Biopharmaceutical Sector

Weekly Update – December 11, 2023

STIFEL | Healthcare

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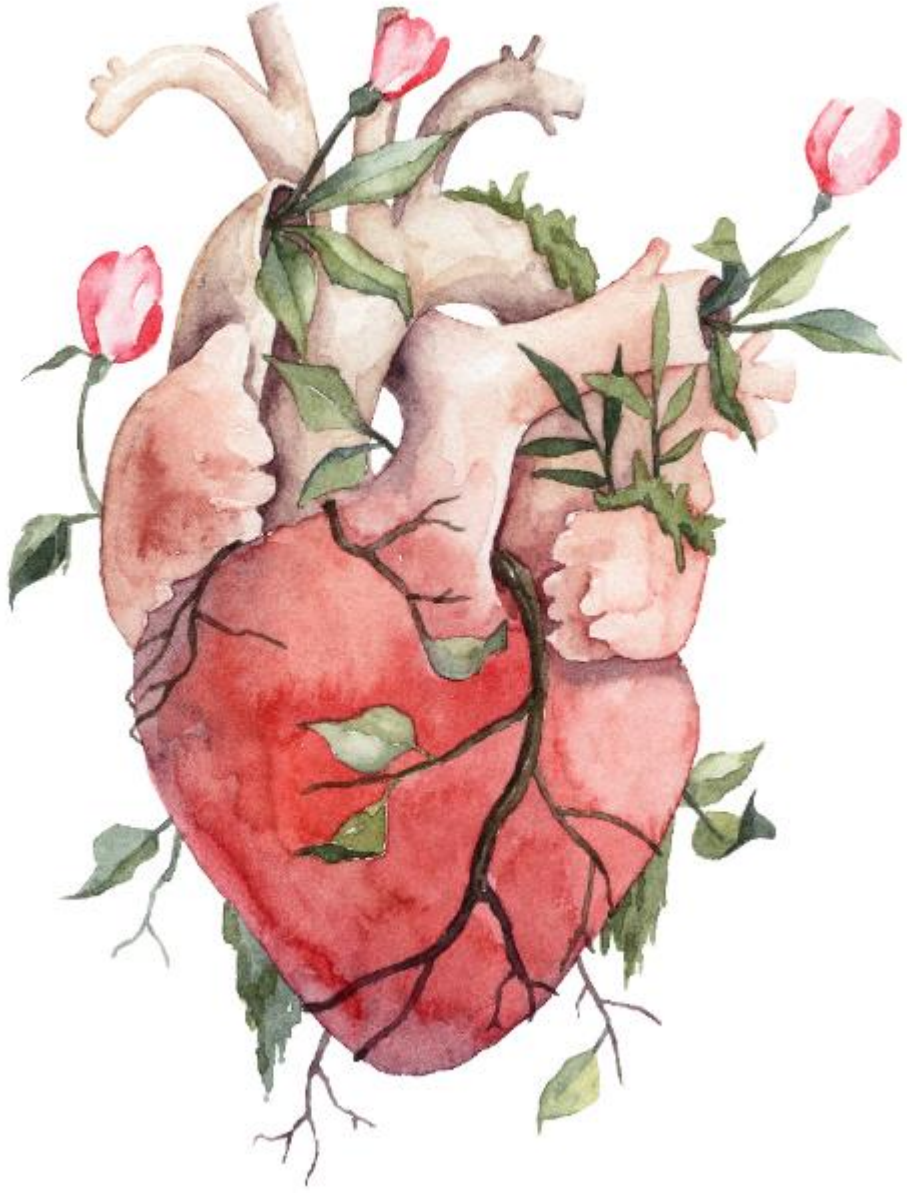

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Excellence in Biopharma Equity Underwriting

$180,000,000	$300,000,000	$185,000,000	$100,000,000	$517,500,000	$100,000,000	$250,070,000
SPYRE THERAPEUTICS	XENON	VIRIDIAN	LEXEO therapeutics	cerevel	Vistagen	Neumora
PIPE	Confidentially Marketed Follow-on Offering	PIPE	Initial Public Offering	Confidentially Marketed Follow-on Offering	Registered Direct	Initial Public Offering
Co-Lead Placement Agent	Joint Bookrunner	Co-Lead Placement Agent	Joint Bookrunner	Joint Bookrunner	Joint Bookrunner	Joint Bookrunner
December 2023	*November 2023*	*November 2023*	*November 2023*	*October 2023*	*October 2023*	*September 2023*

Raising equity capital in this market has not been easy. Stifel's Global Healthcare Group has remained focused on supporting equity issuance by biopharma companies throughout the market downturn with our deep platform comprised of bankers, sales professionals, traders and capital markets professionals.

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Recent issues in case you missed and want to read:

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 8, 2023.

The next event will be on December 15, 2023.

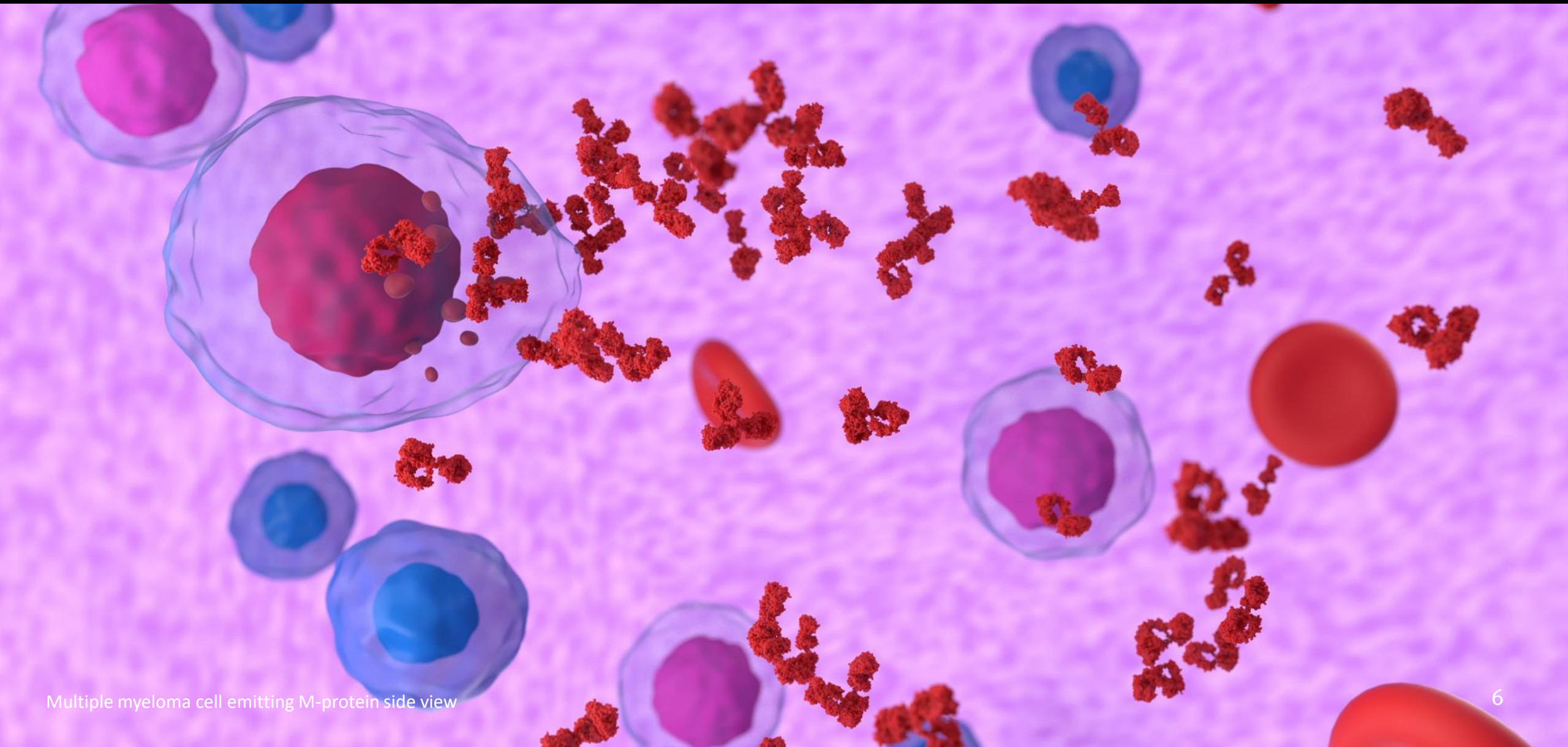
Please join us.

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. Stifel will be hosting an industry cocktail party on Jan 7th.

To meet with Stifel
yeungn@stifel.com

Macro Update



Multiple myeloma cell emitting M-protein side view

U.S. BUREAU OF LABOR STATISTICS

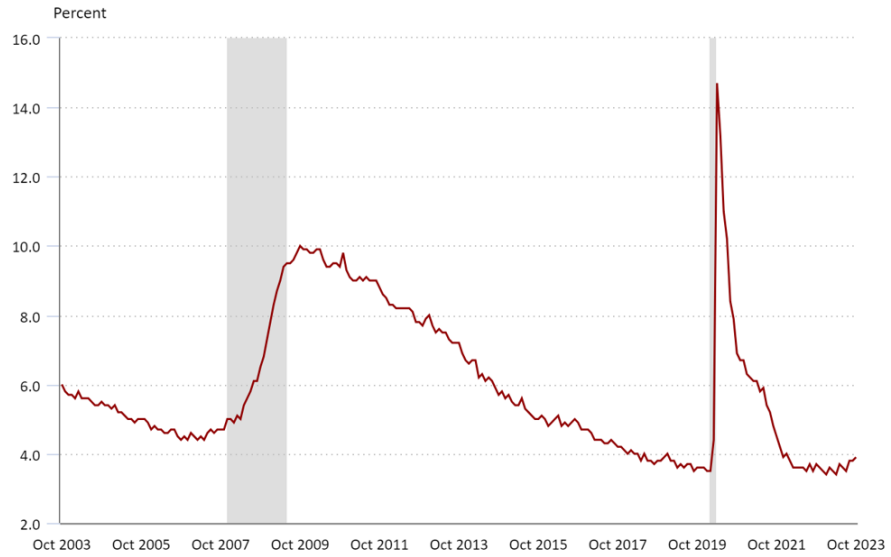
Last Week's October U.S. Jobs Report Positive for Inflation Outlook and Biotech

December 5, 2023

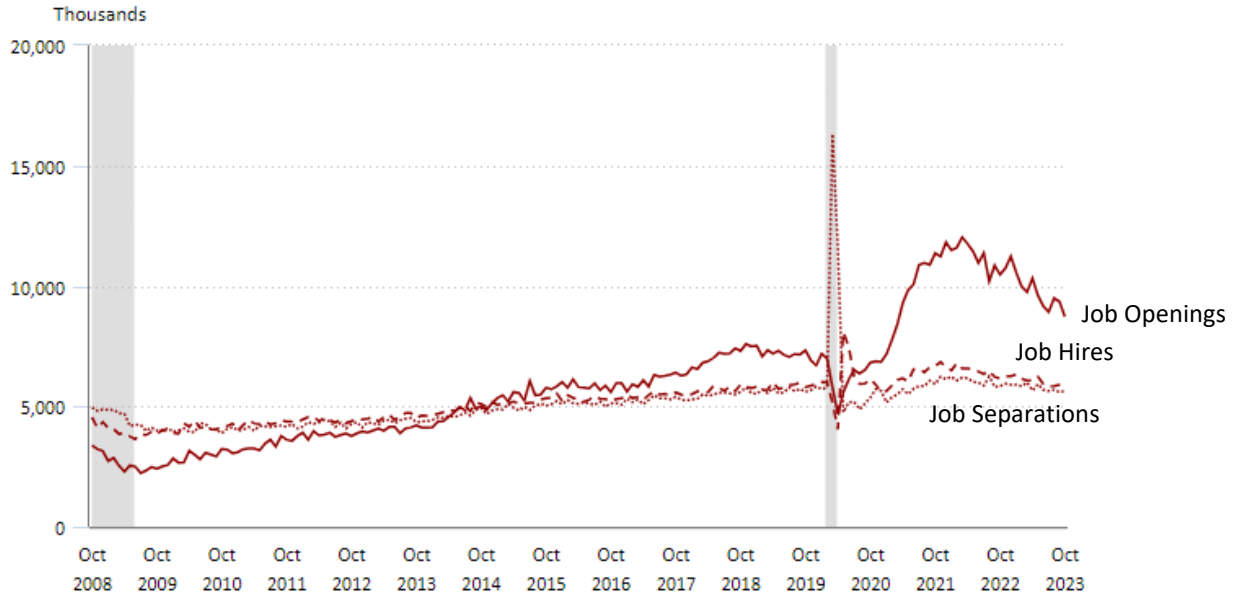
JOB OPENINGS AND LABOR TURNOVER – OCTOBER 2023

The number of job openings decreased to 8.7 million on the last business day of October, the U.S. Bureau of Labor Statistics reported today. Over the month, the number of hires and total separations changed little at 5.9 million and 5.6 million, respectively. Within separations, quits (3.6 million) and layoffs and discharges (1.6 million) changed little. This release includes estimates of the number and rate of job openings, hires, and separations for the total nonfarm sector, by industry, and by establishment size class.

Civilian Unemployment Rate Starting to Move Up



Job Openings Falling Quickly in the U.S. Economy



Source: https://www.bls.gov/news.release/jolts.nro.htm

Solid US Job Growth, Drop in Unemployment Rate Underscore Labor Market Resilience

Lucia Mutikani, Reuters, December 8, 2023

WASHINGTON, Dec 8 (Reuters) - U.S. job growth accelerated in November while the unemployment rate fell to 3.7%, signs of underlying labor market strength that suggested financial market expectations of an interest rate cut early next year were probably premature.

The Labor Department's closely watched employment report on Friday, however, did not change views that the Federal Reserve's rate-hiking cycle was complete as annual wages rose moderately last month. Inflation has been cooling in recent months.

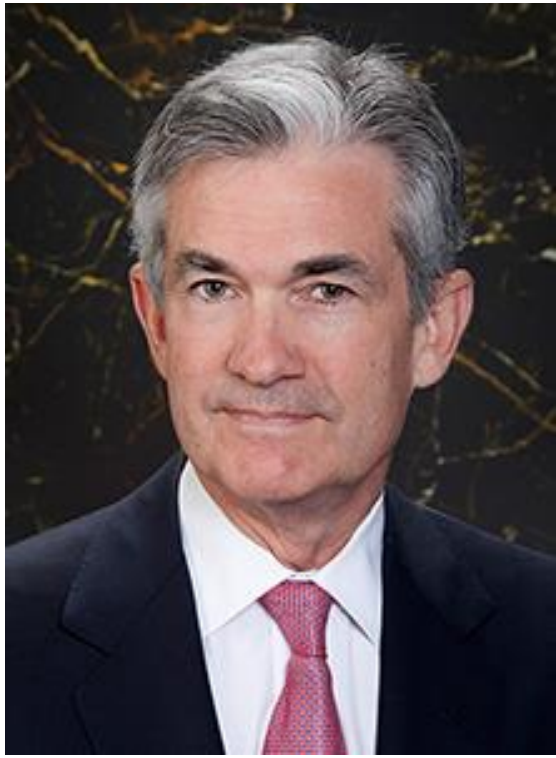
The drop in the jobless rate from a nearly two-year high of 3.9% in October alleviated fears that the economy was close to tipping into recession. The U.S. central bank is expected to keep rates unchanged next Wednesday.

"This was a relatively healthy report and will help to push back some of the excitement around imminent and aggressive rate cuts," said Richard de Chazal, macro analyst.

Source: https://www.reuters.com/markets/us/us-job-growth-accelerates-november-unemployment-rate-drops-37-2023-12-08/

Fed Chairman Powell Comments on Inflation

Jay Powell Talk at Spelman College, December 1, 2023 (excerpt)



Over the six months ending in October, core inflation ran at an annual rate of 2.5 percent, and while the lower inflation readings of the past few months are welcome, that progress must continue if we are to reach our 2 percent objective. High inflation initially emerged from a collision between very strong demand and pandemic-constrained supply. The normalization of supply and demand conditions has played a critical role in the disinflation so far, as has the substantial tightening of monetary policy and overall financial conditions over the past two years. The strong actions we have taken have moved our policy rate well into restrictive territory, meaning that tight monetary policy is putting downward pressure on economic activity and inflation. Monetary policy is thought to affect economic conditions with a lag, and the full effects of our tightening have likely not yet been felt. The forcefulness of our response to inflation also helped maintain the Fed's hard-won credibility, ensuring that the public's expectations of future inflation remain well-anchored. Having come so far so quickly, the FOMC is moving forward carefully, as the risks of under- and over-tightening are becoming more balanced.

As the demand- and supply-related effects of the pandemic continue to unwind, uncertainty about the outlook for the economy is unusually elevated. Like most forecasters, my colleagues and I anticipate that growth in spending and output will slow over the next year, as the effects of the pandemic and the reopening fade and as restrictive monetary policy weighs on aggregate demand. The FOMC is strongly committed to bringing inflation down to 2 percent over time, and to keeping policy restrictive until we are confident that inflation is on a path to that objective. **It would be premature to conclude with confidence that we have achieved a sufficiently restrictive stance, or to speculate on when policy might ease. We are prepared to tighten policy further if it becomes appropriate to do so.**

Source: https://www.federalreserve.gov/newsevents/speech/powell20231201a.htm

Economists See No Fed Rate Cuts Until July 2024

Colby Smith and Eva Xiao, *Financial Times*, December 5, 2023 (excerpt)

The US central bank will hold off on interest rate cuts until at least July 2024 and deliver less relief than financial markets expect, according to leading academic economists polled by the Financial Times. While most of those surveyed thought the rate-raising phase of the Federal Reserve's historic monetary tightening campaign was now over, almost two-thirds of the respondents thought the central bank would only begin to cut its benchmark rate by the third quarter of 2024 or later.

Three-quarters of the economists, polled between December 1 and December 4, also expect the Fed to lower the federal funds rate from its current 22-year high of 5.25-5.5 per cent by just half a percentage point or less next year.

That is a much later and smaller move than Wall Street is wagering, with traders in futures markets ramping up bets that the Fed will begin to cut as early as March and will lower the federal funds rate to about 4 per cent by the end of the year — more than a full percentage point below its current level.

Source: https://www.ft.com/content/8c8fdc12-960f-4c91-bda6-e1a578db44ec

Bank of England Warns That Higher Rates ‘Have Yet to Come Through’ to an Already Weak Economy

Elliot Smith, *CNBC*, Dec 6, 2023

LONDON — The Bank of England on Wednesday warned that although household finances are faring better than expected, higher borrowing costs have yet to fully feed through to the economy.

In its half-yearly Financial Stability Report, the central bank noted that “the overall risk environment remains challenging” amid a sluggish domestic economy, further risks to global growth and inflation and heightened geopolitical tensions.

The Bank of England hiked interest rates by more than 500 basis points between December 2021 and August 2023, taking its main rate to a 15-year high in a bid to combat soaring inflation. Its Financial Policy Committee highlighted in the report that long-term interest rates in both the U.K. and the U.S. are now around their pre-2008 levels.

“The full effect of higher interest rates has yet to come through, posing ongoing challenges to households, businesses and governments, which could be amplified by vulnerabilities in the system of market-based finance,” the FPC said.

“So far, and while the FPC continues to monitor developments, U.K. borrowers and the financial system have been broadly resilient to the impact of higher and more volatile interest rates.”

Source: https://www.cnbc.com/2023/12/06/bank-of-england-warns-that-higher-rates-have-yet-to-come-through.html

Inflation, Disinflation and Vibeflation

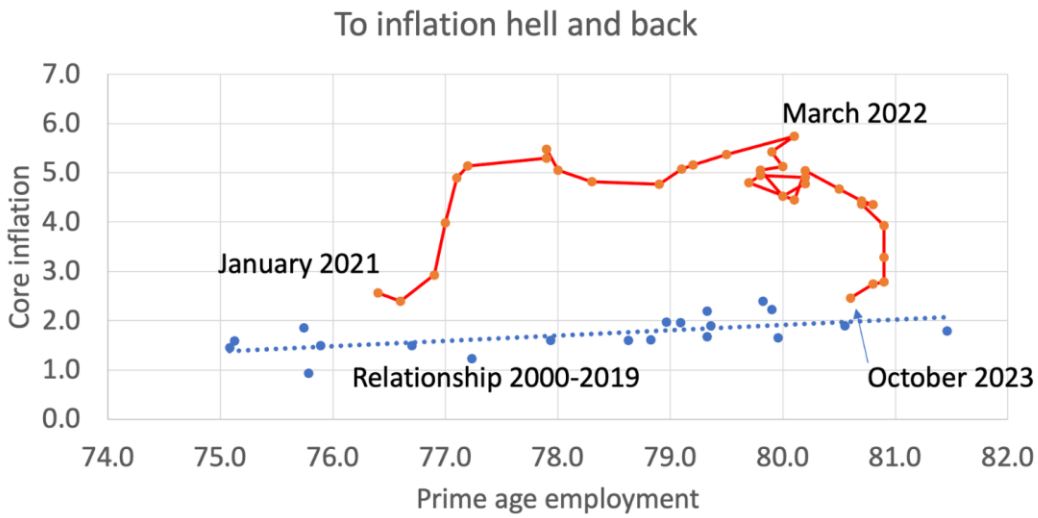
Paul Krugman, "Inflation, Disinflation and Vibeflation," *NYT*, Opinion, Dec 5, 2023

What's remarkable isn't just the fact that we've made so much progress against inflation, but also the fact that this progress has seemed to come without any visible cost. So far, this has been "immaculate disinflation," requiring neither a recession nor a large rise in unemployment.

Here's a chart I find helpful for telling the story of inflation in recent years. The horizontal axis shows the fraction of adults between 25 and 54 who are employed, an indicator that is closely correlated with the unemployment rate but has seemed to be a bit better at measuring how "hot" the labor market is running. The vertical axis shows core inflation. The blue dots at the bottom are annual numbers from 2000 to 2019, while the red line above shows the path since January 2021. Prepandemic, there was on average a modest positive relationship between employment and inflation, shown by the dotted line. But inflation went far higher than this relationship would have led you to expect, then rapidly came down without any significant loss in jobs.

So, what explains this history, and how does it compare with economists' predictions?

There were some big disagreements among economists here. Almost everyone, I think, was surprised by how easily we reduced inflation. But some were more surprised than others.



This suggests that inflation may have had less to do with overspending than it did with pandemic-related disruptions; see the article by Claudia Sahm in "Quick Hits" below. But my big question is why so many economists predicted that the rapid initial rise in inflation would be followed by protracted stagflation. The thing is, we have a standard story about why '70s inflation was so hard to end, which relies on the way persistent inflation had become entrenched in expectations. But this clearly wasn't the case in 2022. So while predictions of inflation in 2021 more or less reflected textbook macroeconomics, predicting stagflation after 2022 meant throwing out the textbook in favor of novel arguments for pessimism.

Source: https://www.nytimes.com/2023/12/05/opinion/inflation-disinflation-economists.html

Decisive Moment Arrives With $4 Trillion Stocks Rally at Stake

Jess Menton, Elena Popina and Carly Wanna, *Bloomberg*, December 9, 2023 (excerpt)

Investors are facing a pivotal week as a key measure of inflation that hits Tuesday and the Federal Reserve's interest-rate decision on Wednesday are expected to set the tone for the stock market and economy heading into 2024.

Growing speculation that the Fed is done hiking rates and will start cutting by mid-year is fueling a sharp drop in Treasury yields and rekindling investors' risk appetite. The S&P 500 Index has added roughly $4 trillion in market value since late October, as traders rush into beaten-down areas of the market like small caps, which typically benefit from falling borrowing costs.

"Stocks have been rallying on optimism the Fed is done raising rates," said Chris Zaccarelli, chief investment officer at Independent Advisor Alliance. "The pricing has been rational considering how much the 10-year yields have dropped since mid-October. It seems like stocks will continue to grind higher as we enter 2024."

That said, a closer look reveals concerns about the week ahead. A measure of expected volatility in the S&P 500 for the next five trading sessions is surging relative to the subsequent five days. At one point this week, the gap reached the widest since March for such a period, signaling rising demand to hedge against turbulence.

Tuesday kicks off the one-two punch of crucial moments next week, with the release of November's consumer price index. Signs of ebbing inflation could buoy shares into year-end by cementing expectations that the Fed will soon shift to easing. Consumer prices likely rose at a 3.1% annual pace, the lowest since June, according to a Bloomberg survey.

The next day, the central bank is projected to keep policy steady for the third straight meeting. With traders anticipating about a percentage point of total easing next year, they'll be watching officials' rate projections particularly closely as well as Chair Jerome Powell's press conference.

Meanwhile, many active managers who sat out this year's rally are trying to make up for lost ground before the end of the year, creating even more stock-market momentum. Large-cap active funds struggled to keep up with last month's rally, with just 41% beating their benchmark, data compiled by Bank of America Corp. show.

Source: https://www.bloomberg.com/news/articles/2023-12-09/stock-market-s-last-decisive-moment-of-2023-fuels-a-wall-of-worry

Biopharma Market Update

The XBI Closed at 79.3 Last Week (Up 1.9%)

The XBI headed up last week for the fifth time in six. Jobs data released on Friday Dec 8th tempered the rise, but, overall, the market rally is very much intact. Next week features a critical FOMC meeting. The XBI remains down while the S&P 500 is now up over 20% for the year.

Biotech Stocks Up Last Week

Return: Dec 2 to Dec 8, 2023

Nasdaq Biotech Index: +1.2%
Arca XBI ETF: +5.7%
Stifel Global Biotech EV (adjusted): 3.7%*
S&P 500: +0.2%

Return: Jan 1 to Dec 8, 2023

Nasdaq Biotech Index: -4.5%
Arca XBI ETF: -4.4%
Stifel Global Biotech EV (adjusted): 5.5%*
S&P 500: +20.4%

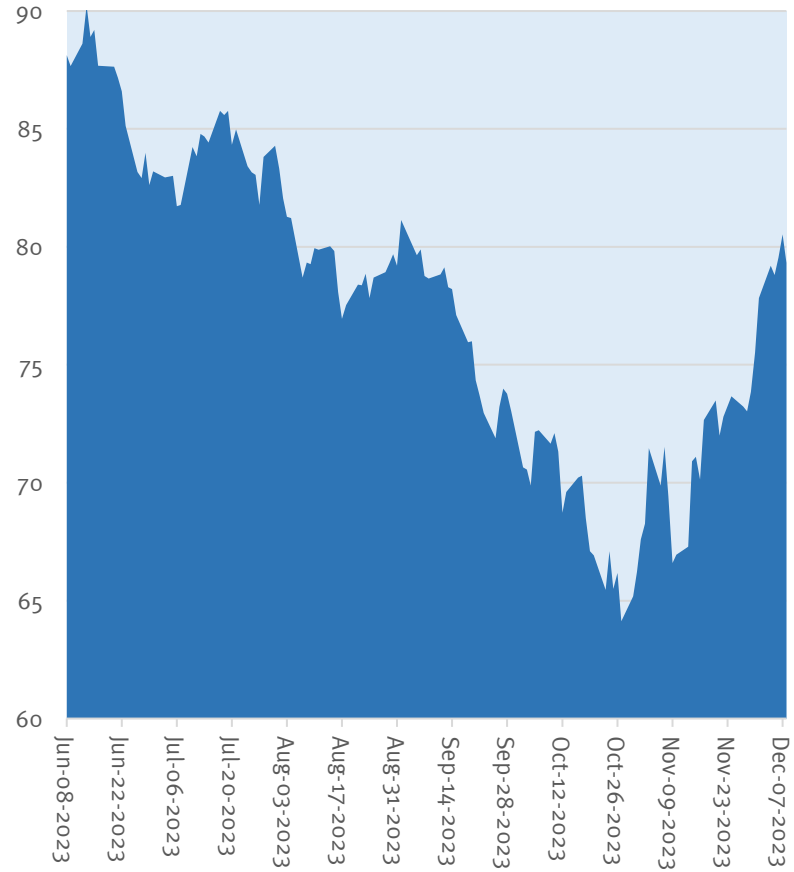
VIX Down

Oct 21: 29.7%
Jan 20: 19.9%
May 26: 18.0%
July 21: 13.6%
Sep 29: 17.3%
Oct 27: 21.2%
Nov 17: 13.8%
Dec 1: 12.6%
Dec 8: 12.35%

10-Year Treasury Yield Flat

Oct 21: 4.2%
Jan 20: 3.48%
May 26: 3.8%
July 21: 3.84%
Sep 29: 4.59%
Oct 27: 4.86%
Nov 17: 4.44%
Dec 1: 4.24%
Dec 8: 4.23%

XBI, June 8 to Dec 8, 2023



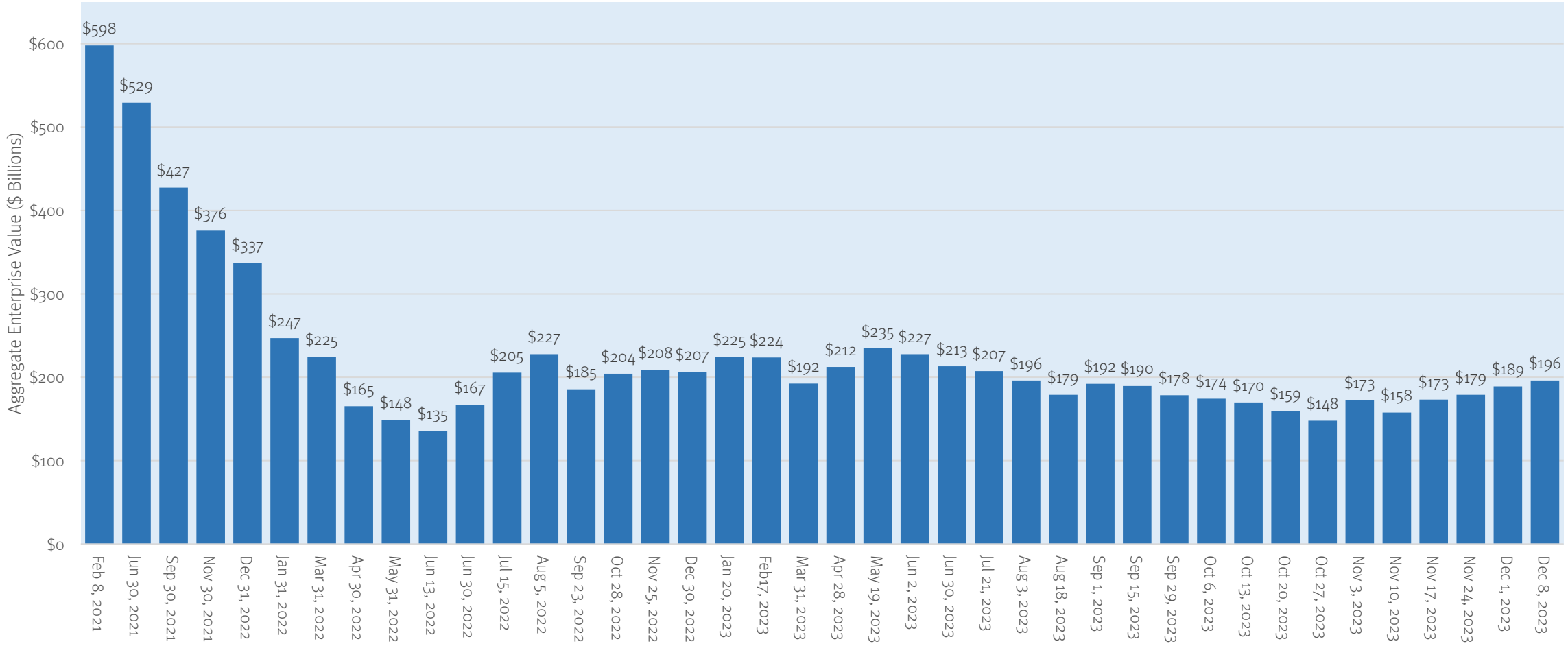
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector is Now Up 33% in Recent Rally

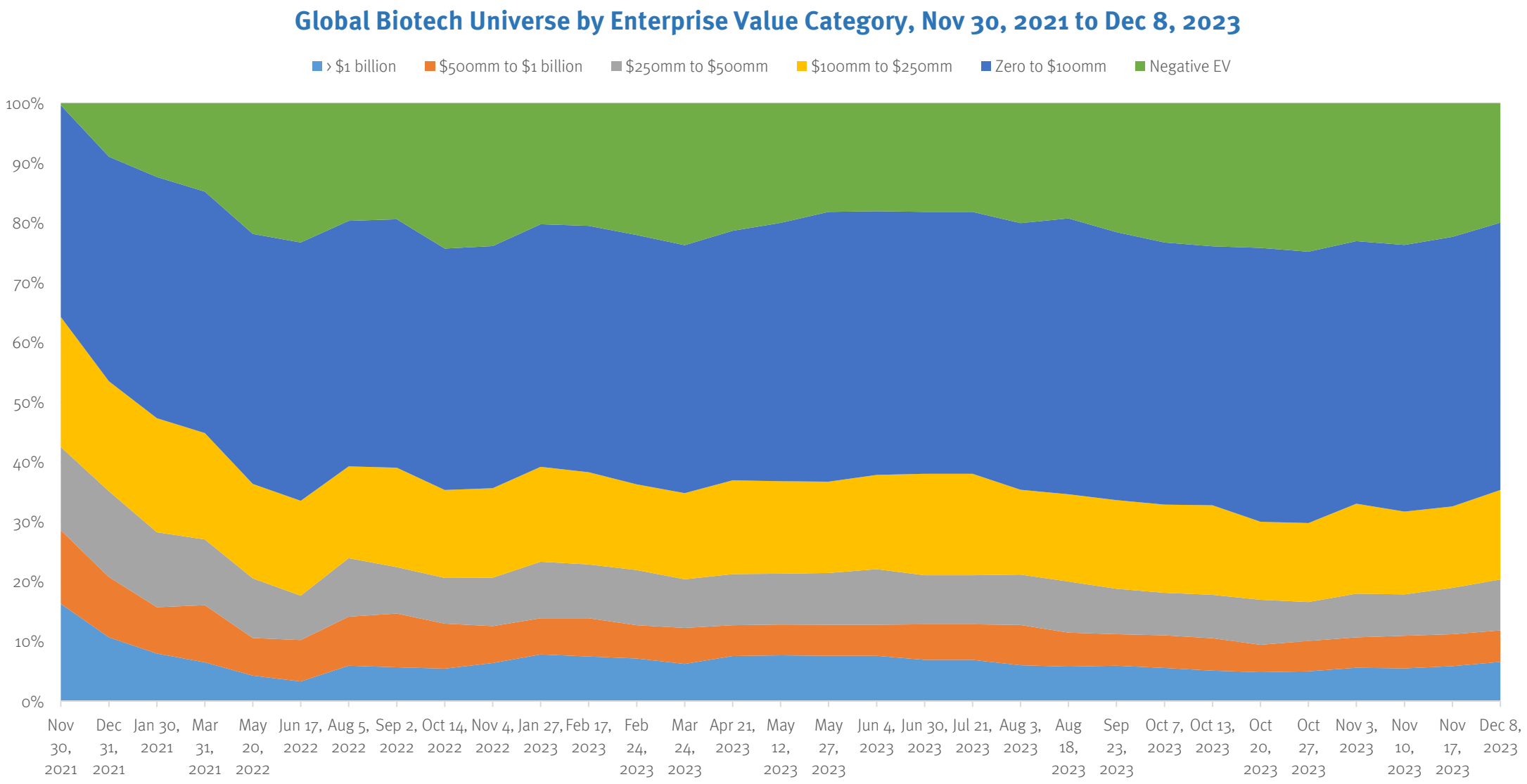
The total enterprise value of the global biotech sector rose by 3.7% last week and is now up 5.5% for the year after adjusting for exits and entries. Biotech values are up 33% since their trough on October 27, 2023.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Dec 8, 2023 ($ Billions)



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

Global Biotech Neighborhood Continuing to Improve



Source: CapitalIQ and Stifel analysis.

Number of Negative Enterprise Value Life Sciences Companies Fell to 176 in Last Week

Source: CapitalIQ

The count of negative EV life sciences companies worldwide fell from 189 one week ago to 176 last Friday.

The negative EV life science company population has shrunk by 24% since peaking on Oct 27, 2023.

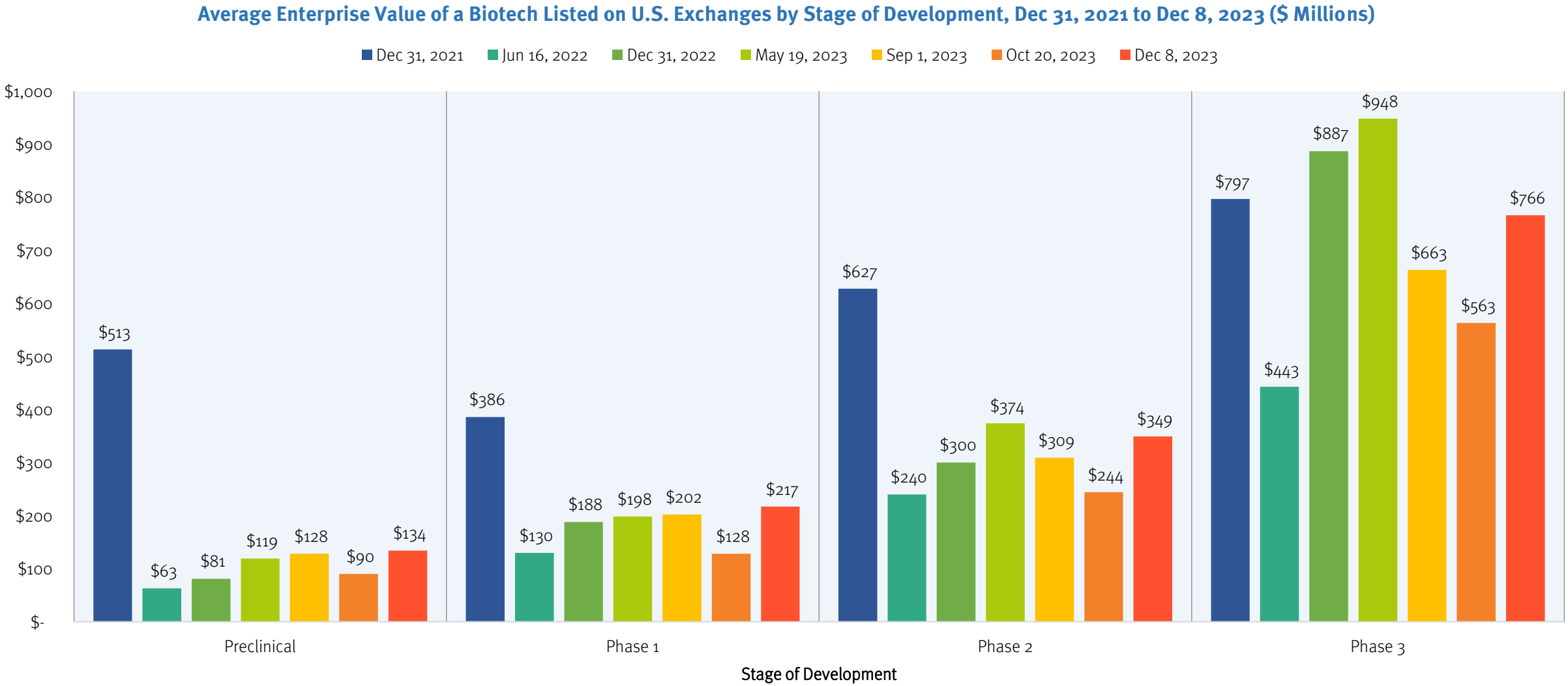
Life Sciences Sector Down 0.7% Last Week

Last week saw a 0.7% drop in life sciences stocks worldwide. The sector's value dropped by $59 billion. Biotech was up the most while CDMO's, pharma services and HCIT stocks dropped the most.

Sector	Firm Count	Enterprise Value (Dec 8, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$84,656	-2.0%	3.6%	0.9%
Biotech	812	$198,707	2.6%	23.8%	-5.1%
CDMO	40	$135,850	-8.0%	-10.2%	-23.7%
Diagnostics	83	$263,575	0.7%	14.7%	1.0%
OTC	31	$27,553	-0.8%	-0.4%	-2.4%
Pharma	724	$5,749,926	-0.4%	2.4%	-2.3%
Services	39	$198,334	-2.9%	0.0%	2.1%
Tools	53	$629,848	-1.1%	9.5%	-17.3%
Devices	181	$1,539,944	-1.0%	8.0%	-2.3%
HCIT	11	$20,844	-3.1%	3.6%	-38.7%
Total	**2055**	**$8,849,237**	**-0.7%**	**4.3%**	**-3.6%**

Source: CapitalIQ

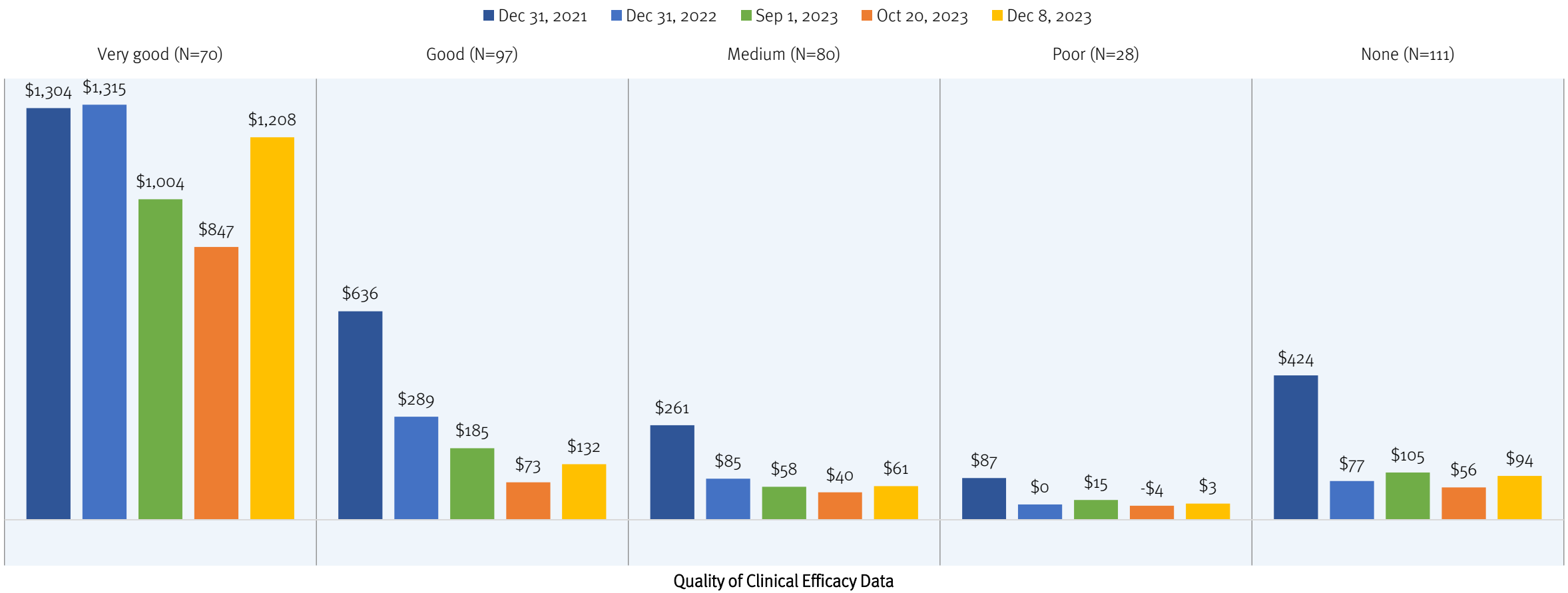
Average US Biotech with Phase 3 Data Up from $563mm in Value to $766mm in Value in Just Six Weeks



Source: CapitalIQ and Stifel analysis.

Biotech Quality Premium is Still Very Much In Place

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Quality of Efficacy Data, Dec 31, 2021 to Dec 8, 2023 ($ Millions)

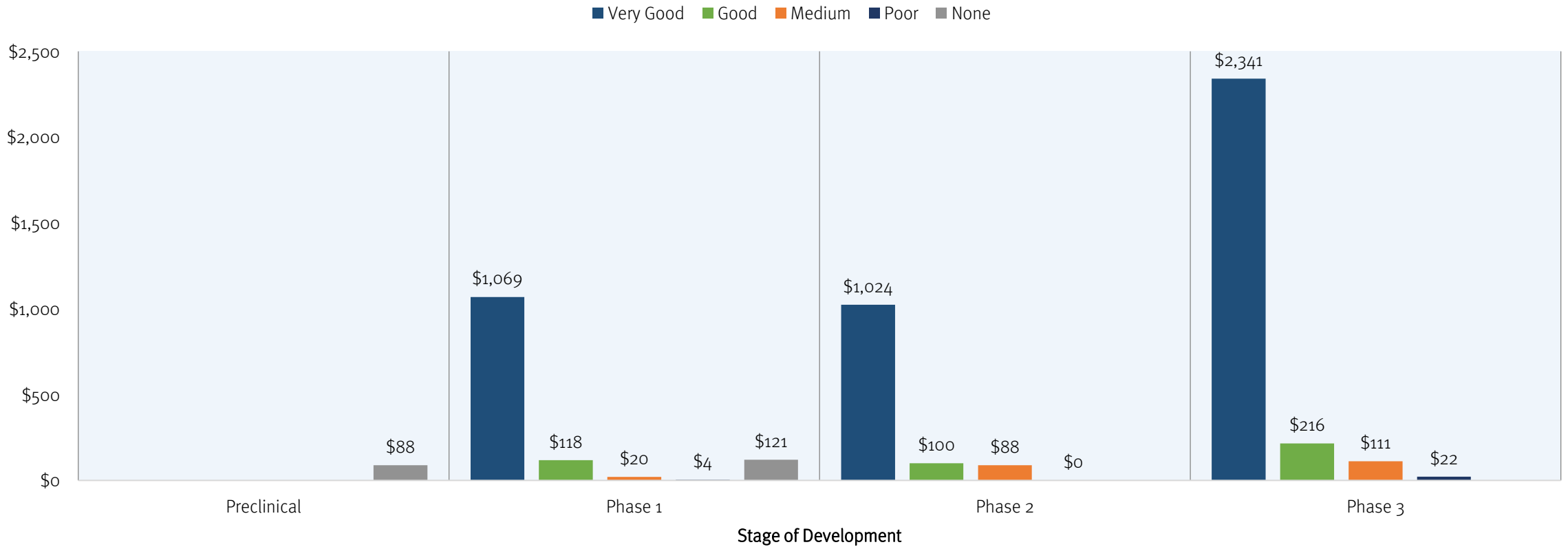


Source: CapitalIQ and Stifel analysis

Late-Stage Companies with Quality Data Garnering a High Premium

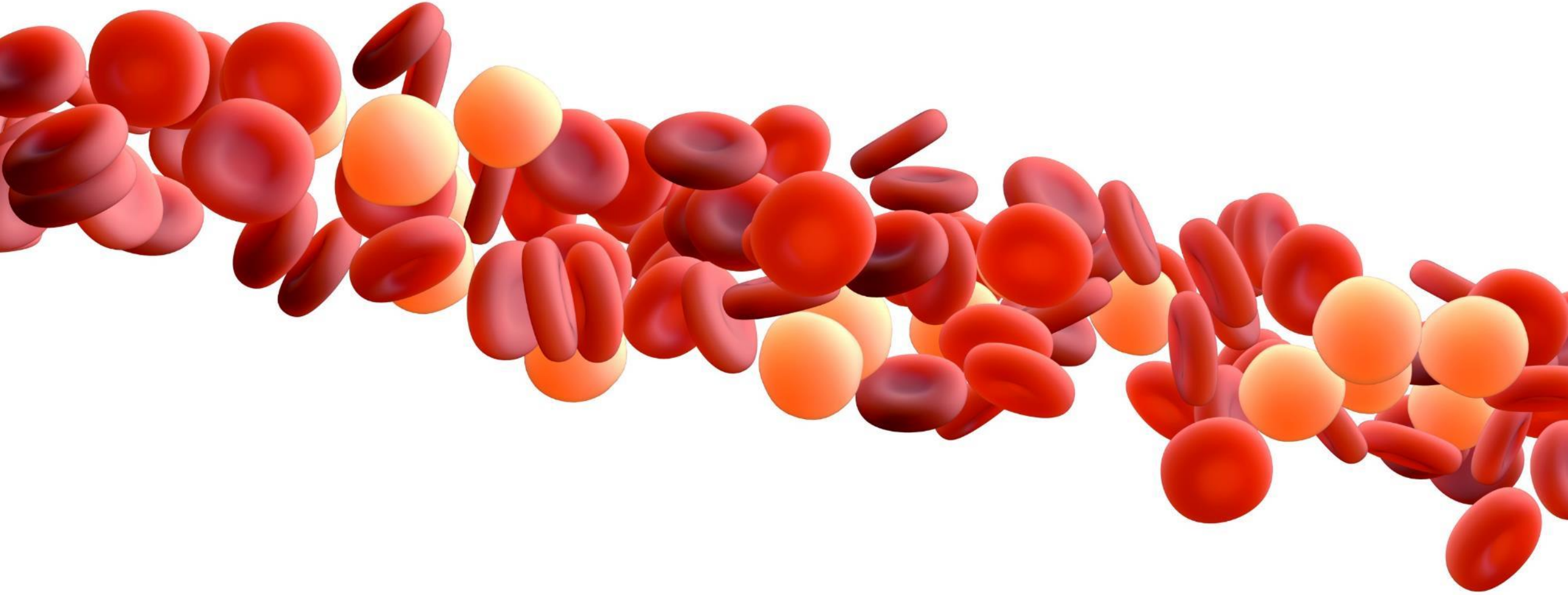
It remains a "winner take all" type of biotech market. Investors are highly discerning, placing much less value on companies with less than excellent datasets.

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Dec 8, 2023 ($ millions)



Source: CapitalIQ and Stifel analysis

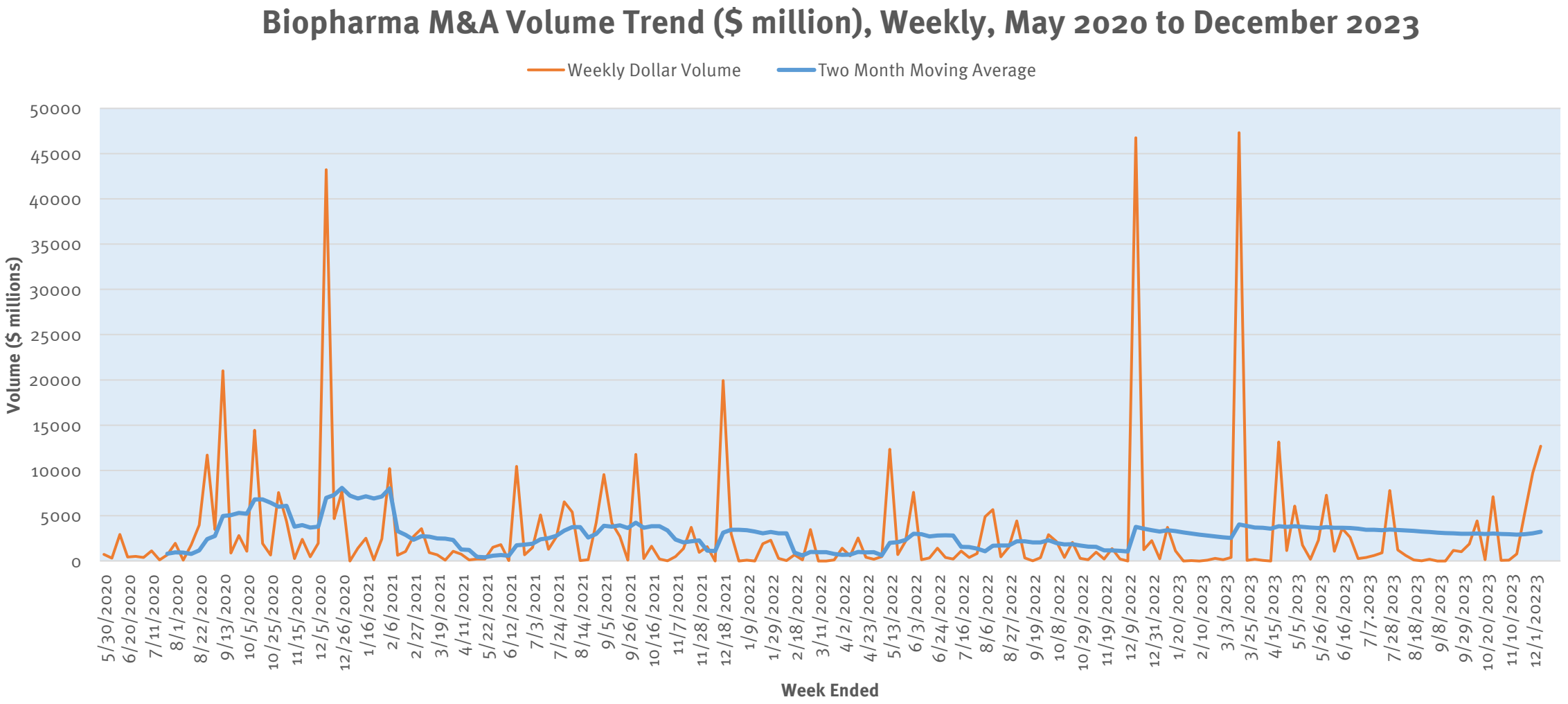
Deals Environment Update



Red blood cells in circulation

M&A Market Strong

The last week has been very strong in M&A with AbbVie buying Cerevel for $8.7 billion and Roche buying Carmot for $2.7 billion.



Source: S&P, CapitalIQ

AbbVie to Acquire Cerevel Therapeutics for $8.7 Billion

NORTH CHICAGO, Ill. and CAMBRIDGE, Mass., Dec. 6, 2023 /PRNewswire/ — AbbVie Inc. (NYSE: ABBV) and Cerevel Therapeutics (NASDAQ: CERE) today announced a definitive agreement under which AbbVie will acquire Cerevel Therapeutics and its robust neuroscience pipeline of multiple clinical-stage and preclinical candidates with potential across several diseases including schizophrenia, Parkinson's disease (PD), and mood disorders. The acquisition complements AbbVie's neuroscience portfolio, adding a wide range of potentially best-in-class assets that may transform standards of care across psychiatric and neurological disorders where significant unmet needs remain for patients.

Under the terms of the transaction, AbbVie will acquire all outstanding shares of Cerevel for $45.00 per share in cash. The transaction values Cerevel at a total equity value of approximately $8.7 billion. The boards of directors of both companies have approved the transaction. This transaction is expected to close in the middle of 2024, subject to Cerevel shareholder approval, regulatory approvals, and other customary closing conditions.

"Our existing neuroscience portfolio and our combined pipeline with Cerevel represents a significant growth opportunity well into the next decade," said Richard A. Gonzalez, chairman and chief executive officer, AbbVie. "AbbVie will leverage its deep commercial capabilities, international infrastructure, and regulatory and clinical expertise to deliver substantial shareholder value with multibillion-dollar sales potential across Cerevel's portfolio of assets."

Cerevel's late-stage asset emraclidine, a positive allosteric modulator (PAM) of the muscarinic M4 receptor, is a potential best-in-class, next-generation antipsychotic that may be effective in treating schizophrenia patients. Schizophrenia impacts more than five million people in the G7 (U.S., France, Germany, Italy, Spain, United Kingdom, and Japan) and a significant opportunity for treatment innovation remains for new and better tolerated therapies. In a Phase 1b study, emraclidine has shown promising efficacy and safety in schizophrenia and is currently completing two Phase 2 trials that were designed to be registration enabling. In addition, emraclidine has potential in dementia-related psychosis in Alzheimer's disease and PD. Emraclidine is currently in a Phase 1 study in elderly healthy volunteers in support of a potential Alzheimer's disease psychosis program.

AbbVie will acquire all outstanding Cerevel common stock for $45.00 per share in cash. The proposed transaction is subject to customary closing conditions, including receipt of regulatory approvals and approval by Cerevel shareholders. The proposed transaction is expected to be accretive to adjusted diluted earnings per share (EPS) beginning in 2030.

Source: https://news.abbvie.com/2023-12-06-AbbVie-to-Acquire-Cerevel-Therapeutics-in-Transformative-Transaction-to-Strengthen-Neuroscience-Pipeline

$19 Billion in a Week: AbbVie Makes Two Big Bets

David Wainer, *Wall Street Journal*, Dec 8, 2023 (excerpt)

The Chicago-area company, best known for selling Botox and immune-disease drug Humira, announced on Thursday of last week it would pay $10.1 billion for biotech ImmunoGen. On Wednesday, it followed up with the acquisition of Cerevel Therapeutics for $8.7 billion.

The timing is also important. These types of target companies frequently either just had their first drug approved or have recently released strong clinical data. In the case of Cerevel, AbbVie's experienced neurology experts think they have enough data from its schizophrenia drug, which is part of a new class of medications that target the muscarinic receptor, to make a call.

Cerevel is currently conducting two mid-stage trials and the results are expected next year. Schizophrenia affects more than five million people in the U.S., France, Germany, Italy, Spain, the U.K. and Japan, according to AbbVie. The company indicated it believes the early results show the drug, emraclidine, can deliver meaningful antipsychotic benefits to patients while avoiding the harsh side effects associated with existing options. AbbVie sounded pretty confident about the study on Thursday. During an analyst call, Roopal Thakkar, the company's chief medical officer, said that while the studies aren't technically late-stage, they are designed in a way to allow the company to file for approval.

AbbVie had been hungry for deals because Humira, one of the top-grossing drugs of all time, started facing lower-priced competition this year. Responding to a question about deal capacity, AbbVie management said it was probably done with midsize deals like these for a while. "We have previously said that our BD [business development] efforts were focused on identifying assets that can drive growth in the next decade," said Robert Michael, president and chief operating officer. "And we've accomplished that…I would not anticipate similar sized transactions for the foreseeable future."

AbbVie has gone from a ravenous customer at the biotech counter to a fully satiated diner. Others remain in line.

Source: https://www.wsj.com/health/pharma/19-billion-in-a-week-abbvie-makes-two-big-bets-0ae90404

Bain Capital Banks Massive Return on Cerevel Deal

Ted Bunker and Ben Glickman, *Wall Street Journal*, Dec 7, 2023 (excerpt)

Bain Capital scored a more than 10-fold return on its investment in creating and fostering neuroscience drug developer Cerevel Therapeutics Holdings, which AbbVie agreed to acquire for $45 a share, giving the company an equity value of about $8.7 billion.

Boston-based Bain Capital initially committed $350 million to the company when it set the business up with drugmaker Pfizer, which contributed compounds that looked promising for the treatment of conditions such as Alzheimer's, epilepsy, schizophrenia and Parkinson's disease.

But the buyout firm's actual investment initially totaled $250 million, a securities filing shows. All in, Bain Capital's bet on the business delivered a return multiple "north of 10" on invested capital, the person said.

Bain Capital increased its commitment to the company about three years ago, participating in a $320 million private investment in public equity deal in conjunction with Cerevel's transition to a public listing by combining with a special-purpose acquisition company backed by life-sciences investment firm Perceptive Advisors. At that point, Bain Capital held about 60 million shares valued at about $10.10 each, or roughly $606 million, and Cerevel's equity value stood at $780 million, a securities filing shows.

The firm raised its bet on the business again less than two months ago, acquiring about 5.5 million Cerevel shares for $22.81 per share, investing a further $125 million, a separate filing shows. That brought the firm's stake to almost 65.7 million shares, or roughly 36.5% of Cerevel's shares, worth more than $2.95 billion at the $45 per share offered by AbbVie

Source: https://www.wsj.com/articles/bain-capital-banks-massive-return-on-cerevel-deal-7a6d1952

Carmot Therapeutics Enters into Agreement to Sell to Roche for $2.7 Billion

BERKELEY, Calif., December 3, 2023 (GLOBE NEWSWIRE) — Carmot Therapeutics Inc. (Carmot), a clinical-stage biotechnology company dedicated to developing life-changing therapeutics for people living with metabolic diseases including obesity and diabetes, today announced that it has entered into a definitive merger agreement for Roche to acquire Carmot at a purchase price of $2.7 billion upfront and the potential for $400 million in milestone payments.

“We are proud of the pipeline that we have built in obesity and diabetes and the strong data we have generated to date,” said Heather Turner, JD, Chief Executive Officer of Carmot. “With distinct routes of administration and the potential for combinations, we feel Carmot’s pipeline has the potential to meet patients where they are in their metabolic journey and have a significant impact on patients’ lives. We are confident that Roche will enable robust development of our programs and help us achieve our goal of delivering life-changing therapeutics for people living with metabolic and potentially other diseases.”

Carmot’s clinical pipeline includes subcutaneous and oral incretins with best-in-class potential to treat obesity in patients with and without diabetes. CT-388 is a weekly injectable, Phase 2 ready, dual GLP-1/GIP receptor agonist for the treatment of obesity in patients with and without type 2 diabetes. CT-996, currently in Phase 1, is a once-daily oral, small molecule GLP-1 receptor agonist intended to treat patients with obesity and type 2 diabetes. CT-868 is a Phase 2, once-daily subcutaneous injectable, dual GLP-1/GIP receptor agonist intended for the treatment of type 1 diabetes patients with overweight or obesity. Carmot also has preclinical programs in development for the treatment of metabolic diseases.

“The obesity epidemic is a worldwide crisis and only continues to worsen. By 2035 it is estimated that nearly half the world’s population will be overweight or obese1,” said Tim Kutzkey, PhD, Chair of Carmot’s Board of Directors. “A health problem of this magnitude requires significant commitment and resources to address, and we believe that patients will be best served with Carmot’s pipeline backed by the drug development expertise, extensive resources and worldwide reach of Roche.”

Source: https://carmot.us/carmot-therapeutics-enters-into-definitive-merger-agreement-with-roche/

Prominent Hedge Funds Stand to Benefit From Carmot Sale

Stephen Taub, *Institutional Investor*, Dec 6, 2023 (excerpt)

So much for going public.

Less than three weeks after Carmot Therapeutics filed initial plans to go public, the fledgling biopharma, which is developing therapeutics for obesity and diabetes, chose a much more lucrative way to monetize its potential. It agreed to be acquired by Roche Holdings for as much as $3.1 billion. Under the deal, Roche will give Carmot $2.7 billion in cash and up to $400 million in milestone payments. The price tag probably exceeds the amount of money Carmot would have raised in its IPO.

And as Institutional Investor recently reported, several prominent hedge funds stand to benefit. In the deal announcement, Roche noted that Carmot has three appealing incretins — gut hormones secreted after food intake that play a role in modulating blood glucose by stimulating insulin secretion and suppressing appetite — in various stages of development.

"The existing clinical data for Carmot's assets, especially the lead asset, CT-388, suggests a best-in-class potential to achieve and maintain weight loss with differentiated efficacy," Roche said. "Moreover, the assets provide an opportunity for combinations with existing Roche pipeline assets, including ones focused on other benefits, such as preserving muscle mass."

Several hedge funds are no doubt cheering the Carmot deal.

Carmot had disclosed in its initial IPO filing that RA Capital Management is its largest outside investor, with 7.2 percent of the shares. They are partly held by hedge fund RA Capital Healthcare Fund, with the bulk of the shares owned by RA Capital Nexus Fund III, a venture capital fund.

Deep Track Biotechnology Master Fund owns 5.8 percent of Carmot's shares.

Last year, RA Capital invested about $30 million and Deep Track about $10 million in Carmot's Series D convertible preferred stock. In May, Deep Track invested $25 million and RA Capital $10 million in Series E convertible preferred stock.

Millennium Management also participated in the Series E financing, although the investment was less than 5 percent.

Source: https://www.institutionalinvestor.com/article/2cjp355m5dqncbfm6hhco/premium/prominent-hedge-funds-stand-to-benefit-from-biopharmas-change-of-plans

Vanda Pharmaceuticals Acquires North American Rights to PONVORY for MS

Stifel was pleased to advise Vanda on its recent asset acquisition transaction last week.

WASHINGTON, Dec. 7, 2023 /PRNewswire/ -- Vanda Pharmaceuticals Inc. (Vanda) (Nasdaq: VNDA) today announced that it has acquired U.S. and Canadian rights to PONVORY® (ponesimod) from Actelion Pharmaceuticals Ltd. (Janssen), a Johnson & Johnson Company. PONVORY® is approved by the U.S. Food and Drug Administration (FDA) and Health Canada to treat adults with relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease. PONVORY® has a proven safety profile with over 10 years of data.

"The acquisition of Ponvory is a significant milestone for Vanda, as it expands our commercial portfolio and gives us access to a versatile immune response modifier that can potentially have broad application in treating a number of autoimmune-based disorders," said Mihael H. Polymeropoulos, M.D., Vanda's President, CEO and Chairman of the Board.

Under the terms of the agreement, Vanda paid $100 million to acquire the U.S. and Canadian rights to PONVORY®. Janssen will continue to operate the business pursuant to a Transitional Business License Agreement, during which time, Vanda and Janssen will transition regulatory and supply responsibility for PONVORY® to Vanda.

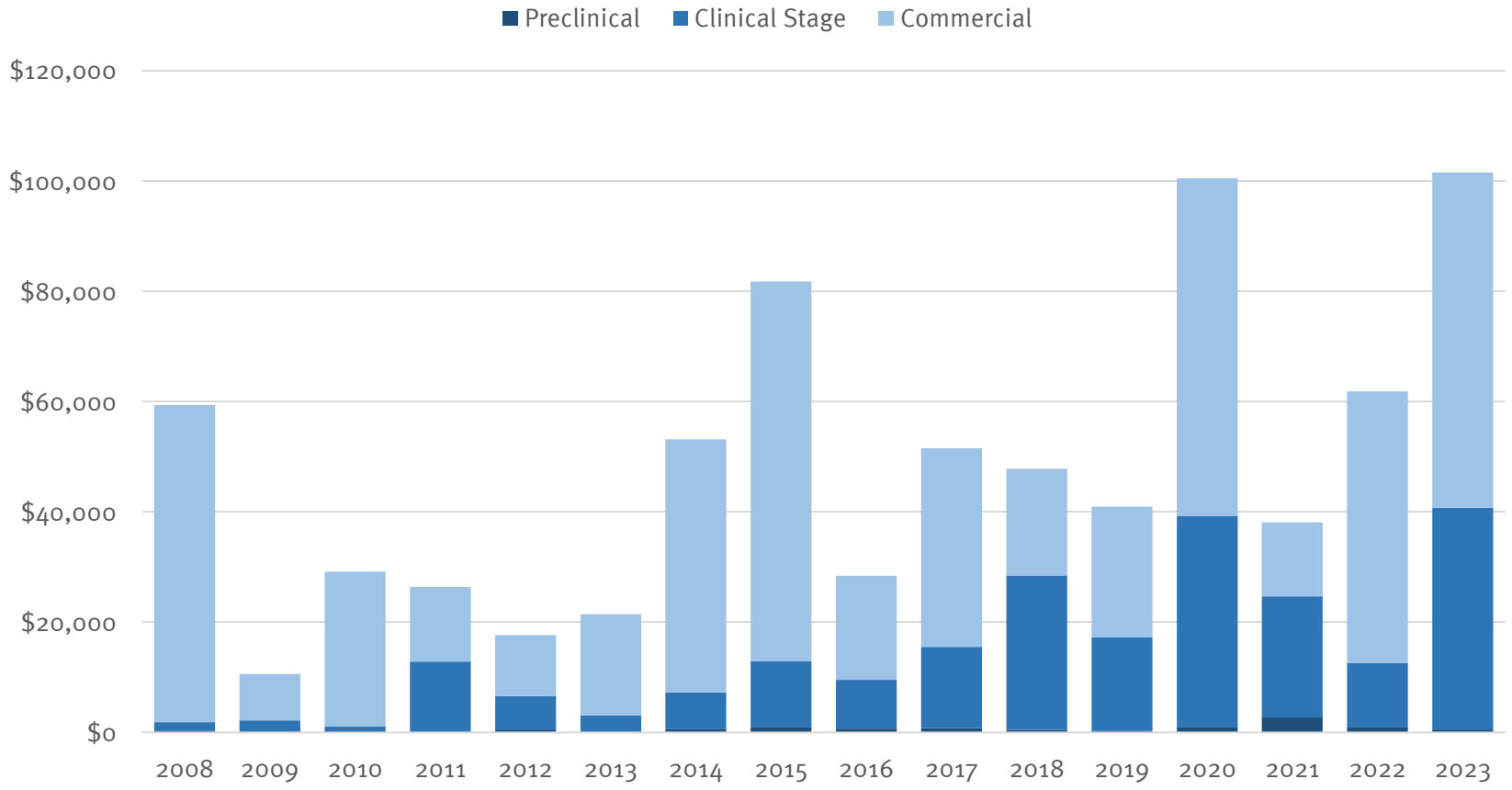
Stifel acted as exclusive financial advisor to Vanda with respect to this acquisition.

Source: https://www.prnewswire.com/news-releases/vanda-pharmaceuticals-acquires-us-and-canadian-rights-to-ponvory-ponesimod-a-selective-s1p1r-modulator-approved-for-patients-with-relapsing-multiple-sclerosis-302008402.html

Big Pharma Biotech M&A Volume at Record Level in 2023

Big Pharma acquisition Volume in 2023 of Biotechs has surpassed record levels despite IRA/FTC uncertainties. The majority of volume in 2023 has been for commercial stage companies.

Dollar Volume of Big Pharma M&A Acquisitions of Biotechs for Between $50 Million and $45 Billion by Stage of Target, 2008 to 2023 ($ millions)



Source: DealForma and Stifel analysis.

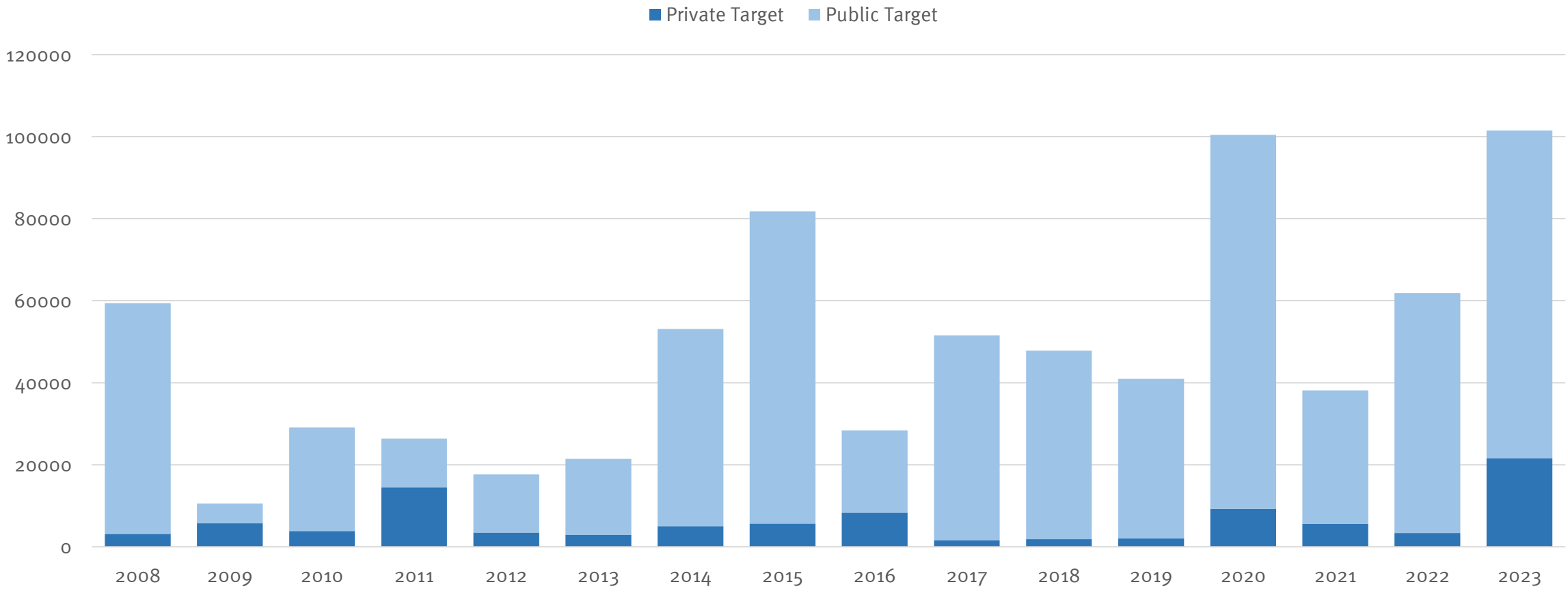
This chart measures sub-$45 billion M&A which we called “Biotech”, leaving out the horizontal “mega deals” like AbbVie / Allergan and BMS / Celgene.

With those larger deals out of the calculus, one can see the cumulative effect of pharma acquisitions of biotech. What becomes apparent is that 2023 has been an exceptionally busy year by any historic measure.

Big Pharma Biotech M&A Volume at Record Level in 2023

We have seen $76.4 billion of public biotech takeouts by big pharma in 2023. While very busy, 2020 saw more public takeout volume than 2023 (so far).

Dollar Volume of Big Pharma M&A Acquisitions of Biotechs for Between $50 Million and $45 Billion by Whether Target is Public, 2008 to 2023 ($ millions)



Source: DealForma and Stifel analysis.

Biotech Deals Are Heating Up. Why 2024 Could Be Even Hotter for M&A.

Josh Nathan-Kazis, *Barron's*, Dec 8, 2023 (excerpt)

Biotech deals are heating up as the year comes to an end, and analysts say the hot streak will likely continue in coming months. That could portend a rebound for the biotech sector, which has performed abominably in recent years.

Large biopharma companies have announced a string of big deals as the year comes to a close. AbbVie said late Wednesday it would buy the neuroscience-focused biotech Cerevel Therapeutics for $8.7 billion—after announcing a week earlier it would acquire the cancer-focused biotech ImmunoGen for $10.1 billion. Roche Holding said Monday it would buy the privately held Carmot Therapeutics for $2.7 billion.

Of the 18 biotech acquisitions worth over $1 billion announced so far this year, a third have come since the start of October, according to the website BioPharma Dive.

More M&A could boost the XBI, as buyouts free up cash from specialist investors to reinvest in the sector and the news flow piques generalist interest.

Where to expect that M&A, however, is tough to guess. Biotechs with obesity, immunology, and cancer assets have been in particular demand this year.

One possibility that drew investor attention earlier this week was that Pfizer could look to make a deal with a biotech developing an anti-obesity pill, given the roadblocks its own internally-developed anti-obesity pill has hit. Shares of Viking Therapeutics, which has an obesity pill under development, are up 47% so far in December, while shares of Terns Pharmaceuticals, which is also testing an obesity pill, are up 62.5% over the same period.

Source https://www.barrons.com/articles/biotech-abbvie-roche-stock-acquisitions-aa44cb59

Reuters Article on Takeda / Shire Merger

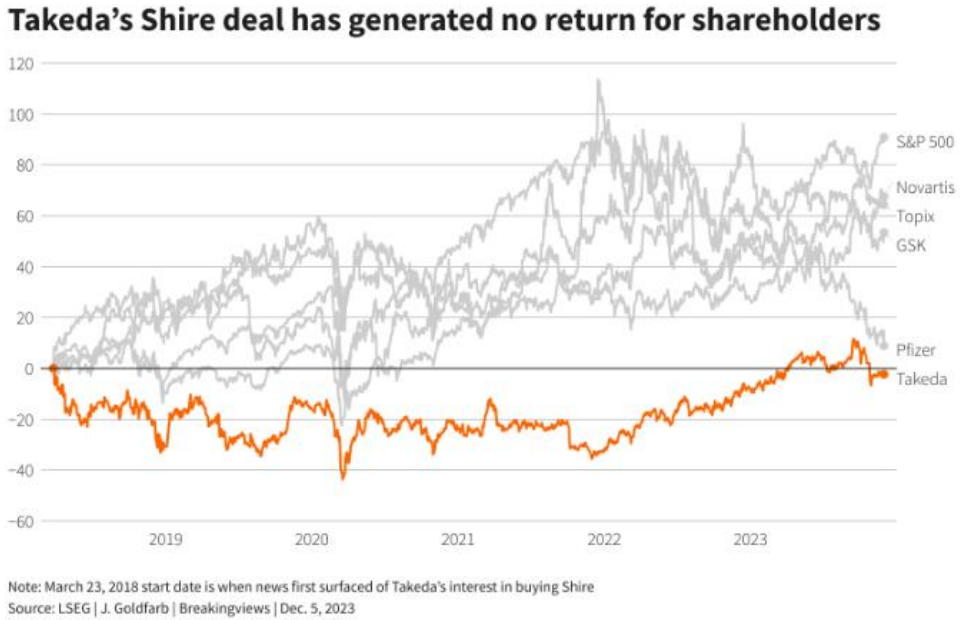
Jeffrey Goldbfarb, Reuters, Dec 6, 2023

Like the quest to discover a new medicine, pulling off a successful mega-deal is a frustrating and elusive experiment. Tokyo-based drugmaker Takeda Pharmaceutical (4502.T) understands the difficulty of both. Although boss Christophe Weber will have plenty to celebrate on the upcoming fifth anniversary of his landmark $62 billion Shire acquisition, the deal has delivered no value to his shareholders.

Despite the long odds, France-born Weber went a long way to accomplishing some of his biggest financial goals. Within a few years, Takeda had offloaded more than $10 billion of product portfolios, including its domestic consumer healthcare arm and a slug of its European over-the-counter and prescription drugs business. The divestitures helped erode the $53 billion mountain of debt the company had accumulated when the deal closed, shrinking it to about $29 billion by September 2023. Takeda's net debt has fallen from 5 times adjusted EBITDA to 2.6 times over that period, nearly meeting its promise of a multiple closer to 2 times. Where synergies are concerned, Weber overdelivered. An initial target of $1.4 billion grew more than 60%, to $2.3 billion. The upwardly revised annual cost savings also came in a year ahead of schedule after Takeda executives swiftly hacked away at Shire's manufacturing and supply expenses, closed and consolidated more than 100 locations and integrated the two companies' worldwide processes. This all helped boost the bottom line.

There were plenty of other benefits, too. Takeda significantly reduced its dependence on Japan, diversifying the location of its workforce while upping the share of revenue from the more lucrative U.S. and European markets. It also bulked up R&D investment, including in promising plasma-derived therapies.

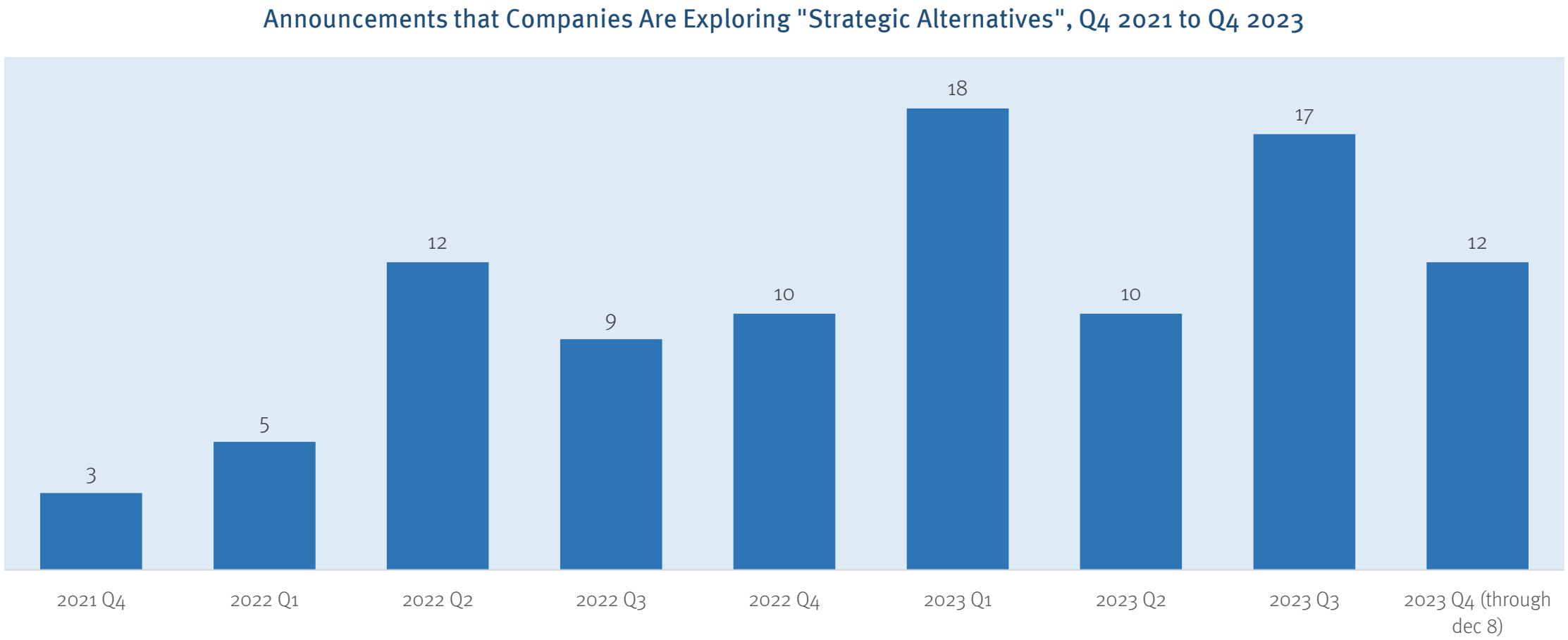
Source: https://www.reuters.com/breakingviews/how-bold-60-bln-deal-went-right-yet-so-wrong-2023-12-06/



This article is quite tough on Takeda, arguing that they overpaid for Shire. We would note that it's very difficult to consider the counterfactual – what would have happened if Takeda hadn't bought Shire. Further, Takeda is only 60 months into the deal. There is still the prospect that substantial incremental value can be created.

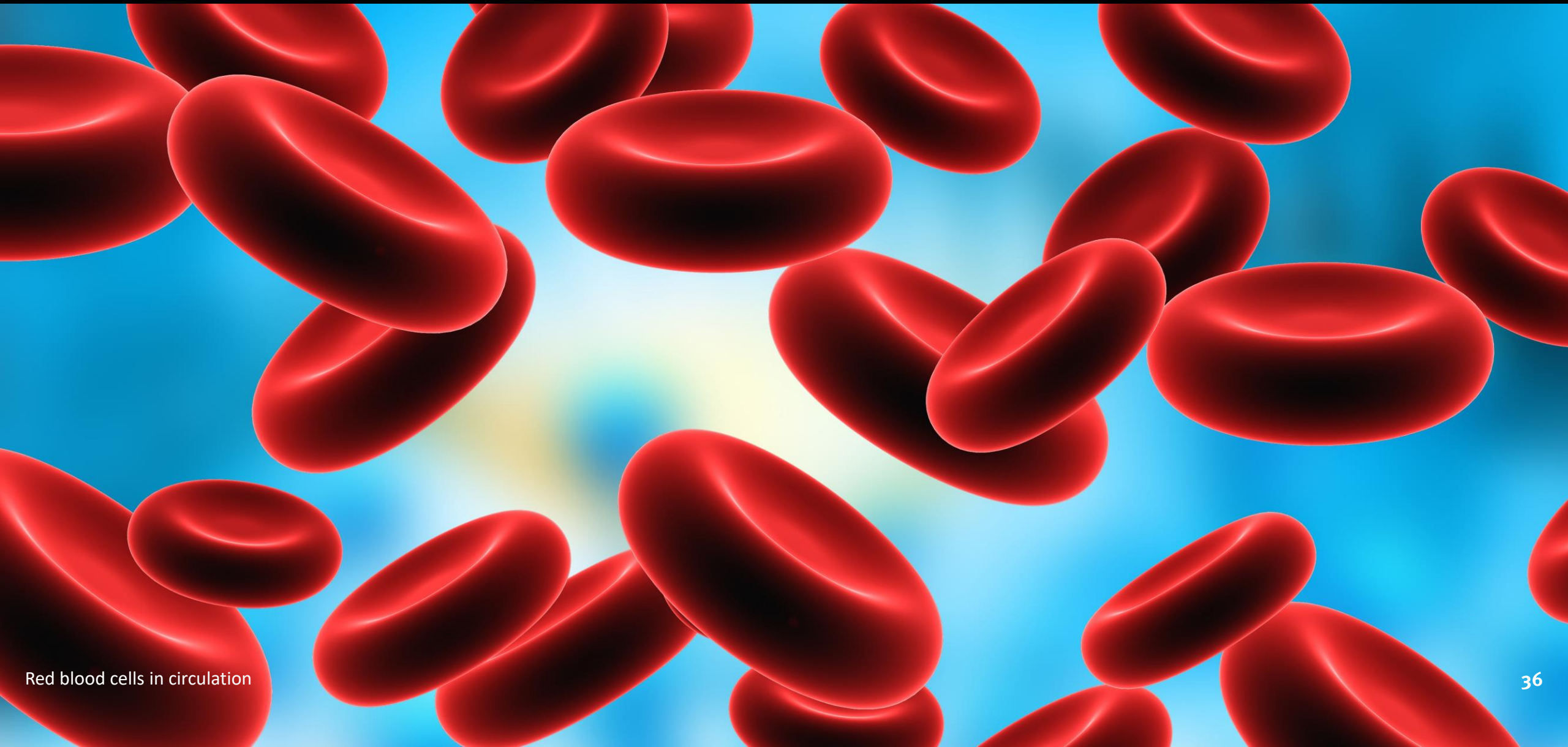
Even More Biopharmas Exploring Strategic Alternatives

With the recent addition of Hepion and Kane to the list we count 49 companies exploring strategic alternatives at present. This is, of course, unprecedented.



Source: Stifel analysis of press releases and SEC disclosures.

Capital Markets Update



Red blood cells in circulation

'No One Was Spared': 2023 Biopharma Funds Projected to Fall $13B YOY, Pitchbook Finds

Gabrielle Masson, *FierceBiotech*, Dec 7, 2023 (excerpt)

By the end of the year, biopharmas are projected to have raised about $24 billion across about 840 transactions—the lowest tally in four years, according to a new PitchBook analysis.

This is compared to annual values of $38.1 billion in 2020, $53.9 billion in 2021 and $36.9 billion for 2022, representing a $12.9 billion drop.

“No one was spared,” senior analyst Kazi Helal, Ph.D., who contributed to the Dec. 7 report, told Fierce Biotech. “Everyone took a bit of a hit.”

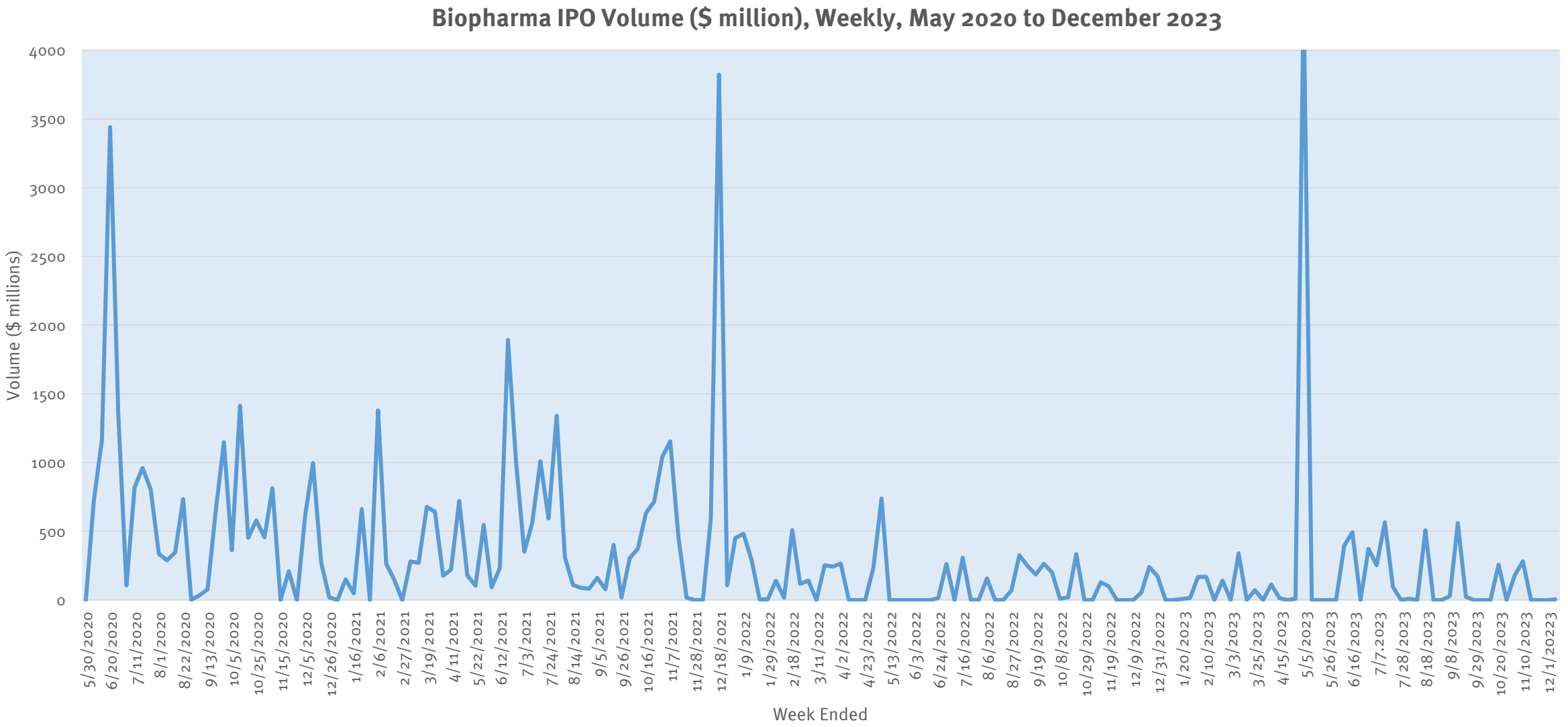
While AI and obesity drugs have proven to be slight exceptions, Helal said the sentiment holds true when looking at the bigger picture.

“As soon as an IPO window opens, we should see a potentially giant wave of companies entering the market,” he said. “There's dry powders there, people are just not spending the money.”

Cracking that window, however, requires more favorable conditions overall, not just for the biotech sector, according to Helal.

Source: https://www.fiercebiotech.com/biotech/no-one-was-spared-2023-biopharma-funds-projected-be-12b-less-last-year-pitchbook-finds

IPO Market Very Slow. One $5mm IPO Last Week in Australia

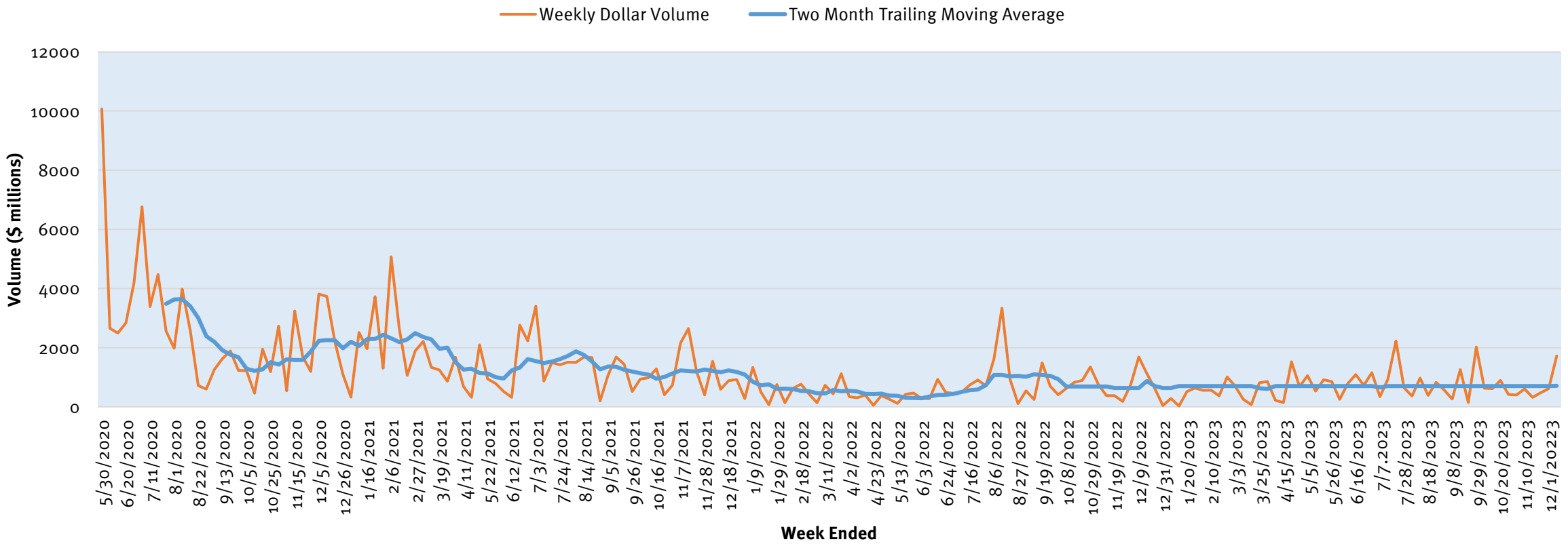


Source: Data from CapitalIQ and Stifel research.

Last Week Very Strong for Follow-On Offerings

Last week saw $1.7 billion in follow-on biopharma volume. This was the third most active week of 2023. The improvement in the equity markets and drop of the VIX helped to support a volume pick up in the market. Key financings including a $300mm raise by Pharvaris, a $275mm raise by Springworks, a $260mm raise by BergenBio, a $200mm raise by Eyepoint and a $180mm PIPE by Spyre.

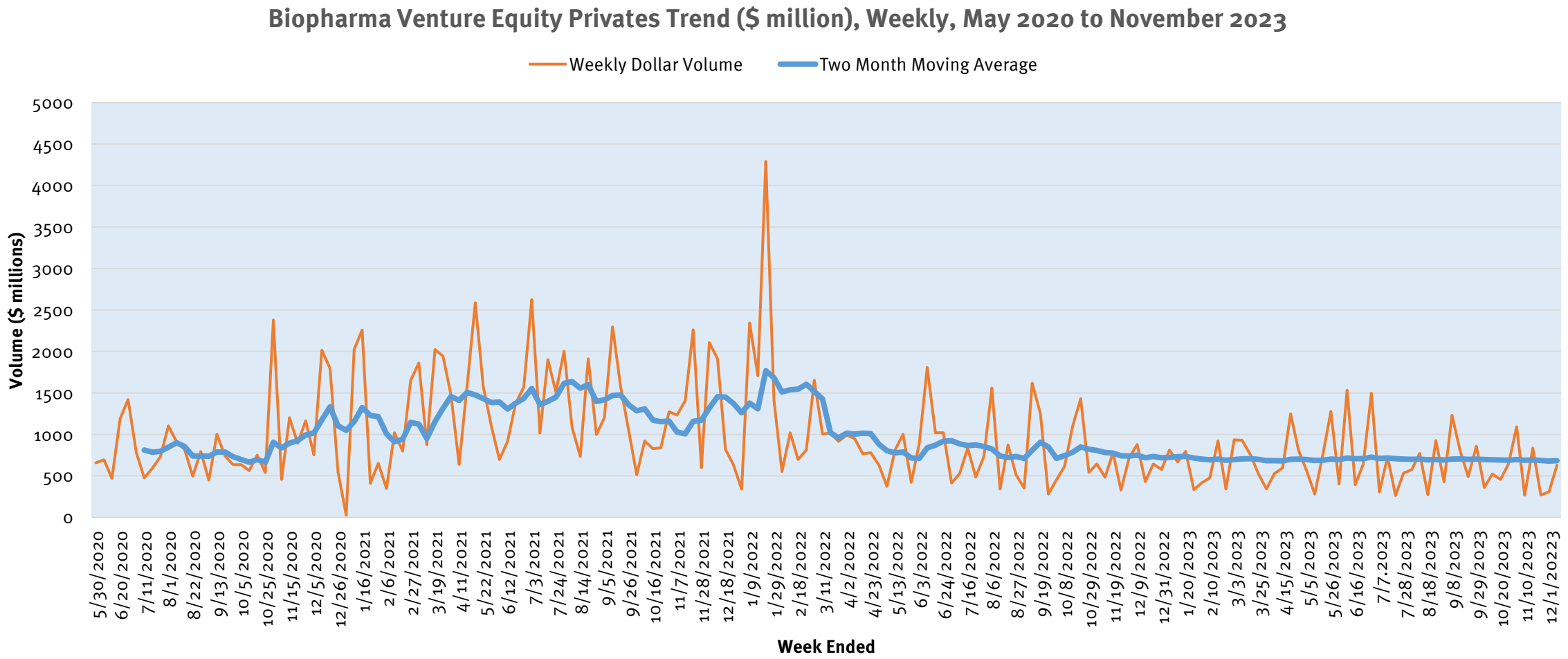
Biopharma Equity Follow-On Volume ($ million), Weekly, May 2020 to December 2023



Source: Data from CapitalIQ and Stifel research.

Last Week Saw $540 Million in Venture Privates

The market picked up substantially from the prior two weeks. The weighted average of private activity continues to decline. The largest deals included a $101 million private for Odyssey Therapeutics and a $90 million private for Artibio (radiopharma company).



Source: Data from CapitalIQ, Crunchbase.

Odyssey Therapeutics Does $101 Million Financing

Boston, Dec. 6, 2023 (BUSINESS WIRE)--Odyssey Therapeutics, Inc., a biotechnology company pioneering next-generation precision immunomodulators and oncology medicines, today announced the closing of a $101 million Series C financing round led by Ascenta Capital with participation from new and existing investors, including OrbiMed, SR One, General Catalyst, Foresite Capital, Woodline Partners LP, HBM Healthcare Investments, Colt Ventures, BlackMars Capital GmbH, Creacion Ventures, funds and accounts advised by Fidelity Management & Research Company, funds and accounts advised by T. Rowe Price Associates, Inc., Catalio Capital Management, Walleye Capital, Alexandria Venture Investments, Racing Beach Ventures LLC, The Healthcare Innovation Investment Fund LLC, an investment fund associated with Leerink Partners, Ab Magnitude Ventures, KB Investment, The Global BioAccess Fund, and multiple leading global investors. This Series C financing brings the total capital raised since founding in late 2021 to $487 million. Proceeds will support the advancement of multiple programs into clinical studies and the continuation of investment in discovery to build a sustainable model for therapeutic innovation.

“Odyssey’s accomplished team of scientists and executives with numerous prior successes in discovery, development and commercialization has made tremendous progress in only two years,” said Lorence Kim, M.D. “Dr. Glick has successfully created a sustainable and capital-efficient model that primes Odyssey to be a hub for immunology and oncology therapeutic innovation, and I look forward to working with him, the board and leaders on the management team in the years ahead.”

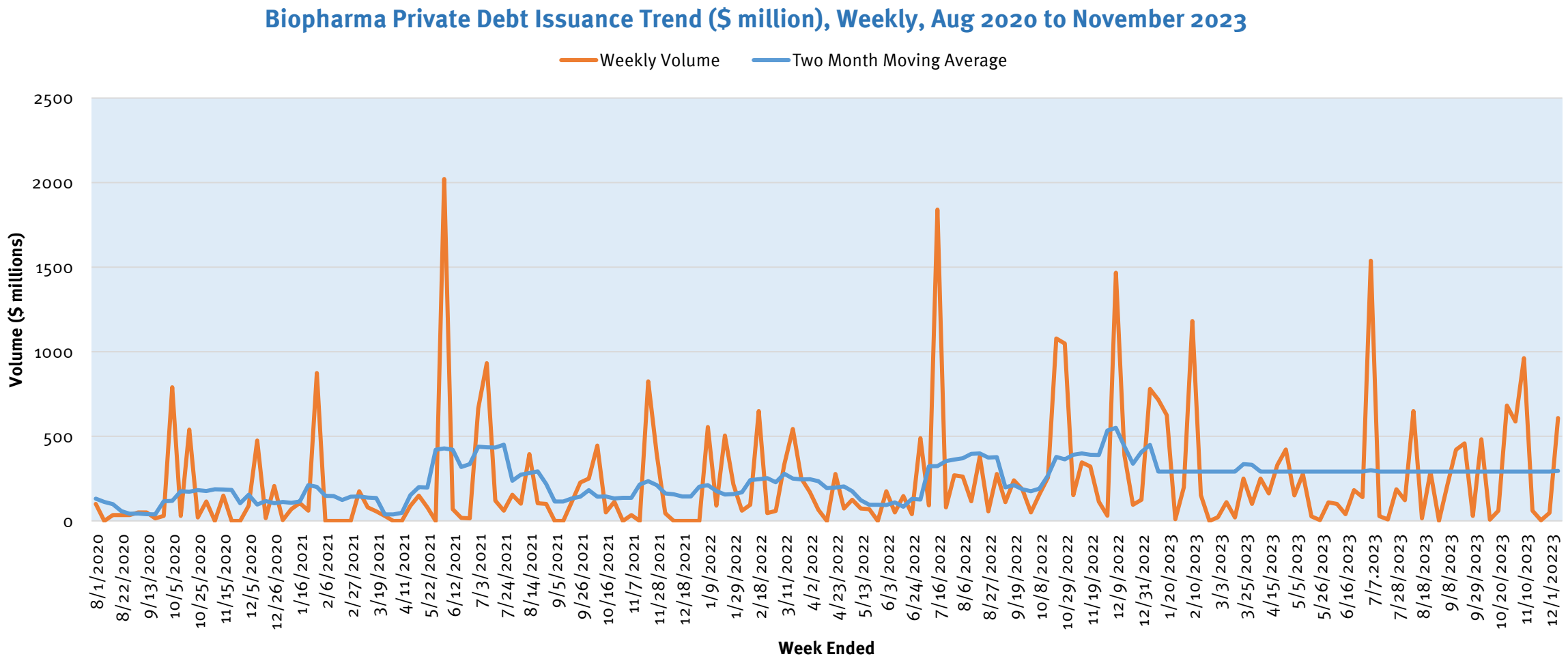
“Odyssey has rapidly advanced a portfolio of immunology and oncology therapeutics with the goal of providing transformative medicines for large numbers of patients in need and several of these molecules have the potential to enter the clinic in the next 12 months. For us, success is defined as bringing safe and effective medicines to patients with serious diseases, with support from Ascenta and our other investors driving our pipeline into the future. We welcome Dr. Lorence Kim, co-founder and managing partner of Ascenta Capital, to our board to join us in achieving this mission.”

Gary Glick
Chief Executive Officer
Odyssey Therapeutics

Source: https://odysseytx.com/odyssey-therapeutics-announces-101-million-series-c-financing/

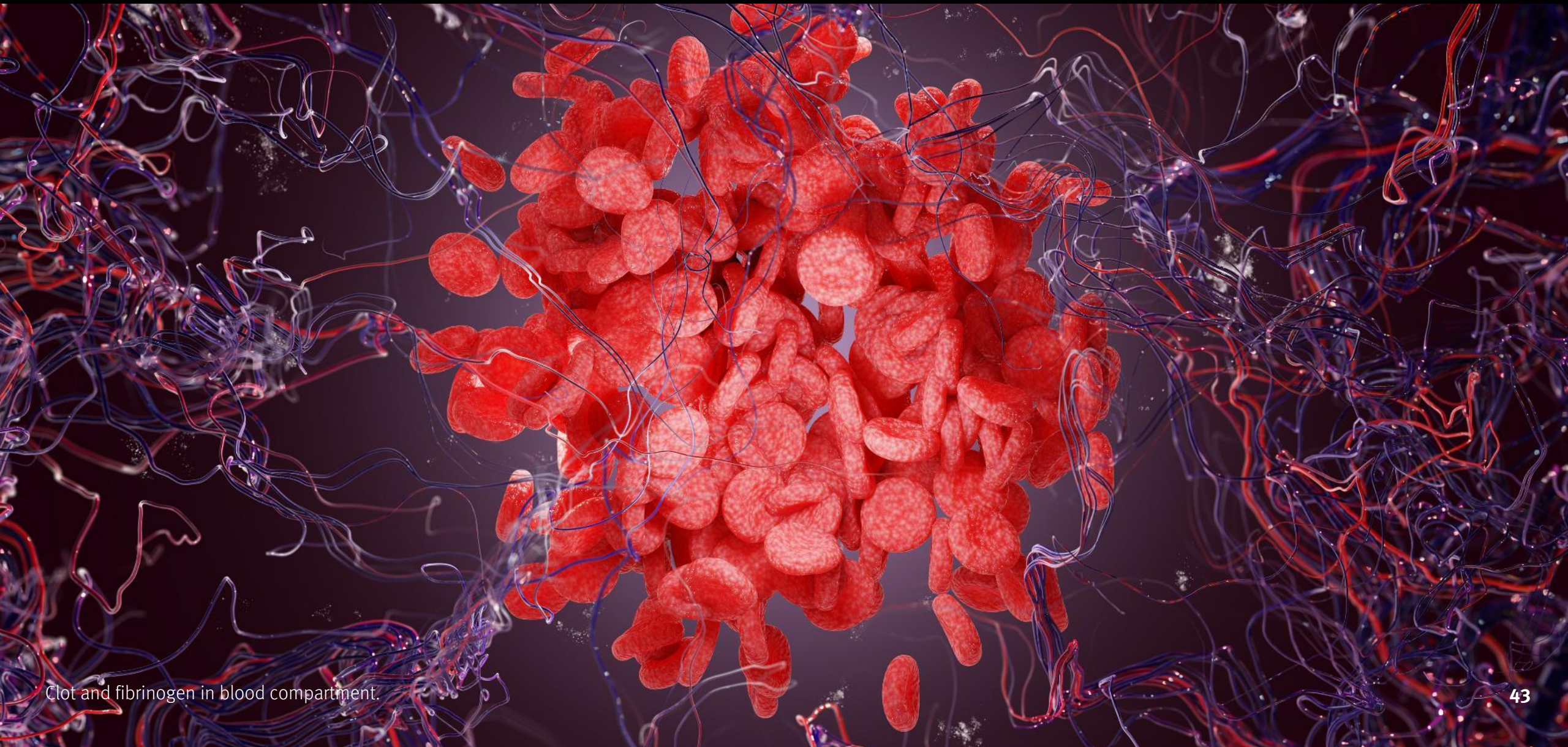
Weekly Global Biopharma Private Debt Placement Volume Slow

We saw $8 million in private debt deals get done last week. The market was quiet. Repligen completed a $600mm private convertible.



Source: Data from CapitalIQ, Crunchbase.

J&J Enterprise Business Review



Clot and fibrinogen in blood compartment.

Johnson & Johnson Targets Sales Growth in Years Ahead

Robb Stewart, *Wall Street Journal*, Dec 5, 2023

Johnson & Johnson is targeting sales growth of as much as 7% a year in the coming years, driven by its innovative medicine and MedTech operations.

The company, which hosts a meeting with investors in New York Tuesday to present its strategy, said it anticipates operational sales growth of 5% to 6% in 2024. Adjusted operational per-share earnings are set to come in at $10.55 to $10.75 for the year, which at the midpoint would mark a rise of 7.3%.

Over the five years through 2030, Johnson & Johnson said it expects compound annual sales growth of 5% to 7%, including at least 3% operational sales growth in 2025 despite the entry into the U.S. of a Stelara biosimilar.

In innovative medicine, the company said it is continuing to focus on areas of high innovation and higher growth while maintaining a pipeline that is expected to deliver more than 20 novel therapies and more than 50 product expansions by 2030.

Johnson & Johnson's medicine pipeline and portfolio is targeting 5% to 7% operational sales growth from 2025 to 2030. The company said more than 10 assets have the potential to deliver over $5 billion in operational "peak-year sales" and 15-plus assets have the potential to generate $1 billion to $5 billion in operational peak-year sales, including Spravato, seltorexant, aticaprant and JNJ-4804.

Grounds of J&J Headquarters

Source: https://www.wsj.com/health/healthcare/johnson-johnson-targets-sales-growth-in-years-ahead-50745d61

2023 Enterprise Business Review

Key Takeaways

Johnson&Johnson

Innovative Medicine Business Overview

Our future growth will be fueled by 20+ novel therapies and 50+ product expansions*

	Select marketed brands	Select anticipated novel therapy approvals & filings through 2030
Assets with **$5B+ Potential**[1,3]	DARZALEX (daratumumab) CARVYKTI (ciltacabtagene autoleucel) Tremfya (guselkumab) TALVEY (talquetamab-tgvs) TECVAYLI (teclistamab) INVEGA SUSTENNA (paliperidone palmitate)	**RYBREVANT / lazertinib** Lung Cancer **CD20-based CAR-T**[2] Lymphoma **Anti-Tau mAb** Alzheimer's Disease **JNJ-2113 Targeted oral peptide** Autoimmune Diseases **milvexian** Thrombosis **nipocalimab** Autoantibody Diseases **TARIS Platform** Bladder Cancer
Assets with **$1 – 5B Potential**[1,3]	Erleada (apalutamide) 60 mg tablets Spravato (esketamine) nasal spray Xarelto rivaroxaban Opsumit[4] macitentan tablets 10 mg Uptravi selexipag tablets Akeega (niraparib/abiraterone acetate)	**JNJ-1887 sCD59** Geographic Atrophy **seltorexant** Major Depressive Disorder **ExPEC** Multivalent Vaccine (9V) **aticaprant** Major Depressive Disorder **Trispecifics**[2] Hematologic Malignancies **JNJ-8114 PSMA / CD3** Prostate Cancer **JNJ-4804**[5] Inflammatory Bowel Disease **RPGR Gene Therapy** Retinitis Pigmentosa **JNJ-8343 KLK2 / CD3** Prostate Cancer **JNJ-6420 ^{225}Ac KLK2** Prostate Cancer **Menin-KMT2A inhibitor** Hematologic Malignancies **JNJ-1459** Psoriasis

$5B+ potential asset in 2021 Analyst Day | ONC | IMM | NS | Select Other Areas

J&J

* Risk-adjusted basis including current-year approvals;
1. Non-risk adjusted peak-year operational sales, including partner sales; 2. Includes multiple assets under development; 3. Select assets shown; 4. Includes sales from fixed-dose combination with tadalafil; 5. Combination therapy

Oncology

J&J in Oncology – leadership, innovation, growth

Portfolio strength

Robust portfolio continues to expand

14 new medicines approved since 2011

Leading with first-in-class and potential best-in-class therapies, breakthrough science, strategic partnerships, global scale and commercial excellence

9 achieved approvals and planned filings in 2023

Pipeline innovation

Pipeline poised to deliver through 2030

~2 novel therapies per year continuing the innovation trajectory

35+ planned filings

Leveraging deep disease expertise to discover novel targets, develop new therapies and progress earlier lines of therapy, regimens and combinations

Driving strategic growth

Striving toward the elimination of disease

7 assets with $5B+ potential[1]

7 assets with $1-$5B potential[1]

#1 Oncology company within the decade

Redefining treatment paradigms in multiple myeloma, B-cell malignancies, lung cancer, bladder cancer and prostate cancer

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1. Non-risk adjusted operational peak year sales, including partner sales

Immunology

Redefining treatment, pioneering pathway science; poised for continued innovation and growth leadership

Unmatched track record of translating science to impact

5 internally developed marketed assets

32 approved indications

$16.9B 2022 sales[1]

4.8% 2022 overall operational sales growth[2]

7.7% 2022 on-patent portfolio operational growth[2,3]

Current portfolio and pipeline of "firsts" drives continued momentum

Tremfya (guselkumab) — **Poised to lead the anti-IL-23 space near- and long-term**

- Demonstrated skin clearance with 6-year data in moderate-to-severe PsO
- Only IL-23i to slow joint damage in PsA
- 30.1% annual operational growth, FY 2022[2]

Stelara (ustekinumab) — **First-and-only anti-IL-12/IL-23 therapy**

- #1 fastest-growing branded product in UC and CD
- 10.4% annual operational growth, FY 2022[2]

7 filings planned through 2025, including 5 first-in-class indications

Clinical-stage pipeline drives future growth

14 first-in-class Phase 2 and Phase 3 programs, including 3 TREMFYA indications

5 novel MOAs in development

3 novel orals in clinical development

1st IBD and PsA biologic combination in Phase 2; novel MOA combinations in planning

10 indications planned for nipocalimab, our entry into autoantibody-driven disease

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1. Reported sales; 2. Non-GAAP measure; excludes the impact of translational currency; Investors section of the company's website; 3. On-patent portfolio includes SIMPONI, SIMPONI ARIA, STELARA, TREMFYA

Neuroscience

Our path to #1 neuroscience company by 2030

We are at a pivotal moment in neuroscience

20+ industry-leading innovations across portfolio

2X neuroscience market to double

2X J&J Neuroscience sales to double

3 new mechanisms of action in launch mode

6 registrational submissions

14 Phase 2 and Phase 3 top line readouts

Six major assets will drive our growth

$1-5B peak year sales potential[1]

- ✓ **SPRAVATO**
  treatment-resistant depression
- Ph3 **Nipocalimab**
  all indications, including gMG and CIDP
- Ph3 **Seltorexant**
  Adjunctive treatment for major depressive disorder in patients with insomnia
- Ph3 **Aticaprant**
  Adjunctive treatment for major depressive disorder in patients with anhedonia

$5B+ peak year sales potential[1]

- ✓ **INVEGA long-acting injectable portfolio**
  schizophrenia
- Ph2 **Posdinemab**
  early Alzheimer's disease

J&J

1. Non-risk adjusted operational peak year sales, including partner sales where applicable

Strongly positioned to deliver long-term shareholder value

Key financial targets

5-7%

Total enterprise operational sales CAGR[1,2] (2025-2030)

Innovative Medicine operational sales CAGR[1,2] (2025-2030)

MedTech is expected to grow operational sales in the upper range of our markets through 2027[3]

22% Free cash flow as a percent of sales by 2026[4]

Adjusted operational EPS growth generally commensurate with sales growth[5]

Key drivers

Continued **acceleration of our in-market portfolios**

Robust Innovative Medicine pipeline; with several first-in-class and best-in-class therapies

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Broad & differentiated MedTech pipeline; upcoming launches & geographic expansion across platforms

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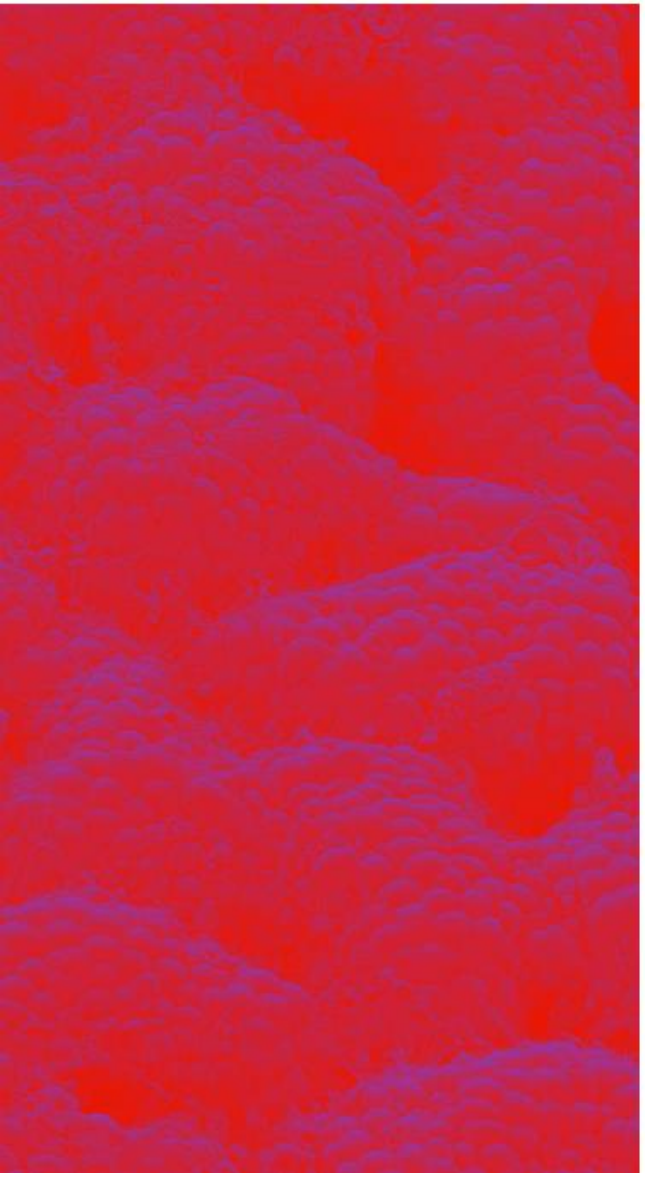
Strong financial foundation & robust free cash flow generation

J&J

1. Represents operational sales; Non-GAAP financial measure; excludes the impact of translational currency; 2. Based on risk-adjusted sales projections; 3. MedTech Market WAMGR reflects the following sources: Internal estimates, Fitch, HRI, Global Data and DRG; 4. Cash flow from operating activities less additions to property, plant and equipment; 5. Non-GAAP financial measure; excludes the impact of translational currency, intangible amortization expense and special items

Enterprise Overview



Johnson&Johnson

5-6%

2024 full year operational sales growth guidance range[1,2]

7.3%

2024 adjusted operational earnings per share growth guidance (midpoint)[3]

>3%

2025 operational sales growth projection[1,2]

5-7%

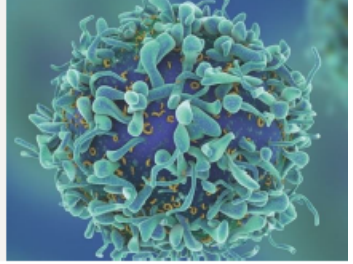
2025 – 2030 projected operational sales CAGR[1,4]

1. Non-GAAP financial measure; excludes the impact of translational currency; 2. Excludes COVID-19 Vaccine; 3. Non-GAAP financial measure; excludes the impact of translational currency, intangible amortization expense and special items; 4. Based on risk-adjusted sales projections

Cell Therapy

J&J is building to be the leader in cell therapy with a foundation in Hematologic Malignancies.

Mission: The elimination of cancer
Our approach: Deliver synergistic, curative treatment regimens to patients.



Substantial cell therapy growth opportunity in Hematologic Malignancies

2022 WW market size	$2.7B
WW market CAGR 2022-2030	27 -29%

Market dynamics

- Multiple Myeloma (MM) patients experience multiple relapses, with many lost between lines of therapy due to attrition (~50% of transplant and <25% of non-transplant patients reach third line of therapy)
- Need for early intervention with highly effective MM treatment regimens
- CARVYKTI has demonstrated the best hazard ratio or clinical outcome for any Phase 3 study in multiple myeloma
- In lymphoma, gaps exist in chimeric antigen receptor T-cell therapy (CAR-T) targeting CD19
- ~60-70% of lymphoma patients receiving CD-19 CAR-T therapy don't respond or face relapse
- CD20 CAR-Ts (licensed from AbelZeta) demonstrated best early clinical data across all Diffuse Large B-Cell lymphoma (DLBCL) therapies to date

Significant unmet need for patients with aggressive or difficult-to-treat blood cancers

Hematologic Malignancies

>1.3M ww incidence >712K ww deaths

107K
People will be diagnosed with MM in the U.S and G7 markets in 2023

49K
People will die from MM in the G7 markets in 2023

187K
People will be diagnosed with Non-Hodgkins Lymphomas (all histologies) in the G7 markets in 2023

58K
People will die from Non-Hodgkins Lymphomas (all histologies) in the G7 markets in 2023

Near-term pipeline/portfolio milestones

CARVYKTI® ($5 billion annual sales potential)*

- Expect approvals of CARTITUDE-4 in 2L-4L RRMM in the U.S. and EU in 2024
- CARVYKTI adoption will be based on the unprecedented efficacy of CARTITUDE-4 and potential to transform care with a one-time infusion once approved
- CARTITUDE-4 demonstrated compelling efficacy in lenalidomide refractory RRMM patients after one to three prior lines of therapy with a Hazard Ratio (HR) of 0.26, the greatest risk reduction for progression or death (74%) shown in any treatment in MM
- Frontline CARTITUDE-5 and CARTITUDE-6 are enrolling

JNJ-4496 (C-CAR039) & JNJ-9530 (C-CAR066)

- AbelZeta presenting data on C-CAR039 (CD19/20 CAR-T) and C-CAR066 (CD20 CAR-T) at ASH 2023
- JNJ-4496: A Phase 1b study in the U.S. is enrolling patients
- JNJ-9530: A Phase 1b study in patients with R/R NHLs is open for enrollment in the U.S.

Our growth strategy

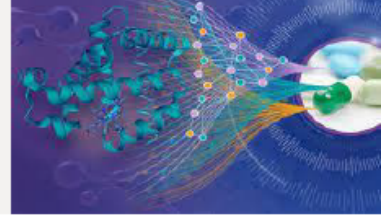
Advance CARVYKTI into earlier lines globally and build next generation cell therapy portfolio

- Ongoing phased launches for CARVYKTI in the U.S. and EU and continued global launches; increased certified treatment centers in the U.S. and growing in EU
- Significant investments to increase production of CARVYKTI:
  - Increased capacity of our Raritan manufacturing site since the beginning of 2023
  - Expect four manufacturing nodes across the U.S. and EU to serve our growing patient demand
  - In-house viral vector production, continued expansion of our internal network and the expectation of increased capacity by end-of-year
- Advancing CD20 CAR-Ts in clinical development as well as pre-clinical assets for hematological and solid tumors

Innovative Medicine

Data Science in R&D

Johnson & Johnson is leveraging the power of data science end-to-end, from R&D to Supply Chain and to Commercial. In R&D, it is helping us bring better, more targeted therapies to patients faster and more efficiently – and make previously impossible science possible.



External dynamics

- Tremendous unmet need: **85% of protein targets** are beyond reach of current medicines[1] and only **10% of drug candidates** reach the market[2]
- Increasing multimodal data: **30% of world's data is healthcare data**, with 26% CAGR (2020-2030)[3]
- Rapid advancements in AI/ML (including **Generative AI**), real-world evidence (RWE), digital tools, and computing power
- Increasing **guidance and acceptance from regulators** on RWE, AI/ML[4]

Our differentiation in R&D

- **Applying AI/GenAI, ML, RWE and digital health from end-to-end across the product lifecycle to:**
  - Co-design novel molecules optimized across multiple parameters
  - Drive precision medicine, enabled by novel endpoints
  - Execute more efficient, targeted and diverse clinical trials
  - Enhance productivity via AI/GenAI-enabled discovery, development, and regulatory enhancement[5]
  - Rapidly evaluate safety signals and generate regulatory-grade RWE
- **150+ world-class 'bilingual' data scientists** working shoulder-to-shoulder with scientists on all asset teams; enterprise-wide focus on data science and digital talent development and upskilling
- **Foundational internal data and analytics platforms** (e.g., 3PB of AI-ready data from internal and external sources, AI and RWE analytics, and applications – sourced from discovery, translational and clinical data systems with our extensive real-world datasets)
- Strong **external collaborations** and relentless enterprise commitment to the **highest data standards** and **ethical application of AI**

Significant near-term milestones

- **Oncology ML-assisted NME:** First-in-human to start recruiting (early 2024)
- **Immunology ML-assisted NME (IL-17 molecule):** Entering Phase 2 in 2024
- **ML-enabled novel endpoint (JNJ-2113):** ML-enabled endoscopy-based UC[9] severity endpoint expected to be deployed in trial (2024/2025)
- **ML-enabled novel endpoint (Tau Active Immunotherapy):** Novel endpoint measuring cognitive and motor function across hundreds of factors planned for deployment in clinical trials (2024)
- **AI/ML, real-world data-driven recruitment:** Scaling from 50 to 75 programs (including milvexian, TAR-200, TECVAYLI®, TALVEYTM, JNJ-2113, and nipocalimab)
- **RWE for full approval in China (IMBRUVICA®):** Leveraged RWE to secure transition from conditional- to full-approval for CLL and SLL[10] in China
- **End-to-end GenAI-Enabled Productivity:** Leveraging GenAI solutions as co-pilots for protocol and regulatory document generation and for adherence to global standards & local requirements for coordinating regulatory compliance across 182 countries

Examples of impact

End-to-end impact
85% of New Molecular Entities (NMEs) and Line Extensions (LEs) leveraging Data Science[6]

50+
Small molecule discovery programs are leveraging AI/ML to guide hit identification via ML-enabled Biosignature platform; generated 15 million images with 2 million compounds tested to date

2 NMEs
in Oncology and Immunology delivered using ML compound optimization in 2023; deploying ML modeling **approaches at scale** to advance high-probability molecules

5+
AI/ML- based novel endpoints being deployed in clinical trials across Oncology, Immunology, and Neuroscience[7]

1.2-2.6x
Higher enrollment at sites highly ranked by AI/ML models[8]; 50+ studies enabled by AI/ML

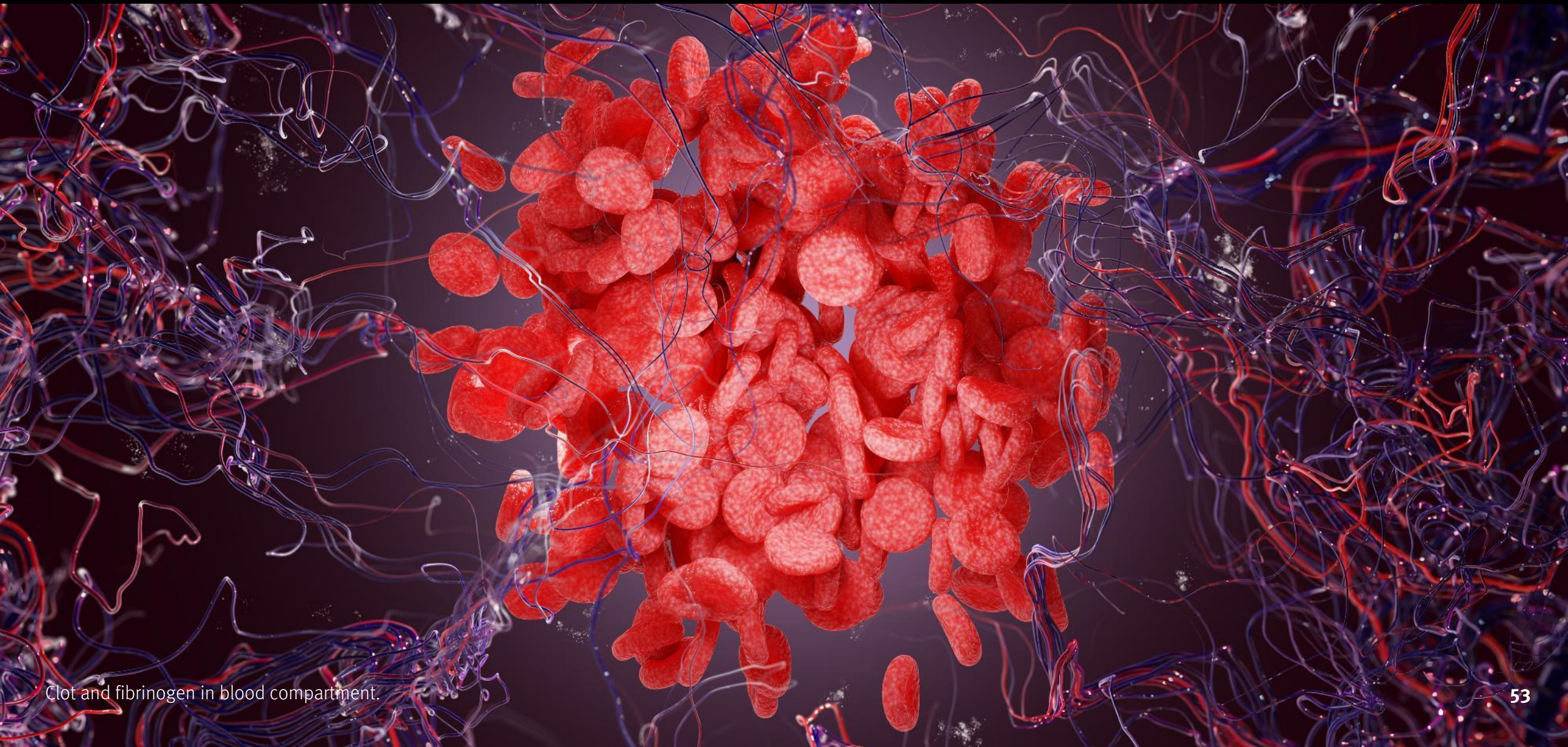
5
Months ahead of schedule in exceeding year-end diversity, equity & inclusion (DEI) goals across 6 Immunology studies, with support from AI/ML

400K
Scientific documents analyzed per year using natural language processing to extract insights on safety in pre-clinical studies and post-marketing surveillance

>100
Post-approval health authority responses informed by ML-enabled real-world data **analyses** each year

95%
Cost avoidance for health authority Post-Approval Safety Study addressed with routinely-collected real-world data instead of a prospective registry

Sanofi R&D Day (December 7, 2023)



Clot and fibrinogen in blood compartment.

Sanofi: Chief Must Prove He Can Win R&D Game

***Financial Times*, Dec 7, 2023 (excerpt)**

Sanofi chief executive Paul Hudson began in sales jobs at groups including GSK. He now needs to draw heavily on those skills to convince investors that Sanofi has what it takes to develop a new breed of blockbuster drugs solo.

His job will be made harder by the fact that some investors have their backs up. Shares in the French pharma company are struggling to recover from their steep fall in October. Hudson spooked the market when he scrapped a 2025 margin target and announced he would spend more on research and development. He has since issued something of a mea culpa, admitting ahead of Sanofi's investor day on Thursday that he should have better explained his plans.

Sanofi's struggles go well beyond communication glitches. Investors remain nervy over its dependence on blockbuster asthma and eczema drug Dupixent. Sales of Dupixent are projected to top €20bn by 2030, up from €8.2bn last year. That would mean it would account for a third of total revenues by the end of the decade. Exclusivity rights run out in the early 2030s.Investor doubts have weighed on Sanofi's valuation.

It trades at a forward price earnings multiple of 11 times. Roche and AstraZeneca trade on 12.4 and 16.56 times respectively. Sanofi insists it has 12 possible blockbusters in the pipeline, with a collective peak sales potential of €33bn to €60bn. If all were approved, that would easily replace Dupixient sales, although analysts at present only forecast peak sales of €8bn from the drugs identified, says Citigroup.

Source: https://www.ft.com/content/05fa7cf0-a1d6-4a5c-b9af-d10ab9ad23a1

Sanofi CEO Defends Extra Spending, Ramping Up Revenue Forecast

***Tim Loh, Bloomberg*, Dec 7, 2023 (excerpt)**

Sanofi laid out ambitious plans to bolster its pipeline of new medicines as the French drugmaker tries to reassure investors after the plan triggered a profit warning and a sell off that wiped out about $25 billion in market value.

Chief Executive Officer Paul Hudson, lauding Sanofi's "new drumbeat," forecast more than €10 billion ($11 billion) in annual sales from recent launches and future medicines by 2030 — almost twice the current expected level, according to Jefferies analysts.

Hudson and his new head of research and development, former entrepreneur Houman Ashrafian, described their vision to create an immunology powerhouse amid concern about spending, but the stock fell as much as 3.3% in Paris trading.

Source: https://www.bloomberg.com/news/articles/2023-12-07/sanofi-says-pharma-sales-set-to-reach-10-billion-by-2030

Sanofi Pipeline:

Unprecedented pipeline of *blockbuster opportunities*

Potential pipeline-in-a-product

€2-5bn peak sales potential each

Pipeline asset	Indication(s)	Expected first submission	Pipeline asset	Expected submission
tolebrutinib *(BTKi)*	Full spectrum of MS - *Ph. 3*	2024	*ExPEC vaccine* - *Ph. 3*	2027+
rilzabrutinib *(BTKi)*	ITP - *Ph. 3* Asthma - *Ph. 2*	2024 *(ITP)*	*RSV mRNA OA combo vaccine* - *Ph. 1/2*	2027+
itepekimab *(Anti-IL-33)*	COPD former smokers - *Ph. 3*	2025	*Acne mRNA vaccine* - *Ph. 1/2*	2027+
lunsekimig *(Anti-IL13/TSLP)*	Asthma - *Ph. 2b*	2027+		
IRAK4 degrader	AD, HS - *Ph. 2*	2027+		
Anti-TL1A	IBD - *Ph. 2*	2027+		

€5bn+ peak sales potential each

Pipeline asset	Main indications	Expected first submission
amlitelimab *(Anti-OX40L)*	Atopic dermatitis - *Ph. 3*	2027
	Asthma - *Ph. 2b*	
frexalimab *(Anti-CD40L)*	RMS, SPMS - *Ph. 3*	2027 *(RMS)*
	Type 1 Diabetes - *Ph. 2b*	
SAR441566 *(Oral TNFR1si)*	Rheumatoid arthritis, Psoriasis - *Ph. 2b*	2027+
	IBD	

Note: non-exhaustive, non-risk-adjusted peak sales estimates, at CER, barring unforeseen events.

Sanofi Impressive in I&I:

Building an *Immunology Powerhouse* driven by new launches, Dupixent and Vaccines

>€10bn

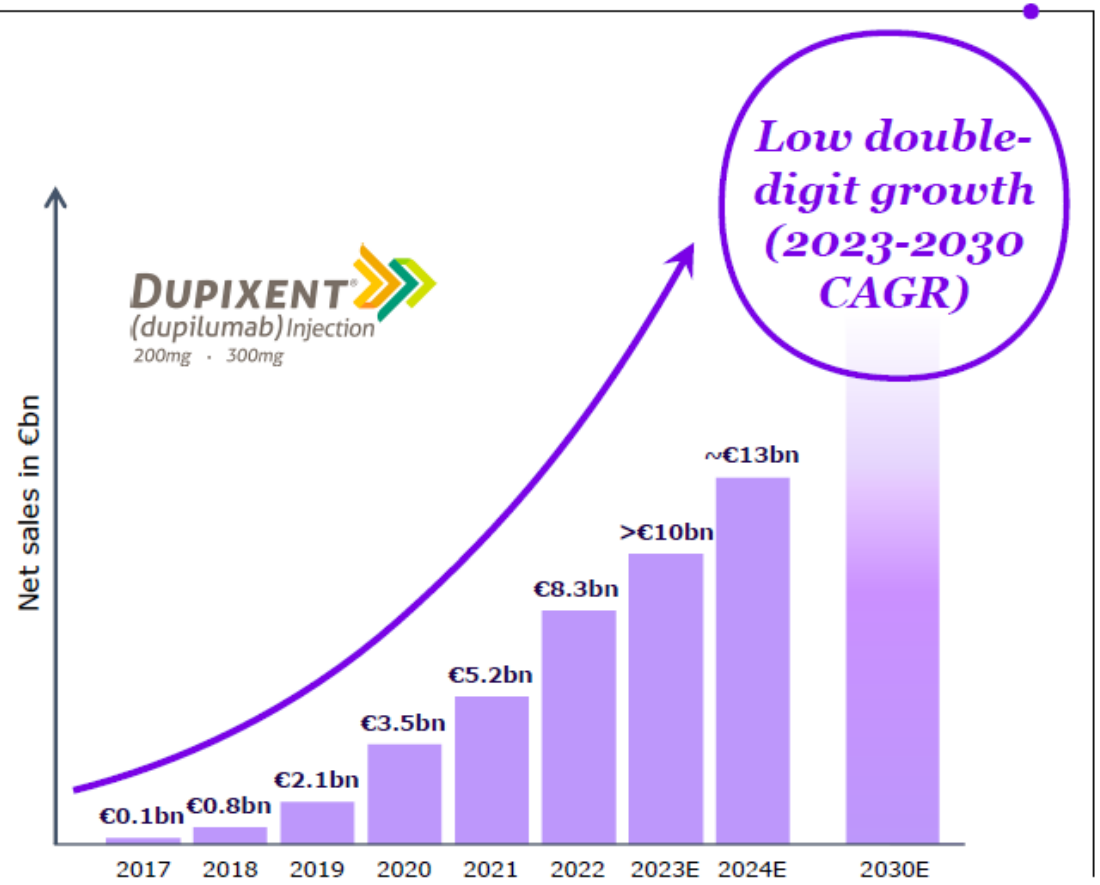
Sales contribution from Pharma launches by 2030[1]

Potential launches

tolebrutinib, itepekimab, amlitelimab, frexalimab, rilzabrutinib, lunsekimig, Oral TNFR1si

Already launched

ALTUVIIIO, TZIELD, Sarclisa, Nexviazyme, Rezurock



>€10bn

Sanofi Vaccines sales by 2030

Already launched

Beyfortus

Vaccines Investor Event, June 29, 2023

Barring unforeseen events. 1 Risk-adjusted net sales, at CER. Pharma already launched also includes net sales from Xenpozyme, Enjaymo, Cablivi.

A development-driven, tech-powered biopharma company committed to serving patients and *accelerating growth*

Execute Play to Win

Continue to deliver on *Dupixent*

Reducing our cost structure, plans to save up to €2bn for reallocation by end-2025

Pharma launches contributing *>€10bn sales*[1] by 2030

Industry-leading immunology pipeline

12 new molecular entities with €2-5bn or €5bn+ peak sales potential

Driving long-term value

Intention to *separate Consumer Healthcare* at the earliest Q4 2024

Strong EPS rebound expected in 2025

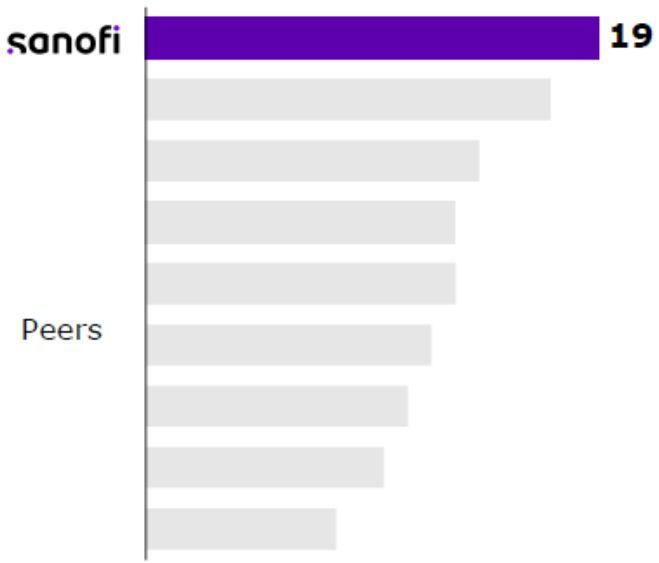
Disciplined *capital allocation* strategy

Barring unforeseen events 1. Risk-adjusted net sales, at CER.

Sanofi portfolio positioned as *leading* I&I franchise

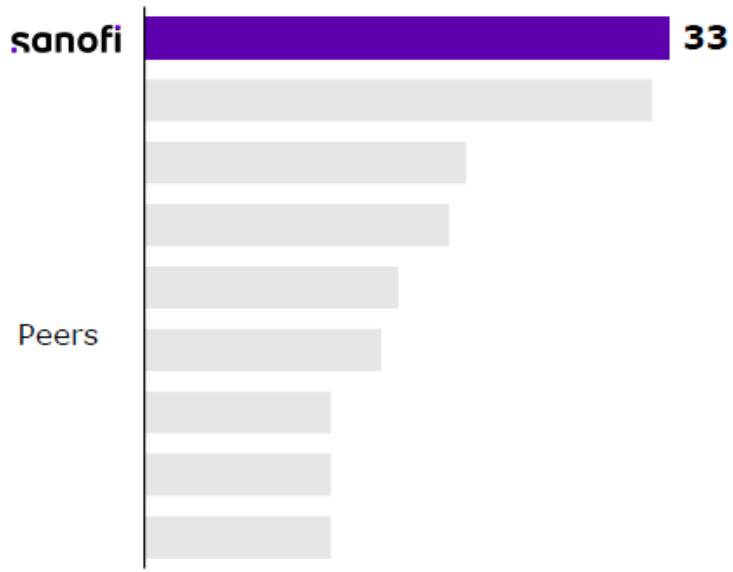
#1 *Total I&I assets*

Total I&I assets
Pipeline and commercial



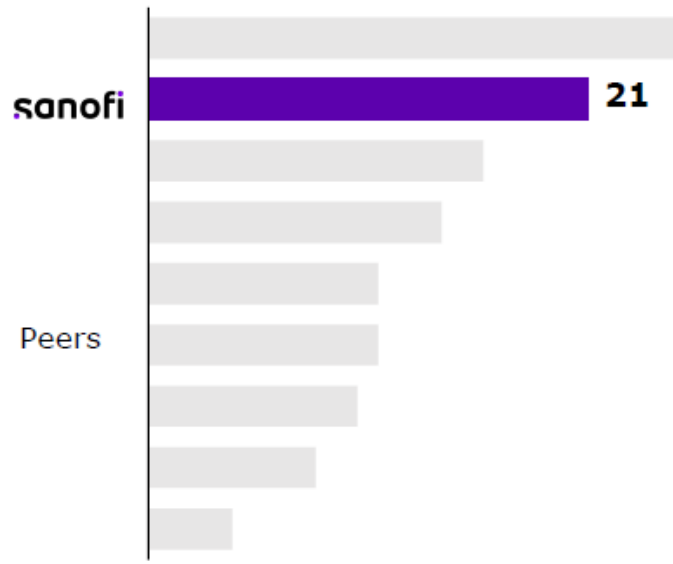
#1 *Asset-indication density*

Number of asset-indication pairs[1]
Pipeline



#2 *First-in-class assets*

Number of potential FIC asset-indication pairs[1]
Pipeline



1. Counting asset-indication pairs (an individual asset may be counted multiple times) and includes FIC in LCM (asset-indication pair is only counted if mechanism and indication are publicly known and that asset is the latest in development in that mechanism-disease); I&I indications include those within Dermatology, Respiratory, Rheumatology, GI and close adjacency disease areas. Source: L.E.K. analysis based on company publicly disclosed pipelines on website or investor materials.

We are *all-in on* Immunology, across therapeutic areas

I&I	Vaccines	Neuro-inflammation	Transplant & Type 1 Diabetes	Oncology	Rare Diseases	Other immune–mediated diseases
Sustain leadership in I&I and Vaccines		*Build up scale* in areas where we can leverage our I&I strengths			*Pursue opportunistically* building upon existing strength & capabilities	Potential *expansion* where *biologically & commercially* relevant, predominantly leveraging our *internal pipeline*

~80% of late-stage assets[1]

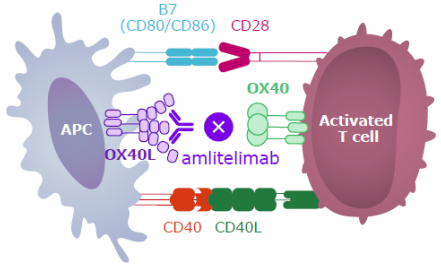
Focus on *FIC / BIC*

1. With at least one indication in I&I, Vaccines, Neuro-inflammation.

Sanofi OX40L mAb Looking Good

(from Kymab M&A)

Amlitelimab: Potential *best-in-class* OX40L pathway blockade, a key pathway in immune diseases



Blocking OX40L on antigen presenting cells, inhibits T-cell dependent inflammation *without immunosuppressive cell depletion*

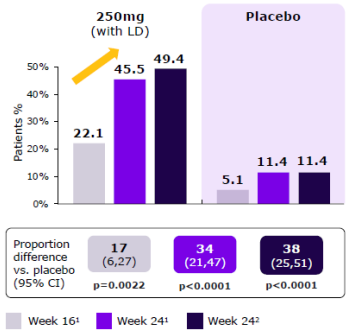
Efficacy across both Type 2 and non-Type 2 pathways, *broadly* eligible population

Pursuing durable *disease modification and long-term control* for best-in-disease Q12W dosing in AD

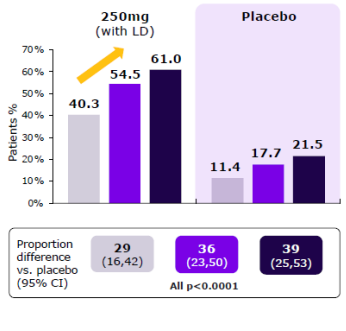
Central controller of inflammation, with potential for pipeline-in-a-product, leading to a *€5bn+ peak sales potential*

Amlitelimab shows significant *improvements* in signs and symptoms of atopic dermatitis

Percentage of patients achieving *IGA 0/1 at Weeks 16 and 24*



Percentage of patients achieving *EASI-75 at Weeks 16 and 24*



Week 16[1] Week 24[1] Week 24[2]

Results support the clinically *meaningful efficacy* with regards to regulatory accepted endpoints

Best efficacy observed in high dose regimen with loading dose, showing progressive improvements to Week 24

Opportunity for *reducing treatment dosing frequency*

1. Data collected after early treatment discontinuation due to reasons other than lack of efficacy prior to endpoint timepoint are included. Data on or after rescue medication or prohibited medications impacting efficacy start date or after the date of treatment discontinuation due to lack of efficacy prior to endpoint timepoint, were considered as non-responders. Any other unobserved values or other missing data are considered as non-responders at Week 16 and Week 24. 2. All data are used for analysis regardless of treatment discontinuation, regardless of rescue/prohibited concomitant medications use. Missing data are considered as non-responders at Week 16/Week 24.
Amlitelimab is currently under clinical investigation, and its safety and efficacy have not been evaluated by any regulatory authority.

Amlitelimab: Potential *Pipeline-in-a-product* targeting core central pathway

Indication	Status	Clinical evidence	Eligible population	Next milestone
AD	Phase 3	Statistically significant improvements in overall efficacy on EASI and IGA scores at 24w	**3.0M**	Phase 3 data in 2026 Submission in 2027
Asthma	Phase 2b	Effect on T2 and non-T2 biomarkers in AD	**1.9M**	Phase 2b data in H2 2024
HS[1]	Phase 2	Target residual B-cell signature[2] after TNF	**0.4M**	Phase 2 data in 2025

More than 5.3M eligible patients

Other indications currently explored adding potentially *another ~1.0M*

Indication	Preliminary evidence	Eligible population	Next milestone
Alopecia Areata	↑ Expression correlated with AA severity (SALT)	**0.6M**	Phase 2 start **in 2024**
Celiac disease	Potential to modulate gluten-specific CD4 T cells	**0.2M**	
Systemic Sclerosis	↑ Soluble Ox40L predictive of pulmonary worsening	**0.2M**	

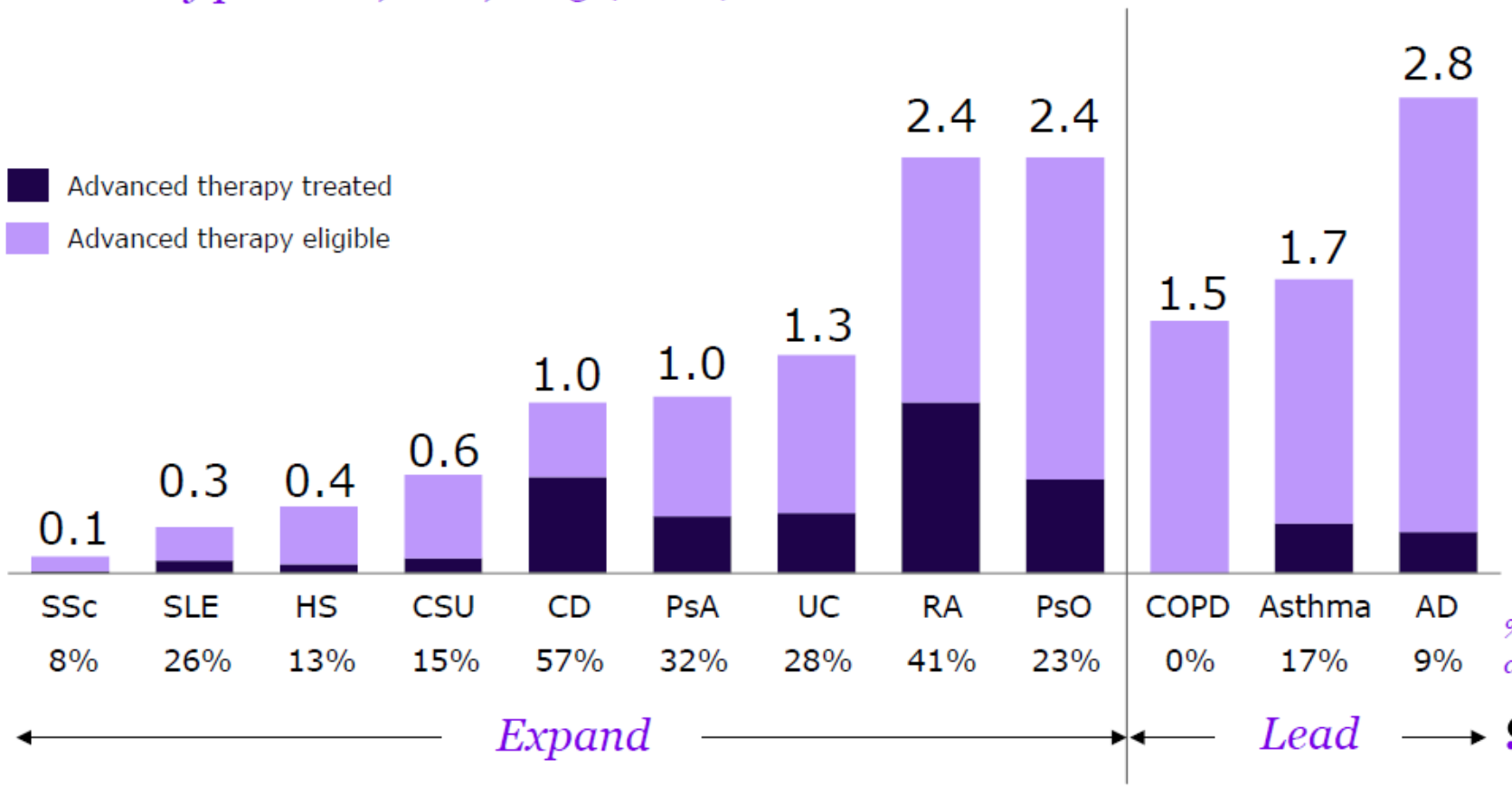
- ✓ Strong science with potential for best-in-class efficacy
- ✓ Fully owned
- ✓ Potential pipeline-in-a-product

>€5bn peak sales potential

Advanced therapy eligible patients across U.S., EU5 (France, Germany, UK, Spain, Italy) and Japan. Additional details in Epidemiology Appendix. 1. Moderate to severe patients. 2. https://pubmed.ncbi.nlm.nih.gov/36689500/.
Amlitelimab is currently under clinical investigation, and its safety and efficacy have not been evaluated by any regulatory authority.

Key immunology markets remain *underpenetrated*

Millions of patients, U.S., EU5 (2022)



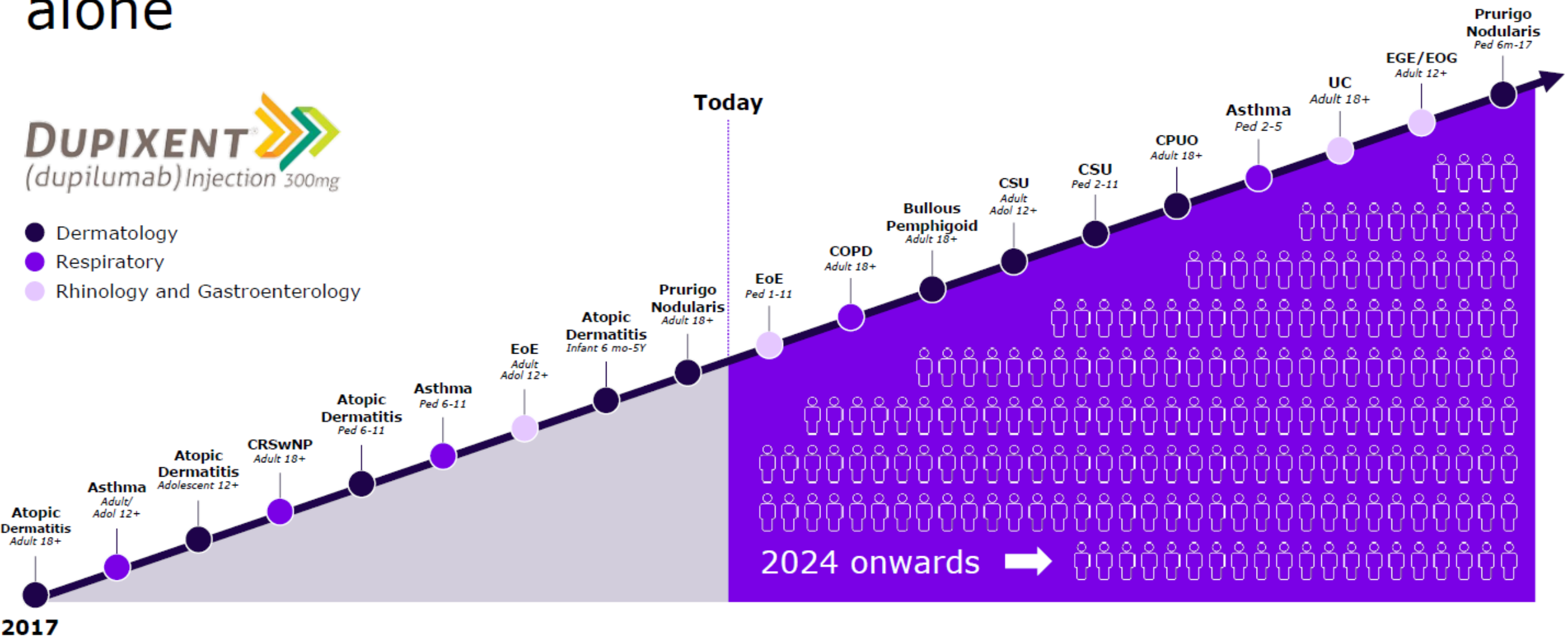
We focus on diseases with *high unmet need* and *high commercial potential*:

- *Large patient populations* / diagnosed prevalence
- *Low penetration* of advanced therapeutics

sanofi

Note: Asthma includes epidemiology data for 12+y. population and COPD for 40+y population, all other diseases 18+. Source: Sanofi estimates. See Appendix for additional details on epidemiology.

Opportunity to add *1 million* eligible patients in the U.S. alone



Itepekimab (IL-33 mAb) Looking Promising in COPD

Potent IL-33 blocker with *best-in-class* and *first-in-class* potential

Phase 2a results in uncontrolled COPD patients fully published

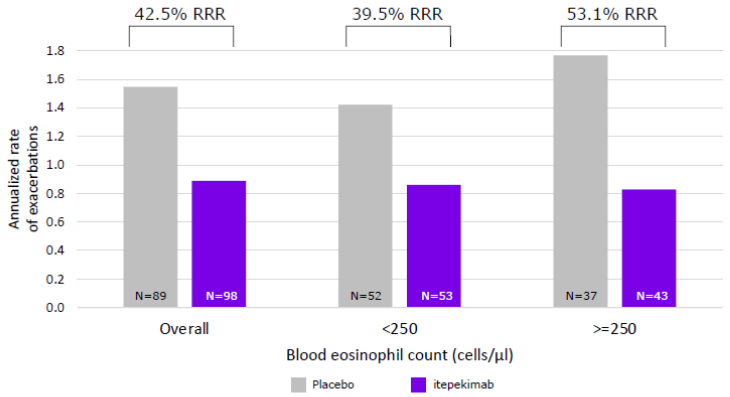
- Numerically lower rate of exacerbations in all patients (not statistically significant)
- >40% reduction in exacerbations in COPD *in former smoker population*
- Generally well tolerated, with an acceptable safety profile

THE LANCET
Respiratory Medicine

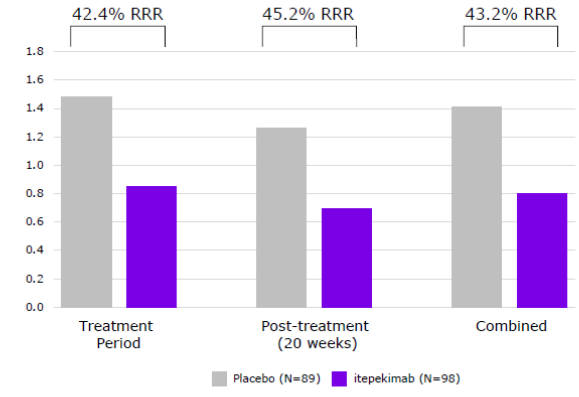
Itepekimab is under investigation and not yet approved by any regulatory agency; Itepekimab is being developed in collaboration with Regeneron. Source: Rabe et al. Lancet Respir Med. 2021

Itepekimab: unprecedented impact in COPD *former smokers* (Phase 2a)

Effect present in *both high and low eosinophil* population



Sustained efficacy 20 weeks post treatment



tepekimab Significantly Reduced Hospitalizations and Emergency Department Visits in Former Smokers With Moderate-to-Severe Chronic Obstructive Pulmonary Disease, Klaus F. Rabe. Rabe et al. Lancet Respir Med. 2021 (Post-hoc analysis). Itepekimab is under investigation and not yet approved by any regulatory agency. Itepekimab was generally well tolerated. Treatment emergent adverse events occurred in 78% of itepekimab patients and 80% of placebo patients. Left graph is showing adjusted values, right graph is showing unadjusted values.

CVS Investor Day (December 5, 2023)

CVS Health Headquarters, Irving, Texas

CVS to Change How It Prices Prescription Drugs with New Pharmacy Reimbursement Model

Annika Kim Constantino, CNBC, Dec 5, 2023

CVS Health on Tuesday said it will revamp how it prices prescription drugs and scrap a complex model that typically sets how much pharmacies get reimbursed and what patients pay for those medications.

The new effort makes CVS the latest company to try to upend the traditional prescription drug pricing system, which has faced years of political scrutiny for what critics call a lack of transparency and inflated health-care costs for U.S. consumers.

CVS will launch a new model for reimbursing its pharmacies on Jan. 1, 2025 for commercial payors, executives said during the company's 2023 investor day. CVS' new model could change the cost of prescription drugs for some patients, but it will not necessarily make all medicine cost less, company executives said. Some drugs may cost less, while prices of others might rise, they noted. But more prescription costs should fall than climb for consumers, employers and health insurers, according to the executives.

Still, CVS is "committed to lowering drug pricing" and making the process more transparent, CEO Karen Lynch said on CNBC's "The Exchange" on Tuesday. "What this does is it essentially aligns the economics of our pricing for drugs to what consumers will pay at the pharmacy counter," Lynch said of the new model. "What people have been saying is, 'We don't understand, it's not transparent, it's not easy to understand how much drugs cost.'" CVS said the plan, named CVS CostVantage, will use a "sustainable and transparent" formula to determine a medication's price and the corresponding reimbursement pharmacies receive from pharmacy benefit managers. Those middlemen negotiate drug discounts with manufacturers on behalf of health insurers, large employers and others that contract them.

Shares of CVS closed nearly 4% higher on Tuesday following the company's investor day, where it also issued a better 2024 revenue forecast than Wall Street expected.

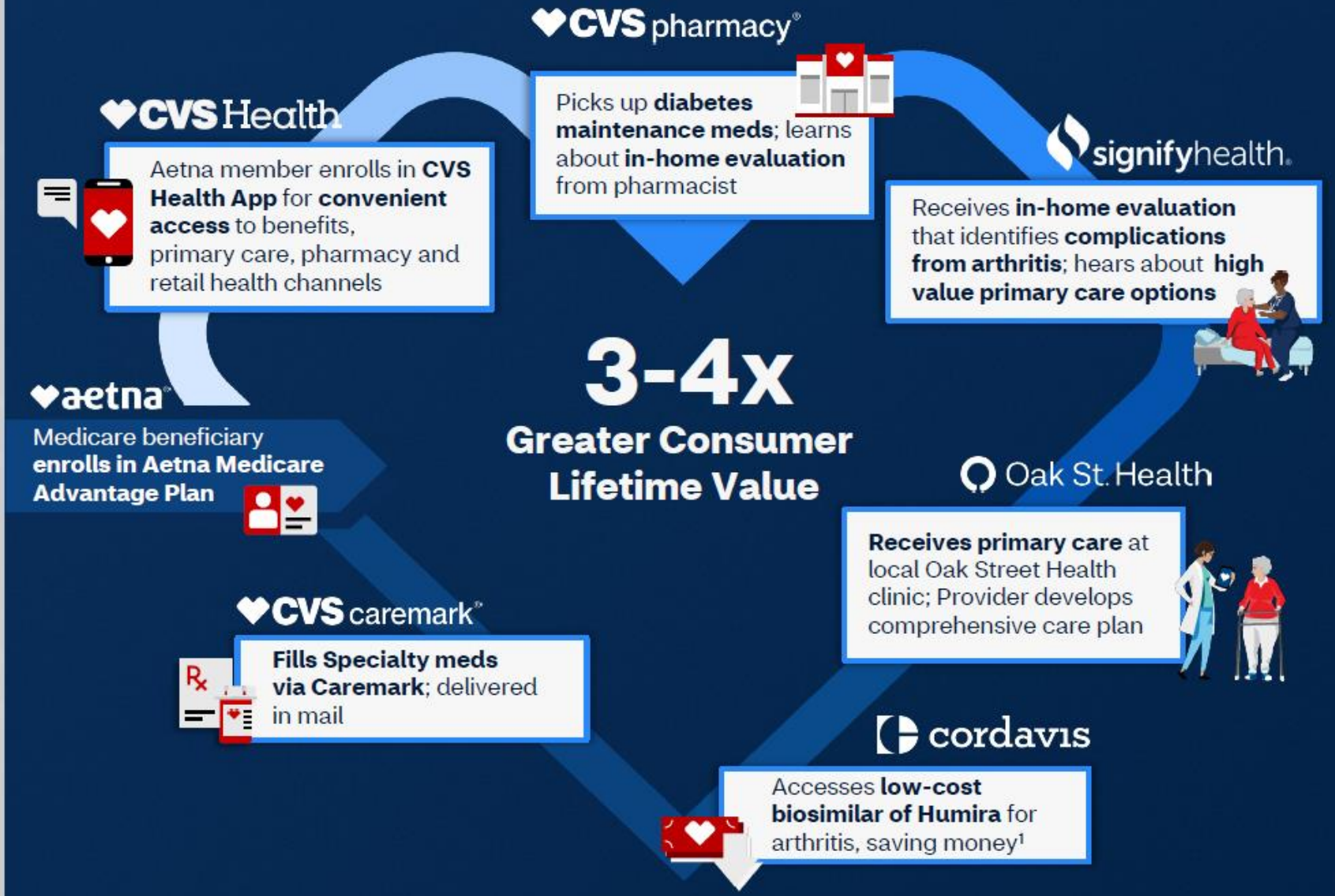
This is a welcome change in pharmacy pricing and aligns CVS with the type of drug pricing approach taken by Mark Cuban's pharmacy.

It's important to note that CVS owns one of the largest PBMs, Caremark, and is, conspicuously *not* offering to make pricing of their PBM more transparent.

Conversations with drug retailers reveal, in fact, that pharmacies are often *losing money* on many drugs and make money from other products (e.g., foods, cosmetics, candy) sold in drug stores.

CVS is designing a pricing scheme that locks in a profit margin on a potentially volatile part of their P&L.

Fully engaged member unlocks sizeable value for payors and CVS Health



1. Available beginning January 1, 2024

Our businesses deliver strong value

aetna®	CVS Healthspire	CVS pharmacy®
Health Care Benefits	**Health Services**	**Pharmacy & Consumer Wellness**
$104.2B Annual revenue[1]	**$182.7B** Annual revenue[1]	**$115.9B** Annual revenue[1]
$5.70B Adjusted operating income[1]	**$7.25B** Adjusted operating income[1]	**$5.81B** Adjusted operating income[1]
35M+ Unique members[2]	**90M+** Members & patients[3]	**120M** Unique customers
50%+ Medicare revenue as a percentage of HCB revenue[1]	**10M+** Annual Health Services visits	**9K+** CVS pharmacies

1. Reflects midpoint of full year 2023 guidance
2. Reflect 2023E total membership, including PDP
3. Projected as of January 1, 2024

CVSHealth

Serving more than a quarter of the U.S. population

provides a unique opportunity to expand engagement

CVS pharmacy®
120M CUSTOMERS[1]

CVS caremark®
90M MEMBERS[2]

aetna®
35M MEMBERS[3]

Our national footprint and local community presence engage **millions of consumers** in high-quality care and help **accelerate growth**

Health Care Delivery

1. Reflects retail pharmacy and front store customers
2. Projected as of January 1, 2024
3. Reflects 2023E total membership, including PDP

CVSHealth.

CVS CostVantage™

We will continue to lower the cost of drugs and will pass through cost improvements to our clients

Drug cost ✕ Markup %

+

Patient management fee

New model benefits the drug supply ecosystem

Retail Pharmacy

- **Transparent pricing**
- **Sustainable** retail economics
- Enables us to **reinvest in our stores and colleagues**
- Clear **growth** drivers

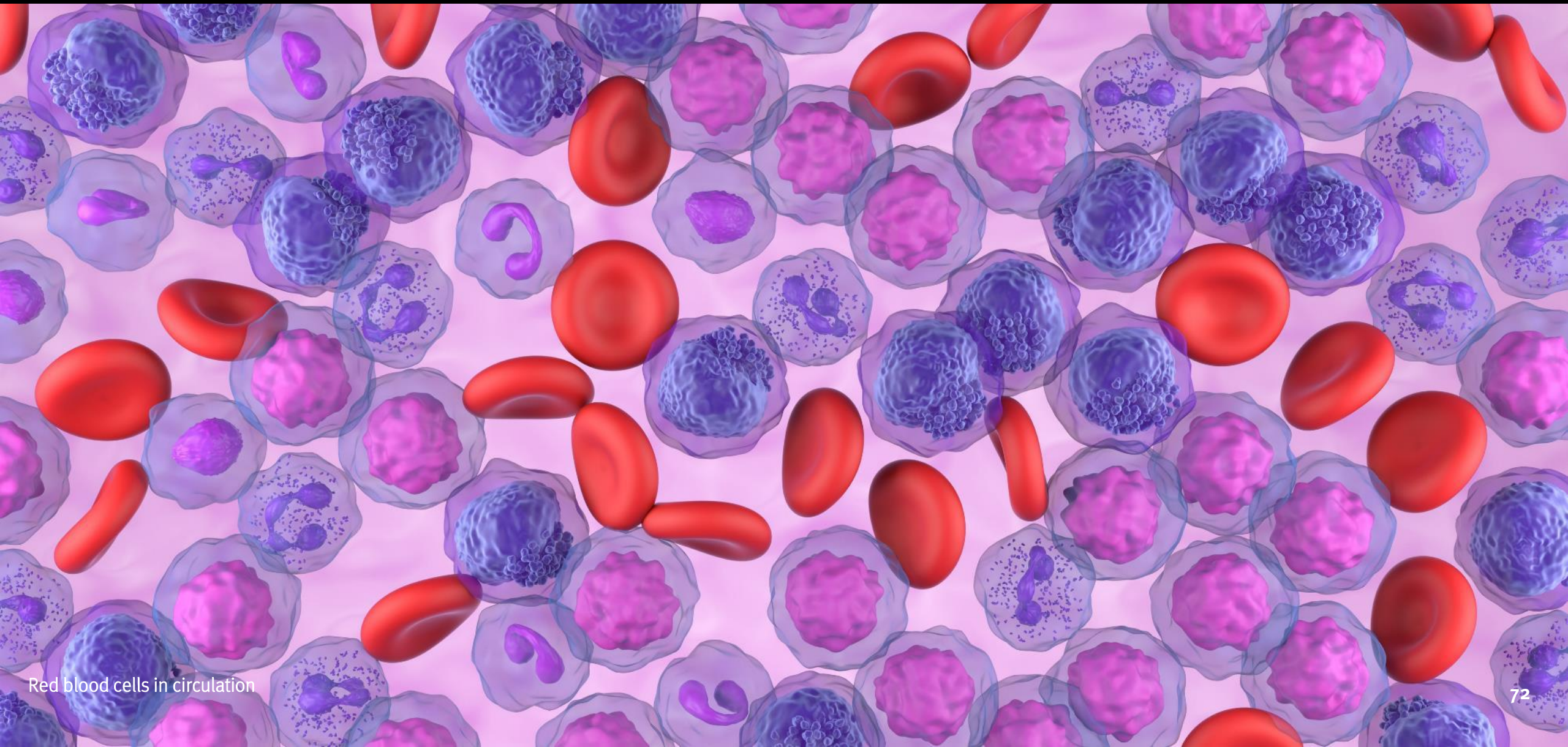
PBMs and Payors

- **Crucial building block** for a more transparent PBM model
- Ensures **access to care**

Consumers

- Provides **foundational step** towards more consumer clarity
- Ensures **access to care**
- Ability to **improve service and quality** for consumers

Industry News



Red blood cells in circulation

Biden Administration Threatens to Exercise March-In Rights

President Joe Biden, Dec 7, 2023 Speech on Instagram:

"Folks, right now, 25 of the largest pharmaceutical companies in America control 70% of the market. This lack of competition drives up prices – making it harder for hardworking American families to access the health care they need.

Today, my Administration is doing something about it. Let me explain:

Hundreds of billions of taxpayer dollars are spent on research, discovery, and development of new prescription drugs. And while I firmly believe that the strength of a nation can be measured by the boldness of its science, the quality of its research, and the progress it helps bring forth, I also believe that the folks who paid for the research – you – ought to be able to access and afford the final product.

That's why my Administration is proposing that if a drug made using taxpayer funds is not reasonably available to Americans, the government reserves the right to "march in" and license that drug to another manufacturer who could sell it for less.

This is an important step toward ending Big Pharma price gouging."

Biden is referring to government rights in the Bayh-Dole Act.

There is the potential to march-in legally.

This appears to be "paper tiger" threat insofar as the practicalities of exercising march-in rights are unimaginable.

How would the government seize control of an NDA? How would it manufacture? Etc.

Source: https://www.instagram.com/reel/Cojdm8GNKTS/

Biden Argument on Lack of Competitiveness Ignores Low Concentration of Pharma Industry

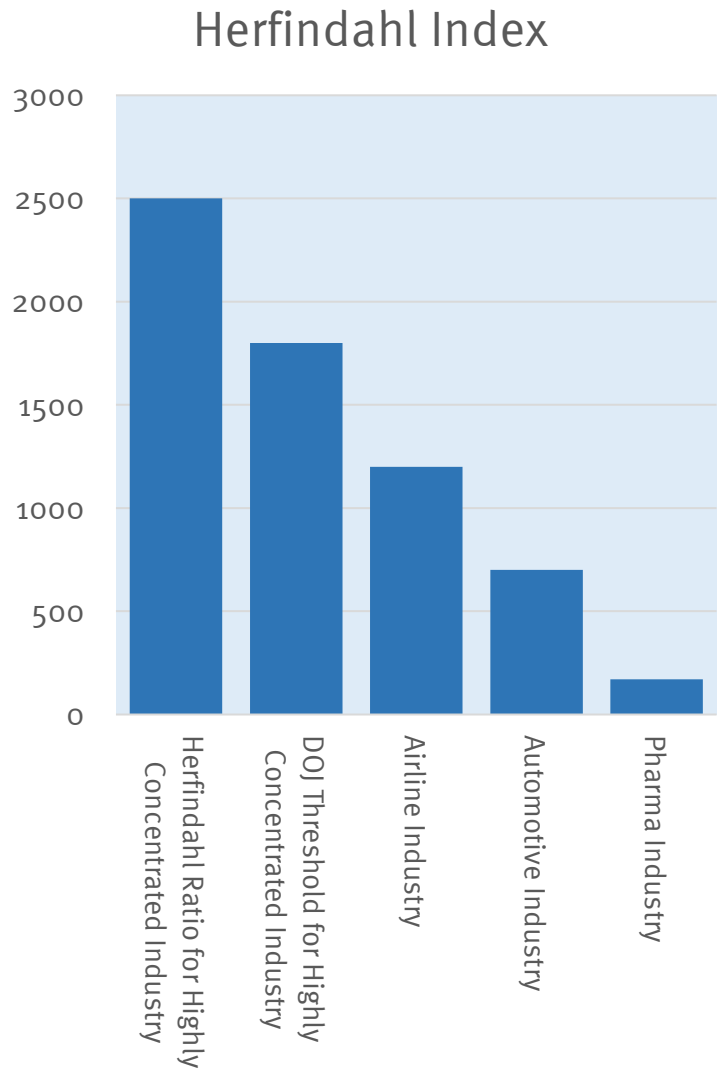
The Biden Administration's position that having 25 companies control 70% of a market is non-competitive and provides pricing power to incumbents is surprising and specious in light of existing economic theory of market competition.

Interestingly, last week's statement by Biden is consistent with the statement given by Holly Vedova, Director of the Bureau of Competition, at the FTC this Spring justifying the antitrust challenge to the Amgen/Horizon combination that "Rampant consolidation in the pharmaceutical industry has given powerful companies a pass to exorbitantly hike prescription drug prices, deny patients access to more affordable generics, and hamstring innovation in life-saving markets." The FTC has taken this type of position consistently in recent years. For example, we were surprised to see two members of the U.S. FTC vote against the AbbVie – Allergan merger on antitrust grounds in 2020. Commissioner Chopra wrote an opinion describing anticompetitive industry behavior in which pharma companies "exploit their dominance, block new entrants, and harm patients in need of life-saving drugs".

The data show that the pharma industry is far from concentrated, at least in an aggregate sense. A widely used measure of industry concentration and competitiveness is the Herfindahl Index (HHI). We compute that the global HHI Index as of May 2023 was 170, well below the U.S. DOJ threshold of 1800 that demarcates a highly concentrated industry – where caution would be exercised by antitrust authorities on horizontal mergers. A perfectly monopolistic industry would have an HHI Index of 10000.

We have been calculating the HHI Index for pharma for a number of years. In Sep 2020, for example, the HHI was 220 – higher than today. The concentration of the pharma industry has been *declining* over time.

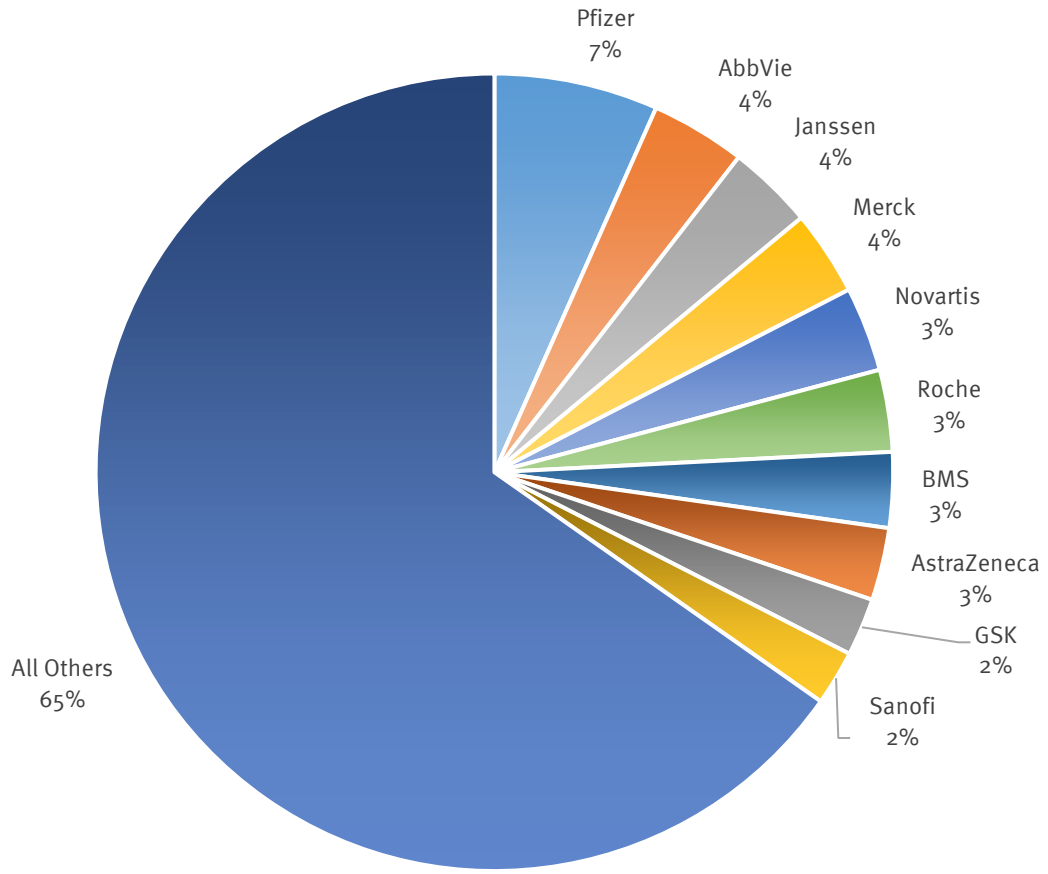
We can only surmise that the Biden Administration is feeling a bit worried about its poor position in the polls for next year's Presidential election and is trying to create an issue. No reasonable economic expert in competition would draw the conclusion that having an HHI index of less than 200 looks anything like a monopolistic industry where pricing power is widespread.



Source: https://ark-invest.com/articles/analyst-research/automotive-consolidation/

Largest Pharma Player Has 7% Market Share

Market Share of Top Ten Pharma Companies and Rest of Industry, 2022 Revenue



Source: updated analysis of the Pharma 1000 database. See https://www.linkedin.com/pulse/pharma-1000-tim-opler/

One has to work really hard to tell a story of anti-competitive behavior in the pharma industry.

The process of developing drugs is fiercely competitive. The process of marketing drugs is even more competitive.

There is no dominant player in the industry. Unlike sectors such as autos, airlines or computer chips, industry concentration in pharma is quite low.

The largest player, Pfizer, had 7% market share in 2022. This number is inflated by Covid vaccine sales. Amgen's market share in the industry is *under 2%*.

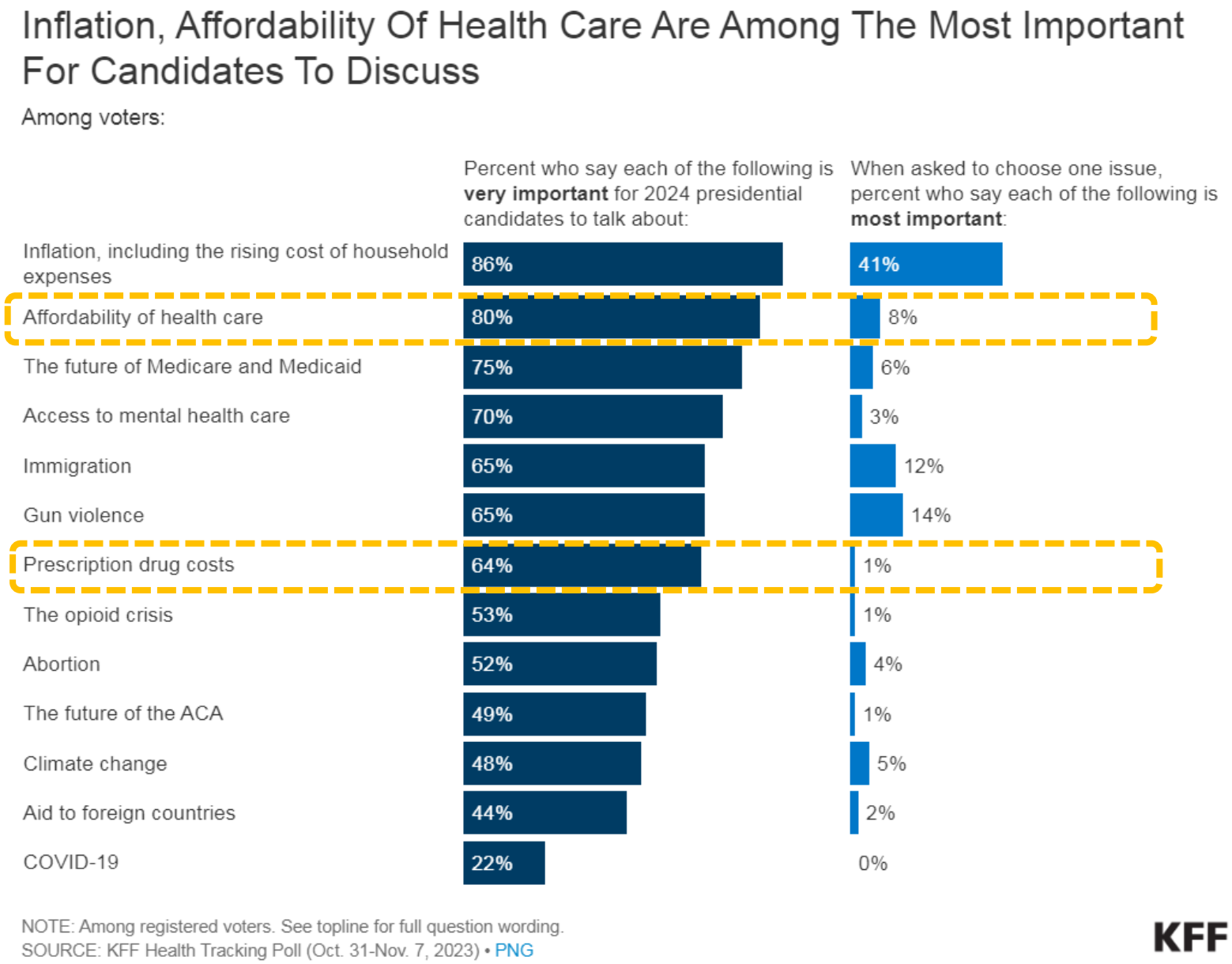
We have argued elsewhere that so-called "large pharma" companies are dwarfed by the "large tech" brethren due to short monopoly periods because of rapid appearance of branded competition, low returns on R&D spend, long timelines for drug development and high risk associated with R&D.

It's hard to think that the Biden Administration is *truly* concerned about lack of competition in the pharma sector given that they could have easily picked on any number of more popular industries that also receive government support. The tech industry and the PBM sector both come to mind.

KFF Poll:

Voters in 2024 U.S. Presidential election most focused on inflation and affordability of healthcare

This chart makes for interesting reading in the context of Biden's recent behavior. Voters in the upcoming election consider healthcare costs to be important. However, only 8% say it's the most important issue. Likewise, only 1% of the populace say that drug costs are their most important issue. One might call prescription drug costs a "dog whistle" issue rather than a core issue for voters at present.



Source: https://www.kff.org/health-reform/poll-finding/kff-health-tracking-poll-november-2023

John Crowley to Lead BIO

Betsy McKay, *Wall Street Journal,* Dec 5, 2023

John Crowley burst into the back hallway of a Cheesecake Factory in New Jersey where his daughter Megan and her nurse had just finished lunch.

Megan, 26, was lying unconscious on the tile floor next to her wheelchair. She was grayish, her lips purple. Nearly a quarter-century after plunging into biotech to find drugs to save Megan and her younger brother, Patrick, from a rare and deadly genetic disease, Crowley feared the battle had suddenly been lost.

A police officer performed CPR and got Megan's pulse back. Crowley grabbed a manual breathing bag and started giving Megan air the way he knew works best for her.

A day later, Megan was home recovering from her most life-threatening emergency since she had pneumonia as a baby. The scare jolted Crowley toward a realization: As far as rare-disease drugs have come, they need to be much better. He resolved to devote the next act of his career to saving not just his children but the biotech industry.

"There is massive unmet need, and the whole ecosystem just isn't coming together," said Crowley, 56, executive chairman of Amicus Therapeutics. He helped develop two drugs to treat Megan, Patrick and others with Pompe disease, which causes heart and skeletal muscles to waste away. The Food and Drug Administration approved the second drug in September.

Crowley will take on his biggest role yet in March, when he becomes chief executive officer of Biotechnology Innovation Organization, a powerful trade group whose members are mostly small health-focused companies. Crowley will succeed Rachel King, who has served as interim CEO since Dr. Michelle McMurry-Heath resigned after disagreements with some BIO board members.

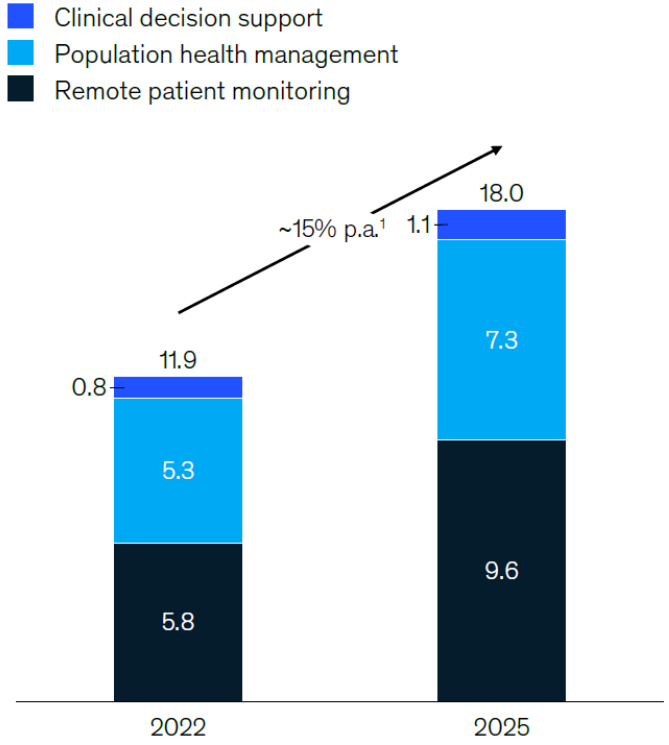
Source: https://www.wsj.com/tech/biotech/john-crowley-biotech-innovation-organization-a1fo8ba2

High Growth Expected in Digital Diagnostics

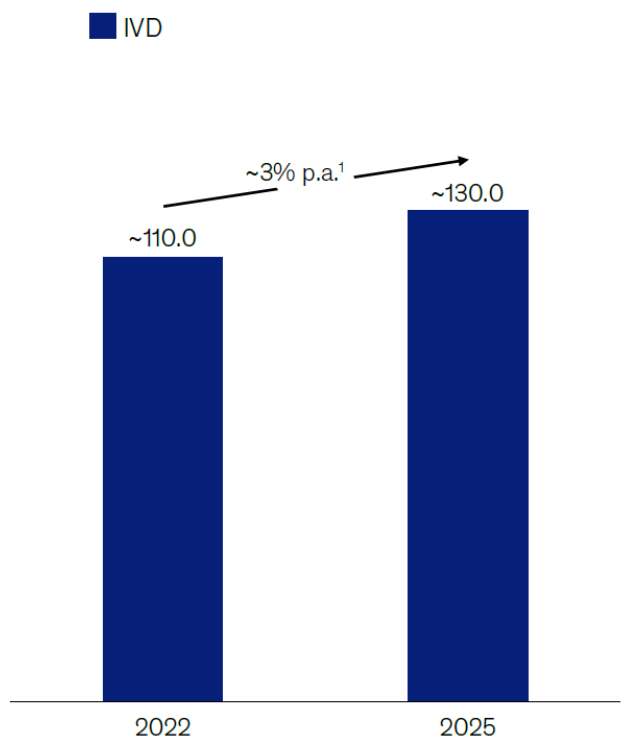
McKinsey Report, Dec 7, 2023

Digital markets adjacent to diagnostics are projected to outgrow the core diagnostics market.

Select global digital market sizes, revenues, $ billion



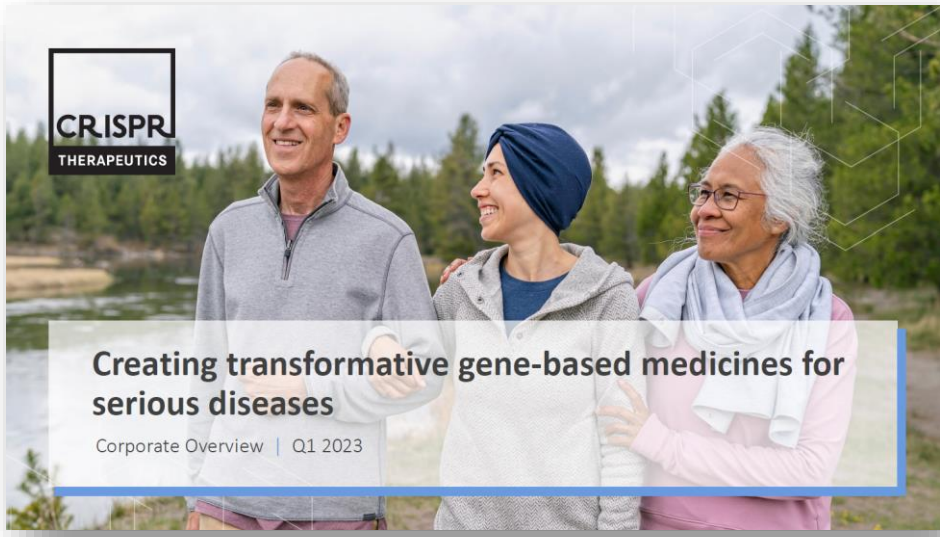
Global in vitro diagnostics (IVD) market size, revenues, $ billion



Source: https://www.mckinsey.com/industries/life-sciences/our-insights/digital-diagnostics-a-path-forward-for-ivd#/

CRISPR eyes Autoimmune Disease in Revamp of Plans

Ben Fidler, *Biopharma Dive,* Dec 5, 2023



CRISPR's most advanced work outside of Casgevy is in cancer, where it has advanced through early clinical testing a pair of similar programs in certain blood cancers and solid tumors. Both are off-the-shelf, or "allogeneic," cell therapy treatments, which use healthy donor cells and are seen as more convenient to the personalized CAR-T cell therapies sold by Gilead Sciences, Novartis and Bristol Myers Squibb.

Like other allogeneic cell therapy developers, CRISPR has struggled to prove its treatments can match up to personalized CAR-T, however. Earlier data for a single dose disappointed, and newly released results on Monday showed an optimized dose regimen wasn't much better. According to the company, preclinical results suggest a pair of newer medicines, dubbed CTX112 and CTX131 and now in Phase 1 testing, should be more potent.

CRISPR also now plans to test its cell therapies in autoimmune disease, a strategy that's seen by large and small drugmakers as a way of expanding the medicines' use. Lupus, in particular, is a disease of interest, following the release of promising data from an academic study in 2022. CRISPR is starting with lupus and could expand into other diseases afterwards, the company said.

It isn't alone. A growing group of companies including startups Kyverna Therapeutics and Cartesian Therapeutics, publicly traded biotech Gracell Biotechnologies, as well as larger companies like Novartis and Bristol Myers, all have lupus cell therapies in development.

Source: https://www.biopharmadive.com/news/crispr-cancer-cell-therapy-autoimmune-lupus/701528/

Bluebird Falls After Its Sickle-Cell Gene Therapy Gets FDA's Strictest Warning

Ike Swetlitz, *Bloomberg*, Dec 8, 2023

Bluebird Bio Inc. fell the most ever after its new gene therapy for sickle cell disease was approved in the US with caveats that may limit revenue.

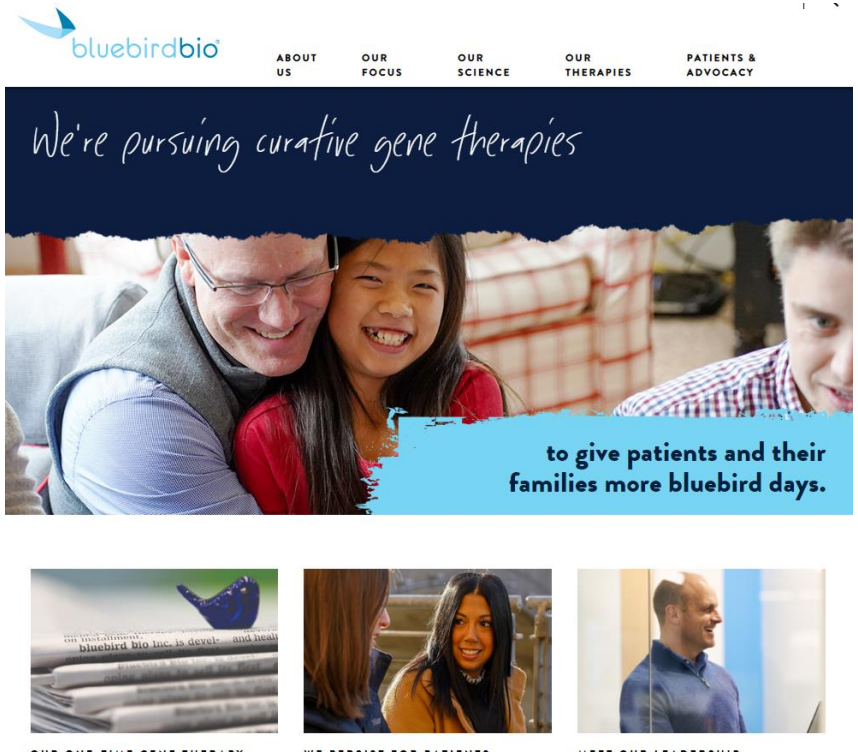
The treatment, Lyfgenia, was approved by the Food and Drug Administration Friday with a boxed warning — the FDA's most severe form of caution — saying that blood cancers have occurred in patients taking the therapy. That risk may push doctors to favor another sickle cell treatment approved at the same time.

The other therapy doesn't carry a boxed warning and is also less expensive. Casgevy, made by Crispr Therapeutics AG and Vertex Pharmaceuticals Inc., will cost $2.2 million, compared with a $3.1 million price tag for Lyfgenia.

Bluebird shares fell 41% Friday, their biggest drop since the stock began trading a decade ago. The Cambridge, Massachusetts-based company has lost 59% of its market value this year.

Making matters worse for Bluebird, the company said it didn't receive a priority review voucher from the FDA along with the approval. Bluebird had already lined up a buyer for the voucher and was expecting to get $103 million for it.

Bluebird investors have weathered a series of setbacks. The company faced safety issues and delays en route to getting FDA approval, and it nearly ran out of money last year.



Source: https://www.bloomberg.com/news/articles/2023-12-08/bluebird-sinks-after-gene-therapy-gets-fda-s-strictest-warning

The First Crispr Therapy Is Just the Start of the Gene-Editing Revolution

Gerry Smith, *Bloomberg,* Dec 9, 2023

Editing DNA with the same ease as spell-checking a Word document is a scientific holy grail. It would allow debilitating and deadly genetic diseases to not only be treated, but cured. The US Food and Drug Administration's approval on Friday of the first treatment using the Nobel-prize-winning technology Crispr is a medical milestone that puts that dream one giant step closer to reality.

Two companies, Vertex Pharmaceuticals Inc. and Crispr Therapeutics AG, are now cleared to sell the cutting-edge gene-editing treatment to potentially cure sickle cell disease. But Crispr's real potential — fixing problematic genetic code inside of the body instead of in a lab — is still in the future.

"I'm looking a few years ahead, to when we can transcend this milestone," said Eric Topol, a physician-scientist and director of the Scripps Research Translational Institute. "This is just the beginning."

Crispr's Nobel prize-winning innovation is the ability to cut and paste DNA with more ease and precision than ever before. Sickle cell, for example, was an early target for the technology because it's caused by a mutation of just one single letter of genetic code. That mutation causes red blood cells to bend in a crescent shape instead of a round one, making it harder for essential oxygen to reach tissues and organs. The therapies extract blood stem cells and edit them in a lab, then return them to patients' bodies. But more recent innovations to the technology, such as what's known as prime editing, have made gene editing even more precise and efficient.

Source: https://www.bloomberg.com/news/articles/2023-12-09/crispr-new-sickle-cell-therapy-is-start-of-dna-editing-revolution

GLP-1 Receptor Agonists and Colorectal Cancer Risk in Drug-Naïve Patients With Type2 Diabetes, With and Without Overweight/Obesity

Wang L, Wang W, Kaelber DC, Xu R, Berger NA, "GLP-1 Receptor Agonists and Colorectal Cancer Risk in Drug-Naive Patients With Type 2 Diabetes, With and Without Overweight/Obesity," *JAMA Oncol.*, Dec 7, 2023

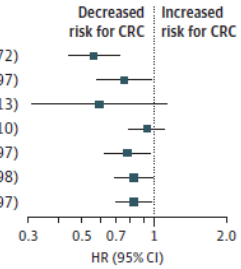
During a 15-year follow-up in 1 221 218 drug-naive patients with T2D, GLP-1RAs were associated with decreased risk for CRC compared with insulin (HR, 0.56; 95% CI, 0.44-0.72), metformin (HR, 0.75; 95% CI, 0.58-0.97), SGLT2 inhibitors, sulfonylureas, and thiazolidinediones, and with lower but not statistically significant risk compared with alpha-glucosidase or DPP-4 inhibitors (Figure, A). Consistent findings were observed in women and in men. GLP-1RAs were associated with a lower risk for CRC in patients with obesity/overweight compared with insulin (HR, 0.50; 95% CI, 0.33-0.75), metformin (HR, 0.58; 95% CI, 0.38-0.89), or other antidiabetics (Figure, B).

In this cohort study, GLP-1RAs were associated with reduced CRC risk in drug-naive patients with T2D with and without obesity/overweight, with more profound effects in patients with obesity/overweight, suggesting a potential protective effect against CRC partially mediated by weight loss and other mechanisms not related to weight loss. Study limitations include potential unmeasured or uncontrolled confounders, self-selection, reverse causality, and other biases inherent in observational studies, and that results need validation from other data and study populations. Further research is warranted to investigate the effects in patients with prior antidiabetic treatments, underlying mechanisms, potential differential effects within GLP-1RAs, and effects of GLP-1RAs on other obesity-associated cancers.

Figure. Risks and Hazard Ratios (HRs) of First-Time Diagnosis of Colorectal Cancer (CRC) in Drug-Naive Patients With Type 2 Diabetes

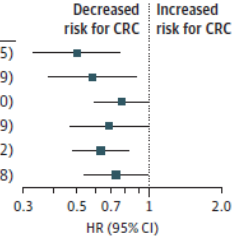
A Overall study population

Exposure cohort (matched)	Comparison cohort (matched)	Exposure cohort No. of cases (overall risk)	Comparison cohort No. of cases (overall risk)	HR (95% CI)
GLP-1RA(+)/insulin(-) (n = 22 572)	GLP-1RA(-)/insulin(+) (n = 22 572)	94 (0.42%)	167 (0.74%)	0.56 (0.44-0.72)
GLP-1RA(+)/metformin(-) (n = 18 518)	GLP-1RA(-)/metformin(+) (n = 18 518)	96 (0.52%)	153 (0.83%)	0.75 (0.58-0.97)
GLP-1RA(+)/AGI(-) (n = 2503)	GLP-1RA(-)/AGI(+) (n = 2503)	14 (0.56%)	26 (1.04%)	0.59 (0.31-1.13)
GLP-1RA(+)/DDP-4(-) (n = 44 146)	GLP-1RA(-)/DDP-4(+) (n = 44 146)	256 (0.58%)	282 (0.64%)	0.93 (0.78-1.10)
GLP-1RA(+)/SGLT2(-) (n = 25 133)	GLP-1RA(-)/SGLT2(+) (n = 25 133)	142 (0.57%)	175 (0.70%)	0.77 (0.62-0.97)
GLP-1RA(+)/SU(-) (n = 36 716)	GLP-1RA(-)/SU(+) (n = 36 716)	207 (0.56%)	293 (0.80%)	0.82 (0.68-0.98)
GLP-1RA(+)/TZD(-) (n = 36 481)	GLP-1RA(-)/TZD(+) (n = 36 481)	222 (0.61%)	378 (1.04%)	0.82 (0.69-0.97)



B Patients with overweight/obesity

Exposure cohort (matched)	Comparison cohort (matched)	Exposure cohort No. of cases (overall risk)	Comparison cohort No. of cases (overall risk)	HR (95% CI)
GLP-1RA(+)/insulin(-) (n = 9398)	GLP-1RA(-)/insulin(+) (n = 9398)	35 (0.37%)	67 (0.71%)	0.50 (0.33-0.75)
GLP-1RA(+)/metformin(-) (n = 8057)	GLP-1RA(-)/metformin(+) (n = 8057)	31 (0.39%)	64 (0.79%)	0.58 (0.38-0.89)
GLP-1RA(+)/DDP-4(-) (n = 16 699)	GLP-1RA(-)/DPP-4(+) (n = 16 699)	96 (0.58%)	125 (0.75%)	0.77 (0.59-1.00)
GLP-1RA(+)/SGLT2(-) (n = 8148)	GLP-1RA(-)/SGLT2(+) (n = 8148)	47 (0.58%)	66 (0.81%)	0.68 (0.47-0.99)
GLP-1RA(+)/SU(-) (n = 15 551)	GLP-1RA(-)/SU(+) (n = 15 551)	85 (0.55%)	154 (0.99%)	0.63 (0.48-0.82)
GLP-1RA(+)/TZD(-) (n = 11 099)	GLP-1RA(-)/TZD(+) (n = 11 099)	71 (0.64%)	124 (1.12%)	0.73 (0.54-0.98)



Patients had no prior CRC and had no prior antidiabetic medication prescriptions between matched cohorts in the overall study population (A) and in patients with obesity/overweight (B). Kaplan-Meier analysis was used to estimate the probability of the outcome (first diagnosis of CRC) at daily time intervals with censoring applied within a 15-year time window starting from the index event (first prescription of glucagon-like peptide 1 receptor agonists [GLP-1RAs] vs other non–GLP-1RA antidiabetic medications). The cohorts were propensity score matched for demographics, adverse socioeconomic determinants of health, preexisting medical conditions, personal and family history of cancers such as CRC and colonic polyps, benign neoplasms of the colon and rectum, lifestyle factors (exercise, diet, smoking, and alcohol drinking), medical encounters, and procedures such as colonoscopy. Overall risk is defined as the number of incidence cases among the number of patients in each cohort at the beginning of the time window. A plus sign (+) indicates that a patient was prescribed a GLP-1RA or non–GLP-1RA antidiabetic medication, while a minus sign (−) indicates that they were not. AGI indicates alpha-glucosidase inhibitors; DPP-4, dipeptidyl-peptidase 4 inhibitors; SGLT2, sodium-glucose cotransporter-2 inhibitors; SU, sulfonylureas, TZD, thiazolidinediones.

Source: https://pubmed.ncbi.nlm.nih.gov/38060218/

The Medicare Gold Rush Is Slowing Down

David Wainer, *Wall Street Journal,* Dec 6, 2023

The popularity of private Medicare plans has been a huge driver of profits for insurance companies in recent years. There are signs the gold rush isn't quite what it once was. Investors have been worried all year as the Biden administration phases in a new system that insurers say will reduce federal payments to Medicare Advantage plans. Developments last week at the top two insurers in the Medicare business, UnitedHealth Group and Humana, raised more questions.

The most immediate red flag came from the industry leader, UnitedHealth. During an investor day last week, it predicted its Medicare Advantage enrollment would grow by 450,000 to 550,000 seniors in 2024. That translates to around 5% growth next year, a significant slowdown from the 11% it grew so far this year, according to TD Cowen analyst Gary Taylor. As UnitedHealth executives were presenting in New York, The Wall Street Journal reported that the second-largest Medicare plan provider, Humana, was in merger talks with Cigna. While Cigna's interest in Humana surely attests to insurers' continued desire to expand into the Medicare market, some investors took it as a sign that Humana isn't so sure about the strength of the business going forward.

The question then becomes at what point do the conversions hit a ceiling. Using Miami as an example, analyst John Ransom at Raymond James noted that once the city reached about 75% market penetration, growth flatlined, suggesting that might be a ceiling for other places. Some seniors, especially wealthier ones less concerned about higher out-of-pocket costs, will continue to prefer regular Medicare coverage, where there is more flexibility in choosing providers and types of care.

As conversions slow down, competition is intensifying. One reason UnitedHealth will have slower growth next year is that CVS Health (which owns insurer Aetna) was more aggressive in its plan offerings. During its investor day Tuesday, CVS said it would add more than 600,000 members to its Medicare Advantage plans next year, confirming that it is grabbing some of the growth away from the industry leaders. The competition is a sign that the market is doing what it should, and that isn't a bad thing for seniors. Beneficiaries are now able to pick from an average of 43 plans based on their location, compared with just 20 in 2018, according to Ransom. As companies compete for market share, supplemental benefits expand while premiums fall, reducing insurers' margins.

Source: https://www.wsj.com/health/healthcare/the-medicare-gold-rush-is-slowing-down-ebc5a4af

Clinical Hold on Roche BTK Inhibitor

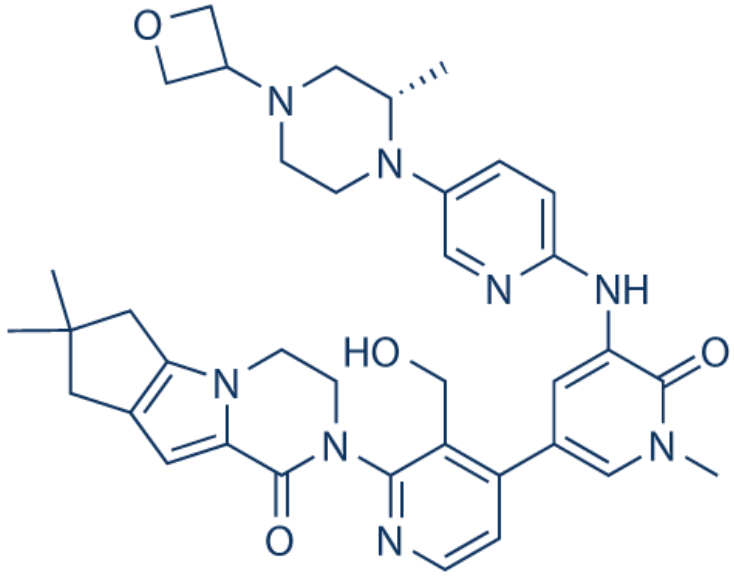
Neurology Live, Dec 5, 2023

According to a recent announcement, the FDA has placed a clinical hold on the development program for fenebrutinib (Roche), an investigational oral, reversible, and noncovalent Bruton tyrosine kinase (BTK) inhibitor in development for patients with multiple sclerosis (MS).

The decision was based on 2 recent cases of hepatic transaminase elevations in conjunction with elevated bilirubin suggestive of drug-induced liver injury that was documented in the blinded phase 3 FENhance studies of relapsing MS. Both patients were asymptomatic and had elevations returned to normal levels following the discontinuation of fenebrutinib.

As a result of the hold, new enrollment for the FENhance 1 trial (NCT04586023) in the US will be paused, while enrollment in countries outside of the US will continue. Participants in the US who received fenebrutinib for more than 70 days will continue treatment in all studies, which comprise the ongoing, fully enrolled FENhance 2 (NCT04586010) and FENtrepid trial (NCT04544449). Roche noted that only a small number of participants in the US who received the treatment for 70 days or less will discontinue treatment.

Fenebrutinib, a BTK inhibitor that blocks the function of BTK, is also a dual inhibitor of both B-cell and microglia activation. Despite the number of BTK inhibitors in the clinical pipeline increasing in recent years, fenebrutinib remains the only reversible inhibitor with this mechanism of action.



Source: https://www.neurologylive.com/view/fda-places-clinical-hold-roche-btk-inhibitor-fenebrutinib-multiple-sclerosis

Axcella Liquidation Via an Assignment to Creditor Process

8-K, Nov 1, 2023

On November 1, 2023 (the “Effective Date”), the Board of Axcella (i) determined that it is in the best interests of Axcella and its stakeholders to effect a transfer and assignment of substantially all of Axcella’s assets to an assignee (the “Assignee”) for the benefit of creditors (the “Assignment”); (ii) determined that it is in the best interests of Axcella and its stakeholders that, following the Assignment, the Company be dissolved in accordance with Delaware General Corporation Law pursuant to a Plan of Dissolution (the “Dissolution”); (iii) approved seeking stockholder approval to proceed with the Assignment and the Dissolution pursuant to Delaware law (the “Assignment and Dissolution Proposals”) at a special meeting of stockholders (the “Special Meeting of Stockholders”) to be held as soon as reasonably practicable following the Effective Date.

Source: https://www.sec.gov/ix?doc=/Archives/edgar/data/0001633070/000110465923113379/tm2329576d1_8k.htm

Why Doctors and Pharmacists Are in Revolt

Noam Scheiber, *New York Times,* Dec 5, 2023

Dr. John Wust does not come off as a labor agitator. A longtime obstetrician-gynecologist from Louisiana with a penchant for bow ties, Dr. Wust spent the first 15 years of his career as a partner in a small business — that is, running his own practice with colleagues.

Long after he took a position at Allina Health, a large nonprofit health care system based in Minnesota, in 2009, he did not see himself as the kind of employee who might benefit from collective bargaining.

But that changed in the months leading up to March, when his group of more than 100 doctors at an Allina hospital near Minneapolis voted to unionize. Dr. Wust, who has spoken with colleagues about the potential benefits of a union, said doctors were at a loss on how to ease their unsustainable workload because they had less input at the hospital than ever before.

At the time he and his colleagues voted to unionize, they were one of the largest groups of private-sector doctors ever to do so. But by October, that distinction went to a group that included about 400 primary-care physicians employed in clinics that are also owned by Allina. The union that represents them, the Doctors Council of the Service Employees International Union, says doctors from dozens of facilities around the country have inquired about organizing over the past few years.

But in each case, the explanation runs deeper: A longer-term consolidation of health care companies has left workers feeling powerless in big bureaucracies. They say the trend has left them with little room to exercise their professional judgment.

“People do feel put upon — that’s real,” said John August, an expert on health care labor relations at the Scheinman Institute at Cornell University. “The corporate structures in health care are not evil, but they have not evolved to the point of understanding how to engage” with health workers.

Source: https://www.wsj.com/tech/biotech/john-crowley-biotech-innovation-organization-a1fo8ba2

EyePoint Pharmaceuticals Announces Positive Topline Data from the Phase 2 DAVIO 2 Trial of EYP-1901 in Wet AMD Achieving All Primary and Secondary Endpoints

WATERTOWN, Mass., Dec. 04, 2023 (GLOBE NEWSWIRE) -- EyePoint Pharmaceuticals, Inc. (NASDAQ: EYPT), a company committed to developing and commercializing therapeutics to improve the lives of patients with serious retinal diseases, today announced positive topline results of its Phase 2 DAVIO 2 trial of EYP-1901, an investigational sustained delivery maintenance treatment for wet age-related macular degeneration (wet AMD) combining vorolanib, a selective tyrosine kinase inhibitor with bioerodible Durasert E™. The clinical trial met its primary endpoint with both EYP-1901 doses demonstrating statistical non-inferiority change in best corrected visual acuity (BCVA) compared to aflibercept control and a favorable safety profile with no EYP-1901-related ocular or systemic serious adverse events (SAEs). The trial also achieved key secondary endpoints with both EYP-1901 doses, including an over 80% reduction in treatment burden, nearly two-thirds of eyes supplement-free up to six months and over 80% receiving only zero or one supplement up to six-months. Additionally, there was strong anatomical control with both EYP-1901 cohorts as measured by optical coherence tomography (OCT).

“We are incredibly pleased by these highly positive Phase 2 results which underscore EYP-1901’s potential as a paradigm-altering maintenance treatment for patients with wet AMD, with a positive safety profile. Since EYP-1901 achieved statistical non-inferiority to the aflibercept control in this trial there is potential for meaningfully lower sized and lower cost pivotal Phase 3 trials,” said Jay S. Duker, M.D., President and Chief Executive Officer of EyePoint Pharmaceuticals. “I would like to thank the patients and the investigators who participated in the DAVIO 2 trial as well as our employees who helped advance us to this important milestone.”

Dr. Duker continued, “the DAVIO 2 clinical trial was designed to support the initiation of Phase 3 clinical trials based on feedback received from the U.S. Food and Drug Administration (FDA) at a Type C meeting last year. The 32-week topline DAVIO 2 data strongly supports our planned Phase 3 non-inferiority design, consistent with the FDA’s recent guidance for wet AMD clinical trials. We look forward to continuing our dialogue regarding our Phase 3 plans with the FDA as we prepare to initiate our first pivotal trial for wet AMD in the second half of 2024.”

Source: https://investors.eyepointpharma.com/news-releases/news-release-details/eyepoint-pharmaceuticals-announces-positive-topline-data-phase-2

Biomea Fusion Updates Diabetes Data

REDWOOD CITY, Calif., Dec. 09, 2023 (GLOBE NEWSWIRE) -- Biomea Fusion, Inc. ("Biomea") (Nasdaq: BMEA), a clinical-stage biopharmaceutical company dedicated to discovering and developing novel covalent small molecules to treat and improve the lives of patients with genetically defined cancers and metabolic diseases, today announced top line data of the 200 mg dose cohorts from the ongoing Phase II clinical study (COVALENT-111) which will be presented in more detail at the International Conference on Advanced Technologies and Treatments of Diabetes (ATTD) in March 2024.

"At WCIRDC over the past days, we had the opportunity to lay out the foundational preclinical work and the data sets which supported that beta cell proliferation and their functional improvement is tractable to BMF-219, not only in animals, but also in the human islets, which we studied together with the Harvard Medical School, Joslin Diabetes Center. When inhibiting menin covalently, we observed some of the key signaling pathways and genes that are known to influence beta cell proliferation and function. As presented at the conference, we have shown for the first time the long-term follow-up data of our 100 mg patient cohorts.

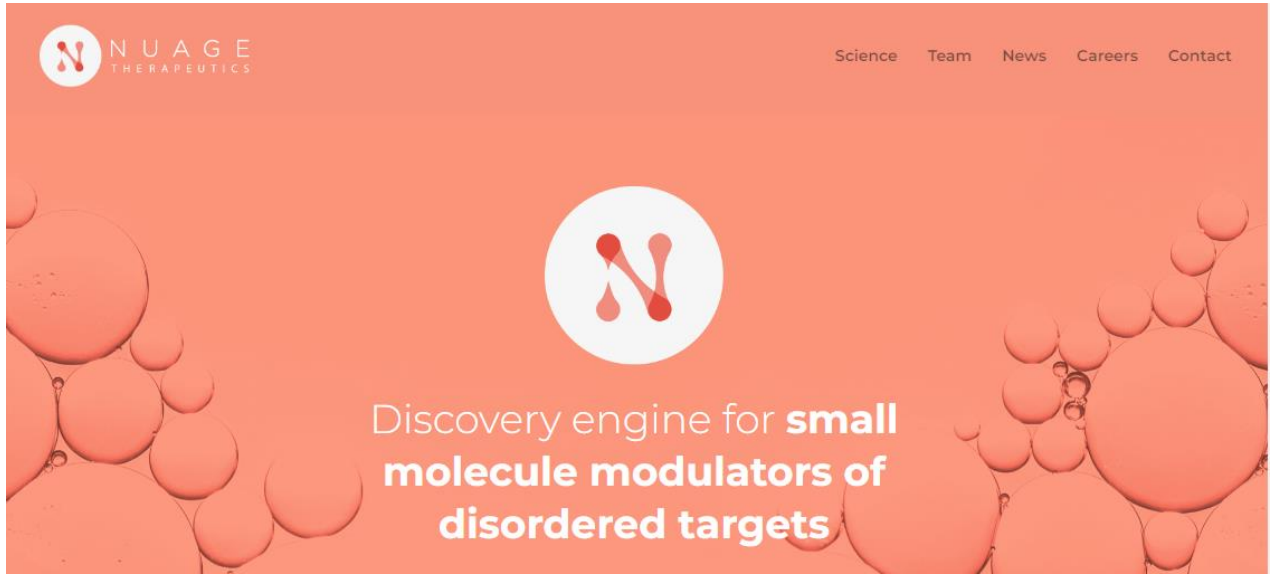
At Week 26, 22 weeks after the last dose of a 4-week treatment with BMF-219, approximately 40% of patients from the 200 mg QD cohorts (4/11) displayed durable reduction in HbA1c of 1% or more; effectively near doubling the percentage of patients as compared to 20% observed in the 100 mg QD cohorts (n=20) presented this week at the World Congress Insulin Resistance, Diabetes & Cardiovascular Disease (WCIRDC). At the ATTD taking place in Florence, March 2024, Biomea will present in an oral poster discussion session, further details of the long-term follow-up data (22 weeks after the last dose of BMF-219) to show durable glycemic control with BMF-219 during the off-treatment period of the 100 mg and 200 mg dose cohorts.

To date, the dose escalation portion has shown, after only 4-weeks of dosing with BMF-219, that patients across all dosing cohorts (n=52) have consistently experienced generally meaningful HbA1c reductions. Patient cohorts at higher dose levels have seen greater pharmacokinetic exposure of BMF-219. Variability seen in HbA1c reduction is viewed as being related to several factors including patients' prior lines of therapies, years since diagnosis, beta cell function scores (Homa-B) and others. Based on the preclinical data, including the WCIRDC published presentations, we believe the responses seen to date will improve with longer dose durations and higher dose levels.

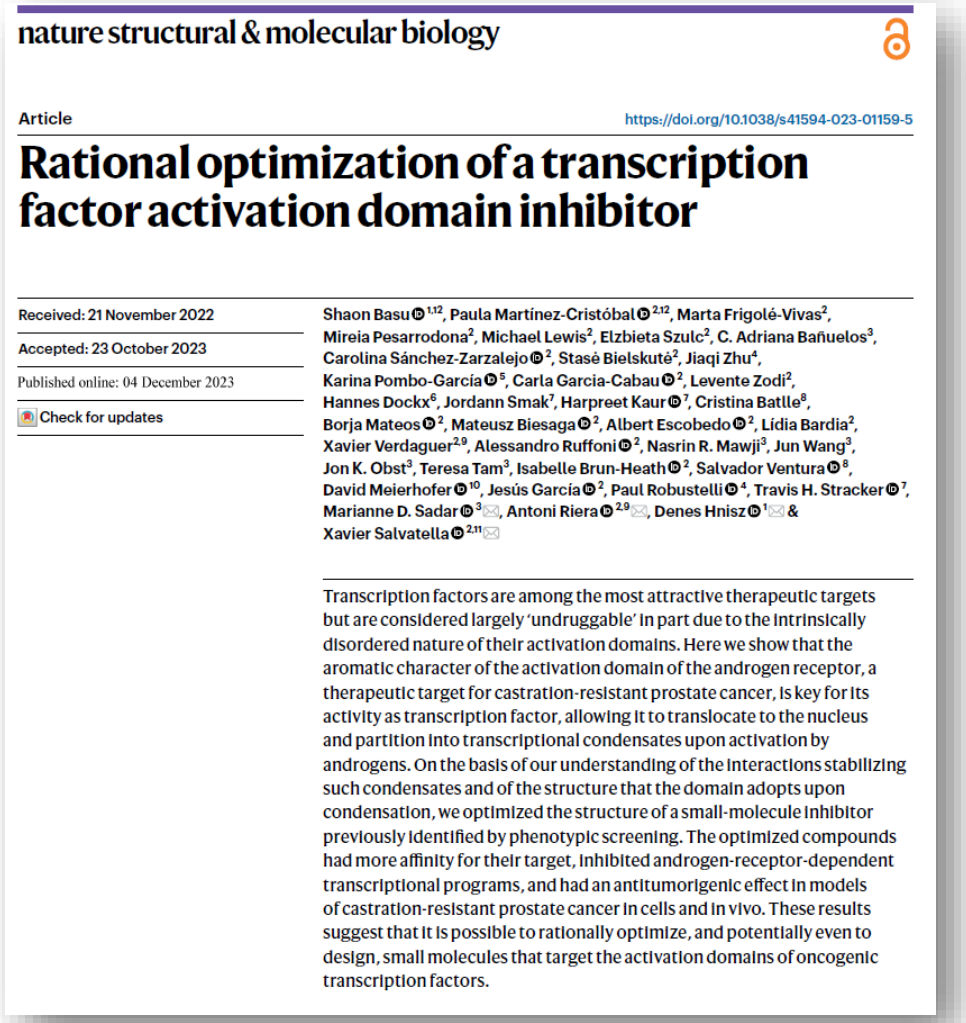
The best performing dosing cohort announced so far is cohort 3 (100 mg without food, n=10), where we reported a mean HbA1c reduction of 0.81% after only 4 weeks of dosing. In cohort 3, we enrolled 90% frontline patients on a single diabetic therapy with a mean HbA1c level reported of 8.1% at baseline; here only 10% of the patients were on two or more therapeutic agents. The dose cohorts we enrolled in addition to the 100 mg cohorts (50 mg, 100 mg BID, 200 mg, n=32) had between approximately 30%-100% of patients on two or more background agents, while failing with above normal HbA1c levels (baseline HbA1c ranging from 7.9% to 8.4%). In these cohorts the mean HbA1c reduction was observed between 0.4% to 0.5%, after four weeks of dosing. Considering the consistency of our responses, we believe we have confirmed clinically meaningful activity across all dosing cohorts.

Source: https://investors.biomeafusion.com/news-releases/news-release-details/biomea-fusion-announces-near-doubling-percentage-patients

Nuage Therapeutics Exploiting Findings Regarding Prostate Cancer Highlighted in Two Articles Out Last Week



The Barcelona based company Nuage Therapeutics is leveraging the work of Xavier Salvatella and Mateusz Biesaga of IRB Barcelona in the field of intrinsically disordered proteins, biomolecular condensation and the structural and functional properties of the transactivation domain of androgen receptor. They are collaborating with Denes Hnisz of the Max Planck and CEO Judit Anido to bring a completely new approach to dealing with mutations in androgen receptor in prostate cancer to market. The article at right is the second publication produced last week by the group. This paper highlights the company's approach to designing its lead drug candidate.



nature structural & molecular biology

Article

https://doi.org/10.1038/s41594-023-01159-5

Rational optimization of a transcription factor activation domain inhibitor

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Check for updates

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Transcription factors are among the most attractive therapeutic targets but are considered largely 'undruggable' in part due to the intrinsically disordered nature of their activation domains. Here we show that the aromatic character of the activation domain of the androgen receptor, a therapeutic target for castration-resistant prostate cancer, is key for its activity as transcription factor, allowing it to translocate to the nucleus and partition into transcriptional condensates upon activation by androgens. On the basis of our understanding of the interactions stabilizing such condensates and of the structure that the domain adopts upon condensation, we optimized the structure of a small-molecule inhibitor previously identified by phenotypic screening. The optimized compounds had more affinity for their target, inhibited androgen-receptor-dependent transcriptional programs, and had an antitumorigenic effect in models of castration-resistant prostate cancer in cells and in vivo. These results suggest that it is possible to rationally optimize, and potentially even to design, small molecules that target the activation domains of oncogenic transcription factors.

Sources: https://nuagetx.com/, https://www.nature.com/articles/s41594-023-01159-5,

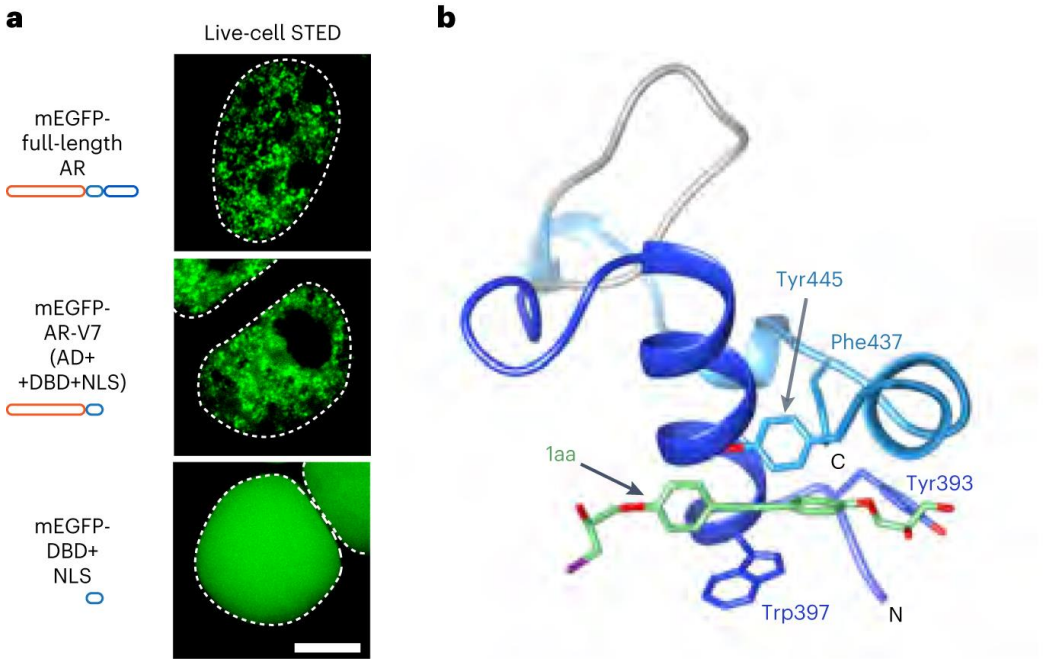
Transient Protein Folding in Condensates Reveals Ways to Target Disordered Oncoproteins

Transient protein folding in condensates reveals ways to target disordered oncoproteins. Nat Struct Mol Biol (2023).

The androgen receptor has long been known to translocate to the nucleus and form mesoscale condensates in the nuclei of hormone-stimulated cells (Fig. 1a). In treatment-resistant prostate cancer, the constitutively active form of the receptor that lacks the hormone-binding domain also forms nuclear condensates. On the basis of these two insights, our central hypothesis was that the ability of the androgen receptor to activate genes is inherently linked to its ability to form condensates in cells. In turn, understanding the molecular basis of condensation could lead to insights into how to develop molecules that interfere with functions of the receptor. We set out to test this model with a team of international collaborators, including labs from four countries and two continents.

On the basis of these results, we took advantage of a small molecule (EPI-001) that was previously shown to bind the activation domain and generated a series of next-generation compounds predicted to be more efficient in binding transient structures within androgen receptor condensates. One of these molecules (termed 1aa) bound strongly to the activation domain under conditions that mimic condensates in vitro, partitioned into condensates and, after further optimization (1ae), inhibited interactions with transcriptional effectors (Fig. 1b). When tested in prostate cancer cells, 1ae was a potent inhibitor of receptor-dependent gene transcription and cell viability. In a mouse xenograft model, the compound showed efficacy against treatment-resistant prostate cancer.

Source: https://www.nature.com/articles/s41594-023-01160-y



a, Live-cell stimulated emission depletion (STED) imaging of HEK293T cells transfected with androgen receptor (AR) constructs tagged with monomeric enhanced green fluorescent protein (mEGFP). The activation domain (AD) is orange, the DNA-binding domain (DBD) is light blue, and the ligand binding domain is dark blue. Dashed line indicates the nuclear periphery. Scale bar, 5 µm. NLS, nuclear localization signal. b. Molecular dynamics simulation of a short fragment within the androgen receptor activation domain interacting with the small molecule 1aa. Helices are colored in blue, the loop between helices in gray. 1aa is shown in green and its chlorine atom in purple.

Extracellular targeted protein degradation: an emerging modality for drug discovery

James Wells and Kaan Kumru, UCSF, *Nature Reviews Drug Discovery*, Dec 7, 2023

Targeted protein degradation (TPD) has emerged in the past decade as a major new drug modality to remove intracellular proteins with bispecific small molecules that recruit the protein of interest (POI) to an E3 ligase for degradation in the proteasome. Unlike classic occupancy-based drugs, intracellular TPD (iTPD) eliminates the target and works catalytically, and so can be more effective and sustained, with lower dose requirements. Recently, this approach has been expanded to the extracellular proteome, including both secreted and membrane proteins. Extracellular targeted protein degradation (eTPD) uses bispecific antibodies, conjugates or small molecules to degrade extracellular POIs by trafficking them to the lysosome for degradation. Here, we focus on recent advances in eTPD, covering degrader systems, targets, molecular designs and parameters to advance them. Now almost any protein, intracellular or extracellular, is addressable in principle with TPD.

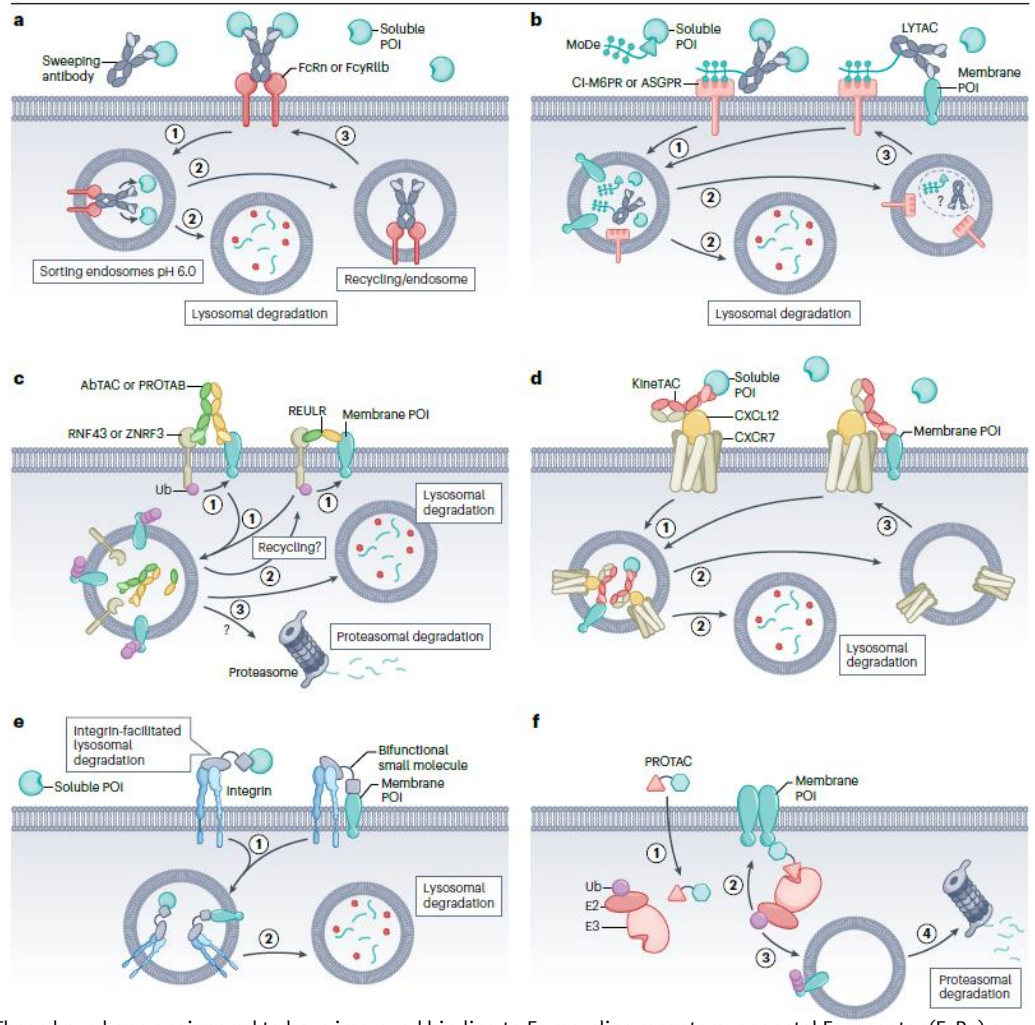


Figure: Six Different Approaches for Degrading Extracellular Proteins: a, Co-opting Fc receptors using IgG molecules called sweeping antibodies. These have been engineered to have improved binding to Fc recycling receptors, neonatal Fc receptor (FcRn) or FcγRIIb, as well as pH-sensitive complementarity-determining regions that bind to the protein of interest (POI) at neutral pH, but release it in acidified endosomes after cellular internalization of the complex, leading to delivery of the POI to the lysosome and degradation. The antibody bound to the Fc receptor is recycled to the cell surface, where it can pick up further cargo. b, Using glycan-targeted recycling receptors such as the cation-independent mannose 6-phosphate receptor (CI-M6PR) or asialoglycoprotein receptor (ASGPR) to promote lysosomal degradation of membrane and soluble POIs. One approach involves the bioconjugation of multiple glycan ligands for the CI-M6PR to an antibody that targets the POI, to produce a construct called a lysosome-targeting chimera (LYTAC). Following binding of the LYTAC–POI complex to the CI-M6PR, it is internalized, leading to degradation of the POI in the lysosome. Biologics, as well as bifunctional small molecules in constructs called MoDE or ASGPR-targeting chimeras (ATACs), have been used for analogous approaches that exploit the ASGPR. c, Exploitation of transmembrane E3 ligases using bispecific antibodies, where one arm binds to the extracellular domain of the E3 ligase and the other arm binds to the extracellular domain of a transmembrane POI (the constructs are called antibody-based proteolysis-targeting chimeras (PROTACs) (AbTACs), proteolysis-targeting antibodies (PROTABs) or receptor elimination by E3 ubiquitin ligase recruitment (REULR)). This brings the degrader and POI into proximity, leading to ubiquitylation (Ub) of the intracellular domain of the POI, which directs it for lysosomal or proteasomal degradation. d, Co-option of natural recycling receptors for cytokines and growth factors using bispecific antibody constructs called KineTACs, where one arm uses the natural cytokine or growth factor and the other arm binds to the POI. KineTACs can work on both membrane-bound and soluble proteins. e, Use of bispecific antibodies that engage recycling integrins, where one arm binds to the integrin and the other binds to the POI in an approach called integrin-facilitated lysosomal degradation. f, Small-molecule PROTACs, where one arm binds to the intracellular kinase domain of a receptor tyrosine kinase (such as EGFR) and the other arm binds to a cytosolic E3 ligase, can lead to ubiquitylation and degradation of the receptor tyrosine kinase in the proteasome.

Source: https://www.nature.com/articles/s41573-023-00833-z

The eTPD field is in its infancy and is rapidly following the iTPD field that inspired it, with a wide range of designs now being investigated (Table 2). Furthermore, other approaches that share facets of classical PROTACs and/or the biologics being used for eTPD are also being pursued.

There are many important questions that remain to be addressed for eTPD. For what targets does eTPD have a clear advantage? What are the most important POIs to degrade and in what therapeutic areas? Will these be more useful for chronic or acute diseases? Will eTPD mostly target soluble or membrane POIs, or both? How important is tissue selectivity for safe and effective drugs for eTPD? Will many degraders work or will there only be a few?

In some ways, the eTPD field is reminiscent of the early days of flight. Many clever flight machines were designed, including bird-like devices, human or motorized, as well as multi-winged and fixed-wing planes. Although few designs survived, the diversity was crucial to advancing the technology and ultimately the broad commercialization of the successful designs.

Table 2 | Summary of extracellular targeted protein degradation strategies and commercialization

Technology	Cellular compartment	Composition	Degrader	Targets	Company	Refs.
Sweeping antibodies	Extracellular	IgG	FcRn, FcγRIIb	IL-6R	Chugai Pharma	39
LYTAC	Extracellular/membrane	Bioconjugate	CI-M6PR, ASGPR	IgG, PDL1, CD71, HER2, EGFR	Lycia Therapeutics	55,64
Tri-GalNAc degraders	Extracellular/membrane	Bioconjugate	ASGPR	Streptavidin, IgG, EGFR	–	65
MoDE-A	Extracellular/membrane	Small molecule	ASGPR	IgG, MIF	Biohaven	66
ATAC	Extracellular	Small molecule	ASGPR	IgG, TNF	Avilar Therapeutics	71
Apt-LYTAC	Extracellular/membrane	Aptamer conjugate	ASGPR	Streptavidin, PDGF, PTK7	–	74
AbTAC	Membrane	Bispecific	RNF43, ZNRF3	PDL1, EGFR	EpiBiologics	79,82
PROTAB	Membrane	Bispecific	RNF43, ZNRF3, plus 4 others	PDL1, IGF1R, HER2	Genentech	85
REULR	Membrane	Bispecific	RNF43, ZNRF3, plus 3 others	PD1, EGFR, EPOR, E3 ligases	InduPro	88
KineTAC	Extracellular/membrane	Bispecific	CXCR7, IL2R	EGFR, HER2, PDL1, PD1, VEGF	EpiBiologics	91
Integrin-based degradation	Extracellular/membrane	Bispecific	$\alpha_v\beta_3$	Streptavidin, PDL1	–	97
PROTAC	Inside/membrane	Small molecule	Cereblon	EGFR	Arvinas, C4 Therapeutics	102,106
ADC PROTAC	Outside in	Bioconjugate	iEF-1	HER2	Orum Therapeutics	NA
Trim-away	Inside	IgG	TRIM21	Many	–	107
bioPROTAC	Inside	Engineered E3	E3 ligases	PCNA	–	108
Nb-PROTAC	Outside in	Cell-permeant Nb	TRIM21	BCL-11a	–	109
Antibody–enzyme conjugates	Extracellular	Nb enzyme	StcE	Mucins	–	110

ASGPR, asialoglycoprotein receptor; AbTAC, antibody-based PROTAC; ATAC, ASGPR-targeting chimera; CI-M6PR, cation-independent mannose 6-phosphate receptor; EGFR, epidermal growth factor receptor; EPOR, erythropoietin receptor; FcRn, neonatal Fc receptor; IGF1R, insulin-like growth factor 1 receptor; LYTAC, lysosome-targeting chimera; NA, not available; Nb, nanobody; PCNA, proliferating cell nuclear antigen; PDGF, platelet-derived growth factor; PROTAB, proteolysis-targeting antibody; PROTAC, proteolysis-targeting chimera; PTK7, protein tyrosine kinase 7; REULR, receptor elimination by E3 ubiquitin ligase recruitment; TRIM21, tripartite motif-containing 21; VEGF, vascular endothelial growth factor.

Source: https://www.nature.com/articles/s41573-023-00833-z

TAF15 amyloid filaments in frontotemporal lobar degeneration

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Check for updates

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Frontotemporal lobar degeneration (FTLD) causes frontotemporal dementia (FTD), the most common form of dementia after Alzheimer's disease, and is often also associated with motor disorders[1]. The pathological hallmarks of FTLD are neuronal inclusions of specific, abnormally assembled proteins[2]. In the majority of cases the inclusions contain amyloid filament assemblies of TAR DNA-binding protein 43 (TDP-43) or tau, with distinct filament structures characterizing different FTLD subtypes[3,4]. The presence of amyloid filaments and their identities and structures in the remaining approximately 10% of FTLD cases are unknown but are widely believed to be composed of the protein fused in sarcoma (FUS, also known as translocated in liposarcoma). As such, these cases are commonly referred to as FTLD–FUS. Here we used cryogenic electron microscopy (cryo-EM) to determine the structures of amyloid filaments extracted from the prefrontal and temporal cortices of four individuals with FTLD–FUS. Surprisingly, we found abundant amyloid filaments of the FUS homologue TATA-binding protein-associated factor 15 (TAF15, also known as TATA-binding protein-associated factor 2N) rather than of FUS itself. The filament fold is formed from residues 7–99 in the low-complexity domain (LCD) of TAF15 and was identical between individuals. Furthermore, we found TAF15 filaments with the same fold in the motor cortex and brainstem of two of the individuals, both showing upper and lower motor neuron pathology. The formation of TAF15 amyloid filaments with a characteristic fold in FTLD establishes TAF15 proteinopathy in neurodegenerative disease. The structure of TAF15 amyloid filaments provides a basis for the development of model systems of neurodegenerative disease, as well as for the design of diagnostic and therapeutic tools targeting TAF15 proteinopathy.

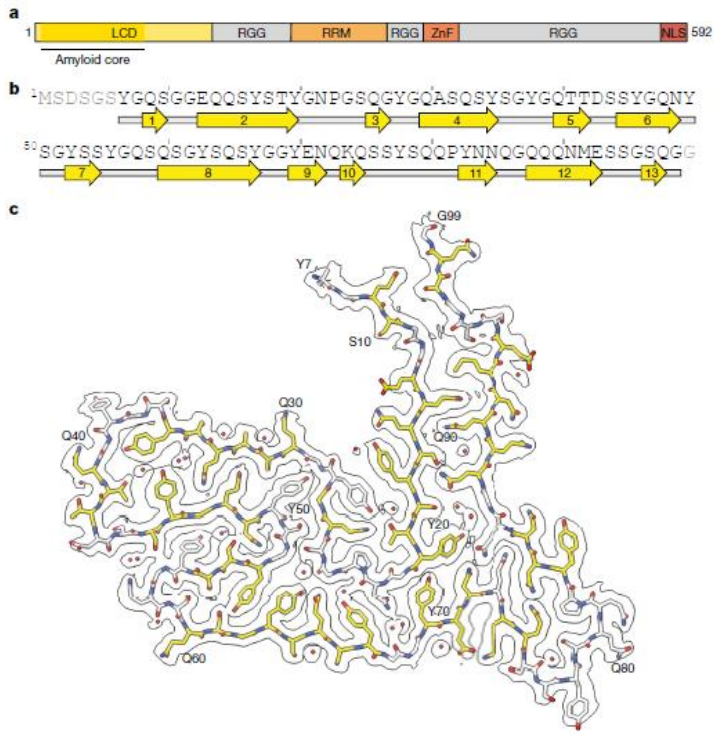
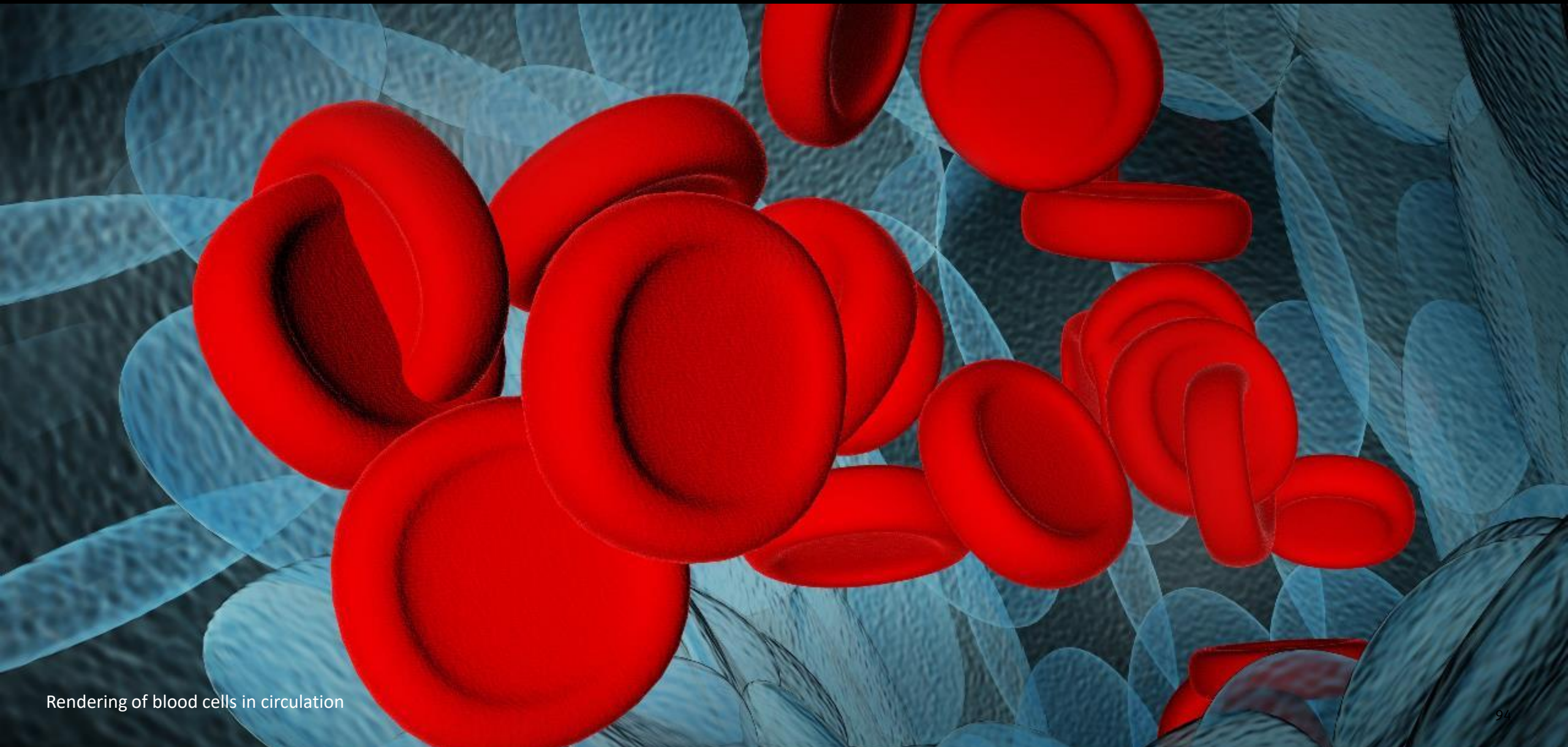


Fig. 3 | Cryo-EM structure of TAF15 amyloid filaments from FTLD–FET. **a**, Domain organization of TAF15. The region comprising the ordered core of TAF15 amyloid filaments is indicated. RRM, RNA recognition motif; ZnF, zinc finger domain. **b**, Sequence alignment of secondary structure elements of the TAF15 amyloid filament fold. Arrows indicate β-strands. **c**, Cryo-EM reconstruction and atomic model of the TAF15 amyloid filament structure, shown for a single TAF15 molecule perpendicular to the helical axis. The carbon atoms of residues forming β-strands are shown in yellow and ordered solvent as red spheres.

This is a pretty cool finding. Frontotemporal dementia (FTD) is a relatively common form of dementia. About 10% of FTD is associated with a specific type of amyloid, previously unknown, called TAF15. The authors of this paper solved for the structure of this protein using CRYO-EM.

Source: https://www.nature.com/articles/s41586-023-06801-2

ASH Conference Updates

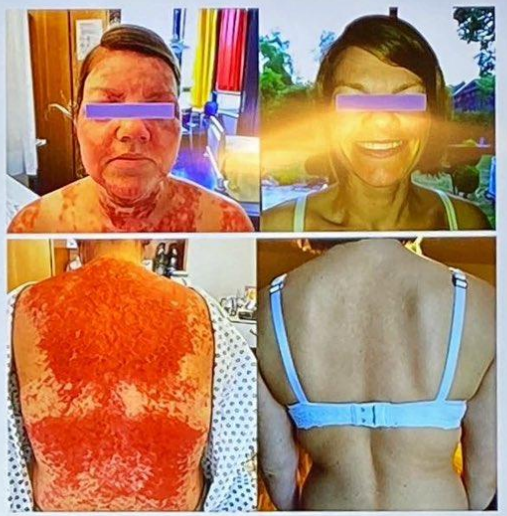


Rendering of blood cells in circulation

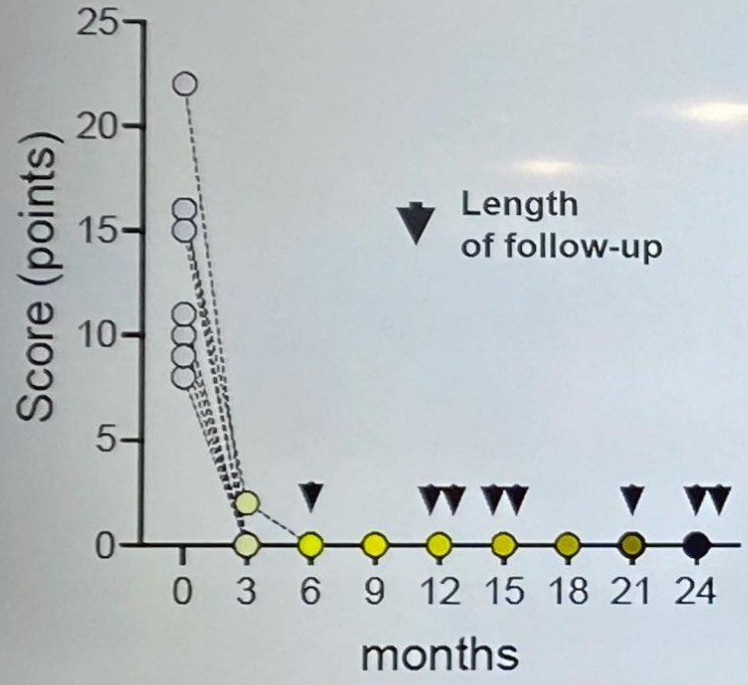
Schett / Cabaletta Lupus Data at ASH Continue to Impress

Embargoed until Saturday, Dec. 9, 2023, at 7:15 a.m. Pacific time

Clinical responses - SLE



SLEDAI-2K



- Disease-activity rapidly abrogated
- Patients remain in complete remission
- No disease-specific therapy since CAR T

➔ CD19 CAR T achieves lasting remission in SLE

➔ More data on efficacy in SSc and IIM this afternoon

➔ Effects of the treatment on B cells

COGENT BIOSCIENCES ANNOUNCES POSITIVE INITIAL DATA FROM PHASE 2 SUMMIT TRIAL EVALUATING BEZUCLASTINIB IN PATIENTS WITH NONADVANCED SYSTEMIC MASTOCYTOSIS (NONADVSM)

WALTHAM, Mass. and BOULDER, Colo., Dec. 09, 2023 (GLOBE NEWSWIRE) -- Cogent Biosciences, Inc. (Nasdaq: COGT), a biotechnology company focused on developing precision therapies for genetically defined diseases, today reported positive initial data from the Company's ongoing Phase 2 SUMMIT trial evaluating bezuclastinib in patients with nonadvanced systemic mastocytosis (NonAdvSM) at the 65th American Society of Hematology (ASH 2023) Annual Meeting & Exposition taking place December 9-12, 2023 in San Diego, CA.

"Nonadvanced systemic mastocytosis is a chronic hematologic disorder that significantly impacts patients' quality of life," said principal investigator, Prithviraj Bose, M.D., professor, Department of Leukemia at The University of Texas MD Anderson Cancer Center. "Significant unmet need remains for these patients and the availability of a well-tolerated, efficacious therapy with rapid symptom improvement could represent an important advancement in treatment."

"The initial data presented today from the SUMMIT trial represent an important step forward in the development of a novel treatment for NonAdvSM patients," said PD Dr. Frank Siebenhaar, M.D., Head University Outpatient Clinic, Institute of Allergology, Charité - Universitätsmedizin Berlin. "Effectively targeting the underlying driver mutation of this disease is critical, and the impressive outcomes generated with bezuclastinib treatment in these patients is very encouraging."

"We are very pleased with the emerging profile bezuclastinib is demonstrating in the NonAdvSM patient population," said Andrew Robbins, Cogent's President and Chief Executive Officer. "Matching the benefit of a selective KIT inhibitor that can potently target overactive and proliferative mast cells, with a safety profile that may support chronic treatment has been elusive up until this point. We are excited to rapidly advance into Part 2 of SUMMIT, a registration-directed, global, randomized placebo-controlled trial, and look forward to presenting additional data from SUMMIT in the first quarter of 2024."

Source: https://investors.cogentbio.com/news-releases/news-release-details/cogent-biosciences-announces-positive-initial-data-phase-2

J&J Menin Data For JNJ-75276617 Competitive

MD Anderson Press Release, Dec 9, 2023

Two clinical trials led by researchers from The University of Texas MD Anderson Cancer Center demonstrated early positive results from novel therapies targeting menin for the treatment of relapsed or refractory acute leukemias with specific genetic alterations. Results from the studies were shared today in oral presentations at the 2023 American Society of Hematology (ASH) Annual Meeting. More information on all ASH Annual Meeting content from MD Anderson can be found at MDAnderson.org/ASH.

Menin inhibitor monotherapy reduces disease burden in majority of relapsed or refractory acute leukemia patients (Abstract 57)

According to data from a Phase I trial led by Elias Jabbour, M.D., professor of Leukemia, the menin inhibitor JNJ-75276617 showed early clinical activity in patients with relapsed or refractory acute leukemias and genetic alterations in KMT2A or NPM1, which are associated with poor clinical outcomes.

Among 66 patients able to be evaluated after one month of treatment, JNJ-75276617 monotherapy reduced bone marrow disease burden in 71%, and 33 of those patients had a decrease in bone marrow blasts of more than 50%. Median time to first response was less than two months. Similar response rates were observed across patient groups with both genetic alterations.

"Patients with relapsed or refractory leukemias and KMT2A or NPM1 alterations often do poorly on currently available therapies, so there is a need to advance more effective options," Jabbour said. "We are encouraged by the antileukemic activity of this monotherapy, which mimics what we saw in the preclinical setting."

Source: https://www.miragenews.com/ash-new-menin-inhibitors-show-potential-in-1140589/

Syndax Menin Data Impressive

MD Anderson Press Release, Dec 9, 2023

The Phase I/II SAVE trial, led by Ghayas Issa, M.D., assistant professor of Leukemia, combined the menin inhibitor revumenib with venetoclax and hypomethylating agent ASTX727, yielding encouraging responses in adult and pediatric patients with relapsed or refractory advanced acute myeloid leukemia (AML) with KMT2A or NUP98 rearrangements or NPM1 mutations.

The overall response rate among nine evaluable patients was 100%. Three patients achieved complete remission, one patient achieved complete remission with partial hematologic recovery, and three patients had complete remission with incomplete platelet count recovery. In addition, one patient had a partial response and one had a morphologic leukemia-free state. Measurable residual disease was undetectable in six of the patients.

"These advanced and acute leukemias often are very difficult to treat and currently have no approved targeted therapies. We believe these early results suggest this treatment will be highly effective in advanced leukemias," Issa said. "This is our first look at an entirely oral combination therapy using menin inhibitors, and the results are very encouraging. If sustained in further trials, this could lead to a change in the standard of care for this patient population, with great potential to improve their quality of life."

Revumenib is a potent, oral, selective inhibitor of the menin-KMT2A interaction. To date, nine patients aged 12 years and older have been enrolled in the trial. Of those, five patients had KMT2A rearrangements, three had NUP98 rearrangements and one had mutant NPM1. On average, patients had received three prior lines of therapy.

Side effects were manageable and consistent with previous studies. The trial is ongoing, with plans to establish the recommended Phase II dose and optimize delivery of the combination before enrolling patients in the Phase II cohort.

This investigator-initiated study was supported by Syndax and Astex. A complete list of collaborating authors and their disclosures can be found with the abstract.

Source: https://www.miragenews.com/ash-new-menin-inhibitors-show-potential-in-1140589/

Agios Presents Positive Results from Phase 2 Portion of the RISE UP Pivotal Study in Sickle Cell Disease

CAMBRIDGE, Mass., Dec. 09, 2023 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq: AGIO), a leader in the field of cellular metabolism pioneering therapies for rare diseases, today presented detailed results from the Phase 2 portion of the global RISE UP study of mitapivat in sickle cell disease in an oral presentation (abstract #271) at the 65th American Society of Hematology (ASH) Annual Meeting & Exposition, which is being hosted Dec. 9-12, 2023, in San Diego.

During the Phase 2 double-blind, placebo-controlled study, treatment with mitapivat demonstrated statistically significant improvement in hemoglobin response across both mitapivat dose levels (50 mg and 100 mg BID), compared to placebo. The safety profile for mitapivat observed in the study was generally consistent with previously reported data in other studies of sickle cell disease and other hemolytic anemias. Improvements were observed in annualized rates of sickle cell pain crises, and markers of hemolysis and erythropoiesis for both mitapivat treatment arms compared to placebo. Improvement in patient-reported fatigue scores was observed with mitapivat 50 mg BID compared to placebo.

The study achieved its primary efficacy endpoint; treatment with mitapivat demonstrated a statistically significant increase in hemoglobin response rate compared to placebo. Hemoglobin response was defined as an increase of ≥1 g/dL in average hemoglobin concentrations from Week 10 through Week 12 compared with baseline.

46.2% of patients (n=12) in the 50 mg BID mitapivat arm and 50.0% of patients (n=13) in the 100 mg BID mitapivat arm achieved a hemoglobin response, compared to 3.7% of patients (n=1) in the placebo arm (2-sided p=0.0003 and 0.0001, respectively).

Source: https://investor.agios.com/news-releases/news-release-details/agios-presents-positive-results-phase-2-portion-rise-pivotal

Regeneron's Linvoseltamab (BCMA x CD3) Generates Strong Response Rate But High AE Rate in Multiple Myeloma

TARRYTOWN, N.Y., Dec. 07, 2023 (GLOBE NEWSWIRE) -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that the primary endpoint analysis from the pivotal trial (LINKER-MM1) investigating linvoseltamab demonstrated high rates of deep and durable responses in patients with relapsed/refractory (R/R) multiple myeloma (MM). These Phase 1/2 results are planned to be submitted to regulatory authorities, including to the U.S. Food and Drug Administration (FDA) this year. Linvoseltamab is an investigational BCMAxCD3 bispecific antibody designed to bridge B-cell maturation antigen (BCMA) on multiple myeloma cells with CD3-expressing T cells to facilitate T-cell activation and cancer-cell killing.

"Multiple myeloma remains an incurable disease, in which patients endure cycles of relapse and remission, resulting in a critical need for innovative medicines," said L. Andres Sirulnik, M.D., Ph.D., Senior Vice President, Translational and Clinical Sciences, Hematology at Regeneron. "With longer follow-up data on linvoseltamab, we're seeing deep and durable responses with a complete response rate nearing 50% in a difficult-to-treat patient population who had received a median of 5 prior lines of therapy. Furthermore, in our trial, the regimen had a short monitoring time and a convenient, response-adapted administration schedule that enabled deep responders to go from every two-week to every four-week dosing. This regimen saved time for clinicians and patients, underscoring the potential for linvoseltamab as a patient-centric option in relapsed/refractory multiple myeloma."

At a median duration of follow-up of 11 months, an objective response rate of 71% as assessed by an independent review committee, with 46% achieving a complete response or better, was observed in patients treated with linvoseltamab 200 mg in the Phase 1/2 trial (n=117). After a minimum of 24 weeks of therapy, patients who achieved a very good partial response (VGPR) or better shifted from every two-week to every four-week dosing. These results build on an earlier data cut, with 8 months of median follow-up, that will be presented at the 65th American Society of Hematology (ASH) Annual Meeting and Exposition from December 9 to 12 in San Diego, CA.

Based on the latest data cut, **all patients treated with 200 mg experienced an adverse event (AE), including 85% who experienced Grade ≥3 adverse events** (AE). The most commonly occurring AE was cytokine release syndrome (CRS; 46%). Of the CRS cases, the majority (35%) were Grade 1, 10% were Grade 2 and there was one case (1%) of Grade 3 CRS. Adjudicated immune effector cell-associated neurotoxicity syndrome (ICANS) events occurred in 9 patients (8% all Grades); Grade 3 ICANS occurred in 3 patients, and no cases of ≥Grade 4 cases. All grade infections were observed in 73% of patients; 34% were Grade 3 or 4. Deaths due to treatment-emergent AEs on-treatment or within 30 days post last dose occurred in 14 patients (12%), of which 11 (9%) were due to infections.

Source: https://investor.regeneron.com/news-releases/news-release-details/updated-linvoseltamab-pivotal-data-demonstrated-strong-rates-and

Early Data from Century Therapeutics Allogeneic CAR NK Therapy

PHILADELPHIA, Dec. 09, 2023 (GLOBE NEWSWIRE) -- Century Therapeutics (NASDAQ: IPSC), an innovative biotechnology company developing induced pluripotent stem cell (iPSC)-derived cell therapies in immuno-oncology and autoimmune and inflammatory disease, today announced the presentation of initial clinical data from a single-patient case study which Century believes support the potential for a multi-dosing strategy for CAR iNK enabled by Allo-Evasion™ edits at the 65th American Society of Hematology (ASH) Annual Meeting and Exposition.

"We are thrilled that the initial clinical evidence for CNTY-101 provides support for the potential for Allo-Evasion™ to enable a multi-dosing regimen without the need for continued lymphodepletion. This is highly encouraging in advancing our goal to increase persistence of the cells during the treatment period and potentially lead to deeper and more durable responses," said Brent Pfeiffenberger, Pharm.D., Chief Executive Officer of Century Therapeutics. "We look forward to advancing the study at both higher and more frequent doses of CNTY-101, and plan to present additional clinical data in mid-2024."

"As the first cell therapy product candidate engineered with six precision gene edits aimed at providing selectivity and persistence, CNTY-101 is positioned to potentially fill a high unmet need among heavily pretreated non-Hodgkin lymphoma patients," said Krish Patel, M.D., Director of Lymphoma Program, Director of Hematologic Malignancies and Cellular Therapy, Swedish Cancer Institute, Seattle. "The encouraging initial data presented today from this patient who received low doses of CNTY-101 exhibits signals of persistence of CNTY-101 cells out of circulation and supports testing at higher doses. I look forward to the continuation of the study and to further investigating the full therapeutic potential of CNTY-101."

Data featured in a single-patient case study presented at ASH involves a 63-year-old patient with relapsed/refractory (R/R) progressive follicular lymphoma previously treated with four prior lines of therapy who was enrolled at Dose Level 1 (100 million cells). As of a data cutoff date of November 13, 2023, the patient has received seven 28-day cycles of a single infusion of CNTY-101 at Dose Level 1. Cycles one and two included three days of lymphodepletion (LD), whereas cycles three through seven were given with no LD. Interleukin-2 (IL-2) was administered for all cycles except for the first. The patient maintained a complete response with a duration of six months before subsequently progressing.

Following administration of two cycles with and three cycles without LD, serum assessments from available data of the first five cycles of CNTY-101 treatment in this patient showed no evidence of functional pre-existing or induced humoral immunogenicity against CNTY-101. Importantly, tumor microenvironment initial analyses demonstrated a vigorous increase in T cells within 8 days of the 1st CNTY-101 cell infusion. Increases in proliferating cytotoxic T cells and TNFα and IFNγ-secreting cells were observed, suggestive of induction of adaptive immune responses within the tumor. Additionally, ddPCR analysis of CNTY-101 genomic DNA and cell-free DNA from Dose Level 1 patient (n=4) samples suggest that CNTY-101 cells were able to traffic out of circulation shortly after infusion and showed persistence in tissues for at least 3 days.

In addition to the preliminary clinical data presented today, the Company will also present additional results from patients treated at Dose Level 1 (100 million cell dose), as well as preliminary data from three patients treated at Dose Level 2 (300 million cell dose) during a conference call and webcast on Monday, December 11 at 7:30 AM PT/10:30 AM ET. In addition, the Company will discuss its planned Phase 1 trial, including supporting preclinical data, for CNTY-101 in systemic lupus erythematosus, the Company's first autoimmune and inflammatory disease indication.

Source: https://investors.centurytx.com/news-releases/news-release-details/century-therapeutics-presents-initial-data-cnty-101-phase-1

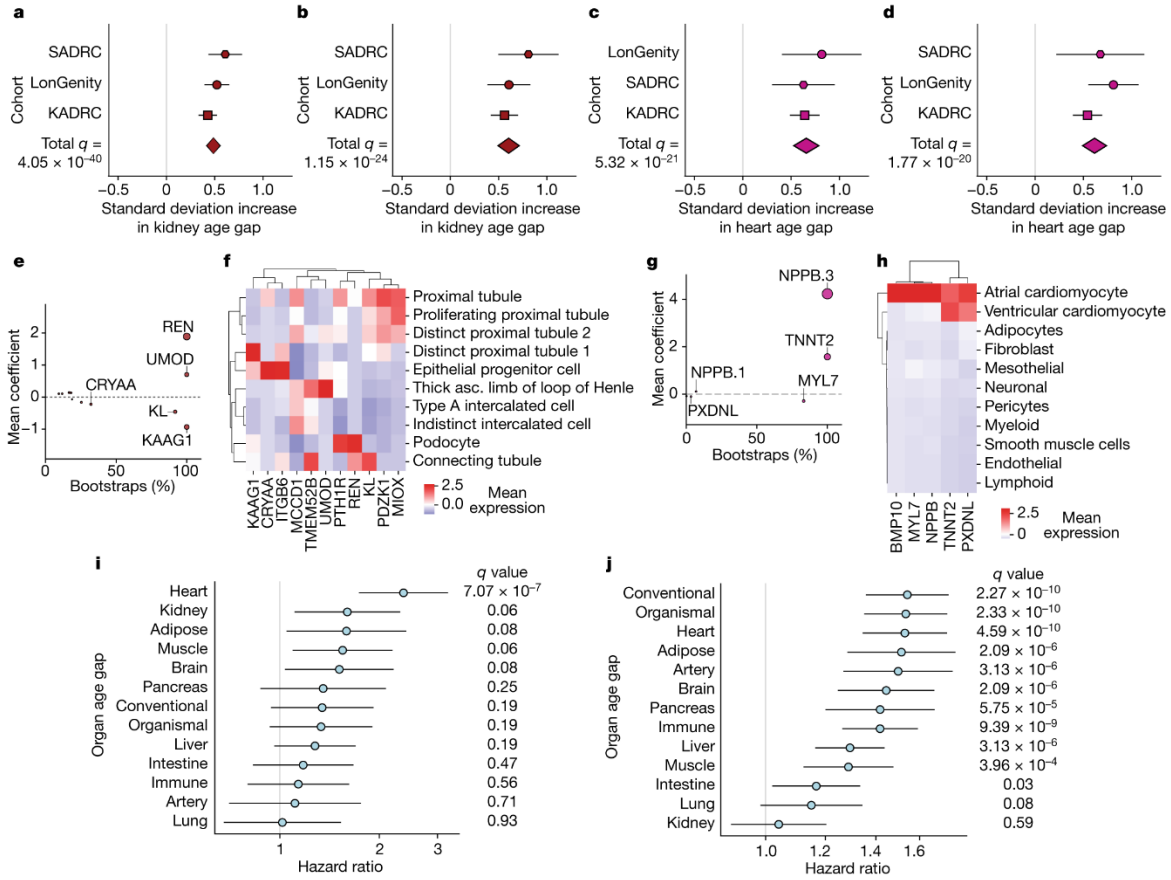
Recent Developments in Proteomics and Aging

Organ Aging Signatures in the Plasma Proteome Track Health and Disease

Wyss-Coray et.al, "Organ aging signatures in the plasma proteome track health and disease," *Nature* 2023 Dec;624(7990):164-172.

Animal studies show aging varies between individuals as well as between organs within an individual, but whether this is true in humans and its effect on age-related diseases is unknown. We utilized levels of human blood plasma proteins originating from specific organs to measure organ-specific aging differences in living individuals. Using machine learning models, we analysed aging in 11 major organs and estimated organ age reproducibly in five independent cohorts encompassing 5,676 adults across the human lifespan. We discovered nearly 20% of the population show strongly accelerated age in one organ and 1.7% are multi-organ agers. Accelerated organ aging confers 20–50% higher mortality risk, and organ-specific diseases relate to faster aging of those organs. We find individuals with accelerated heart aging have a 250% increased heart failure risk and accelerated brain and vascular aging predict Alzheimer's disease (AD) progression independently from and as strongly as plasma pTau-181, the current best blood-based biomarker for AD. Our models link vascular calcification, extracellular matrix alterations and synaptic protein shedding to early cognitive decline. We introduce a simple and interpretable method to study organ aging using plasma proteomics data, predicting diseases and aging effects.

Source: https://www.nature.com/articles/s41594-023-01160-y



a, A cross-cohort meta-analysis of the association (linear regression) between the kidney age gap and hypertension (with hypertension n = 1,566, without n = 1,561). False discovery rate (FDR) P valuemeta = 4.05 × 10−40, effect sizemeta = 0.486. (Supplementary Table 10). b, As in a, kidney age gap versus diabetes (with diabetes n = 335, without n = 2,839). FDR P valuemeta = 1.15 × 10−24, effect sizemeta = 0.604. c, As in a, heart age gap versus atrial fibrillation or pacemaker (with atrial fibrillation n = 239, without n = 2,936). FDR P valuemeta = 5.32 × 10−21, effect sizemeta = 0.657. d, As in a, but for heart age gap versus heart attack (with heart attack history n = 280, without n = 2,904). FDR P valuemeta = 1.77 × 10−20, effect sizemeta = 0.615. e, All kidney aging model coefficients. x axis shows % of model instances in the bagged ensemble that include the protein. Size of bubbles is scaled by the absolute value of the mean model weight across model instances (absolute value of y axis) (Supplementary Table 7). f, Single-cell RNA expression of kidney51 aging model proteins. Mean normalized expression values shown. g, As in e, but for the heart aging model. h, Human heart single-cell RNA expression of heart52. Mean normalized expression values shown. i, Cox proportional hazard regression analysis of the relationship between organ age gap and future congestive heart failure risk over 15 years of follow-up in the LonGenity cohort for those without heart failure history at baseline (n = 26 events in 812 individuals). FDR P valueHeart = 7.07 × 10−7, hazard ratioHeart = 2.37. (Supplementary Table 11). j, Cox proportional hazard regression analysis of the relationship between organ age gap and future mortality risk, over 15 years of follow-up in the LonGenity cohort (n = 173 events in 864 individuals). FDR P valueConventional = 2.27 × 10−10, hazard ratio

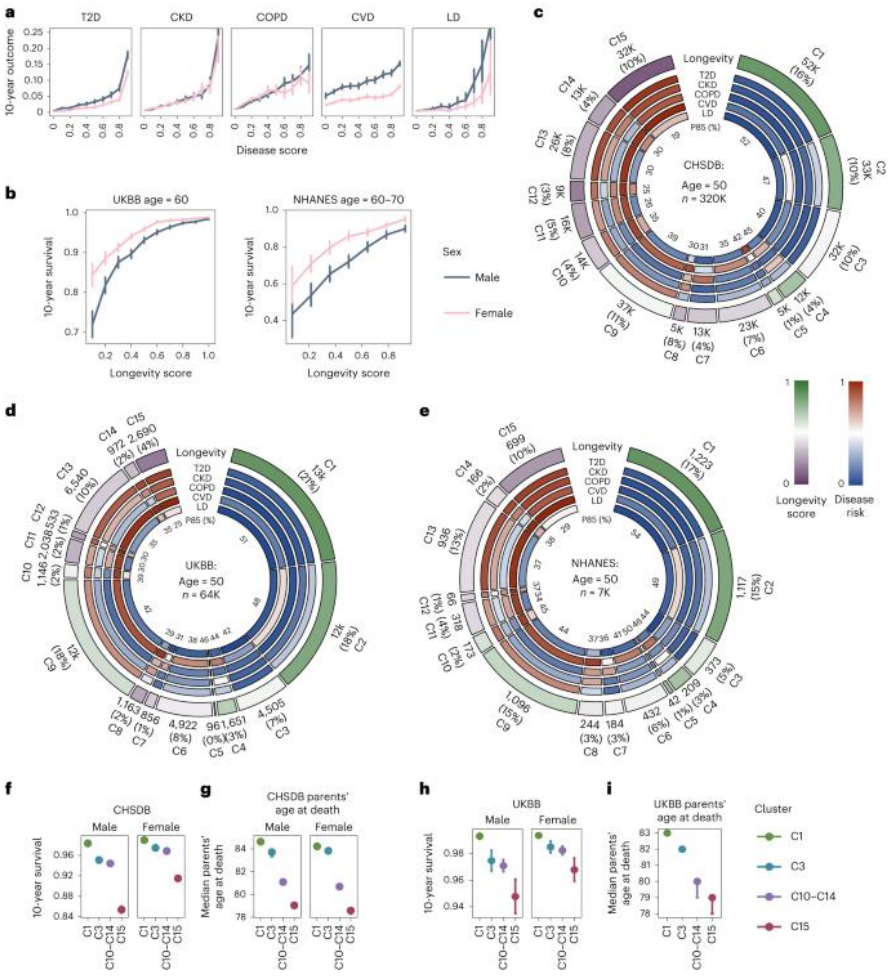
Longitudinal Machine Learning Uncouples Healthy Aging Factors from Chronic Disease Risks

Cohen, N.M., Lifshitz, A., Jaschek, R. et al., "Longitudinal machine learning uncouples healthy aging factors from chronic disease risks," *Nat Aging* (2023).

Animal studies show aging varies between individuals as well as between organs within an individual, but whether this is true in humans and its effect on age-related diseases is unknown. We utilized levels of human blood plasma proteins originating from specific organs to measure organ-specific aging differences in living individuals. Using machine learning models, we analysed aging in 11 major organs and estimated organ age reproducibly in five independent cohorts encompassing 5,676 adults across the human lifespan. We discovered nearly 20% of the population show strongly accelerated age in one organ and 1.7% are multi-organ agers. Accelerated organ aging confers 20–50% higher mortality risk, and organ-specific diseases relate to faster aging of those organs. We find individuals with accelerated heart aging have a 250% increased heart failure risk and accelerated brain and vascular aging predict Alzheimer's disease (AD) progression independently from and as strongly as plasma pTau-181, the current best blood-based biomarker for AD. Our models link vascular calcification, extracellular matrix alterations and synaptic protein shedding to early cognitive decline. We introduce a simple and interpretable method to study organ aging using plasma proteomics data, predicting diseases and aging effects.

Source: https://www.nature.com/articles/s43587-023-00536-5

a, Disease models performance in the UKBB. The 10-year cumulative incidence probability estimations (center points) are shown, with death as the competing risk for all patients without disease at age 60 (n = 89,124) according to the disease risk score (x axis). The error bars indicate the 95% CIs. b, Longevity models performance in the UKBB and NHANES. The Kaplan–Meier 10-year survival estimates for patients at age 60 or 60–70 in the UKBB/NHANES are shown according to the longevity score (x axis), n = 89,124/10,046. The error bars indicate the 95% CIs. c, Population distribution according to lifelong longevity and disease potential. All patients aged 50 in the CHSDB were clustered according to the quantile-normalized longevity score and disease risk. Color-coded clusters with the number of patients in each cluster (outer annotation) and probability of surviving to age 85 (P85, inner annotation) are shown. d, Population distribution in the UKBB (like c but for the UKBB data). Clustering was performed using precomputed CHSDB clusters and assigning the cluster with minimal distance to the cluster centroid. e, Population distribution in the NHANES (like d but for the NHANES data), including patients aged 50–60. f, Patient 10-year survival according to predisposition groups. The 10-year Kaplan–Meier probability estimates for survival (center points) for males (left, n = 81,872) and females (right, n = 110,528) are shown according to the predisposition groups shown in c. The error bars indicate the 95% CIs. g, Parental survival according to child longevity and disease potential clustering. Kaplan–Meier estimates for median age at death of the patients' parents according to the patients' predisposition groups (males, n = 27,023 /14,096 /54,737 /23,109; females, n = 48,305 /32,170 /50,966 /21,376) for clusters C1, C3, C10–C14 and C15) are shown. The error bars indicate the 95% CIs. h,i, As in f,g for the UKBB (n = 13,157 males and 18,765 females). Males and females combined, given a smaller sample size:



Article https://doi.org/10.1038/s41588-023-01600-x

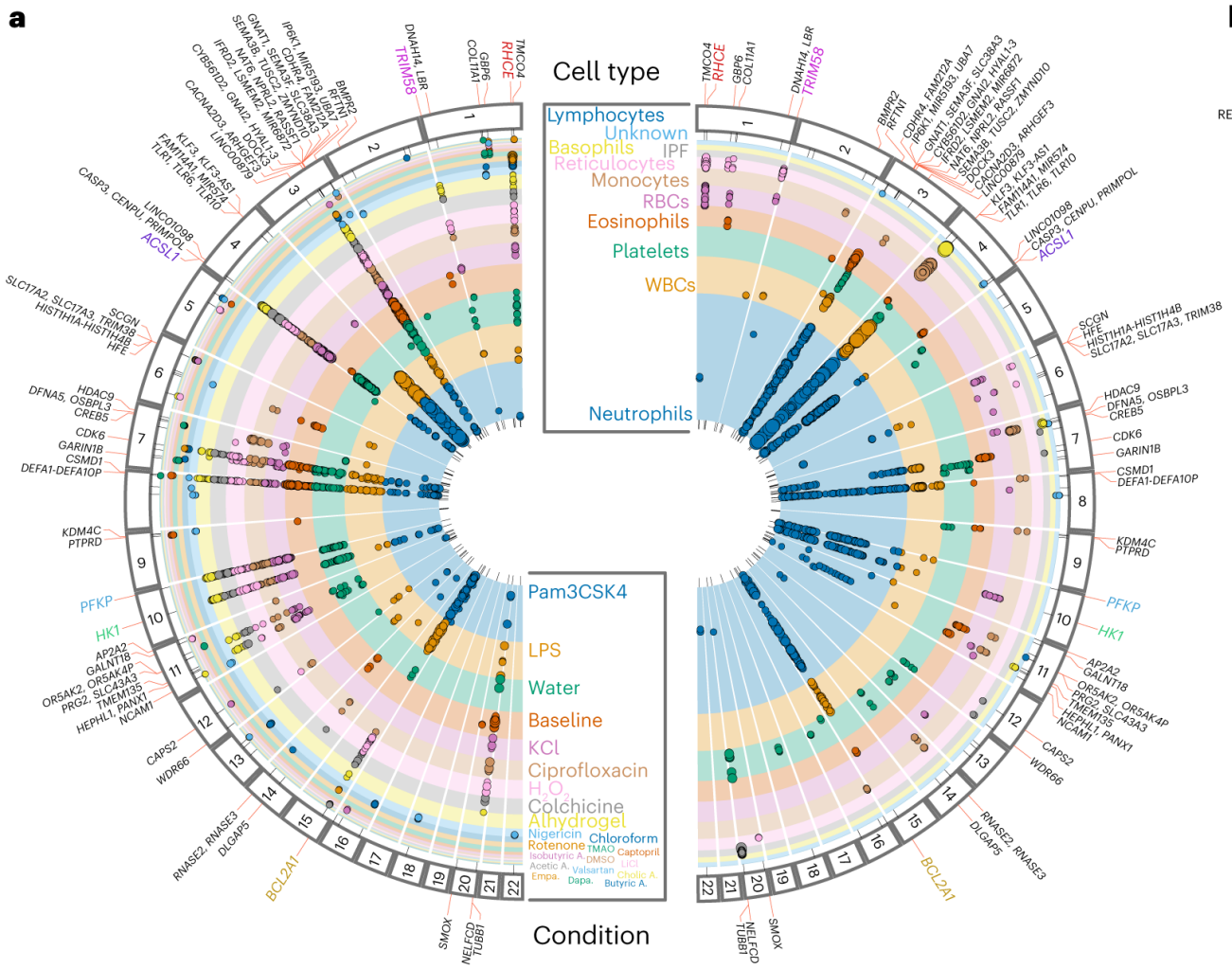
Perturbational phenotyping of human blood cells reveals genetically determined latent traits associated with subsets of common diseases

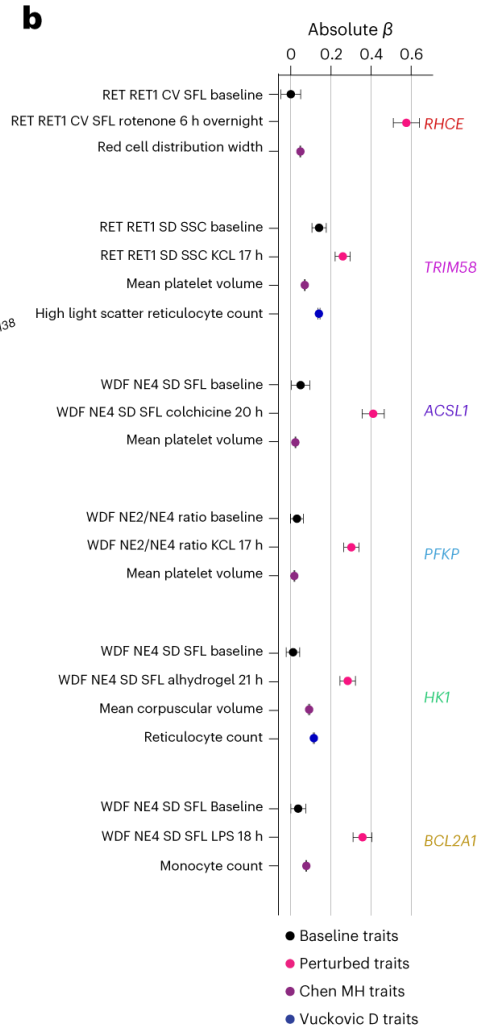
Nature Genetics, Dec 4, 2023

Although genome-wide association studies (GWAS) have successfully linked genetic risk loci to various disorders, identifying underlying cellular biological mechanisms remains challenging due to the complex nature of common diseases. We established a framework using human peripheral blood cells, physical, chemical and pharmacological perturbations, and flow cytometry-based functional readouts to reveal latent cellular processes and performed GWAS based on these evoked traits in up to 2,600 individuals. We identified 119 genomic loci implicating 96 genes associated with these cellular responses and discovered associations between evoked blood phenotypes and subsets of common diseases. We found a population of pro-inflammatory anti-apoptotic neutrophils prevalent in individuals with specific subsets of cardiometabolic disease. Multigenic models based on this trait predicted the risk of developing chronic kidney disease in type 2 diabetes patients. By expanding the phenotypic space for human genetic studies, we could identify variants associated with large effect response differences, stratify patients and efficiently characterize the underlying biology.

Source: https://www.nature.com/articles/s41588-023-01600-x

Whole-Blood Perturbational Profiling Yields a Wide Range of Genetic Associations for Specific Conditions and Cell Types





a, Genome-wide significant associations with P < 5 × 10−8 colored by perturbation condition (left) and cell type (right). Two-sided P values are based on t tests in linear regression models and are not adjusted for multiple testing. Circle size is proportional to −log10(P value). Nearby genes are annotated based on proximity. For clarity, only a subset of readouts is shown for loci with many significant associations (see Table 1 for an overview of traits, cell types, candidate genes and previously reported blood-trait associations and Supplementary Data 1 for a full listing of associations). b, Comparison of β coefficients for six of the most significant variants across multiple traits and genes. For these readouts, perturbation conditions led to large effect size changes that were not observed at baseline. For our study, the variants shown are rs644592 (RHCE, n = 943), rs3811444 (TRIM58, n = 1,410), rs12513029 (ACSL1, n = 1,296), rs34538474 (PFKP, n = 1,339), rs6480404 (HK1, n = 1,378) and rs67760360 (BCL2A1, n = 1,424). For the studies in refs. 17,18, which included over 400,000 individuals, the variants shown are the reported variants with the lowest P value for each gene. Data are presented as absolute estimated β coefficient +s.e.m.

Source: https://www.nature.com/articles/s41588-023-01600-x

Recent Developments in Type 1 Diabetes

Baricitinib and β-Cell Function in Patients with New-Onset Type 1 Diabetes

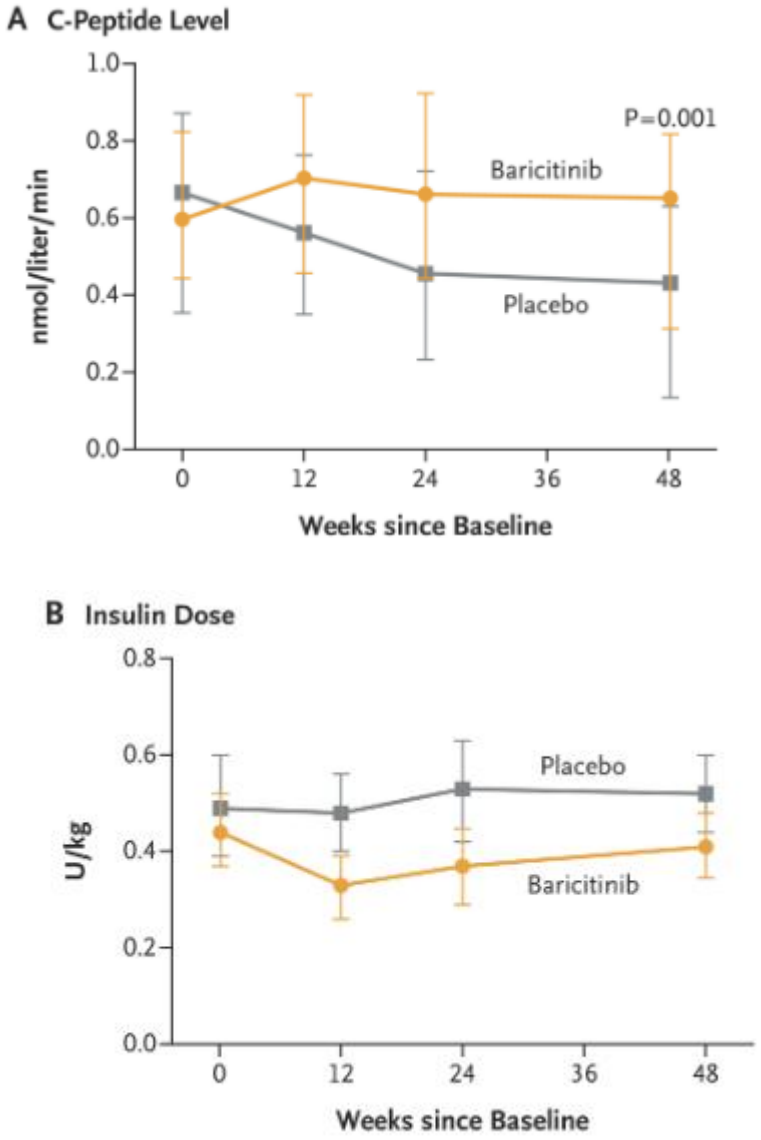
Baricitinib and β-Cell Function in Patients with New-Onset Type 1 Diabetes

Michaela Waibel, Ph.D., John M. Wentworth, M.B., B.S., Ph.D., Michelle So, M.B., B.S., Ph.D., Jennifer J. Couper, M.D., Fergus J. Cameron, M.D., Richard J. MacIsaac, M.B., B.S., Ph.D., Gabby Atlas, M.B., B.S., Alexandra Gorelik, M.Sc., Sara Litwak, Ph.D., Laura Sanz-Villanueva, B.Sc., Prerak Trivedi, Ph.D., Simi Ahmed, Ph.D., et al., for the BANDIT Study Group*

***New England Journal of Medicine*, Dec 7, 2023**

A total of 91 patients received baricitinib (60 patients) or placebo (31 patients). The median of the mixed-meal–stimulated mean C-peptide level at week 48 was 0.65 nmol per liter per minute (interquartile range, 0.31 to 0.82) in the baricitinib group and 0.43 nmol per liter per minute (interquartile range, 0.13 to 0.63) in the placebo group (P=0.001). The mean daily insulin dose at 48 weeks was 0.41 U per kilogram of body weight per day (95% confidence interval [CI], 0.35 to 0.48) in the baricitinib group and 0.52 U per kilogram per day (95% CI, 0.44 to 0.60) in the placebo group. The levels of glycated hemoglobin were similar in the two trial groups. However, the mean coefficient of variation of the glucose level at 48 weeks, as measured by continuous glucose monitoring, was 29.6% (95% CI, 27.8 to 31.3) in the baricitinib group and 33.8% (95% CI, 31.5 to 36.2) in the placebo group. The frequency and severity of adverse events were similar in the two trial groups, and no serious adverse events were attributed to baricitinib or placebo. In patients with type 1 diabetes of recent onset, daily treatment with baricitinib over 48 weeks appeared to preserve β-cell function as estimated by the mixed-meal–stimulated mean C-peptide level.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2306691



Teplizumab and β-Cell Function in Patients with Newly Diagnosed Type 1 Diabetes

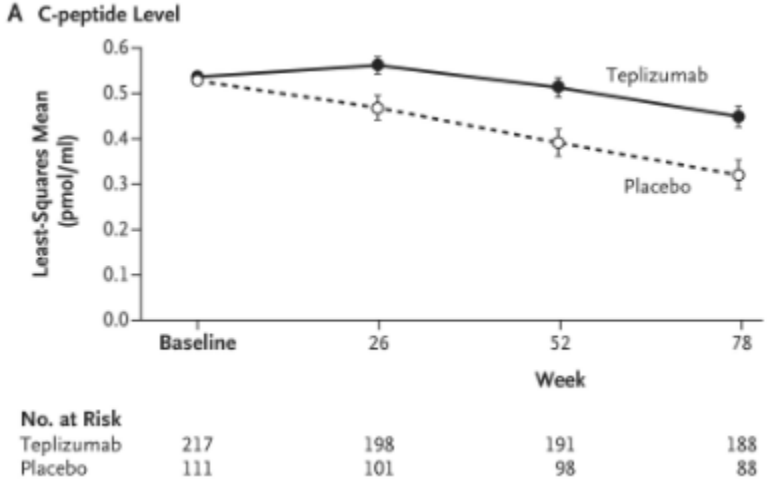
Teplizumab and β-Cell Function in Newly Diagnosed Type 1 Diabetes

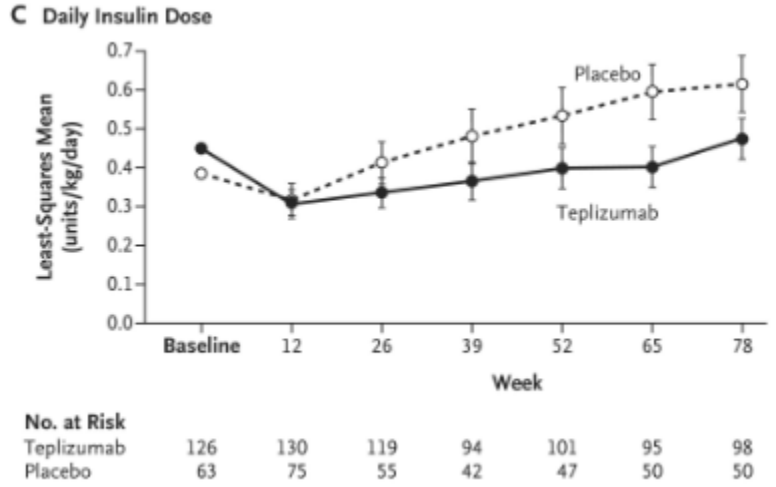
Eleanor L. Ramos, M.D., Colin M. Dayan, M.B., B.S., Ph.D., Lucienne Chatenoud, M.D., Ph.D., Zdenek Sumnik, M.D., Ph.D., Kimber M. Simmons, M.D., Agnieszka Szypowska, M.D., Ph.D., Stephen E. Gitelman, M.D., Laura A. Knecht, M.D., Elisabeth Niemoeller, M.D., Wei Tian, Ph.D., and Kevan C. Herold, M.D. for the PROTECT Study Investigators*

***New England Journal of Medicine*, Dec 7, 2023**

Patients treated with teplizumab (217 patients) had significantly higher stimulated C-peptide levels than patients receiving placebo (111 patients) at week 78 (least-squares mean difference, 0.13 pmol per milliliter; 95% confidence interval [CI], 0.09 to 0.17; P<0.001), and 94.9% (95% CI, 89.5 to 97.6) of patients treated with teplizumab maintained a clinically meaningful peak C-peptide level of 0.2 pmol per milliliter or greater, as compared with 79.2% (95% CI, 67.7 to 87.4) of those receiving placebo. The groups did not differ significantly with regard to the key secondary end points. Adverse events occurred primarily in association with administration of teplizumab or placebo and included headache, gastrointestinal symptoms, rash, lymphopenia, and mild cytokine release syndrome.

Two 12-day courses of teplizumab in children and adolescents with newly diagnosed type 1 diabetes showed benefit with respect to the primary end point of preservation of β-cell function, but no significant differences between the groups were observed with respect to the secondary end points.





Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2308743

Editorial on the Two Articles on Type 1 Diabetes

Immune Interventions at Onset of Type 1 Diabetes — Finally, a Bit of Hope

New England Journal of Medicine*, Dec 7, 2023** Johnny Ludvigsson, M.D., Ph.D. ***Excerpt

One reason for the lack of progress is that care has focused almost completely on the consequences of the disease (particularly blood glucose control) with very limited attention to dying pancreatic β cells. Few clinicians would treat thyroid disease without measuring thyroid hormones, but very few clinicians have been interested in measuring or even considering residual β-cell function. Clinicians and diabetes teams are occupied with helping their patients obtain good glycated hemoglobin levels, and they are less willing to spend time on intervention trials.

Although baricitinib, in contrast to teplizumab, must be given daily and continuously, no serious adverse events were seen. In fact, this treatment has been used for many years as a treatment for juvenile idiopathic arthritis, and the safety profile of JAK inhibitors has been acceptable.

Taken together, these trials indicate that, finally, we have promising treatments that may soon be offered to patients with type 1 diabetes at the onset of their disease, and more studies are on their way. With sufficient health care resources, these treatments will be pragmatically feasible. Will clinicians, patients, or parents of children with diabetes see these treatments as justified? For patients with cancer, the alternative to treatment is death, and for some patients with certain autoimmune diseases, treatment is the only way to decrease suffering. For patients with type 1 diabetes, immunologic interventions to preserve β-cell function arrive in parallel with glucose sensors, smart insulin pumps, and even closed-loop systems. Although modern devices are expensive and not an option for all patients, immunologic interventions can be expected to be accepted and successful if clinicians are able to explain the great value for the patient of residual insulin secretion. In addition, the interventions to preserve β-cell function must be proved to be safe and to not cause serious adverse events in both the short and the long term.

Source: https://www.nejm.org/doi/full/10.1056/NEJMe2312091

Under-the-Skin Implant Could Treat Type I Diabetes

***Cornell Chronicle*, Dec 5, 2023**

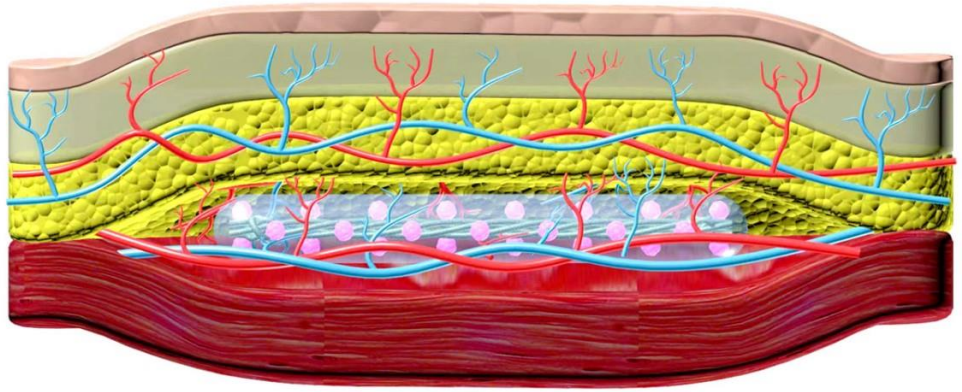
A collaboration between researchers from Cornell and University of Alberta, Edmonton, has created a new technique to treat Type 1 diabetes: implanting a device inside a pocket under the skin that can secrete insulin while avoiding the immunosuppression that typically stymies management of the disease.

The approach would offer an easier, long-term and less invasive alternative to insulin injections or traditional transplants that require immunosuppression.

The group's paper, "Inflammation-Induced Neovascularization of the Subcutaneous Tissue for the Long-Term Survival of Encapsulated Islets Without Immunosuppression," published Dec. 5 in Nature Biomedical Engineering. The co-lead authors are former postdoctoral researcher Long-Hai Wang and Braulio A. Marfil-Garza of University of Alberta, Edmonton.

In Type 1 diabetes, the body's immune system goes rogue and destroys insulin-producing pancreatic cell clusters, known as islets, thereby depriving the body of a way to usher glucose, i.e., sugar, into muscle and tissue cells to generate energy. The standard treatment for the disease is insulin therapy in the form of daily injections or insulin pumps.

Source: https://news.cornell.edu/stories/2023/12/under-skin-implant-could-treat-type-i-diabetes



Researchers created a thread-like device that can be implanted under the skin to secrete insulin via islet cells (the tiny pink balls) while receiving nutrients and oxygen from blood vessels.

Showed successful reversal of diabetes in mice.

nature biomedical engineering

Article

https://doi.org/10.1038/s41551-023-01138-7

Week-long norm glycaemia in diabetic mice and minipigs via a subcutaneous dose of a glucose-responsive insulin complex

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Check for updates

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Glucose-responsive formulations of insulin can increase its therapeutic index and reduce the burden of its administration. However, it has been difficult to develop single-dosage formulations that can release insulin in both a sustained and glucose-responsive manner. Here we report the development of a subcutaneously injected glucose-responsive formulation that nearly does not trigger the formation of a fibrous capsule and that leads to week-long normoglycaemia and negligible hypoglycaemia in mice and minipigs with type 1 diabetes. The formulation consists of gluconic acid-modified recombinant human insulin binding tightly to poly-L-lysine modified by 4-carboxy-3-fluorophenylboronic acid via glucose-responsive phenylboronic acid–diol complexation and electrostatic attraction. When the insulin complex is exposed to high glucose concentrations, the phenylboronic acid moieties of the polymers bind rapidly to glucose, breaking the complexation and reducing the polymers' positive charge density, which promotes the release of insulin. The therapeutic performance of this long-acting single-dose formulation supports its further evaluation and clinical translational studies.

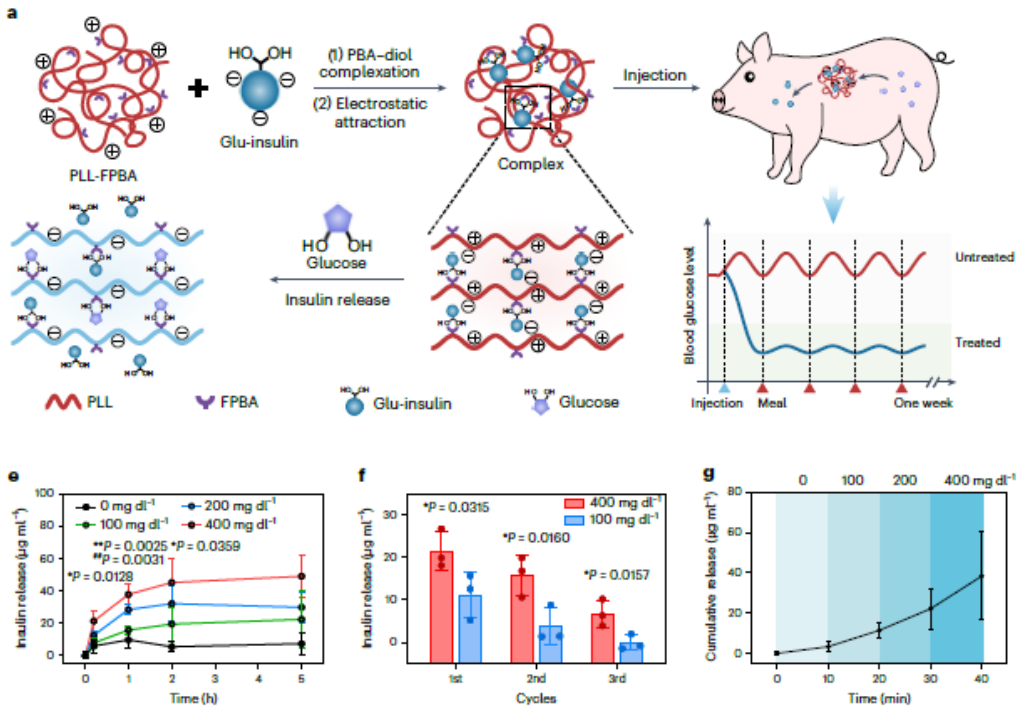
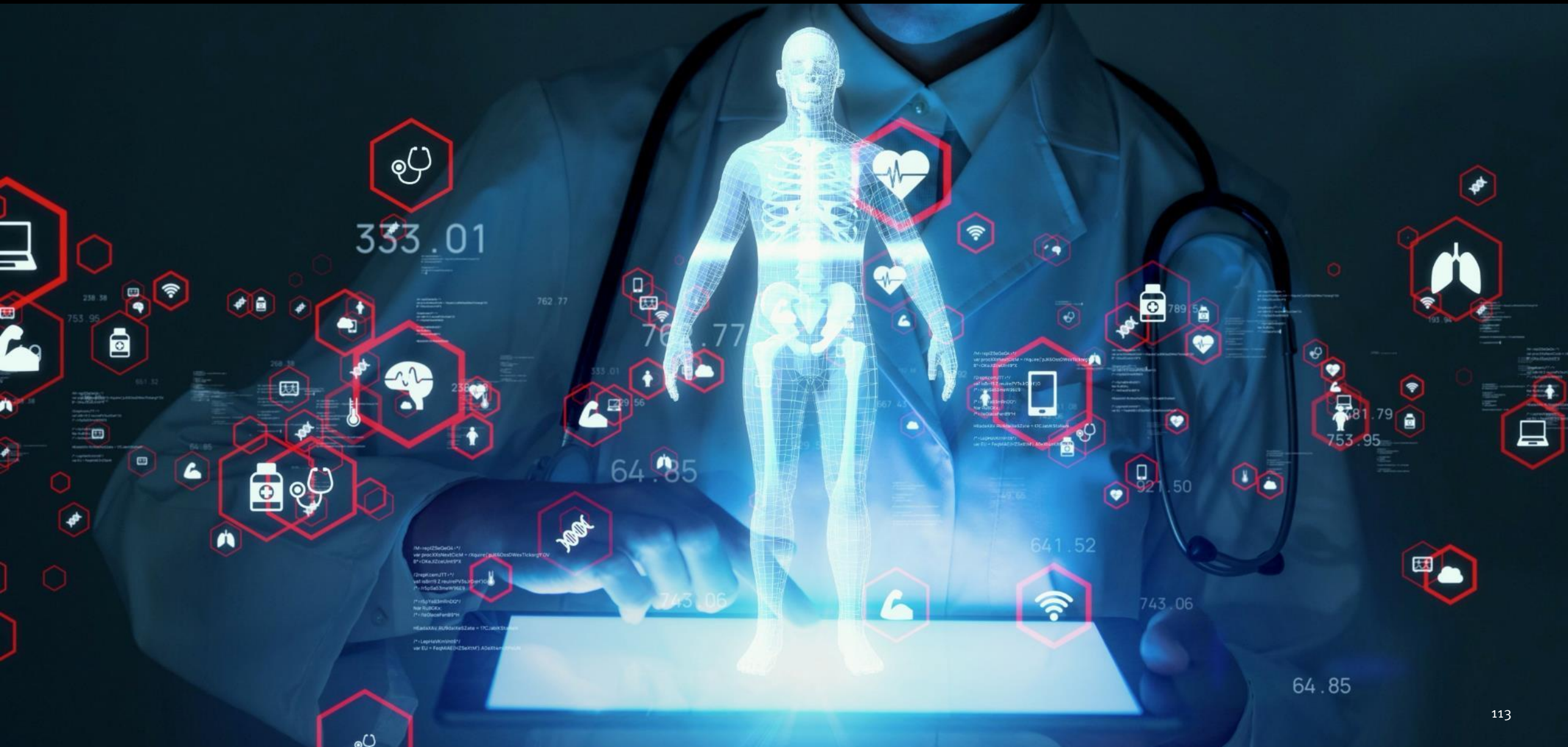


Fig. 1 | Dually glucose-responsive complex for insulin delivery. **a**, Schematic of complex formation and insulin release with dual glucose-responsive mechanisms. The negatively charged diol moiety-containing Glu-insulin and the positively charged PBA moiety-containing PLL-FPBA can form a complex through electrostatic attraction and PBA–diol binding. Upon exposure of the complex to a solution with a high level of glucose, binding of glucose to the FPBA moiety instantly reduces the positive charge density on PLL-FPBA and disrupts the PBA–diol bonds, resulting in immediate insulin release. **b**, Representative pictures of the complex. The complexes were prepared using FITC-labelled Glu-insulin (orange) and unlabelled PLL-FPBA, Cy5-labelled PLL-FPBA (blue) and unlabelled Glu-insulin, or FITC-labelled Glu-insulin and Cy5-labelled PLL-FPBA. Equal weights of Glu-insulin and PLL-FPBA were used. **e**, GRI release from the complex when exposed to a solution containing 0 (black), 100 (green), 200 (blue) and 400 mg dl−1 glucose (red). Data points are means.

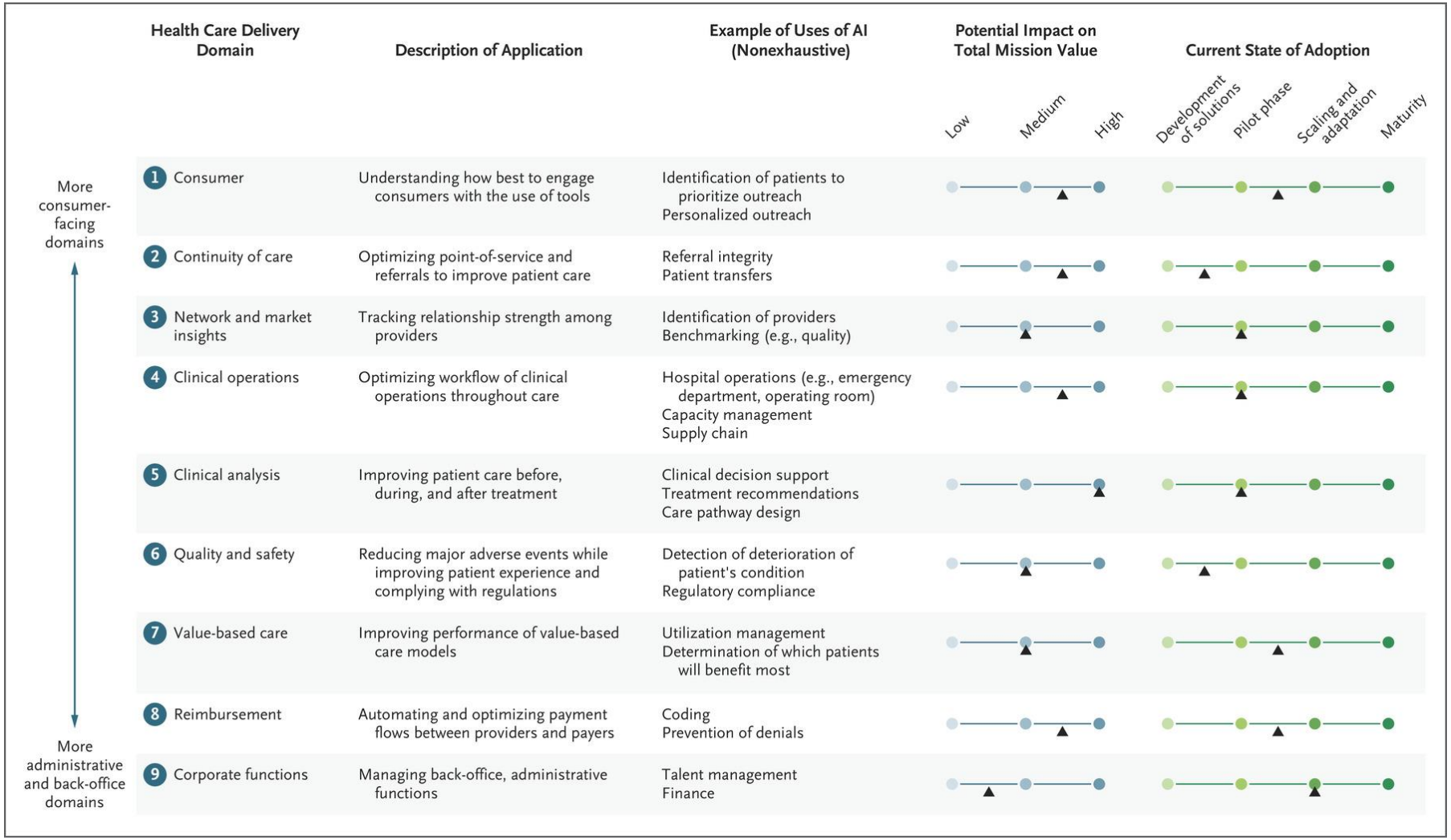
Source: https://www.nature.com/articles/s41551-023-01138-7

The Future: AI is Coming to Healthcare Delivery



Adoption of AI in Healthcare Remains Nascent

Sahni NR, Carrus B. Artificial Intelligence in U.S. Health Care Delivery. *N Engl J Med*. 2023 Jul 27;389(4):348-358.



	Health Care Delivery Domain	Description of Application	Example of Uses of AI (Nonexhaustive)	Potential Impact on Total Mission Value (Low / Medium / High)	Current State of Adoption (Development of solutions / Pilot phase / Scaling and adaptation / Maturity)
More consumer-facing domains	1 Consumer	Understanding how best to engage consumers with the use of tools	Identification of patients to prioritize outreach Personalized outreach		
	2 Continuity of care	Optimizing point-of-service and referrals to improve patient care	Referral integrity Patient transfers		
	3 Network and market insights	Tracking relationship strength among providers	Identification of providers Benchmarking (e.g., quality)		
	4 Clinical operations	Optimizing workflow of clinical operations throughout care	Hospital operations (e.g., emergency department, operating room) Capacity management Supply chain		
	5 Clinical analysis	Improving patient care before, during, and after treatment	Clinical decision support Treatment recommendations Care pathway design		
	6 Quality and safety	Reducing major adverse events while improving patient experience and complying with regulations	Detection of deterioration of patient's condition Regulatory compliance		
	7 Value-based care	Improving performance of value-based care models	Utilization management Determination of which patients will benefit most		
	8 Reimbursement	Automating and optimizing payment flows between providers and payers	Coding Prevention of denials		
More administrative and back-office domains	9 Corporate functions	Managing back-office, administrative functions	Talent management Finance		

Israeli Study Shows that AI-Generated Diagnoses in a Primary Care Setting Generally Get it Right

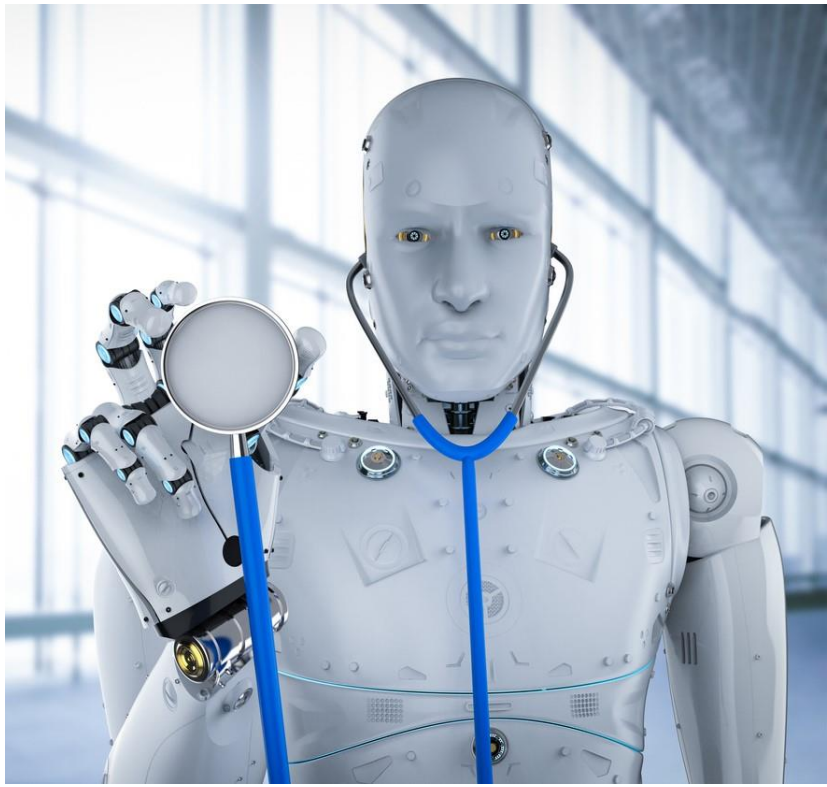
Zeltzer et.al., "Diagnostic Accuracy of Artificial Intelligence in Virtual Primary Care," *Mayo Clinic Proceedings: Digital Health*, Sep 20, 2023.

Objective: To evaluate the diagnostic accuracy of artificial intelligence (AI)-generated clinical diagnoses.

Patients and Methods: A retrospective chart review of 102,059 virtual primary care clinical encounters from October 1, 2022, to January 31, 2023 was conducted. Patients underwent an AI medical interview, after which virtual care providers reviewed the interview summary and AI-provided differential diagnoses, communicated with patients, and finalized diagnoses and treatment plans. Our accuracy measures were agreement between AI diagnoses, virtual care providers, and blind adjudicators. We analyzed AI diagnostic agreement across different diagnoses, presenting symptoms, patient demographic characteristics such as race, and provider levels of experience. We also evaluated model performance improvement with retraining.

Results: Providers selected an AI diagnosis in 84.2% (n = 85,976) of cases and the top-ranked AI diagnosis in 60.9% (n = 62,130) of cases. Agreement rates varied by diagnosis, with greater than or equal to 95% provider agreement with an AI diagnosis for 35 diagnoses (47% of cases, n = 47,679) and greater than or equal to 90% agreement for 57 diagnoses (69% of cases, n = 70,697). The average agreement rate for half of all presenting symptoms was greater than or equal to 90%. Adjusting for case mix, diagnostic accuracy exhibited minimal variation across demographic characteristics. The adjudicators' consensus diagnosis, reached in 58.2% (n = 128) of adjudicated cases was always included in the AI differential diagnosis. Provider experience did not affect agreement, and model retraining increased diagnostic accuracy for retrained conditions from 96.6% to 98.0%.

Conclusion: Our findings show that agreement between AI and provider diagnoses is high in most cases in the setting of this study. The results highlight the potential for AI to enhance primary care disease diagnosis and patient triage, with the capacity to improve over time.

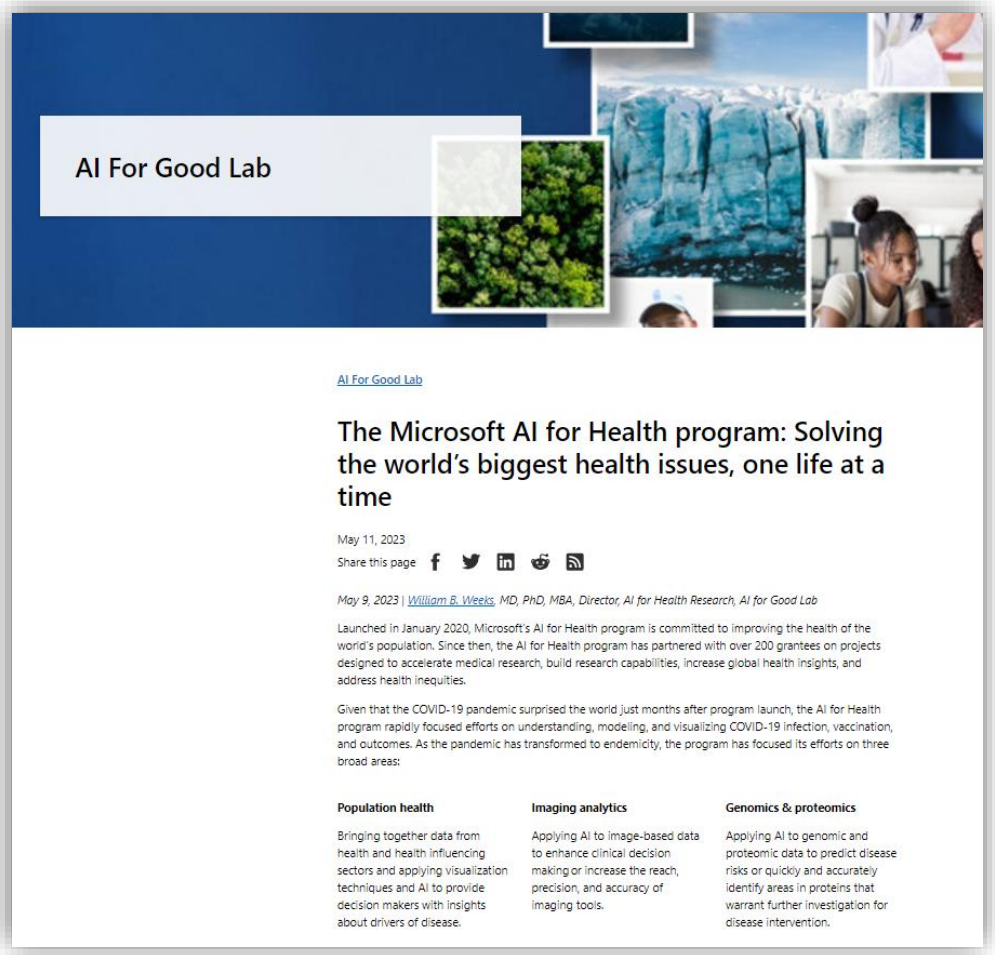


Source: https://www.mcpdigitalhealth.org/article/S2949-7612(23)00070-6/fulltext

Microsoft Perspective

Bajwa J, Munir U, Nori A, Williams B. Artificial intelligence in healthcare: transforming the practice of medicine. Future Healthc J. 2021 Jul;8(2):e188-e194.

“Advances in AI have the potential to transform many aspects of healthcare, enabling a future that is more personalised, precise, predictive and portable. It is unclear if we will see an incremental adoption of new technologies or radical adoption of these technological innovations, but the impact of such technologies and the digital renaissance they bring requires health systems to consider how best they will adapt to the changing landscape. For the NHS, the application of such technologies truly has the potential to release time for care back to healthcare professionals, enabling them to focus on what matters to their patients and, in the future, leveraging a globally democratised set of data assets comprising the ‘highest levels of human knowledge’ to ‘work at the limits of science’ to deliver a common high standard of care, wherever and whenever it is delivered, and by whoever.”

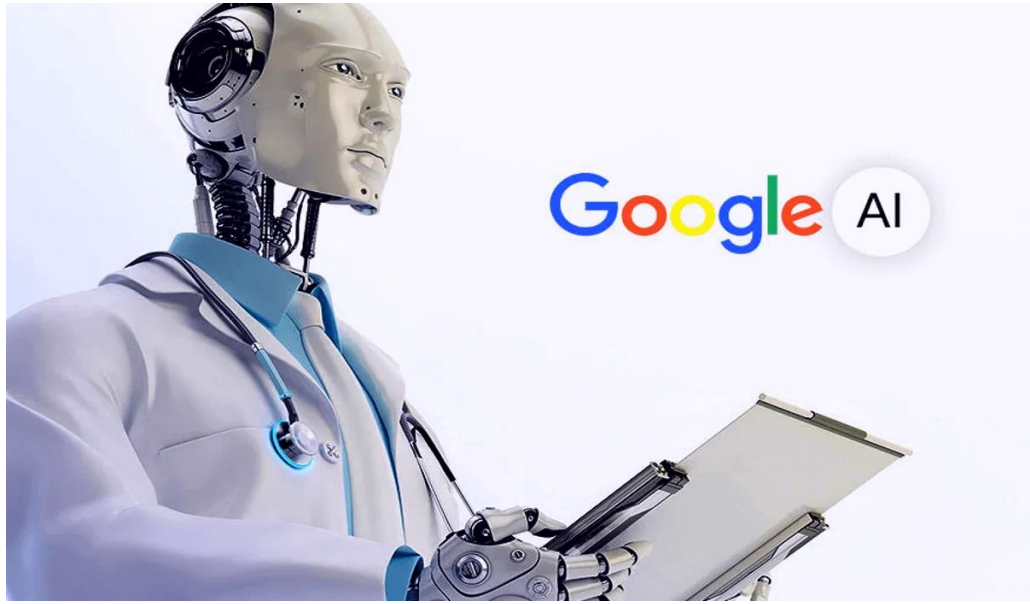


Google Perspective

Google's Exploration of Large Language Models in Medicine, *NEJM Podcast*, May 2023

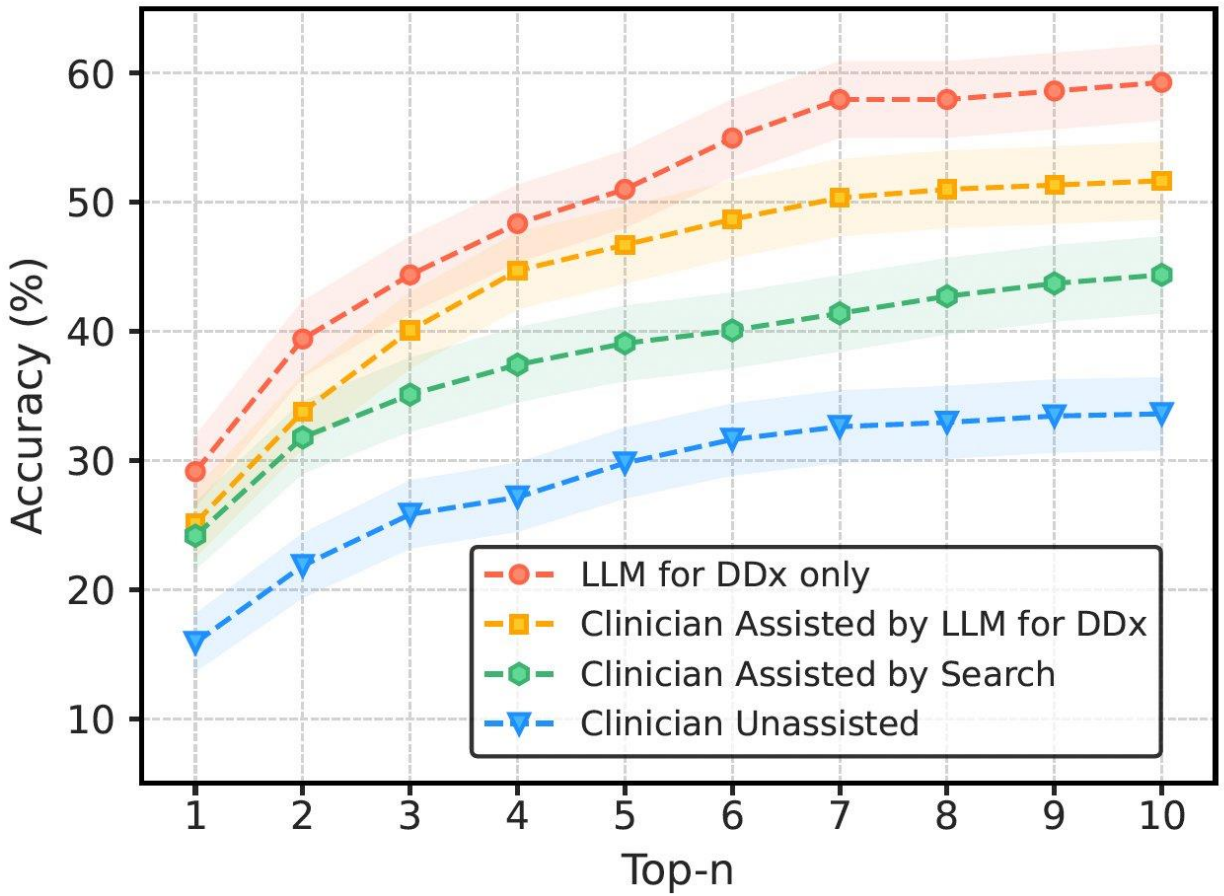
It was a lot of fun to chat with Alan and Vivek of Google AI about their groundbreaking work... One of the highlights of the conversation for me was learning about the large language models performance on step one style practice questions, which are questions that are used to test med students' clinical knowledge.

This model achieved a remarkable 70% accuracy, significantly surpassing previous models that were limited to only 40 to 50% accuracy. It's worth noting that since we recorded this conversation, Vivek and Alan's team have released an updated model called Med-PaLM 2 that now scores over 80%.



Source: https://ai-podcast.nejm.org/e/google-s-exploration-of-large-language-models-in-medicine/

Google AI Team: Towards Accurate Differential Diagnosis with Large Language Models



LLM alone was more accurate than clinicians

arXiv:2312.00164, Dec 5, 2023

An accurate differential diagnosis (DDx) is a cornerstone of medical care, often reached through an iterative process of interpretation that combines clinical history, physical examination, investigations and procedures. Interactive interfaces powered by Large Language Models (LLMs) present new opportunities to both assist and automate aspects of this process. In this study, we introduce an LLM optimized for diagnostic reasoning, and evaluate its ability to generate a DDx alone or as an aid to clinicians. 20 clinicians evaluated 302 challenging, real-world medical cases sourced from the New England Journal of Medicine (NEJM) case reports. Each case report was read by two clinicians, who were randomized to one of two assistive conditions: either assistance from search engines and standard medical resources, or LLM assistance in addition to these tools. All clinicians provided a baseline, unassisted DDx prior to using the respective assistive tools. Our LLM for DDx exhibited standalone performance that exceeded that of unassisted clinicians (top-10 accuracy 59.1% vs 33.6%, [p = 0.04]). Comparing the two assisted study arms, the DDx quality score was higher for clinicians assisted by our LLM (top-10 accuracy 51.7%) compared to clinicians without its assistance (36.1%) (McNemar's Test: 45.7, $p < 0.01$) and clinicians with search (44.4%) (4.75, $p = 0.03$). Further, clinicians assisted by our LLM arrived at more comprehensive differential lists than those without its assistance. Our study suggests that our LLM for DDx has potential to improve clinicians' diagnostic reasoning and accuracy in challenging cases, meriting further real-world evaluation for its ability to empower physicians and widen patients' access to specialist-level expertise.

Source: https://arxiv.org/abs/2312.00164

Disclosure

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