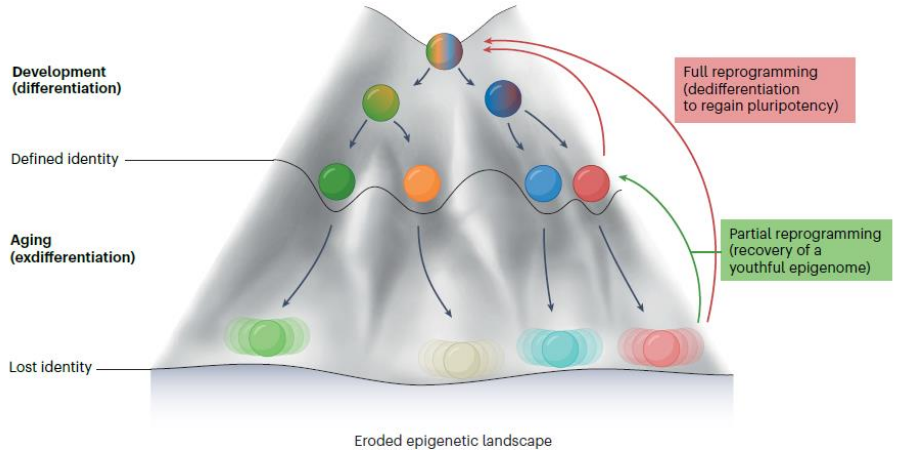
Source: https://a16z.com/ai-healthcare-economics/

The Information Theory of Aging

Yuancheng Ryan Lu, Xiao Tian & David A. Sinclair, *Nature Aging, Dec 15, 2023*

According to the information theory of aging (ITOA), the progressive deterioration of organismal function culminating in mortality, the process we call ‘aging’, is primarily attributed to the gradual loss of information established during development.

There are a number of predictions the ITOA makes, the testing of which will help to support or refute the theory. An increasing number of studies indicate that dysregulation of developmental pathways and loss of cell identity are common occurrences in mammalian aging. In aging human brain tissue, for example, there is a general upregulation and alteration of CpG methylation near developmental genes. As our mouse model with inducible epigenetic changes showed, developmental genes are hotspots for epigenetic changes during aging, including those caused by DSBs10. We suggested this might occur because developmental genes are activated as part of the RCM response when cells are damaged, as a way to temporarily increase cell repair and survival. This on-and-off cycling makes them more susceptible to epigenetic changes over time. A recent interpretation of these findings that aging is a programmed extension of development, a proposition that is in alignment with a recent analysis showing that developmental genes are hotspots for DNA methylation changes. If so, then enhancing DNA DSB repair would be unlikely to affect the rate of epigenetic aging or lifespan. Yet, long-lived species have more efficient DSB repair and overexpression of Sirt6, a DSB repair factor, makes mice live longer, arguing that DSB repair is a part of the normal aging process and aging is not simply an extension of development. The ITOA predicts that reducing other types of cellular damage that alter the epigenome will also lead to lifespan extension.



The epigenetic landscape of development, aging and rejuvenation In the original Waddington landscape metaphor, valleys represent cell-type specificity, starting with a pluripotent cell at the highest point and ending at the lowest point when a differentiated state is reached. During development, a complex set of epigenetic changes, including DNA methylation and posttranslational histone modifications, dictates patterns of gene expression, providing cells with a defined cellular identity. By extending this landscape forward to include post-developmental events, we can represent changes to celltype specificity that occur during aging. Distinct from another theory suggesting aging is an intrinsic feature of the developmental program103, the ITOA posits that DNA damage and various cellular insults lead to temporary alterations in the epigenetic landscape that induce a specific pattern of gene expression aimed at enhancing cell survival. These changes, however, are not fully reset after insults, leading to the landscape becoming eroded over time and cellular identities drifting away from their original state of differentiation10, a process called exdifferentiation or dysdifferentiation.

Source: https://www.nature.com/articles/s43587-023-00527-6

Mechanisms, Pathways and Strategies for Rejuvenation Through Epigenetic Reprogramming

Cipriano, A. et al. Mechanisms, pathways and strategies for rejuvenation through epigenetic reprogramming. *Nat Aging* (2023).

Over the past decade, there has been a dramatic increase in efforts to ameliorate aging and the diseases it causes, with transient expression of nuclear reprogramming factors recently emerging as an intriguing approach. Expression of these factors, either systemically or in a tissue-specific manner, has been shown to combat age-related deterioration in mouse and human model systems at the cellular, tissue and organismal level. Here we discuss the current state of epigenetic rejuvenation strategies via partial reprogramming in both mouse and human models. For each classical reprogramming factor, we provide a brief description of its contribution to reprogramming and discuss additional factors or chemical strategies. We discuss what is known regarding chromatin remodeling and the molecular dynamics underlying rejuvenation, and, finally, we consider strategies to improve the practical uses of epigenetic reprogramming to treat aging and age-related diseases, focusing on the open questions and remaining challenges in this emerging field.

Source: https://www.nature.com/articles/s43587-023-00539-2

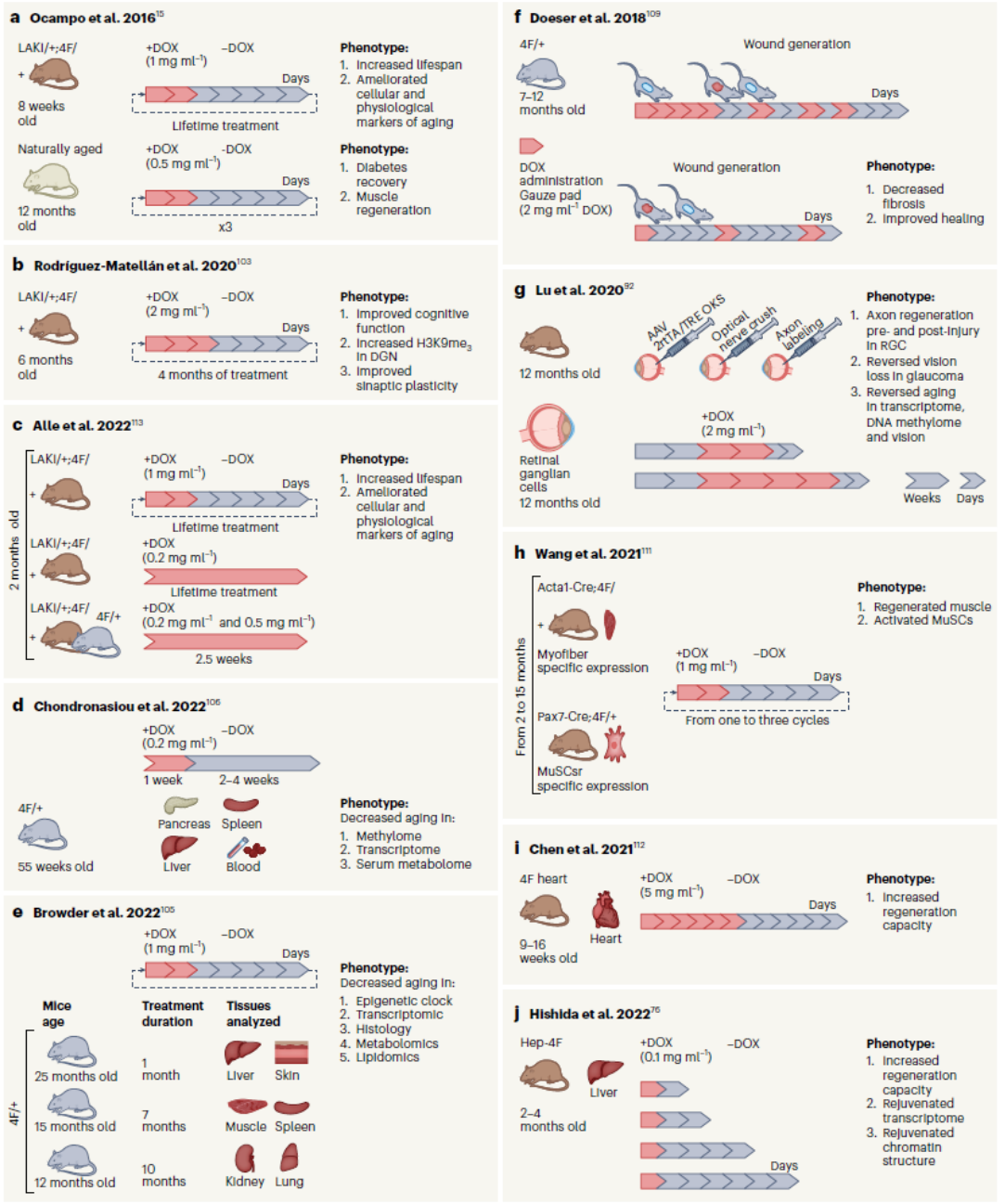


Fig. 3 | Summary of detailed in vivo whole-organism partial reprogramming protocols. a–e, Whole-organism partial reprogramming for Ocampo et al. 2016 (ref. 15) (**a**), Rodríguez-Matellán et al. 2020 (ref. 103) (**b**), Alle et al. 2022 (ref. 104) (**c**), Chondronasiou et al. 2022 (ref. 106) (**d**) and Browder et al. 2022 (ref. 105) (**e**). **f–j**, Tissue-specific partial reprogramming for Doeser et al. 2018 (ref. 109) (**f**), Lu et al. 2020 (ref. 92) (**g**), Wang et al. 2021 (ref. 111) (**h**), Chen et al. 2021 (ref. 112) (**i**) and Hishida et al. 2022 (ref. 76) (**j**). Each panel shows the strain of mice used and the respective ages (left), the tissues analyzed and the protocol of partial reprogramming (center) and the phenotype analyzed (right). Pink and grey arrows indicate days or weeks (specified below or above the arrow) of DOX administration and DOX removal, respectively. Created with BioRender.com.

Iron Accumulation Drives Fibrosis

Maus M et.al., "Iron accumulation drives fibrosis, senescence and the senescence-associated secretory phenotype," *Nature Metabolism*, Dec 14 2023.

Fibrogenesis is part of a normal protective response to tissue injury that can become irreversible and progressive, leading to fatal diseases. Senescent cells are a main driver of fibrotic diseases through their secretome, known as senescence-associated secretory phenotype (SASP). Here, we report that cellular senescence, and multiple types of fibrotic diseases in mice and humans are characterized by the accumulation of iron. We show that vascular and hemolytic injuries are efficient in triggering iron accumulation, which in turn can cause senescence and promote fibrosis. Notably, we find that senescent cells persistently accumulate iron, even when the surge of extracellular iron has subdued. Indeed, under normal conditions of extracellular iron, cells exposed to different types of senescence-inducing insults accumulate abundant ferritin-bound iron, mostly within lysosomes, and present high levels of labile iron, which fuels the generation of reactive oxygen species and the SASP. Finally, we demonstrate that detection of iron by magnetic resonance imaging might allow non-invasive assessment of fibrotic burden in the kidneys of mice and in patients with renal fibrosis. Our findings suggest that iron accumulation plays a central role in senescence and fibrosis, even when the initiating events may be independent of iron, and identify iron metabolism as a potential therapeutic target for senescence-associated diseases.

Source: https://pubmed.ncbi.nlm.nih.gov/38097808/

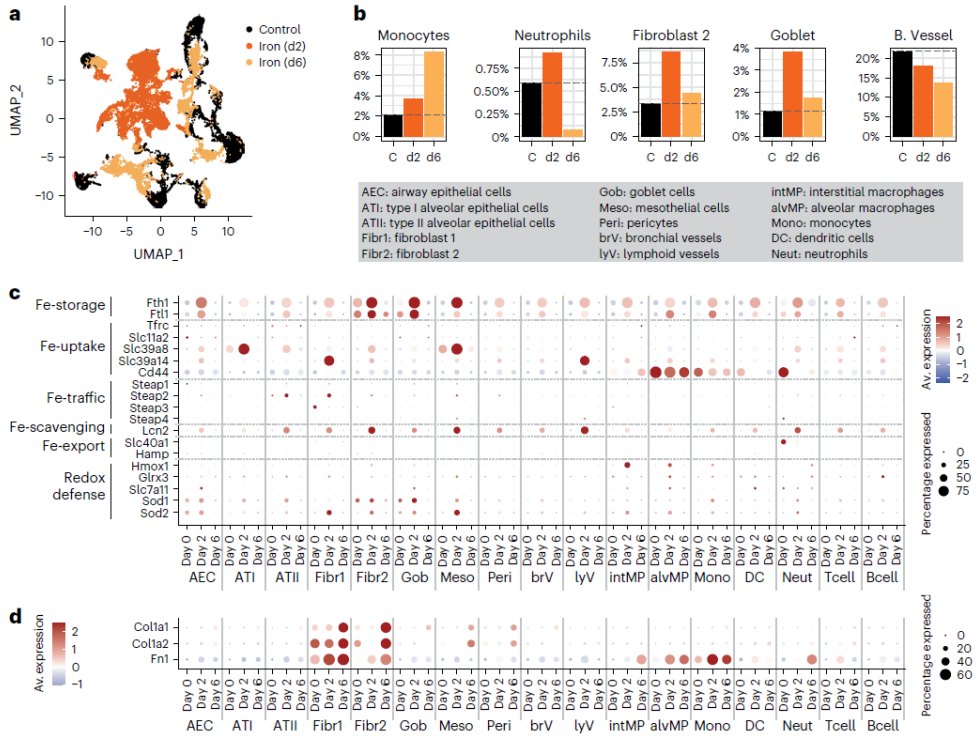


Fig. 6 | Single-cell dynamics of iron accumulation in lung fibrosis.
a–f, snRNA-seq analysis of cells from lungs of control mice receiving intratracheal administration of PBS (6 d; n = 1) and mice receiving iron intratracheally (500 nM) 2 d (n = 1) or 6 d (n = 1) before analysis. UMAP visualization of cells (a). Percentages of cell types with robust change in abundance in response to iron (b). Average expression and percentage of cells expressing genes regulating iron homeostasis (c), type I collagens (d) and fibronectin in individual cell types. Dot plot showing the scaled average expression of an individual gene across all cell types and conditions. Percentage expressed shows the percentage of cells that showed detectable expression of the analyzed gene within a specific cell type at a specific condition. Scatter-plots showing the expression of a cell proliferation signature

Expectations for 2024

Janus Henderson: Healthcare Stocks: Positioned for a Smoother Ride in 2024?

Andy Acker and Dan Lyons, Janus Henderson, Nov 29, 2023

In the wake of recent underperformance, healthcare is entering the new year with compressed valuations just as innovation picks up and a post-COVID reset winds down. That should make for a positive outlook, say Portfolio Managers Andy Acker and Dan Lyons.

Looking ahead, we think the road could begin to smooth out. Attractive valuations, numerous medical advances, and positive long-term demographic trends have put the sector into a position of unusual strength in our view – with the potential to reward long-term investors.

Normalizing markets

For much of 2023, the healthcare sector had to nurse a COVID-19 hangover, as some companies saw their revenues decline sharply following the end of the public health emergency. Demand for diagnostics and the "picks and shovels" used to manufacture vaccines, for example, waned, weighing on tools and services companies, which also suffered from excess inventories at their clients. In biopharma, sales of COVID-19 vaccines and therapeutics topped $90 billion in 2022, roughly 20% of all blockbuster biotech drug sales that year.

This deceleration was necessary and something we expected. It should also start to improve as we head into 2024, making for easier year-over-year sales comparisons. Encouragingly, excluding COVID products, many biopharma earnings have continued to grow. Firms have also acted to right-size cost structures, which is expected to support profit margin expansion over the coming year. In short, after a rare year of earnings declines for the healthcare sector, we expect earnings to stage a recovery in 2024.

Clarity around GLP-1s

It was hard to miss the enthusiasm for a new class of weight-loss drugs known as GLP-1 agonists this year. These therapies work by mimicking gut hormones that regulate appetite and have achieved unprecedented levels of weight loss in patients – anywhere from 15% to more than 20%.

Data suggest the drugs could have other health benefits, too. In clinical trials, Wegovy – the first GLP-1 indicated for obesity – reduced the risk of heart attack, stroke, and death in people with cardiovascular disease and obesity by 20%. GLP-1s have been marketed for more than a decade for diabetes, and additional beneficial effects are still being uncovered, including in cardiovascular, liver, and kidney diseases.

We believe GLP-1s could be the biggest market opportunity yet in biopharma, with sales topping $100 billion before the end of the decade. But the drugs have also raised alarm bells about the future of medical device products and drugs that treat related diseases, anything from sleep apnea and heart disease to orthopedics.

We think the reality will be far more nuanced and that the knee-jerk reaction, which has driven down medical device and select biotech stocks, is overdone. For one, it could take decades for GLP-1s to bend demand curves. For an overweight 60-year-old with osteoarthritis, a GLP-1 prescribed today is unlikely to eliminate the need for a knee procedure since osteoarthritis may have built over decades and is largely irreversible. What's more, GLP-1s might help drive demand if people live longer (as device usage is heavily related to age) or enable more people to qualify for procedures, thanks to weight loss.

In short, we think GLP-1s represent a tremendous medical advancement, but we are not writing off the rest of the sector. On the contrary, we think many affected companies are still set up for long-term growth given the complexity of healthcare and the high unmet medical need.

Source: https://www.janushenderson.com/en-us/advisor/article/healthcare-stocks-positioned-for-potentially-smoother-ride-in-2024/

Janus Henderson on 2024 (continued)

Janus Henderson INVESTORS

Attractive valuations

Volatility has pushed down valuations of tools and device firms, as well as traditionally defensive areas of healthcare, such as managed care. These stocks hit bumps in 2023 as new regulation lowered reimbursement rates in Medicare Advantage (the private version of the federal health plan for the elderly) and reduced enrollment in Medicaid (which provides health coverage for low-income households). Rising utilization costs were another challenge, as people once again leaned on their insurance to catch up on routine medical care (yet another COVID hangover).

But these issues could find a resolution in 2024. Insurers, for instance, can raise premiums annually to offset costs (and have done so in recent months). An aging population makes Medicare Advantage still the fastest growth area of the industry, while former Medicaid members could qualify for federally subsidized private insurance.

In biotech, many stocks trade at even bigger discounts – by some measures, the biggest we have ever seen. After a record drawdown in 2021 and 2022, small- and mid-cap biotech stocks got caught up in the sell-off of long-duration growth assets as 10-year Treasury yields started to rise in 2023. This is not unusual, as we tend to see biotech underperform amid rising rates, with less focus on stock-specific developments. But some market moves seemed extreme as even positive news – such as one company's announcement of approval for its new therapy for phosphate management in dialysis – would sometimes result in negative returns

Once again, we think the selling is overdone. While the industry was due for some rationalization, many companies are making significant medical breakthroughs. In fact, in 2023, more than 55 novel therapies were approved by the Food and Drug Administration, with dozens more applications pending review as of mid-November.3 At that pace, it could be a record year for drug launches.

Furthermore, many of these new drugs address large disease categories where few treatment options existed before, including Alzheimer's and Duchenne muscular dystrophy (an often fatal, muscle-wasting hereditary disease that afflicts children). These drugs are now beginning what could be a 10-year period of revenue growth, given patent protections. More breakthroughs are on the horizon, too, including the first oral therapy for fatty liver disease and a new type of treatment that inhibits KRAS mutations, which are widely found in pancreatic, colorectal, and lung cancer tumors.

An improving rate backdrop

Meanwhile, an end to the Federal Reserve's rate-tightening cycle could be a boon to biotech. Rate cuts could also be welcome even if they signal we are headed for an economic slowdown or recession. Historically, biotech has tended to outperform during such periods, benefiting from a lower discount rate and, most importantly, innovative drivers that are independent of economic growth.

In fact, the healthcare sector overall has held up well during downturns. Since 2000, the MSCI World Health Care Index, on average, has captured just 47% of the downside when the MSCI World Index fell 15% or more.4 With valuations now generally attractive across the sector, we think healthcare could be well positioned to offer resilience should the economic outlook deteriorate.

That kind of defense can be rare to find in a sector that can also offer substantial growth opportunities. We think it all adds up to a potentially better ride for healthcare investors in 2024.

Source: https://www.janushenderson.com/en-us/advisor/article/healthcare-stocks-positioned-for-potentially-smoother-ride-in-2024/

Eleven Clinical Trials that Will Shape Medicine in 2024

Carrie Arnold and Paul Webster, *Nature Medicine*, Dec 7, 2023

Base editing for hypercholesterolemia	**AI for early lung cancer diagnosis**	**T cell vaccine for HIV**	**App therapy for perinatal depression**
Stem cells for Parkinson's disease	**Machine learning for patient triage**	**Immunotherapy for melanoma**	**R21 malaria vaccine**
Enhertu ADC for brain metastasis	**Intervention model for infant mental health**	**CT screening for lung cancer**	

Source: https://www.nature.com/articles/s41591-023-02699-5

The Weight Loss Drug Boom Isn't Over Yet — Here's What to Expect in the Year Ahead

Annika Kim Constantino, *CNBC*, Dec 17, 2023 (excerpt)

Weight loss drugs exploded into the public eye this year, and 2024 will bring more change to the evolving market.

The drugs skyrocketed in popularity in 2023 as they helped patients shed significant weight, despite hefty price tags, mixed insurance coverage and a handful of unpleasant side effects.

Demand for the drugs is unlikely to slow down in 2024, especially as treatments gradually become more accessible. Much of Wall Street believes the weight loss drug market will only expand, with some analysts projecting that it will be worth $100 billion by the end of the decade. Goldman Sachs analysts expect 15 million U.S. adults to be on obesity medications by 2030.

But next year, investors will be watching how the dominant players in the market, Novo Nordisk and Eli Lilly, navigate supply issues plaguing their treatments. Patients have been struggling to get their hands on Novo Nordisk's weight loss injection Wegovy, its diabetes treatment Ozempic, and Eli Lilly's diabetes injection Mounjaro.

Analysts expect supply constraints to improve but note that the broader issue will take years to resolve.

Outside of supply headwinds and the lack of broader insurance coverage for weight loss drugs, Novo Nordisk and Eli Lilly have a big year ahead of them.

Source: https://www.cnbc.com/2023/12/17/weight-loss-drugs-2024-expectations-for-wegovy-ozempic-zepbound.html

Novo Nordisk could win approvals for expanded use of Wegovy in the U.S. and Europe. Eli Lilly's newly approved weight loss drug, Zepbound, could garner more than a billion dollars in sales in its first year on the market.

Both companies are also expected to release new data that could show other potential health benefits of their drugs beyond weight loss and diabetes management, which may increase insurance coverage down the line.

Next year may mean even more to the other companies hoping to join what's so far been a two-horse race to make weight loss treatments.

New drug data from Pfizer and Amgen, and the potential for more buyouts or collaborations between larger companies and smaller makers of obesity drugs, could alter the market's competitive landscape in the coming months.

Novo Nordisk during its third-quarter earnings call in November said it is "looking at significantly scaling our supply" of Wegovy in the U.S. in 2024. TD Cowen analyst Michael Nedelcovych told CNBC that the company during the call appeared to suggest that such a change wouldn't look like a big jump in supply but rather steady improvements over time.

Supply could increase more significantly years from now: Novo Nordisk in November said it would invest $6 billion to expand its manufacturing facilities in Denmark, noting it will finish construction from the end of 2025 through 2029. The company also said it would spend around $2.3 billion to expand another production site in France.

Predictions for 2024 from Venrock

Brian Roberts and Bob Kocher, Venrock, "AI will live up to the hype and more unicorns will lose their horns: 10 health care predictions for 2024 from top investors," Nov 2023. (excerpt)

Now on to 2024. Here is what we think is going to happen:

1. GLP-1s prove cost-effective and are prescribed as freely as statins
Wegovy's cardiovascular outcomes data was stunning, and now there is the CKD trial success. The whole class will ride these cardiovascular disease benefits and future data will reveal benefits for liver disease, some cancers, and as prophylaxis for pre-diabetics. The effect could all be due to weight loss–no matter how you get there. We think the magnitude of their benefits, excellent safety profiles, and high level of demand for weight loss will lead GLP-1s (once cost-effectiveness is known) to become the next statins. In five to seven years, oral formulations will make this even more the case, but competition and direct-to-consumer advertising will take much of the economics out of the class for pharma.

2. Nothing happens to Pharmacy Benefit Managers (PBMs)
Despite pharma buying ads accusing PBMs of being middlemen that are restricting access to medication and driving up drug prices by adding fees (notably 53% of the price of Insulin are PBM fees), and endorsing nine bills aimed at curtailing PBM practices, we think nothing will pass and nothing will change. It is better politics, in an election year, to vilify PBMs rather than disrupt them. Any change to PBMs will be met with worries that patients will not get their medicines. Moreover, bills that go after PBMs may not lead to lower prices for patients. As Trump learned when he proposed the elimination of rebates for Part D drugs, it would only lead to higher premiums.

3. Supreme Court protects access to Mifepristone
While the Supreme Court made conservatives happy with the Dobb's decision, we think that they will not go further by trying to pull Mifepristone from the market. We do not think that the court will take authority to approve and regulate drugs away from the FDA.

4. Payors play hardball with hospitals and drop systems who refuse to negotiate
Normally, after much bluster, hospitals win payor negotiations since payors are unwilling to drop hospitals from their networks. This is because employers insist on broad networks which leads to payors acquiescing when push comes to shove.

5. CMS completes drug price negotiations on 10 drugs by the 9/1/24 deadline
Despite lawsuits, needing to hire a team to build a new capability, and threats of government shutdowns, we believe that CMS will hit the deadline and successfully negotiate lower prices on the first 10 drugs they tackle.

6. Medicare Advantage plans' underperformance leads to leadership turnover
Poor acquisitions, failing to hit 4 stars, and sub-par risk adjustment will likely decimate several income statements. Centene and CVS/Aetna have struggled with Stars and this will cost these plans many millions–or even billions.

7. The Federal Trade Commission (FTC) sets its sights on healthcare monopolies
The mere mention of the word "Epic" normally elicits a groan from anyone who uses, connects with or exchanges data in healthcare.

8. More unicorns lose their horns, deemed to be bad businesses
The frothy private markets of 2020-2021 created 66 health tech unicorns–and many of these companies raised money at nonsensical multiples. Some will grow into their multiples since 50x revenue becomes a more plausible 10x revenue multiple after 4 years of 50% growth.

9. AI/large language models (LLMs) are useful and adopted for many use cases
At first glance, this may seem obvious. The non-obvious part of our prediction will be the breadth of use cases ranging from cancer genomic data interpretation, call center support, chronic disease management, and clinical documentation. Unlike many new healthcare technologies, user satisfaction will be high. AI/LLMs will live up to the hype.

10. VC-backed brick-and-mortar healthcare services startups crumble
In recent years, Warby Parker-esque-inspired retail healthcare was all the rage, led by One Medical. However, it turns out that capital-intensive, low-margin structures and high patient churn make these businesses smaller and harder to scale than people thought–especially in a world with a higher cost of capital and where growth is too expensive.

Source: https://www.cnbc.com/2023/12/17/weight-loss-drugs-2024-expectations-for-wegovy-ozempic-zepbound.html

Deloitte Survey: 2024 Outlook for Life Sciences GenAI, Drug Prices, Economy Likely to Influence Strategy

By Pete Lyons, National Life Sciences sector leader, Deloitte Consulting LLP, and Leena Gupta, senior manager, Deloitte Center for Health Solutions, Deloitte Services LP

Digital transformation, generative artificial intelligence (AI), and the adoption of virtual health/digital tools are the three trends most likely to impact medical device manufacturers in 2024, according to a survey of C-suite executives conducted by the Deloitte Center for Health Solutions. Overall, biopharmaceutical executives expect that drug pricing, regulatory changes, and out-of-pocket costs for consumers to have the most significant impact on their companies next year (click here to see complete results of our survey). Deloitte's 2024 Health Care and Life Sciences Outlook is based on responses from 121 C-suite executives representing U.S. biopharmaceutical companies, medical device manufacturers, health systems, and health plans.

Drug pricing is top concern for biopharma

Every pharmaceutical executive who participated in this year's Outlook survey expects drug pricing to have either a "great impact" (58%) or a "moderate impact" (43%) on their organization. We're not surprised by the responses. In August, the Centers for Medicare and Medicaid (CMS) identified the first high-cost drugs that will be subject to price negotiation under the Inflation Reduction Act (IRA). (See How might IRA's drug-pricing provisions affect stakeholders.) In addition to that federal law, a growing number of states adopting Prescription Drug Affordability Boards (PDABs) to manage drug costs. PDABs seek to cap and control what drug manufacturers can charge for their products. In addition, more than 20 states have passed drug-pricing transparency laws.

While the IRA was signed into law more than a year ago, some drug manufacturers might have been surprised by the drugs that were picked for negotiation and have begun to understand the impact the law could potentially have on their pipelines. The increased focus on drug prices this year seems to have caused some trepidation across the industry and there are questions about what it might mean for research and development (R&D) prioritization. There are also concerns about the impact new laws and regulations could have on products already on the market, according to survey results. Over the next year, we expect that biopharma companies will focus on cell and gene therapies, new oncology regimens, and therapies to treat rare diseases. These products are associated with comparatively high per-patient pricing.
6 more factors likely to influence biopharma and medtech in '24

Based on our survey findings, and conversations with our life sciences clients, here's what may have the most profound impact on biopharmaceutical companies and medtech manufacturers in 2024:

Generative AI: Last year, we suggested that the rise of AI was a trend to watch (see 2023 Outlook for Life Sciences). More than 90% of biopharma and medtech respondents said they expect generative AI to have an impact on their organizations next year. A year ago, it seemed like few people had even heard of generative AI. It now dominates many of the conversations we have with

Source: https://www2.deloitte.com/us/en/blog/health-care-blog/2023/outlook-for-life-sciences.html

Deloitte Survey (continued)

leaders from life sciences companies. A majority of life sciences companies surveyed (66%) said they are experimenting with generative AI to test ideas and to build use-cases. They are exploring ways the technology could automate repetitive back-office functions, reimagine supply chains, or support compliance and regulatory affairs (see Can Life Sciences companies unlock the full value of GenAI?). Twenty-five percent of biopharma executives said their companies have established governance and an oversight structure for generative AI and another 50% expect to have something in place within the next 12 months. Nearly 70% of biopharma respondents said using generative AI for research and discovery is a top priority. Medtech executives appear to be slightly behind with 20% having governance and an oversight structure in place, and 57% expecting to get there in 2024. About half of our medtech respondents said research and discovery is a priority for generative AI next year. About 25% of medtech executives, and 18% of biopharma executives, said they are waiting for more evidence before they invest in generative AI. According to results from our Medtech Digital Innovation survey, more than 80% of medtech leaders said their organization's largest digital investments were going toward AI.

The economy and inflation: Last year, half of all life sciences respondents expected that inflation would have a profound impact on their organizations as consumers put off purchasing prescription drugs or medical devices. Inflation appears to have stabilized, falling from 4.9% in 2022 to 3.6% this year.1 And the economy hasn't fallen into a recession as some economists had predicted.2 However, 36% of this year's life sciences respondents expect the economy and inflation will continue to influence their strategy in 2024. Among medtech manufacturers, 43% said the economy and inflation would have a "great impact" on their 2024 strategy, and 57% thought it would have a "moderate impact." Respondents from the biopharma side were a bit more optimistic, with 33% expecting a "great impact" and 60% predicting a "moderate impact."

Investment in innovations: Last year, 95% of biopharma executives said the development of next-generation therapies and other innovative products was a top priority for 2023. This year, 20% biopharma respondents said investing in innovative products was a top priority for 2024, and 23% said it was not important. However, about 30% of biopharma respondents pointed to R&D productivity as a key priority. And while 38% of this year's medtech executives said R&D productivity was a top strategy, that percentage is down from 75% a year ago. The drop this year is a bit surprising given that innovation is generally at the heart of the life sciences. Despite the decline from 2023, it seems likely that investing in innovation and improving R&D productively will remain priorities.

Workforce and talent: The workforce shortages that continue to affect hospitals and health systems have not had the same impact on life sciences companies. In our meetings with life sciences leaders, the topic of talent and workforce challenges typically doesn't come up as often as it did a year ago. A year ago, the sector was still feeling aftershocks from the COVID-19 pandemic, and medtech and biopharma executives predicted talent challenges and shortages would have an impact on their 2023 strategy. There appears to be less concern about workforce heading into 2024. But that doesn't mean talent is not important. What seems to matter is the type of talent. The battle for scientific talent in life sciences tends to be an important topic because it can drive competitive advantage.

Health equity: Sixty percent of biopharma executives, and 57% of medtech executives, said addressing health equity would influence their strategies in 2024. The percentages are down a little from a year ago, which might be a reflection of recent regulations. An omnibus spending bill enacted in late 2022 (Public Law 117-328) requires diversity strategies for clinical trials used by the Food and Drug Administration (FDA) to decide whether drugs are safe and effective. Nearly 80% of patients who participate in clinical trials are white, according to a multi-year FDA study. Moreover, less than 20% of approved drugs have data that evaluated the treatment benefits or side-effects on Black patients.

Employer Weight Management Programs

Huge Demand for GLP-1's at Work

- Employees want access to obesity drugs in a huge way
- Excess weight is a big problem in employment ages (20 to 60)
- Overweight employees, on average, have twice the healthcare costs as healthy employees
- Most health plans have heavy access restrictions to GLP-1s. Only 25% of employees today have plans that cover GLP-1s
- A recent survey found that 44% of people with obesity would change jobs to gain coverage for treatment.
- And more than half of workers would stay at a job they didn't like to retain that coverage, according to the survey from the Obesity Action Coalition.

Employers Wrestling with Covering Weight-Loss Drugs

GBS Benefit Group, Dec 12, 2023

The explosion in demand for new, costly and highly effective weight-loss and diabetes drugs is poised to play an outsized role in increasing the cost of health care, and in turn, health insurance in America. These groundbreaking drugs — the most popular sold under the brand names Mounjaro, Ozempic and Wegovy — are partly to blame for overall pharmaceutical benefit costs jumping 8.3% in 2023, compared to an increase of 6.4% in 2022, according to a report by Mercer.

The effects are amplified because of the high cost of these drugs — around $1,000 a month — as well as the growing legion of patients being prescribed them. On the other hand, these GLIP-1 drugs, as they are known, show great promise in helping tackle the obesity epidemic in the country, which contributes significantly to medical costs.

Employers and insurers are now faced with the prospect of exploding drug costs if demand continues to boom and doctors write more prescriptions for them. To head that prospect off, they are trying to formulate approaches that could keep costs from spiraling while still attending to the demand for weight-loss regimens.

Mercer's "National Survey of Employer-Sponsored Health Plans 2023" survey with 500 or more workers found:

- 35% cover GLP-1 drugs for treating obesity with prior authorization and/or reauthorization requirements.
- 7% said they cover the drug with no special requirements.
- 19% said they don't cover these drugs but are considering it.
- 40% said they are not considering covering these medications.

For employers who want their plans to cover GLP-1 drugs but need to cap their health care costs, experts recommend a step program for people struggling with obesity as it can help patients lose weight at a lower cost:

Step one — Focuses on helping the patient change their lifestyle through dietary changes and exercise.
Step two — Focuses on education and ancillary services, such as food delivery or mental health support.
Step three — If they still need help, doctors can prescribe less expensive first-generation anti-obesity medications
Step four — If all else fails, doctors prescribe GLP-1s if the plan covers them, fully or partially.

Employers are working incredibly hard to deal with the onslaught of demand from employees for the new GLP-1 drugs.

Only 7% of employers cover the drugs outright.

Others are using step edits and forced education/lifestyle change programs.

Source: https://gbsbenefitsgroup.com/employers-wrestling-with-covering-weight-loss-drugs/

A New Generation of Companies Has Popped Up to Ration Demand

Heather Landi, "Employers face soaring demand for obesity care benefits. Virtual care players are jumping in with a slew of offerings," *FierceHealth*, May 26, 2023

Employers are seeing surging demand from their workers for benefits that cover obesity treatment and this is opening up considerable market opportunities for virtual care players.

"I think very much that where we were on mental health as an employee benefit 10 years ago is where we are today on metabolic health. In 10 years, employees will move with their feet to employers who cover holistic metabolic health benefits," said Isabelle Kenyon, founder and CEO of Calibrate, a digital metabolic health platform.

Health plan sponsors are facing increasing pressure to cover these medications. If these drugs are used by a substantial portion of those with obesity, the increase in medical costs will be high, according to Jeff Levin-Scherz, M.D., managing director and population health leader at insurance services company Willis Towers Watson (WTW). And these advances in game-changing obesity drugs come as employers are already facing the highest medical inflation rate in decades.

Virtual care companies are now jumping into the market as they see big opportunities to combine prescriptions for GLP-1 drugs with online programs that focus on lifestyle and behavior change. The idea, digital health executives say, is to improve long-term clinical outcomes and ultimately reduce costs by helping people keep the weight off.

"When we talk to employers, it's not, 'I don't want to cover these drugs.' In fact, I literally have never heard that from an employer," said Kenyon, whose company, Calibrate, launched an enterprise business late last year. "What I hear from employers is, 'I want to cover these drugs and I want to do it in a way that guarantees outcomes and I want to do it in a way that contains cost.' And that does not mean one-way prescribing of GLP-1s."

She added, "Employers are feeling this already. They see it in their Ozempic spend, they see it in their Trulicity spend. I would say two-thirds of employers that we meet want a solution for this category today. And a solution means cost control and it means outcomes."

Employees are being told you better eat right and exercise if you want to get coverage for your semaglutide.

Source: https://www.fiercehealthcare.com/digital-health/employers-grapple-soaring-demand-obesity-care-benefits

Key Players in Virtual Obesity Management at the Employer

Calibrate

- Behavioral Therapy plus GLP-1 access
- Comes with a cellular-connected scale
- $138 / month but employee pays for their GLP-1s
- Strong efficacy (almost all employees on GLP-1s)

OPTUMRx®

- Tailored programs that include patient monitoring and motivation and support tools on top of GLP-1s
- Employees only get GLP-1s after working with an obesity specialist / weight loss coach

Teladoc™ HEALTH

- Sets up counseling and provider oversight for patients taking GLP-1s.
- Creates broader clinical programs to achieve lasting weight loss.

wondr HEALTH™

- Behavioral Therapy through digital tools
- Members get an app (similar to Noom)
- Access to doctors and an online community
- Members don't get access to GLP-1s

See https://www.fiercehealthcare.com/payers/optum-rx-rolls-out-new-weight-management-program, https://www.teladoc.com/health-talk/a-whole-person-care-approach-to-weight-loss-medications/

Behavioral Health Application for Employees

wondr HEALTH

Reimagine weight loss & well-being

Get better health outcomes while reducing costs.

Our clinically proven behavior-change program treats the root cause of chronic metabolic conditions to improve quality of life and health outcomes while reducing costs.

GET STARTED

Skills-based, science-backed program

- Clinically proven, virtual-first behavior change solution features videos, digital tools and coaching support to promote results that last.
- Expert doctors and clinicians instruct participants every step of the way, with unlimited access to our online community, tools, and resources for support.
- Ongoing assessments personalize app engagement with tailored messaging, content recommendations, tracking tools and more.

Source: https://wondrhealth.com/

Calibrate

How It Works | Pricing | Program | Medication | Results | FAQs | For Business | For Employees | Sign In | Am I Eligible?

BACKED BY SCI

LASTING WEIGHT LOSS PROVEN BY DATA

Did you know: Calibrate is the first and only program to drive 15% sustained weight loss in the real world, outside of clinical trials. Even better? Those who continue with Masters Programs sustain the same average 15% weight loss at 18 months and our earliest members have sustained an average of 15% weight loss at 24 months.

See Results Report

92% of Calibrate Members Get GLP-1's

From Calibrate's Real World Evidence Study, March 2023

The cohort of 2,643 members was determined as follows: 4,440 members enrolled in Calibrate as of October 2021, and 321 did not have GLP1 access. GLP-1 access for purposes of this cohort meant initial pathway to GLP-1 coverage and at least one month of medication access; members may not have been on medications for the entirety of the program and may have been impacted by supply challenges. For these 4119 members with initial GLP-1 access, 793 dropped out for reasons other than a medical contraindication, and 501 had not yet completed the One Year Metabolic Reset program "OYMR" as of the data freeze date, two weeks after the data analysis deadline (the first 12 months of the Calibrate's program is called the One Year Metabolic Reset; members received program extensions to support supply challenges encountered summer 2022, and members also have an opportunity to go "on pause" for up to 90 days if a medical, personal, or other life event warrants a break from the program). Finally, 103 members completed the OYMR after the data analysis deadline but before the data freeze date of 11/01/2022

Source: https://www.joincalibrate.com/pages/member-results, https://calibrate.cdn.prismic.io/calibrate/783fc9aa-801f-48ce-8941-86494e86e09c_Calibrate+2023+Second+Annual+Results+Report.pdf

Calibrate Recently Taken Over in Bankruptcy

Shelby Livingston and Rebecca Torrence, *Business Insider*, Nov 2, 2023 (excerpt)

Facing the threat of bankruptcy, weight-loss startup Calibrate was forced to make a tough deal with private equity firm Madryn Asset Management, according to company documents reviewed by Insider.

Under the terms of the deal, Madryn took a 70% stake in Calibrate in exchange for just $20 million, the documents show. Madryn had already lent the troubled weight-loss startup more than $60 million, giving it leverage to dictate the terms of the transaction.

Insider first reported on October 20 that Calibrate, which prescribes popular drugs such as Ozempic and Wegovy, was selling itself to Madryn and undergoing a restructuring, after struggling with patient complaints and refunds.

Calibrate's founder, Isabelle Kenyon, stepped down as CEO in the restructuring. She's left with a 2.5% stake, per the documents. The documents, which are dated October 17, include the merger agreement and a list of Calibrate investors, and were sent to shareholders as part of the deal. The deal terms are especially bleak for a startup that raised about $170 million from investors including Tiger Global, Founders Fund, and Optum Ventures, according to Pitchbook. The figure also includes some previous lending by Madryn.

Madryn's takeover caps a tumultuous year for Calibrate. While it was one of the first companies built to prescribe new weight-loss drugs, the startup ran into problems getting patients their medications on time and responding to their messages, and paid out millions of dollars in refunds in the first half of the year, Insider reported previously. Some longtime patients have regained much of the weight they lost after Calibrate failed to get them medications, Insider reported on Thursday.

Source: https://www.businessinsider.com/calibrate-deal-madryn-asset-management-bankruptcy-2023-11

VC’s Much More Picky on Weight Loss After Calibrate Fall

Rebecca Torrence, Business Insider, Dec 11, 2023 (excerpt)

With the Ozempic craze in full swing, investors are getting picky about the weight-loss startups they want to back.

GLP-1 agonists like Ozempic, Wegovy, and Mounjaro have taken off this year for their potential to induce life-changing weight loss, and healthcare startups have flooded the market to get a piece of the pie. Now some venture capitalists say they want to put their money behind startups that benefit from the drugs' rise but don't rely on prescribing them.

Investors' hesitation about the market for prescribing drugs like Ozempic has grown as challenges like insurance denials and drug shortages have plagued their distribution.

VCs are especially heeding the warning of Calibrate's fall. Calibrate, which banked on prescribing drugs like Ozempic and providing coaching, sold itself to a private-equity firm in October after giving back millions of dollars in refunds to unhappy customers in the first half of 2023.

"You can see what happened with Calibrate — it's not that easy if you're relying on prescribing a medication but then you can't get it to patients," Kaganoff said.

Other companies have run into similar roadblocks. Business Insider reported in June that the $7 billion digital-health startup Ro was facing patient complaints of long response times and medication denials after launching a weight-loss program that included GLP-1 prescriptions.

Ro told Business Insider in a December email that the company has "continued improving and enhancing our patient experience and look forward to helping even more patients soon with the launch of Zepbound.“ Hims & Hers launched a weight-loss program in December, but its CEO told Business Insider in November that the healthcare company wouldn't prescribe Ozempic or Wegovy to avoid the challenges of widespread insurance denials and drug shortages. Instead, Hims & Hers plans to prescribe only generic medications for weight loss, which can be cheaper and easier to access but typically less effective.

With so many startups crowding the weight-loss market, some VCs said the opportunity to back a company that could actually succeed over its competitors has passed.

Instead, she said, she'd be more likely to back a startup that can provide significant support for weight loss without relying on prescribing medications, such as a company promising an off-ramp for people who want to stop taking the drugs while maintaining weight loss.

Source: https://www.businessinsider.com/why-vcs-getting-selective-next-weight-loss-investment-ozempic-2023-12

Behavioral Therapy for Weight Loss Only Modestly Effective

Kurnik Mesarič, K., Pajek, J., Logar Zakrajšek, B. et al. Cognitive behavioral therapy for lifestyle changes in patients with obesity and type 2 diabetes: a systematic review and meta-analysis. Sci Rep 13, 12793 (2023).

The aim of this systematic review and meta-analysis was to examine the contribution of cognitive behavioral therapy (CBT) to the implementation of lifestyle changes, considering health-related and behavioral outcomes. A systematic literature review was performed using multiple databases (PsycInfo, PubMed and MEDLINE). The inclusion criteria comprised randomised controlled trials of CBT for lifestyle changes in patients with obesity and/or type 2 diabetes. The quality of study reporting was assessed with the revised Cochrane Collaboration's risk of bias tool. A meta-analysis was conducted on studies with appropriate outcomes. Nine randomised controlled trials, with a total sample size of 902 participants, met the inclusion criteria. The meta-analysis has shown a medium, significant effect size of CBT interventions for weight loss and weight maintenance, and a low, non-significant effect size of CBT interventions for reducing glycated hemoglobin (HbA1c) levels. A separate, combined, meta-analysis for all nine calculated effect sizes has yielded a medium and significant overall effect size for the model. Our review of the studies about the effectiveness of CBT in implementing lifestyle changes has, in comparison to usual control groups, proven the efficacy of CBT interventions in implementing lifestyle changes, especially for weight loss and weight maintenance.

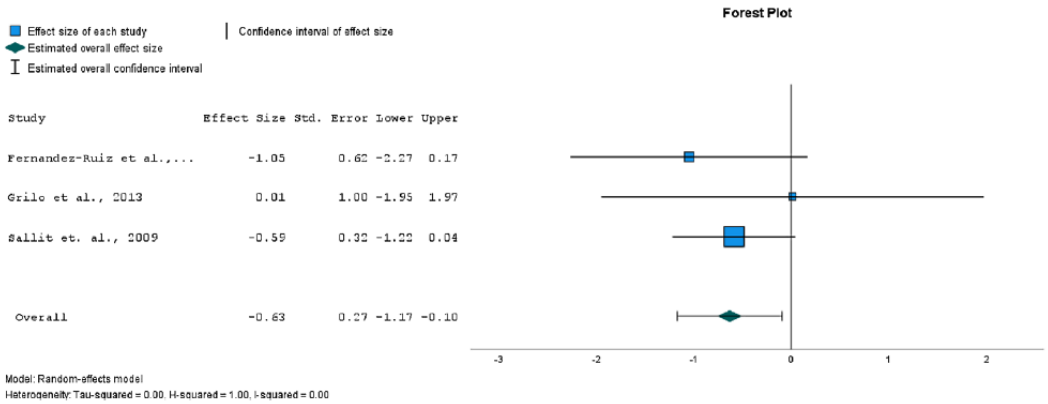


Figure 3. Forest plot comparing effect sizes between intervention and control groups, outcome: weight loss (expressed as BMI change).

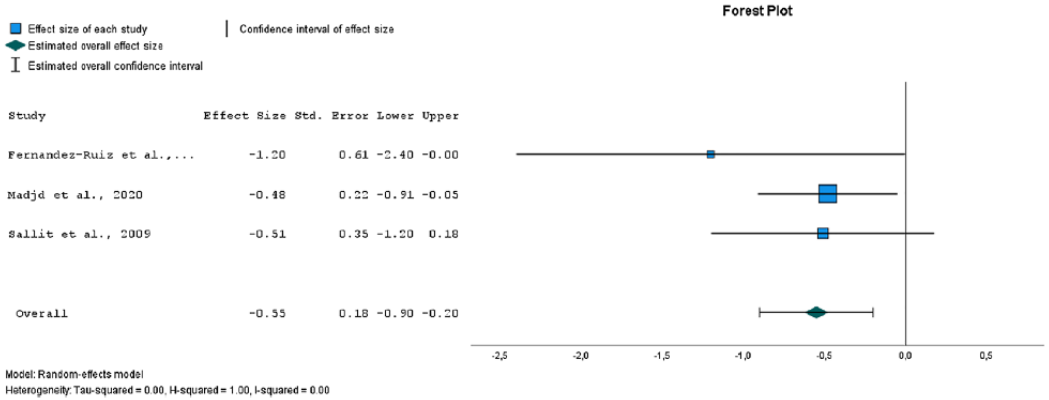


Figure 4. Forest plot of comparison of effect sizes between intervention and control groups, outcome: weight maintenance (BMI).

Source: https://www.nature.com/articles/s41598-023-40141-5

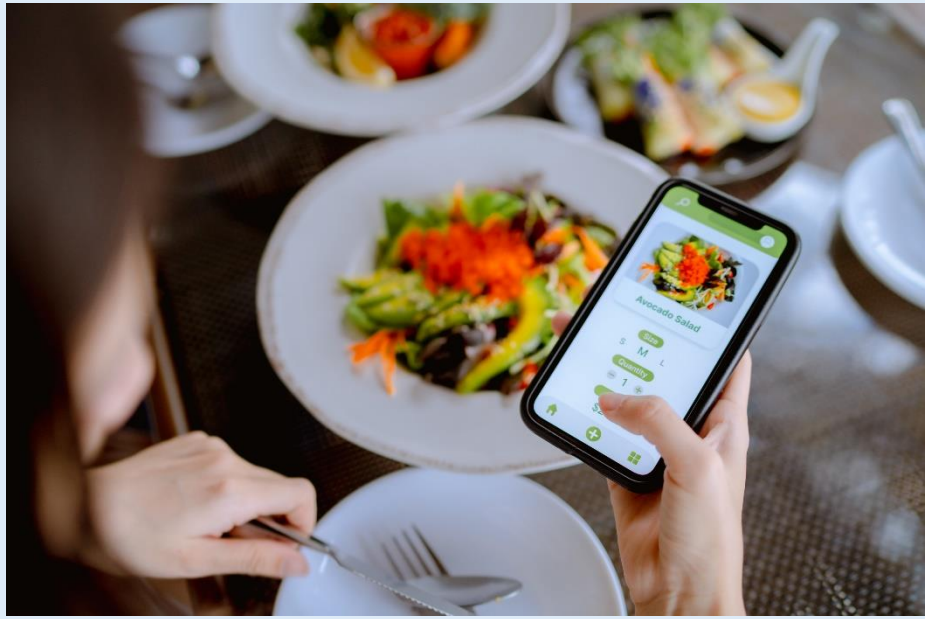
Critique of Current Employer Approaches to Obesity

We have reached an era where a new crop of medications allows employees to dramatically change their health through weight loss. However, employers are rapidly adopting a subtle form of a step edit: get this app, take this class and get to the gym before we pay for your GLP-1 (if we pay at all). This has a moral overtone with a scientific patina: “You, Mr. Employee are the problem. You need to avoid cheeseburgers and start eating your carrot and lettuce. If you don’t change, why should we pay for your drugs?”

We can’t help notice that the only provider that gives any evidence of efficacy of their program is Calibrate and their data looks suspiciously like the weight loss curves from using GLP-1’s alone. Conspicuously, Calibrate has not run a trial of their program + GLP-1 versus GLP-1 alone. In fact, none of the programs have.

From a public health perspective, employers are using the scientific sounding programs from groups like Teladoc and Wondr to force employees into largely ineffective behavioral and nutritional counseling. We believe that the effect of this is to work against the high-risk employee who may have had difficult life circumstances, perhaps poverty, and ends up overweight and risky to the employer’s health bottom line. One can argue that the new virtual weight management programs are there to give employers an excuse to throttle back access to needed medications. There must be a better way than to waste employee and employer resources on behavioral therapy that everyone knows is unlikely to do much in order to deny access to GLP-1 medications.

Perhaps employers should just come out and say that they won’t cover these medications and let employees then decide whether to stay in their positions.



Employers’ wish to avoid paying for GLP-1’s is creating a whole new cottage industry of obesity and nutrition counseling programs + apps. It does not appear to be a coincidence that the growing strength of medical data supporting use of GLP-1’s has been an associated with an explosion in less expensive but less effective behavioral therapy options.

Breakthrough on Hyperemesis Gravidarum

Hyperemesis Gravidarum

Affects

1 to 2%

of all pregnancies

Over 200,000 sufferers a year in US and Europe.

Persistent and uncontrolled vomiting in pregnancy.

Has serious life-altering implications for mother and baby.

No good treatments on the market.

Women are frequently told to suffer through it and that it might be psychological.

Source: Hyperemesis Gravidarum Foundation

Hyperemesis Gravidarum

- Hyperemesis Gravidarum (HG) is a potentially life-threatening condition characterized by severe nausea and vomiting during pregnancy
- HG can start after just 3 weeks and last for months leading to extreme weight loss and nutritional disturbances akin to starvation in pregnancy
- Well known sufferers include Charlotte Brontë, Maria Shriver, the Princess of Wales, Kelly Clarkson and, most recently, Amy Schumer

Maternal Impact

- 26% of mothers lose more than 15% of their pre-pregnancy weight
- 22% experience symptoms until term
- 18% full criteria PTSD
- 37% no more children
- Detached retinas, collapsed lungs, esophageal tears, rib fractures, brain damage, pulmonary embolism, heart attack and even death

Fetal Impact

- 6% therapeutic termination rate
- 4x increased risk of poor outcome (preterm birth)
- 3.6x increased risk of emotional/behavioral disorders
- Increased risk of neurodevelopmental delay, attention problems and autism spectrum disorder
- Vitamin K deficient embryopathy

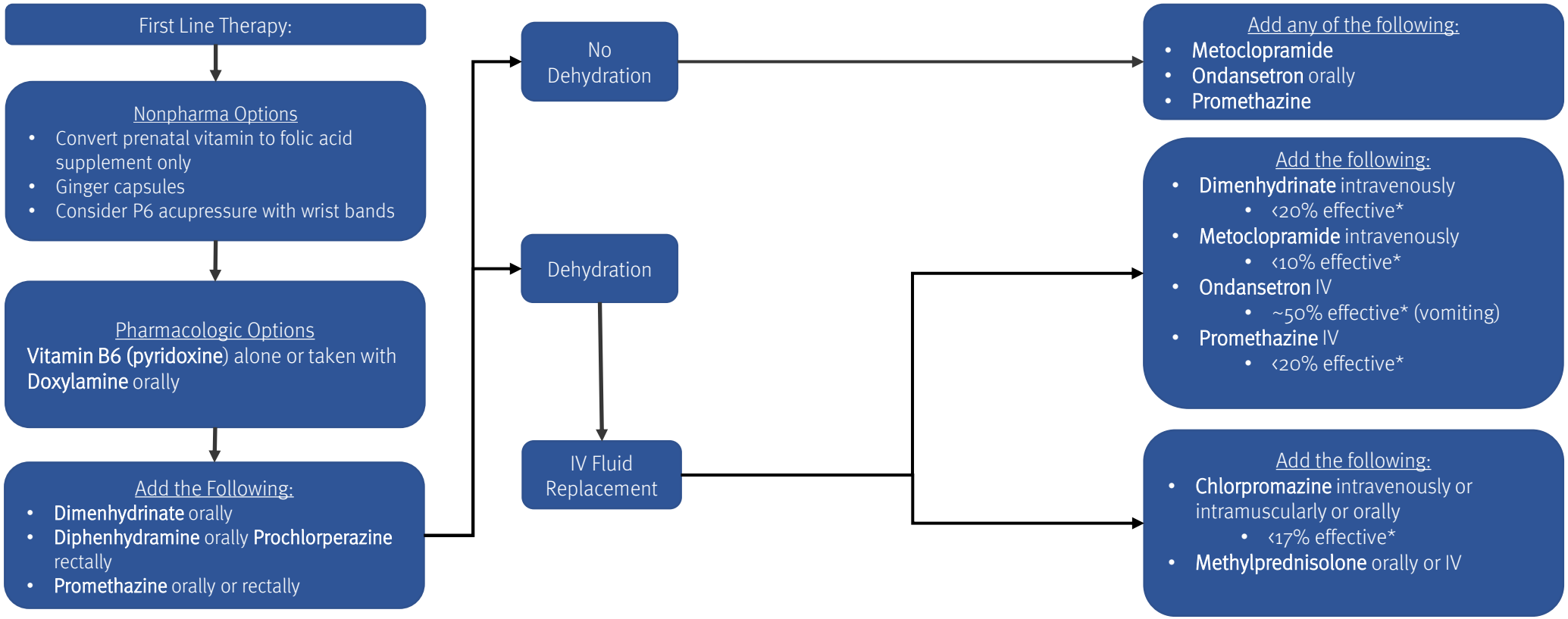
Financial Impact

- 2nd leading cause of hospitalizations in the fetal/maternal health area after preterm birth
- 2012 total estimated cost in US is $1.8 billion
- $215 million inpatient charges 2014
- $290 million medication cost
- 10-15% require tube feeding (>$1000/day and high risk of infection)

Source: Hyperemesis Gravidarum Foundation

Today's HG Treatment Landscape

- There are **no medications** approved for HG treatment
- Current medications used for HG are largely ineffective and all are used "off-label"
- Pipeline for HG treatments is weak, representing opportunity for effective therapy to enter the market



*Efficacy is self-reported

Nature Paper Last Week:
GDF-15 That Induces HG is From Feto-Placental Unit

Nature, Dec 13, 2023

Fetally-encoded GDF15 and maternal GDF15 sensitivity are major determinants of nausea and vomiting in human pregnancy

M Fejzo,[1,*] N Rocha,[2,*] I Cimino,[2,*] SM Lockhart,[2,*] C Petry,[2,*] RG Kay,[2,3] K Burling,[2,4] P Barker,[2,4] AL George,[3] N Yasara,[5] A Premawardhena,[6,7] S Gong,[8,9] E Cook,[8] K Rainbow,[2] DJ Withers,[2] V Cortessis,[1,10] PM Mullin,[1] KW MacGibbon,[11] E Jin,[1] A Kam,[1] A Campbell,[12] O Polasek,[13] G Tzoneva,[14] FM Gribble,[2] GSH Yeo,[2] BYH Lam,[2] V Saudek,[2] IA Hughes,[15] KK Ong,[15,16] JRB Perry,[2,16] A Sutton Cole,[17] M Baumgarten,[17] P Welsh,[18] N Sattar,[18] GCS Smith,[8,9,*] DS Charnock Jones,[8,9,*] AP Coll,[2,*] CL Meek,[2,*] S Mettananda,[5,19,*] C Hayward,[20,*] N Mancuso,[21,22,23,*] and S O'Rahilly[24,*^]

Here we report that fetal production of GDF15, and maternal sensitivity to it, both contribute substantially to the risk of HG. We found that the great majority of GDF15 in maternal circulation is derived from the feto-placental unit and that higher GDF15 levels in maternal blood are associated with vomiting and are further elevated in patients with HG.

Conversely, we found that lower levels of GDF15 in the non-pregnant state predispose women to HG. A rare C211G variant in GDF15 which strongly predisposes mothers to HG, particularly when the fetus is wild-type, was found to markedly impair cellular secretion of GDF15 and associate with low circulating levels of GDF15 in the non-pregnant state. Consistent with this, two common GDF15 haplotypes which predispose to HG were associated with lower circulating levels outside pregnancy. The administration of a long-acting form of GDF15 to wild-type mice markedly reduced subsequent responses to an acute dose, establishing that desensitisation is a feature of this system.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10312505/

Nature Paper Last Week:
Scientists Pinpoint Cause of Severe Morning Sickness

Azeen Ghorayshi, *New York Times*, Dec 13, 2023

The nausea and vomiting that often define the first trimester of pregnancy are primarily caused by a single hormone, according to a study published on Wednesday in the journal *Nature*. Researchers said that the discovery could lead to better treatments for morning sickness, including rare, life-threatening cases of it.

The study confirms prior research that had pointed to the hormone, called GDF15. The researchers found that the amount of hormone circulating in a woman's blood during pregnancy — as well as her exposure to it before pregnancy — drives the severity of her symptoms.

More than two-thirds of pregnant women experience nausea and vomiting during the first trimester. And roughly 2 percent of women are hospitalized for a condition called hyperemesis gravidarum, which causes relentless vomiting and nausea throughout the entire pregnancy. The condition can lead to malnutrition, weight loss and dehydration. It also increases the risk of preterm birth, pre-eclampsia and blood clots, threatening the life of the mother and the fetus.

Perhaps because nausea and vomiting are so common in pregnancy, doctors often overlook hyperemesis, dismissing its severe symptoms as psychological, even though it is the leading cause of hospitalization during early pregnancy, experts said. Although celebrities like Kate Middleton and Amy Schumer have raised the condition's profile in recent years by sharing their experiences, it remains understudied.

"I've been working on this for 20 years and yet there are still reports of women dying from this and women being mistreated," said Dr. Marlena Fejzo, a geneticist at the University of Southern California Keck School of Medicine and a co-author of the new study.

She knows the pain of the condition firsthand. During her second pregnancy, in 1999, Dr. Fejzo was unable to eat or drink without vomiting. She rapidly lost weight, becoming too weak to stand or walk. Her doctor was dismissive, suggesting she was exaggerating her symptoms to get attention. She was eventually hospitalized, and miscarried at 15 weeks.

Dr. Fejzo said she asked the National Institutes of Health to fund a genetic study of hyperemesis, but was rejected. Undeterred, she convinced 23andMe, a popular genetic testing company, to include questions about hyperemesis in surveys of tens of thousands of customers. In 2018, she published a paper showing that customers with hyperemesis tended to carry a variant in a gene for GDF15.

Source: https://www.nytimes.com/2023/12/13/health/morning-sickness-hyperemesis-gravidarum.html

Nature Paper Last Week:
GDF-15 Levels Associated with Hyperemesis Gravidarum

Alice E. Hughes & Rachel M. Freathy, "Pregnancy sickness linked to hormone from fetus," *Nature*, Dec 13, 2023

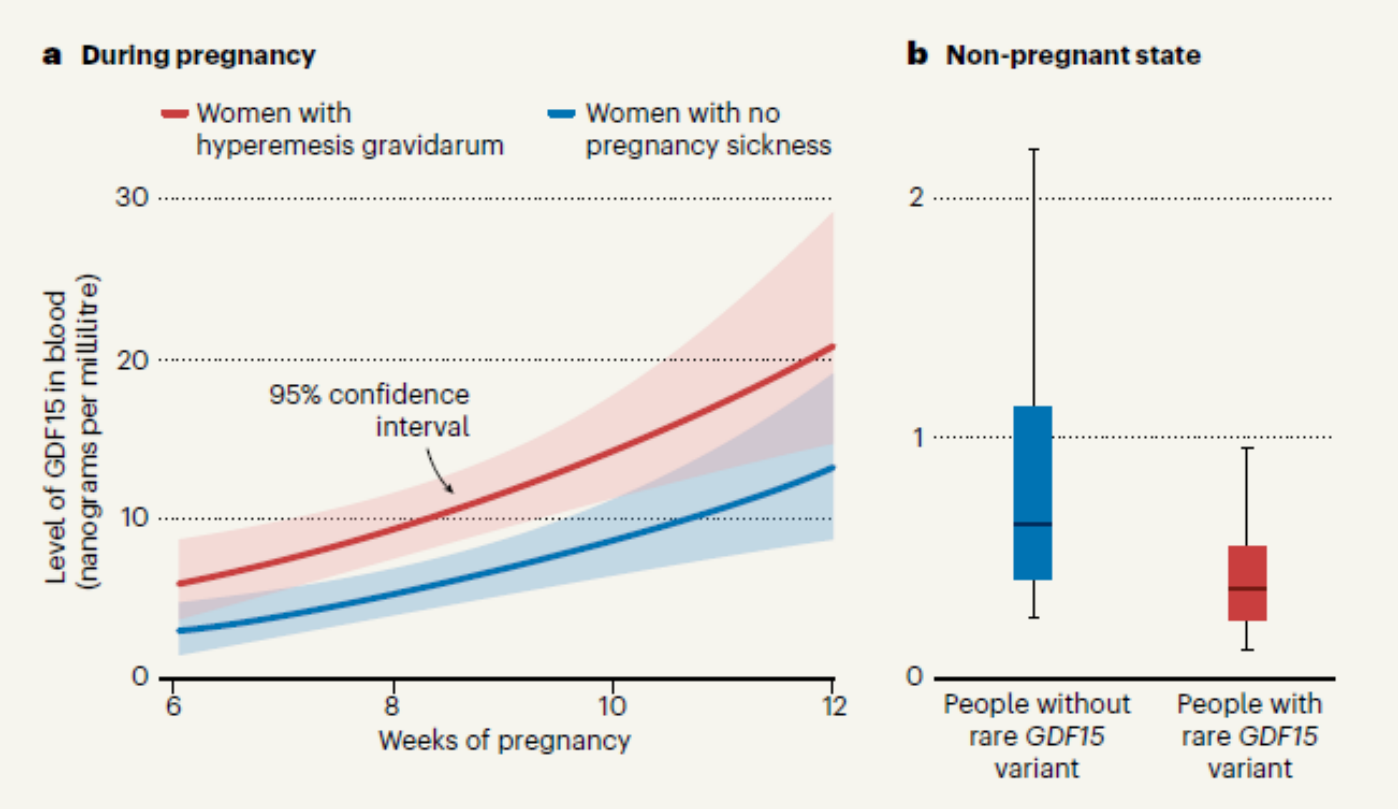
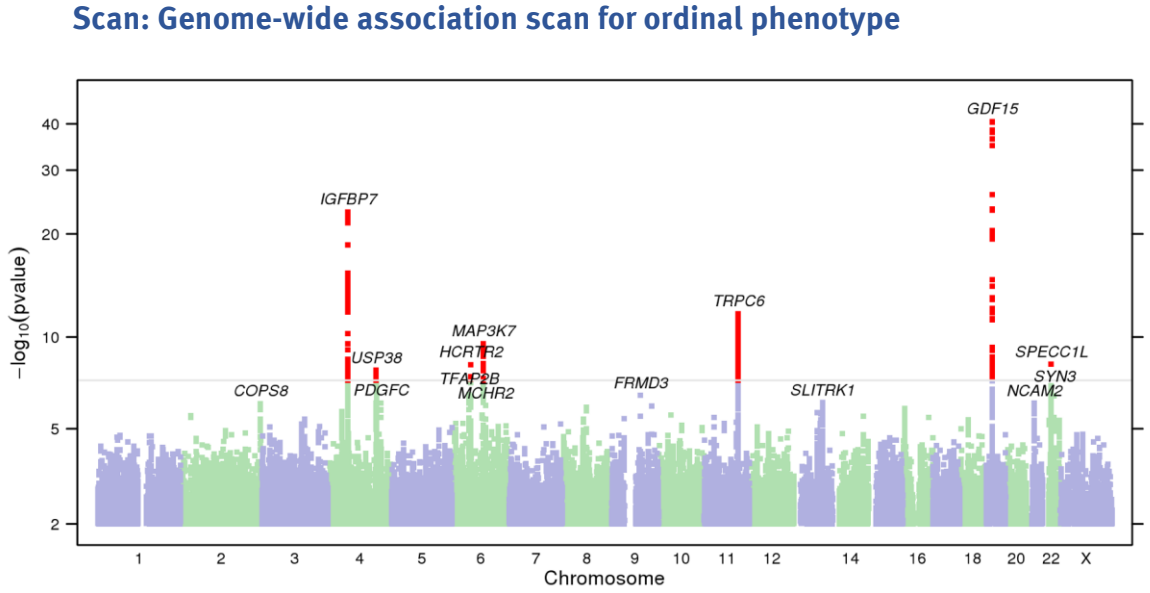
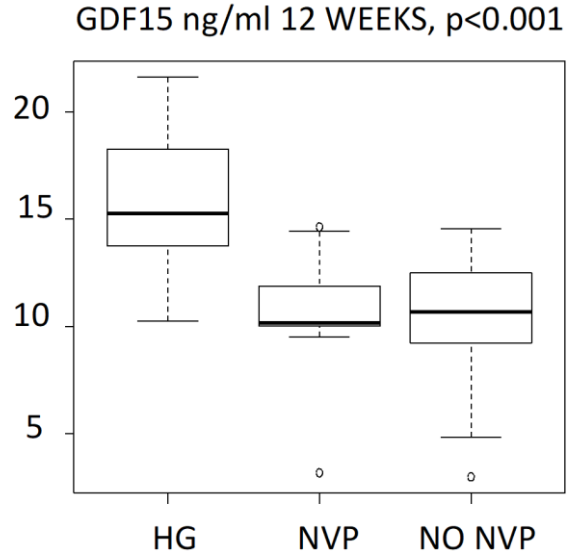


Figure 1 | The hormone GDF15 is responsible for excessive nausea and vomiting during pregnancy. a, Fejzo et al. find that the levels of GDF15 in the mother's bloodstream increase during the first 12 weeks of pregnancy, and that most of this GDF15 originates from the fetus and placenta. Women with a condition called hyperemesis gravidarum (HG), who experience severe nausea and vomiting, have higher levels of GDF15 than those who don't experience pregnancy sickness — suggesting that high levels of GDF15 are linked to symptoms of HG. People with a rare GDF15 variant have lower basal levels of GDF15 than those who do not have the variant. Individuals with this genetic variant are predisposed to HG. Lower levels of GDF15 in the non-pregnant state could explain why these people are sensitive to the increase in GDF15 during pregnancy, and so experience HG.

Source: https://www.nature.com/articles/d41586-023-03940-4

Strong Link between GDF-15 and HG





- Over 15 million variants scanned in >53,000 women revealed a strong association between GDF-15 and HG
- There is a 10^{-41} chance that the association between GDF-15 and Hyperemesis Gravidarum is random

- Hyperemesis Gravidarum (HG) cases display serum GDF-15 at 12 weeks of pregnancy that is well above that in women who are suffering from nausea and vomiting of pregnancy (NVP) or morning sickness
- Women with no NVP have roughly the same levels of GDF-15 as those with normal NVP
- The first quartile GDF-15 ELISA measure in HG patients is well above the third quartile (and close to the 95th percentile) of GDF-15 in other pregnant women

Source: Fejzo et al., *Nature Communications* (2018), Fejzo et al., *Geburtshilfe Frauenheilkd* (2019).

C211G mutation in GDF15 have at least a 10-fold increased risk of developing HG

Fejzo MS, MacGibbon KW, First O, Quan C, Mullin PM. Whole-exome sequencing uncovers new variants in GDF15 associated with hyperemesis gravidarum. *BJOG*. 2022 Oct;129(11):1845-1852.

The paradigm-changing finding that GDF15 is the greatest genetic risk factor for HG is now supported by a second genetic technique, WES, in an independent cohort.

This study provides mounting genetic evidence that variants in GDF15 are associated with HG. This study is the first to identify missense variants within GDF15 (rs1058587 and rs372120002) associated with HG.

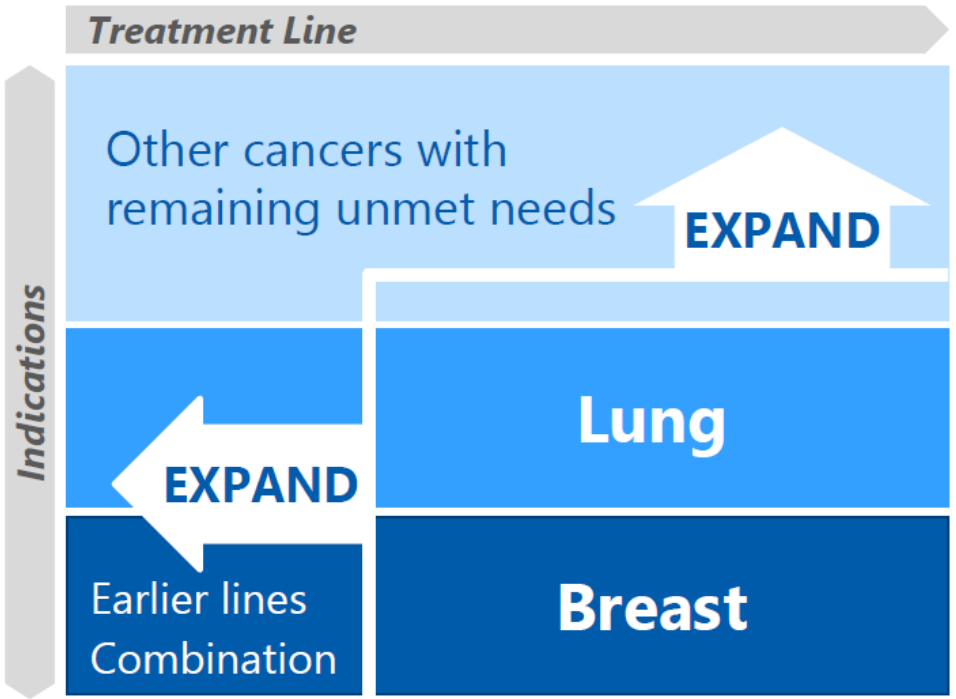
As no other exome-wide significant nor causal variants in ≥10 cases were identified, this study does not support the two predominant historical theories that HG has a psychological origin or is caused by the pregnancy hormone hCG.

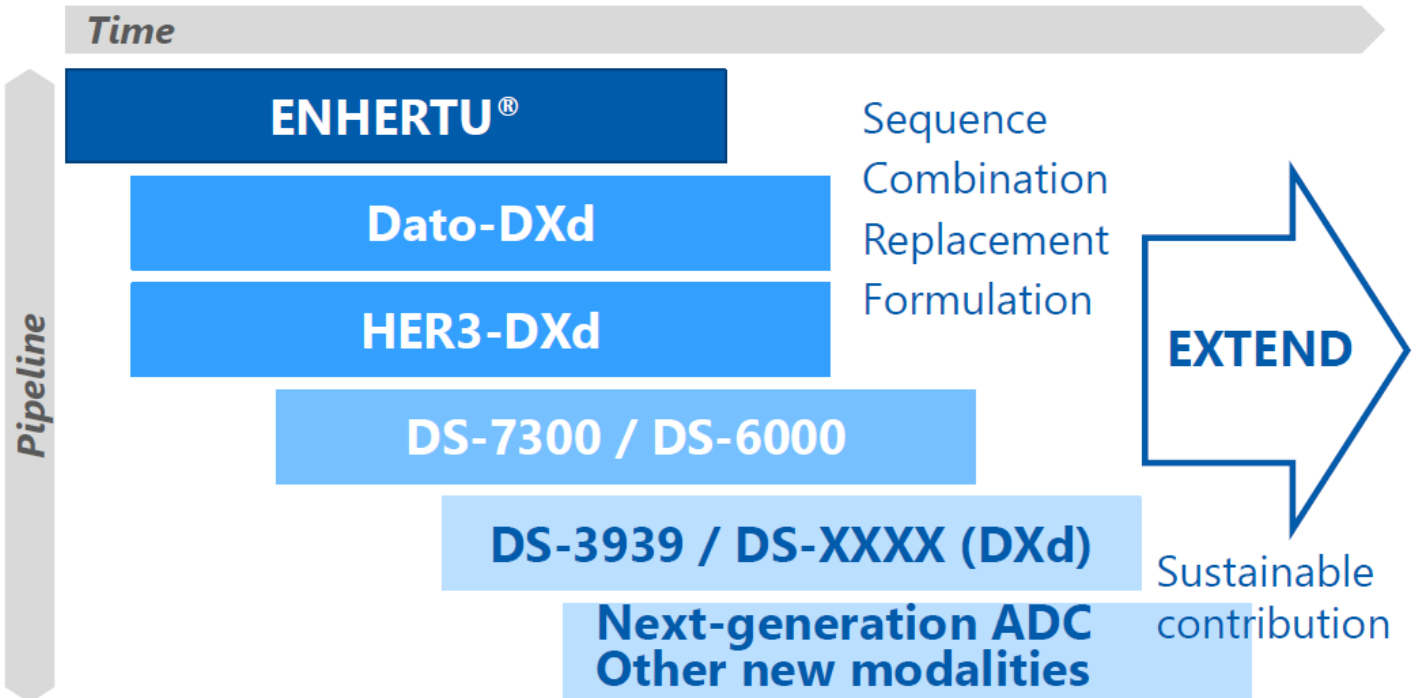
Indeed, this study did not identify any rare pathogenic variants coding for hCG occurring in two or more cases and in no controls, nor any that were even close to reaching exome-wide significance.

Source: https://pubmed.ncbi.nlm.nih.gov/35218128/

Daiichi Sankyo R&D Day – Dec 12, 2023

EXPAND & EXTEND to deliver our technology to more patients





- Establish and expand DXd ADC therapies in **Breast** and **Lung** cancers
- **Go Earlier:** explore early lines of therapy/ stage of diseases; replace chemotherapy
- **Go Wider:** into new diseases beyond currently focusing areas to serve more patients in needs

- Address unmet needs **after ENHERTU®** treatment
- Seek effective **treatment sequencing, novel combination, or formulation** to enhance efficacy and improve treatment
- **Grow early pipeline** following 5DXd ADCs to contribute to more patients in the future

Long history behind the birth of DXd ADC

1990 | 2000 | 2010 | 2020 | 5 DXd ADC & Next Wa

Sankyo Co., Ltd.

Biologics

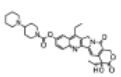
1990s
Humanization
Small-scale manufacturing
(Anti CD95, anti-DR5)

2000s
Establishment of mAb screening / Expansion of mAb portfolio / Establishment of large-scale manufacturing / M&A (Denosumab etc.)

Daiichi Pharmaceutical Co., Ltd.

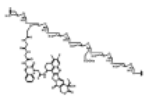
Topo I inhibitors

1980s
Irinotecan（CPT-11）
Co-development w/ Yakult



1990s
Potent Top I inhibitor, Exatecan
（Ph3 terminated）

2000s
R&D of DDS
（DE-310, Ph1 terminated）



2007 merged

Cross-functional activity for ADC research

R&D of ENHERTU®

2013	2015	2019
Preclinical studies	Clinical trial initiated	1st indication approved

Our research culture includes…

Great history of delivering unique value for patients

Insatiable passion in the pursuit of new science & technology

Emphasis creativity and insistence on perfection

DXd ADCs
+"Beyond DXd ADC" drugs

Several inventors of ENHERTU® have been involved in other launched products

- They have long tenure at DS, leveraged their expertise and are now research leaders growing our future talent

Swift. Decisive. Courageous.

Only nine years

Between DS ADC Working Team launch and ENHERTU® approval

History of ADCs

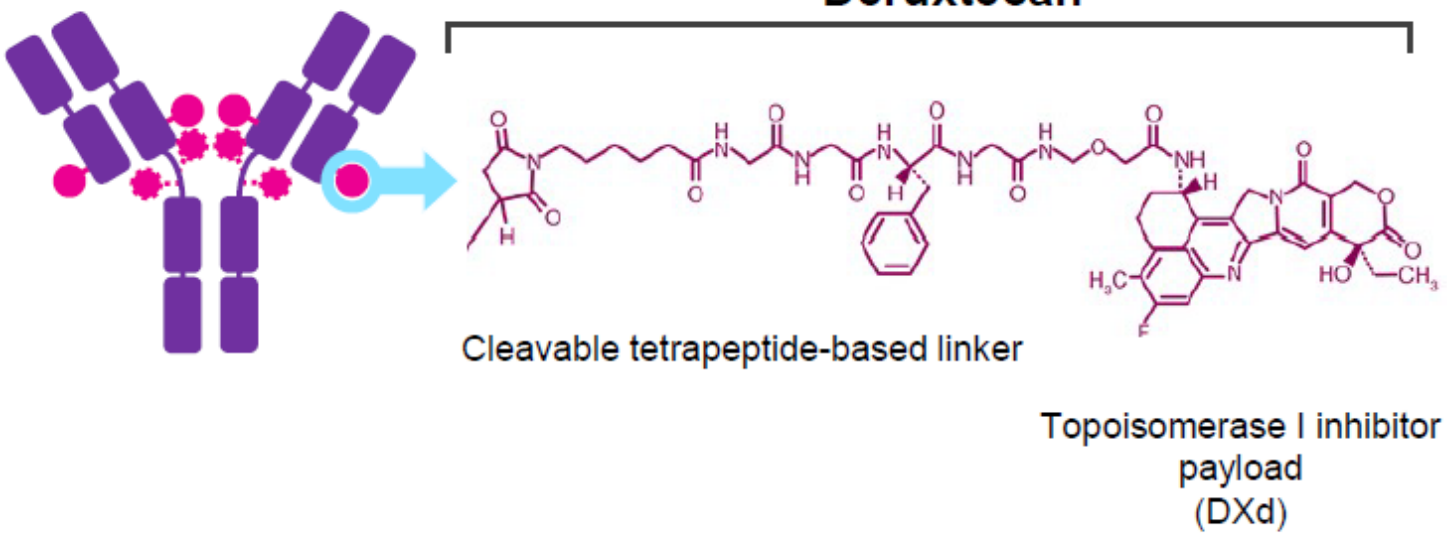
Source: *Nakada T, et al. Chem Pharm Bull (Tokyo). 2019*

ADC: antibody-drug conjugate, mAb: monoclonal antibody

Daiichi Sankyo's DXd ADC technology solved conventional challenges

Widely applicable platform

DXd ADC Technology



7 Key Attributes[a] of DXd ADC

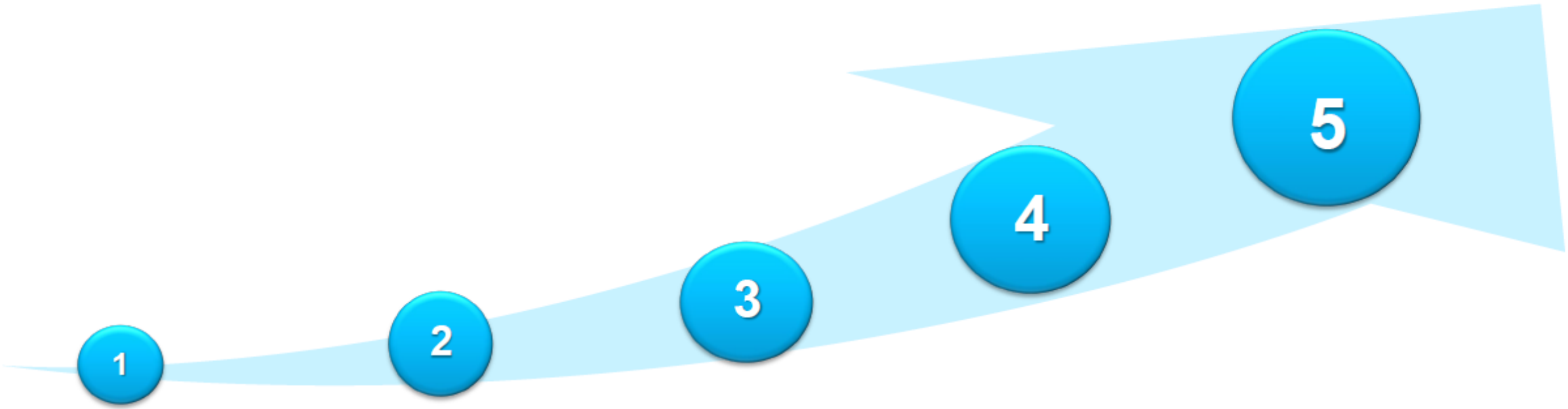
- Payload MOA: Topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio (DAR)
- Stable linker-payload
- Payload with short systemic half-life
- Tumor-selective cleavable linker
- Bystander antitumor effect

[a]The clinical relevance of these features is under investigation.

Source: *Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185; Ogitani Y, et al. Clin Cancer Res. 2016;22(20):5097-5108; Trail PA, et al. Pharmacol Ther. 2018;181:126-142; Ogitani Y, et al. Cancer Sci. 2016;107(7):1039-1046.*

ADC: antibody-drug conjugate

Sustainable ADC Development



DXd ADC

ENHERTU®
Dato-DXd
HER3-DXd
DS-7300 (I-DXd)
DS-6000 (R-DXd)
DS-3939
DS-XXXX

Next Generation ADC

- **DS-9606**
- Multiple projects in IND enabling & discovery stage

New Concept ADC 1

Multiple projects in IND enabling stage

New Concept ADC 2

Multiple projects in discovery stage

New Concept ADC 3

Multiple projects in discovery stage

cept 4

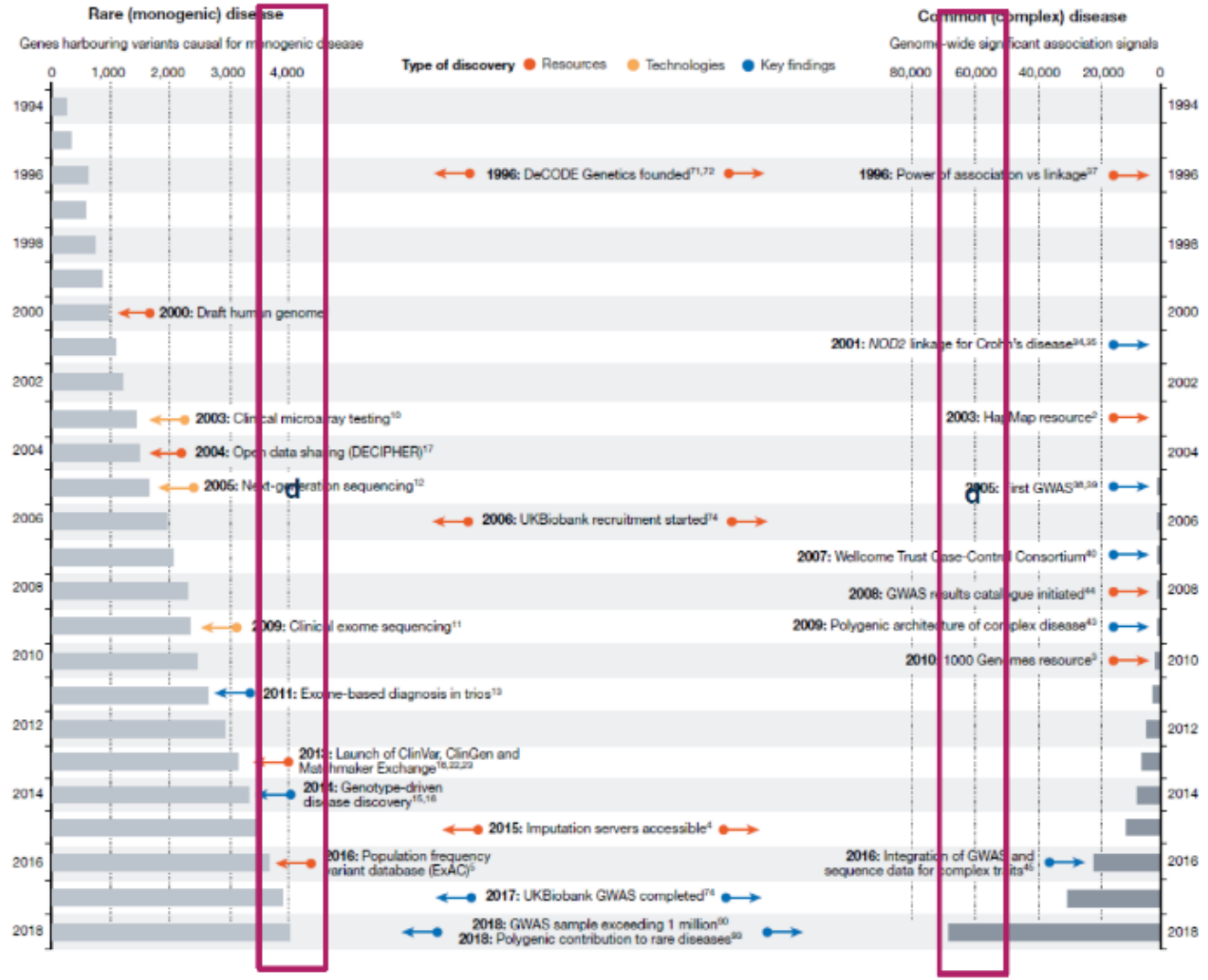
cept 5

ADC: antibody-drug conjugate, IND: investigational new drug application

Alnylam R&D Day

Growth in Discovery of Disease-Associated Genetic Variation

1994-2018



Claussnitzer et al., Nature, 2020; 577:179-189

- Deeper understanding of molecular basis of human disease
- Dramatic increase in number of genetically validated targets
- Highlights needs for new approaches to treatment of vast array of disorders

Alnylam

Advancing a Robust and High-Yielding Pipeline of RNAi Therapeutics

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1]	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis with PN*			●	Global
amvuttra (vutrisiran)	*hATTR Amyloidosis with PN*			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*			●	Global
LEQVIO (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[2]
Vutrisiran	*ATTR Amyloidosis with CM*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Cemdisiran (+/- Pozelimab)[3*]	*Complement-Mediated Diseases*		●		Global; Milestone/Royalty
ALN-TTRsc04*	*ATTR Amyloidosis*	●			Global
Belcesiran[4*]	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[5*]	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran*	*Hypertension*	●			U.S. 50-50; Ex-U.S. Royalties
ALN-HSD[6*]	*NASH*	●			Royalty
ALN-APP*	*Alzheimer's Disease; Cerebral Amyloid Angiopathy*	●			50-50
ALN-PNP*	*NASH*	●			50-50
ALN-KHK*	*Type 2 Diabetes*	●			Global

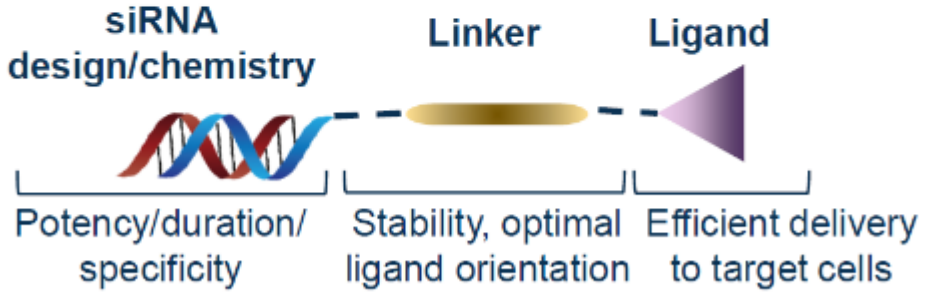
[1] Includes marketing application submissions; [2] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [3] Alnylam and Regeneron are evaluating potential combinations of the investigational therapeutics cemdisiran and pozelimab; [4] Novo Nordisk is leading and funding development of belcesiran; [5] Vir is leading and funding development of ALN-HBV02; [6] Regeneron is leading and funding development of ALN-HSD; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established. **As of December 2023**

Alnylam®

Achieving Best-in-Class Extrahepatic Delivery

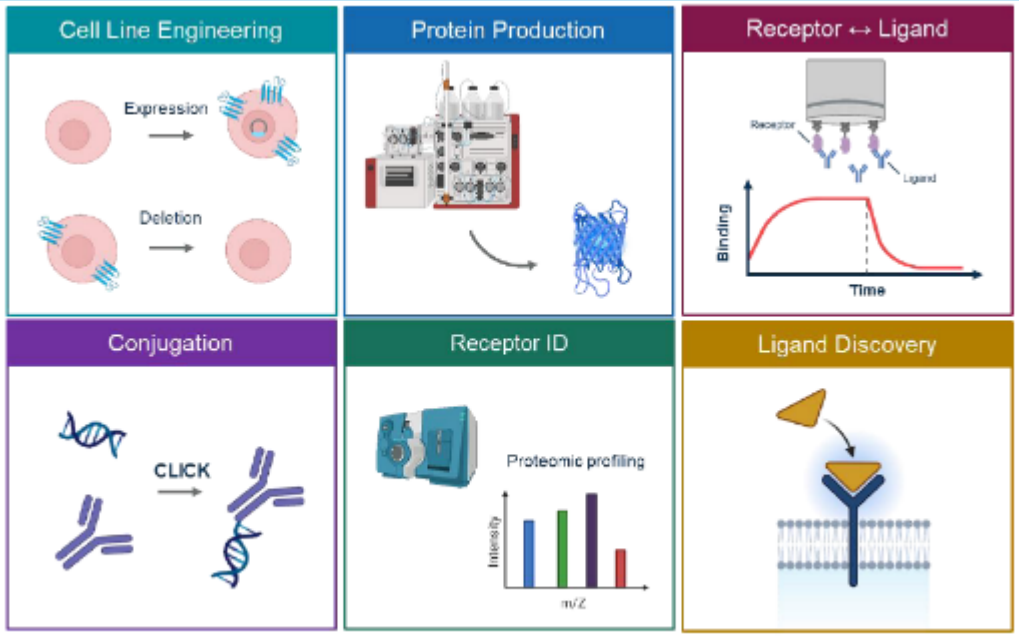
Excellence in Delivery for Liver and Now CNS, and Expanding to Additional Tissues

Extensive knowhow from earlier delivery efforts



Range of ligands for tissue-specific delivery

Fueled by core capabilities



Differentiated profile

- Extensive preclinical characterization provides high confidence in human translation
  - ✓ Safety
  - ✓ Efficacy
  - ✓ CMC
- Minimize liver sink to improve exposure in tissue of interest
- Potential for targeting multiple tissues (e.g., liver + adipose/muscle)
- Desired features for best-in-class differentiating profile

SC dosing → ≤ 3 mg/kg ED_{90} → Efficient Manufacturing

Alnylam

Driving a Large Multi-Organ Pipeline to Clinic by 2025

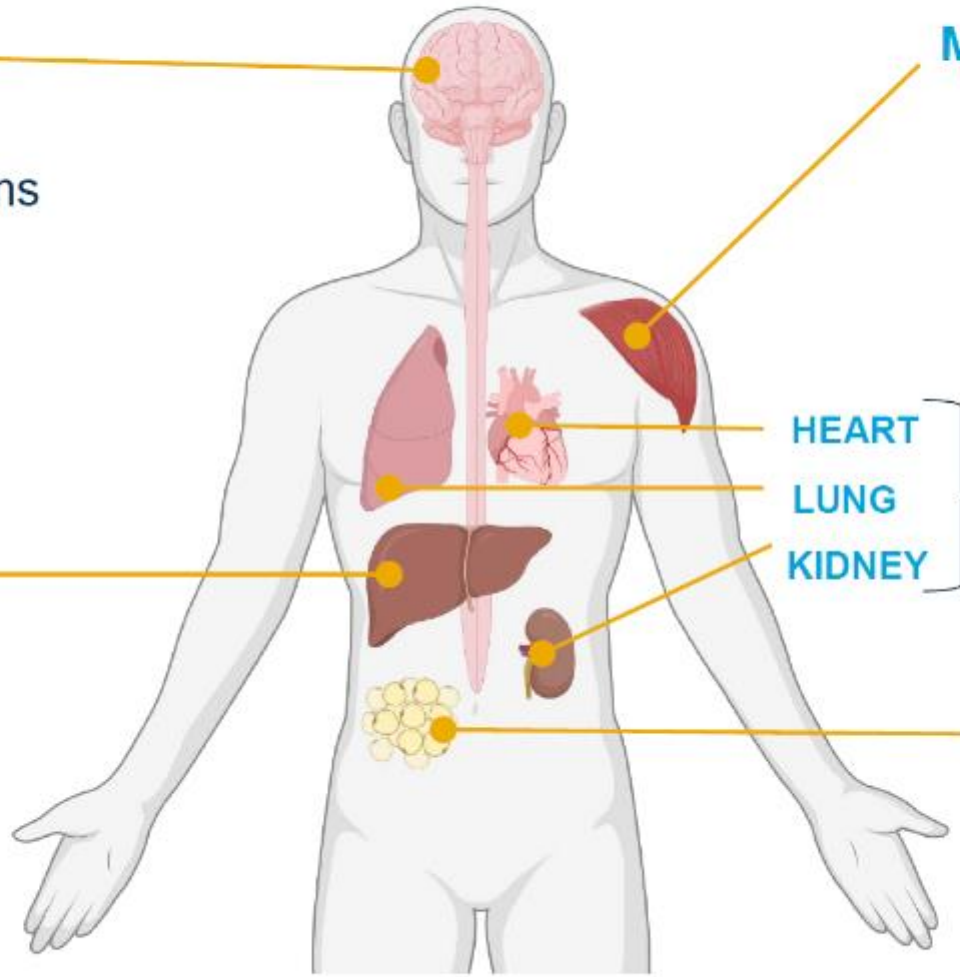
From Liver Delivery to CNS Human PoC; Now Advancing to Adipose, Muscle, and More

CNS

2 new ALNY-led CNS INDs
3+ including partnered programs

LIVER

5 new ALNY-led liver INDs
10+ including partnered programs



MUSCLE

First ALNY
IND by 2025

HEART
LUNG
KIDNEY

Preclinical PoC;
IND timelines TBD

ADIPOSE

First ALNY
IND by 2025

Going forward, we will also be targeting multiple tissues simultaneously

Alnylam

Disclosure

STIFEL | Healthcare

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