Biopharmaceutical Sector

Weekly Update – Feb 12, 2024

STIFEL | Healthcare

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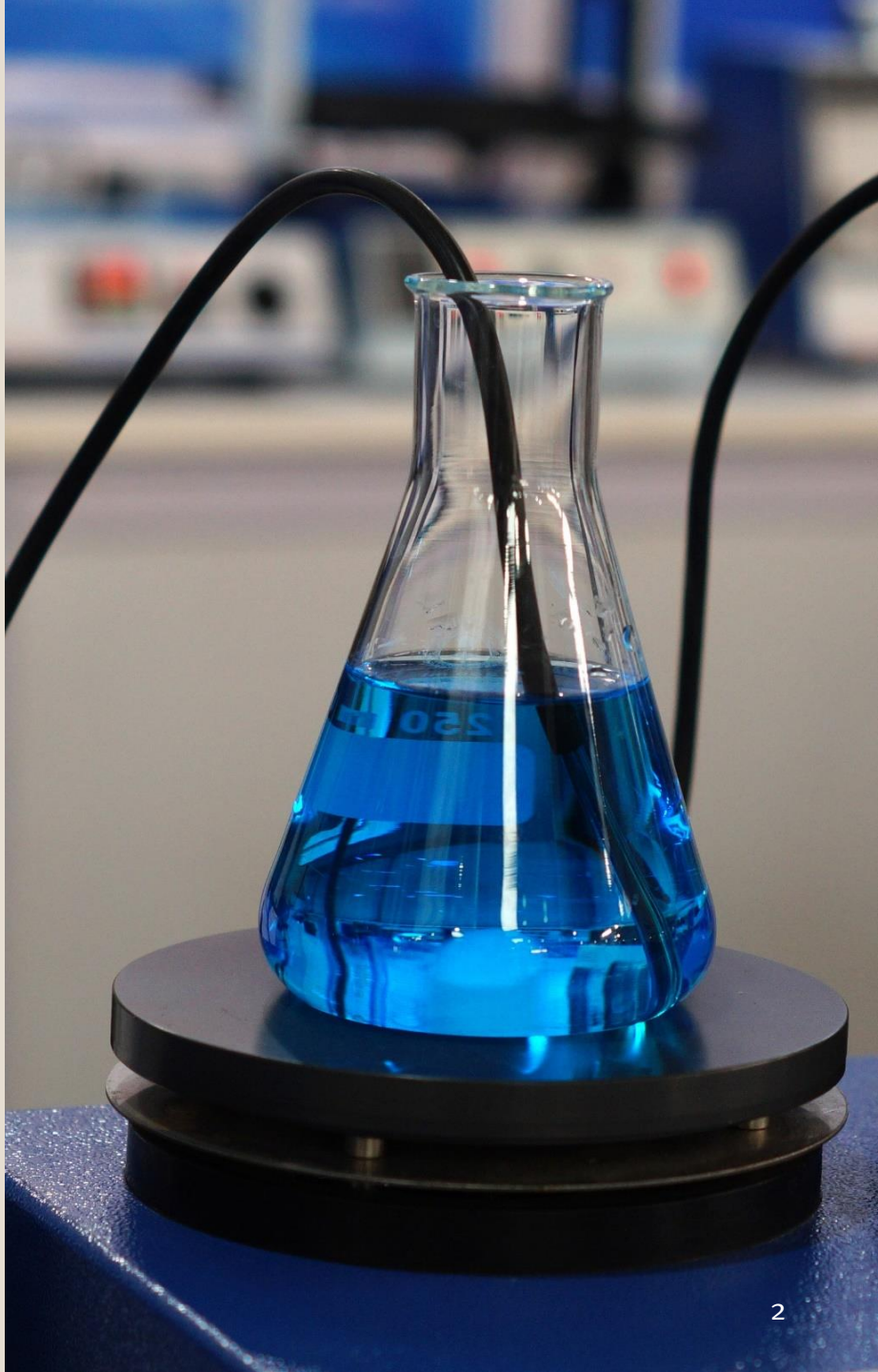

Accessing Past Issues

If you wish to be added to mailing list for this publication, please notify Natasha Yeung (yeungn@stifel.com).

Recent issues in case you missed and want to read:

Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Jan 22, 2024 (AI in medicine)
Jan 15, 2024 (FDA Commissioner Priorities)
Jan 5, 2024 (Sector Outlook for 2024)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 22, 2023 (Bullish on Biotech)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Changing Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on Feb 9, 2024.

The next event will be on February 16, 2024.

Feb 9, 2024. Session: https://twitter.com/i/spaces/1YqxoDZNLyBKv
Feb 16, 2024. Session: https://twitter.com/i/spaces/1kvKpvZaddPJE

Please join us.

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

The week of March 18 will feature over 5,000 biopharma professionals in Barcelona for Bio-Europe. We hope to meet you there.

To meet with Stifel @ Bio-Europe
yeungn@stifel.com

Stifel Active in Biophama Sector Advisory and Financing Transactions

Today, biopharma companies find themselves in a fast-moving environment characterized by great risk and great opportunity. This environment calls for getting the best possible advisor by your side. Stifel's Global Healthcare Group brings senior level attention and intense focus on execution to its clients. The group has been active in 2024's dynamic financing and deal environment. Since the formation of the Global Healthcare Group in 2010, Stifel's team has helped to raise over $115 billion in over 600 transactions and has advised on over 150 strategic transactions.

UPSHER-SMITH

Has agreed to be acquired by

Bora Pharmaceuticals

Advisor to Seller

Pending

€50,500,000

Sensorion

PIPE

Lead Placement Agent

February 2024

$147,900,000

ALTO NEUROSCIENCE

Initial Public Offering

Joint Bookrunner

February 2024

$230,000,000

DIANTHUS THERAPEUTICS

PIPE

Joint Placement Agent

January 2024

$345,144,000

Dyne THERAPEUTICS

Follow-On Offering

Joint Bookrunner

January 2024

$175,000,000

PROPELLA

Has been acquired by

astellas

Advisor to Seller

December 2023

$230,000,000

Syndax

Confidentially Marketed Follow-on Offering

Joint Bookrunner

December 2023

$180,000,000

SPYRE THERAPEUTICS

PIPE

Co-Lead Placement Agent

December 2023

$100,000,000

VANDA PHARMACEUTICALS INC.

Has acquired U.S. and Canada rights to

Ponvory (ponesimod)

from

Johnson&Johnson

Advisor to Buyer

December 2023

$245,000,000+

TEIJIN

In-Licensing of the Japan Rights to Three Rare Endocrinology Drugs From

ascendis pharma

Advisor to Licensee

November 2023

$300,000,000

XENON

Confidentially Marketed Follow-on Offering

Joint Bookrunner

November 2023

$185,000,000

VIRIDIAN

PIPE

Co-Lead Placement Agent

November 2023

$100,000,000

LEXEO therapeutics

Initial Public Offering

Joint Bookrunner

November 2023

$517,500,000

cerevel

Confidentially Marketed Follow-on Offering

Joint Bookrunner

October 2023

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Macroeconomics Update

Mixed US Consumer Price Revisions Leave Slowing Inflation Trend Intact

Lucia Mutikani, *Reuters*, Feb 9, 2024 (excerpt)

U.S. monthly consumer prices rose less than initially thought in December, but the overall inflation revisions were mixed, and did not shift expectations on the timing of an anticipated interest rate cut from the Federal Reserve this year.

The annual revisions published by the Labor Department on Friday also showed the consumer price index increasing slightly more than previously reported in October and November.

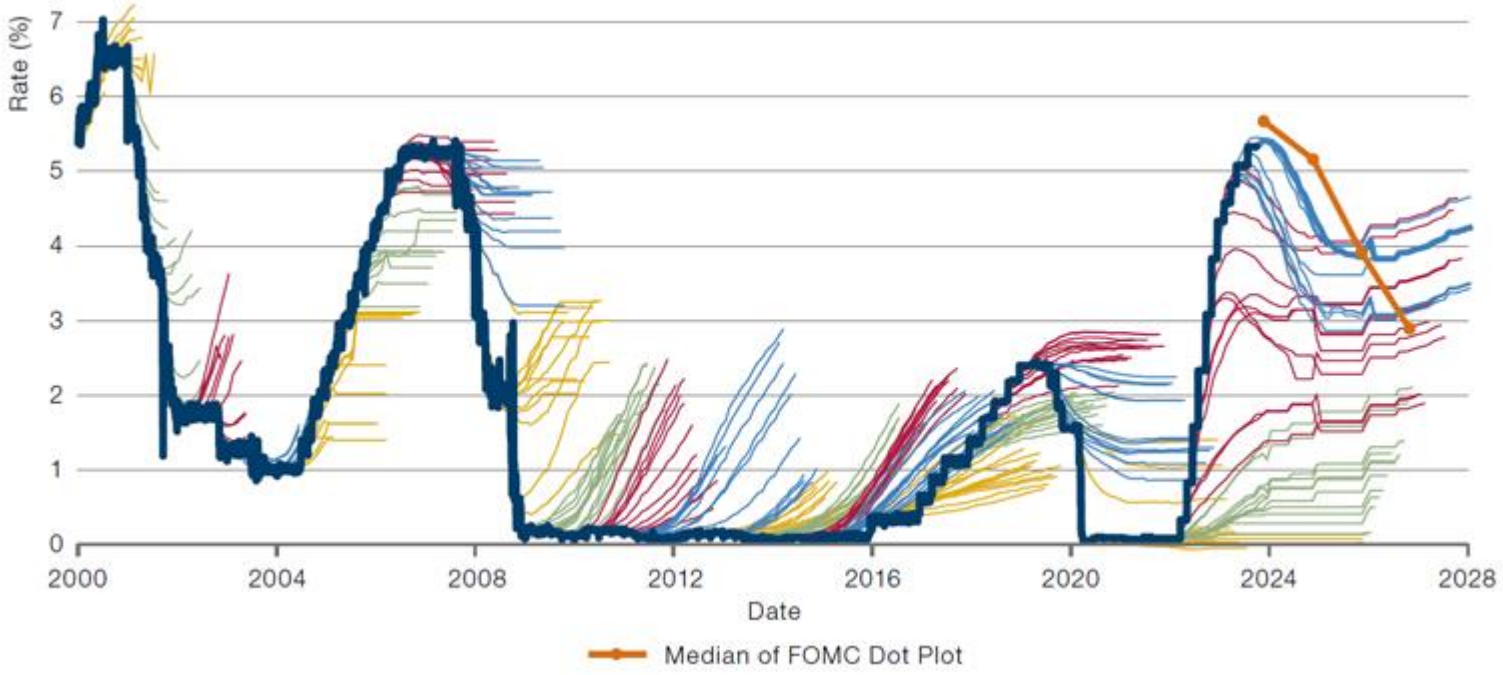
Prices excluding the volatile food and energy components were unrevised, after rounding, from October through December. All told, the revisions did not materially alter the path of inflation, which is moderating after surging in 2022.

The revised CPI data had been eagerly awaited by financial markets and economists after Federal Reserve Governor Christopher Waller last month flagged them as among the key data pieces he would be watching as policymakers try to gauge progress in their fight against inflation.

Source: https://www.reuters.com/markets/us/us-december-consumer-prices-revised-lower-2024-02-09/

Market Usually Wrong About Fed's Direction for Rates

Man Group, Effective Fed Funds rate versus market expectations



At first glance, the market seems to believe that the Fed will hold for the rest of 2023, keeping rates unchanged, which as we've shown, Fed officials in aggregate do not seem to agree with. Beyond this, there seems to be agreement on the cuts out to 2025, with the slight deviation being the steeper gradient of cuts expected by the market. Interestingly, after 2025, there is broad divergence between the two, with the market expecting rates to land on a higher long-term or r* level, plateauing from 2025.

Source: https://www.man.com/maninstitute/views-from-the-floor-2023-October-10

S&P 500 Tops 5,000

Samantha Subin and Yun Li, *CNBC*, Feb 9, 2024 (excerpt)

Stocks rose on Friday after December's revised inflation reading came in lower than first reported, and the S&P 500 closed above the key 5,000 level as strong earnings and economic news chugged on.

The S&P 500 rose 0.57% to end at 5,026.61, while the Nasdaq Composite rallied 1.25% to close at 15,990.66. The Dow Jones Industrial Average slipped 54.64 points, or 0.14%, to settle at 38,671.69.

For the week, the S&P added 1.4%, while the Nasdaq gained 2.3%. The Dow finished flat. All three major averages notched their fifth straight winning week and 14th positive week in 15.

"At the end of the day, we're still seeing whopping good news on an economic front, and the market is reacting to that," said Dana D'Auria, co-chief investment officer at Envestnet. "The longer that story plays out, the more likely it seems to the market that we actually are sticking a landing here."

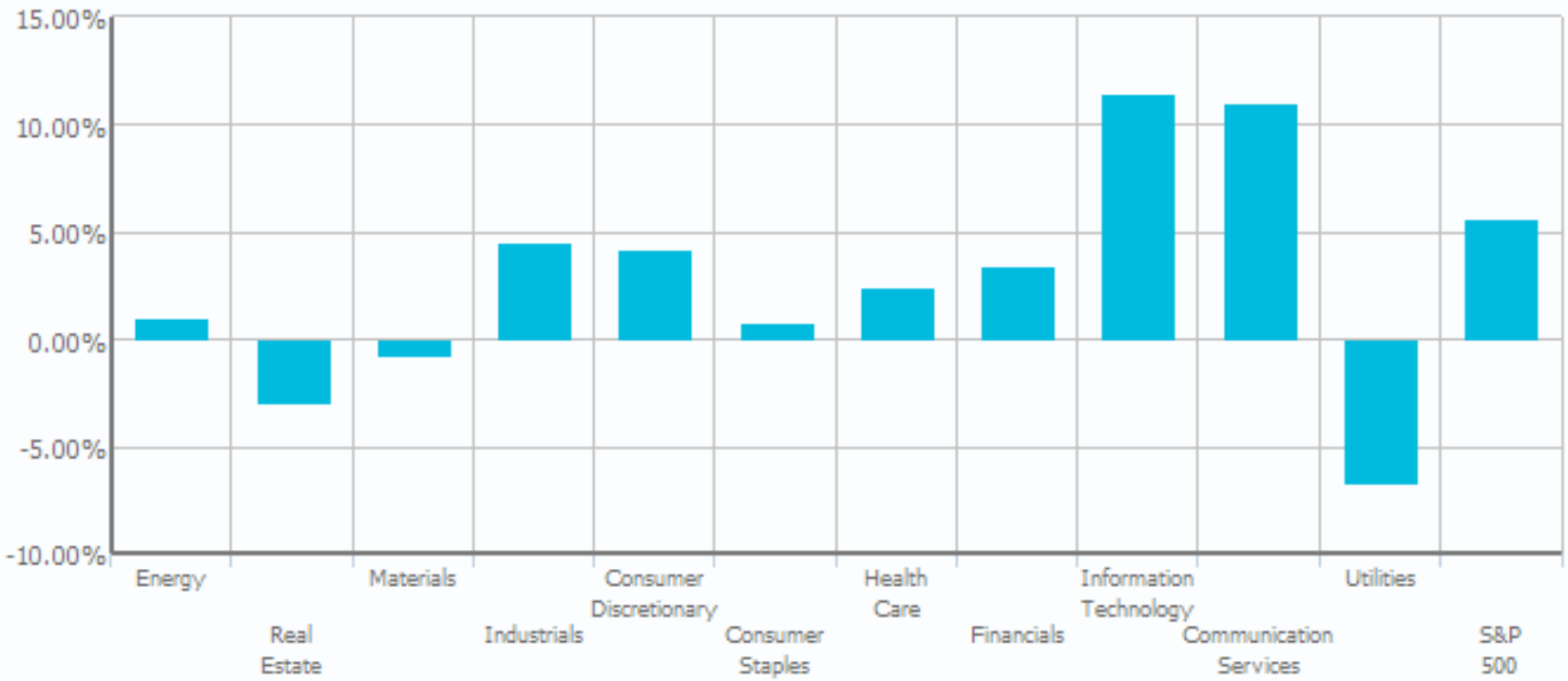
A solid earnings season, easing inflation data and a resilient economy have charged 2024's market rally. It's also propelled the S&P to close above the 5,000 level after first touching the milestone during Thursday's session. The index first crossed 4,000 in April 2021.

Source: https://www.cnbc.com/2024/02/08/stock-market-today-live-updates.html

Total Global Stock Market Performance, Jan 9 to Feb 9, 2024, by Sector

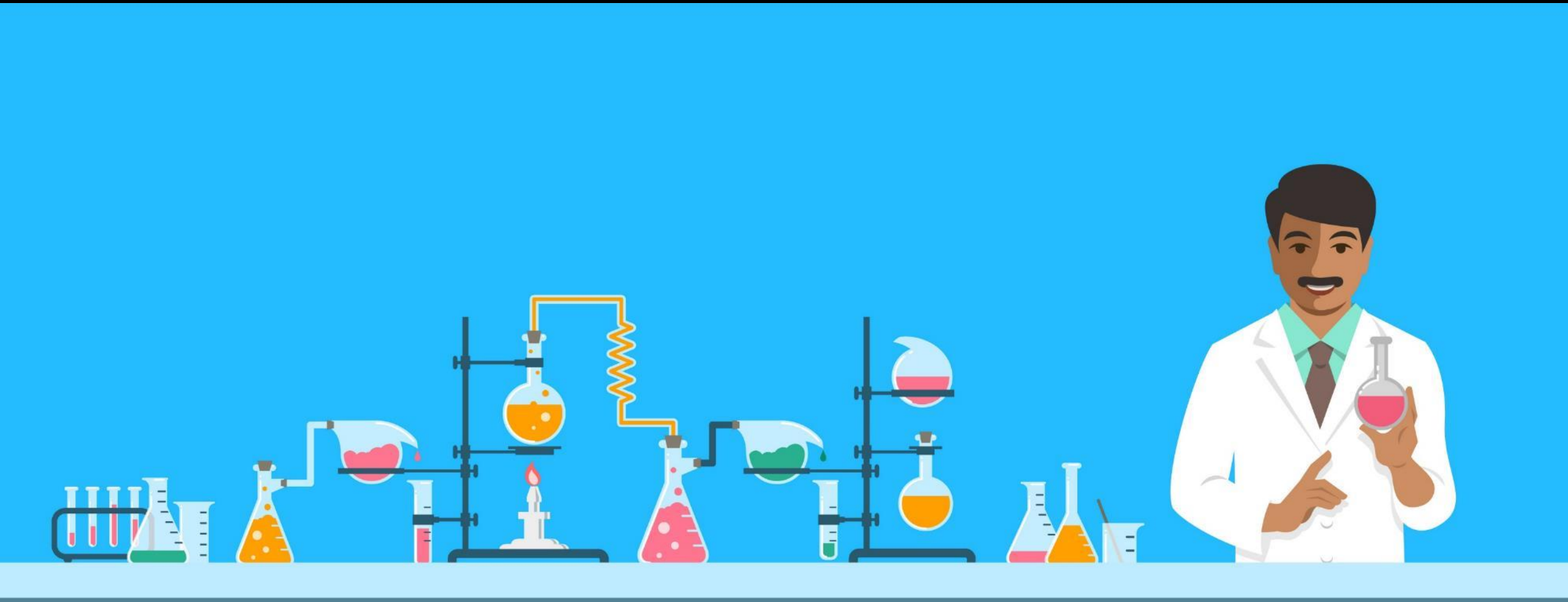
As we see a “risk on” attitude take hold in the market, we are seeing a renaissance in riskier stocks including IT, communication services, industrials and consumer discretionary recovery.

In contrast, sectors that are “safer”, particularly utilities, have underperformed over the last thirty days. Healthcare is up but nowhere near what has happened in the information technology sector.



Source: S&P Capital IQ

Biopharma Market Update



The XBI Closed at 91.04 Last Friday (Feb 2), Up 3.5% for the Week

Last week the XBI was up 3.5% and is up 2% YTD. Our measure of total biotech market value rose by 8.5% and is now up 13.7% for the year to date. Note that the XBI continues to give a distorted view of what is going on in the overall biotech market.

Biotech Stocks Up Last Week

Return: Feb 3 to Feb 9, 2024

Nasdaq Biotech Index: -0.3%
Arca XBI ETF: +3.5%
Stifel Global Biotech EV (adjusted): +8.5%*
S&P 500: +3.5%

Return: Jan 1 to Feb 9, 2024

Nasdaq Biotech Index: +0.1%
Arca XBI ETF: +2.0%
Stifel Global Biotech EV (adjusted): 13.7%*
S&P 500: +5.4%

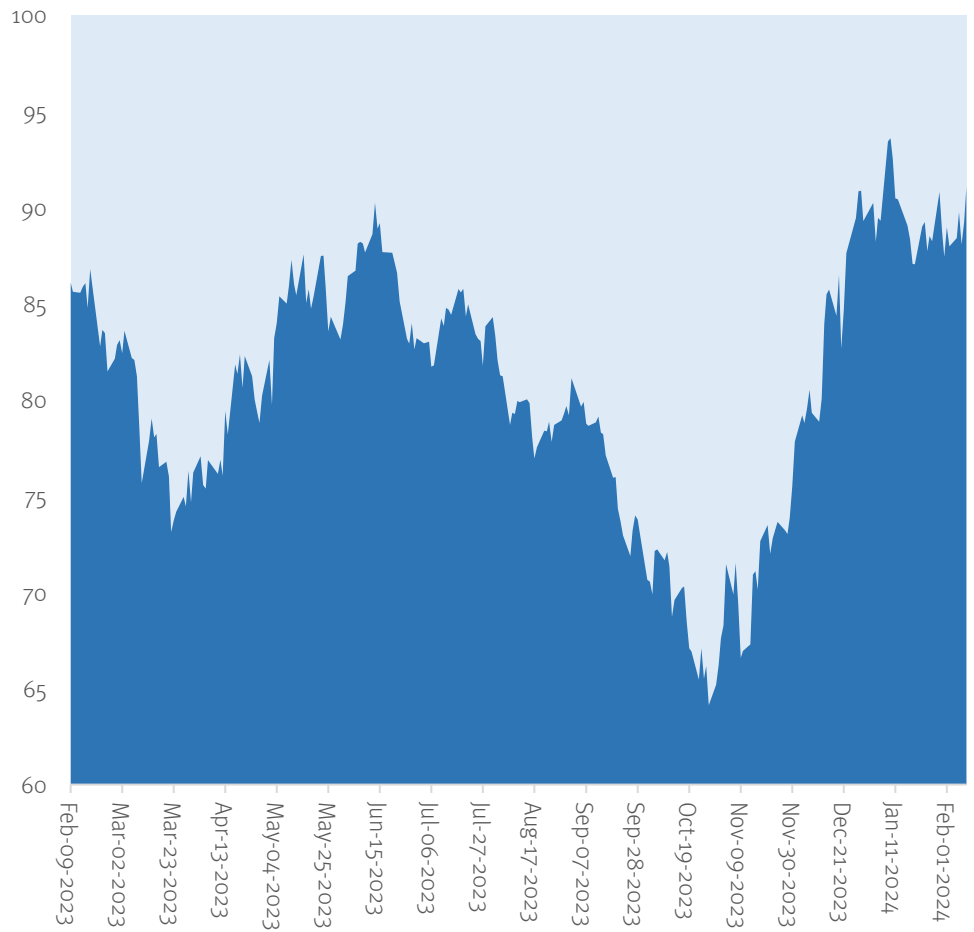
VIX Down Slightly

Jan 20: 19.9%
May 26: 18.0%
July 21: 13.6%
Sep 29: 17.3%
Oct 27: 21.2%
Dec 29: 12.45%
Jan 26, 2024: 13.26%
Feb 2, 2024: 13.8%
Feb 9, 2024: 12.9%

10-Year Treasury Yield Up

Jan 20: 3.48%
May 26: 3.8%
July 21: 3.84%
Sep 29: 4.59%
Oct 27: 4.86%
Dec 29: 3.88%
Jan 26, 2024: 4.15%
Feb 2, 2024: 4.02%
Feb 9, 2024: 4.17%

XBI, Feb 9, 2023 to Feb 9, 2024



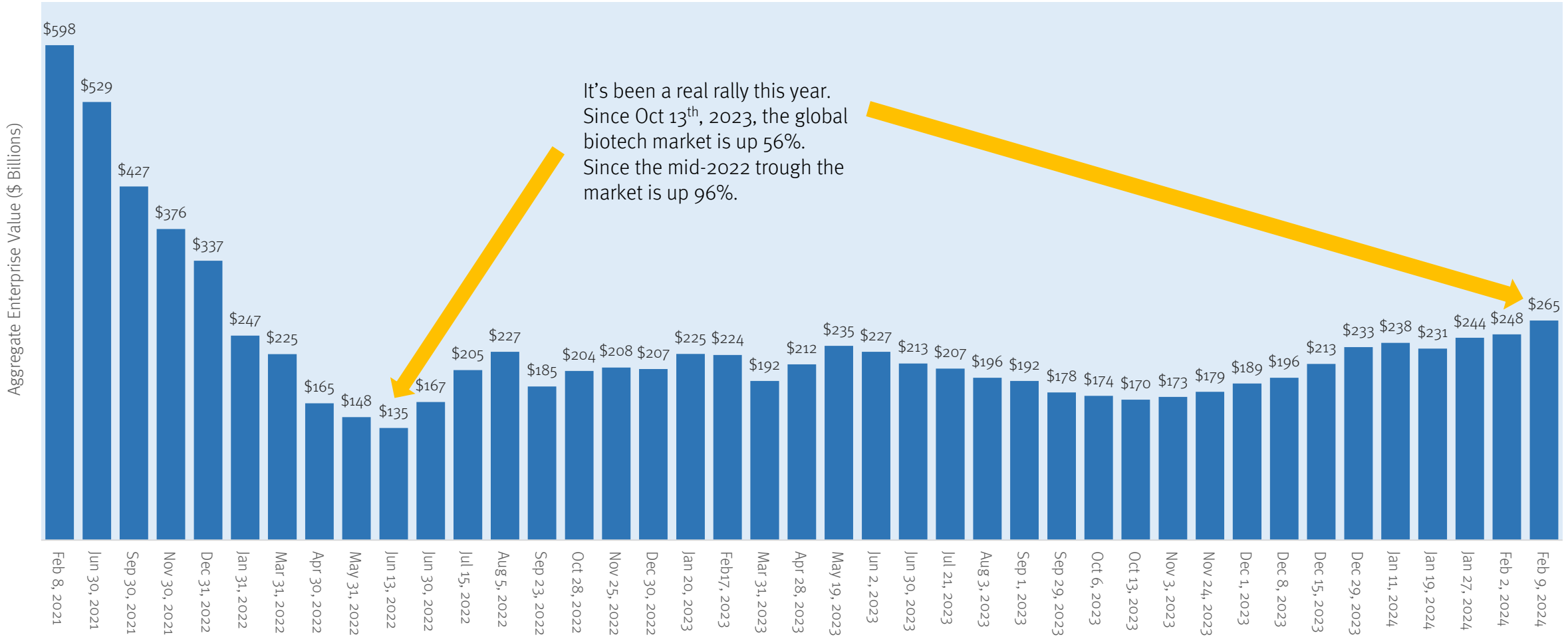
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Rose 8.5% Last Week

The total enterprise value of the global biotech sector is up 13.7% for the year to date on an addition/exit corrected basis. The rally that started 15 weeks ago picked up more momentum last week. The biotech market has been up 13 of the last 15 weeks.

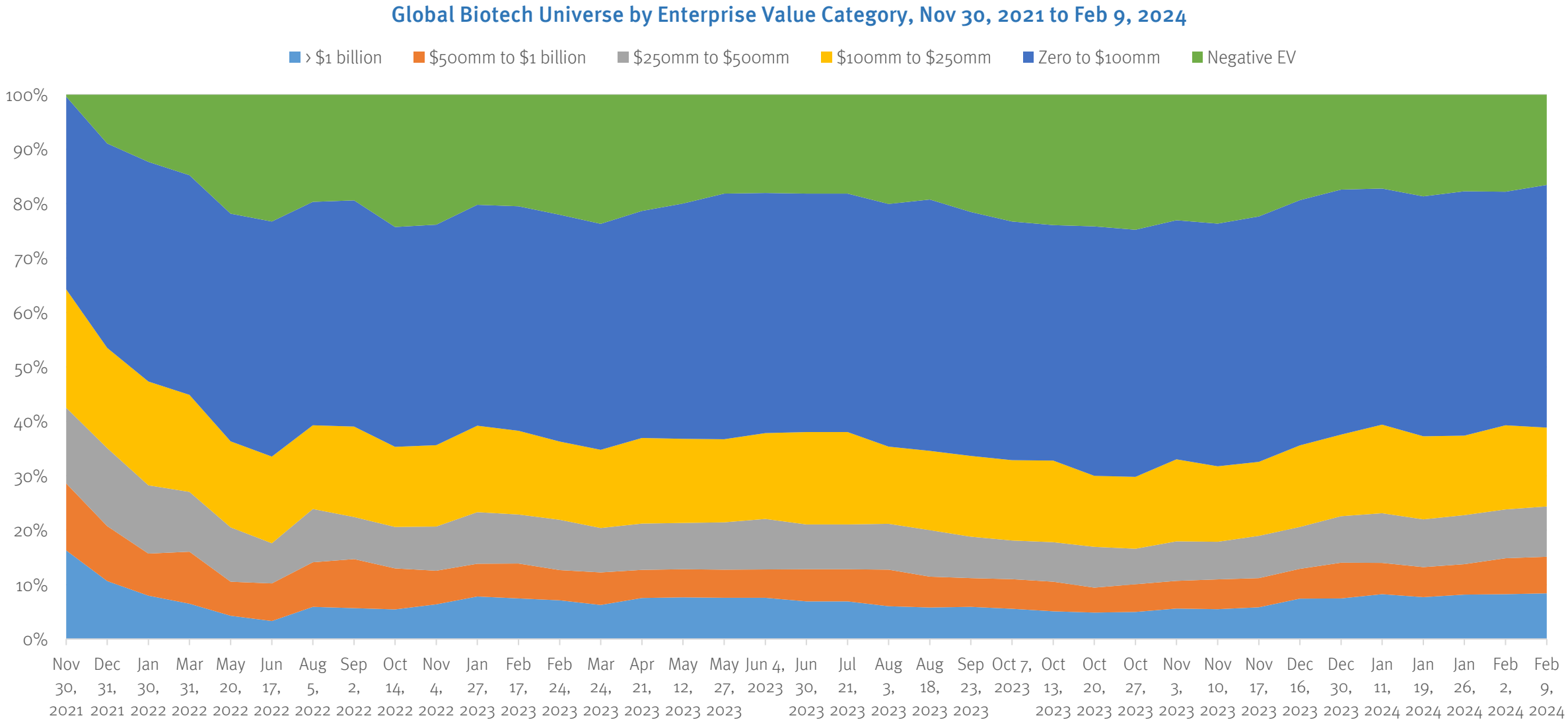
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Feb 9, 2024 ($ Billions)



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

Global Biotech Neighborhood Analysis

Last week saw rapid shrinkage of the negative EV population sector in biotech.

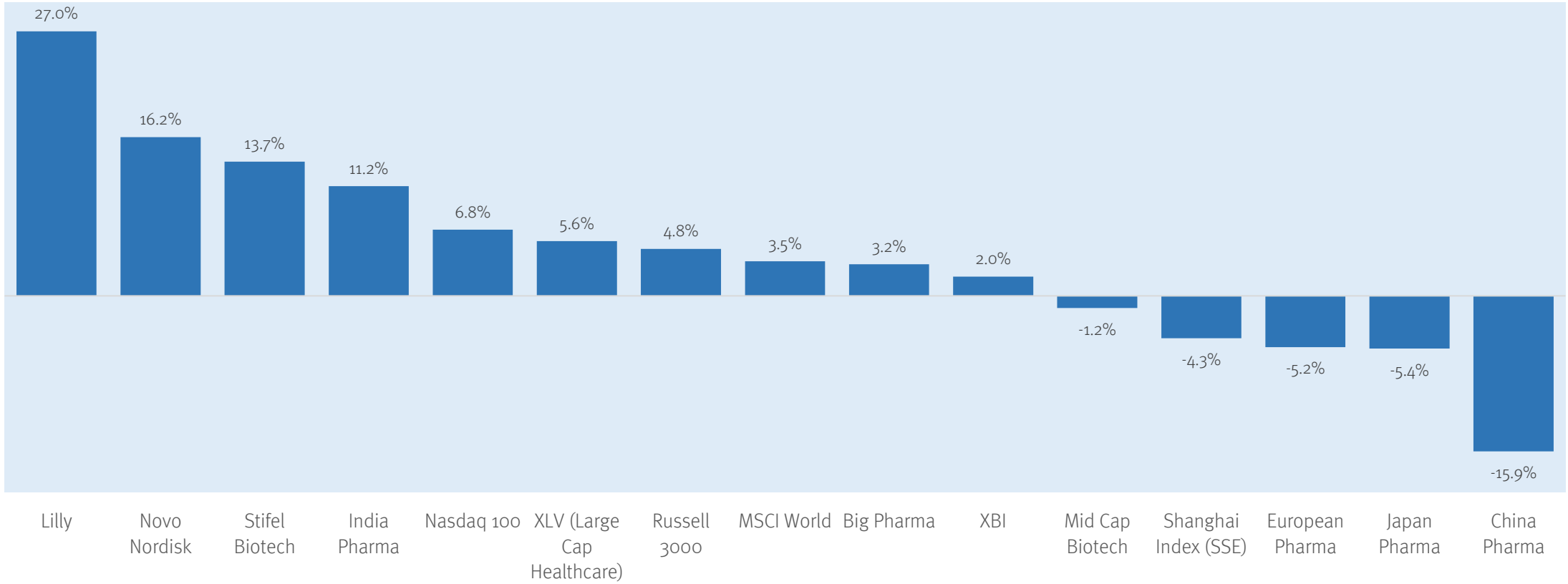


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Where Has the Pharma Market Done Best?

Japan, Europe and China pharma have underperformed in 2024. Big pharma is up slightly but this is driven entirely by returns of Novo Nordisk and Eli Lilly. The XBI is up 2% and Stifel's biotech value tracker is up much more. The Stifel value tracker is tied to enterprise value rather than market cap and so is leveraged to the rally. India pharma and the Nasdaq 100 have also done well thus far in 2024. Strength in the dollar versus the Yen and Euro explain some but not all of the decline in the value of European and Japan pharma thus far in 2024.

Group Share Price Return, Dec 30, 2023 to Feb 9, 2024



Notes: These data are from S&P CapitalIQ and are compiled into equal-weighted indices. Big pharma includes PFE, LLY, MRK, ABBV, NOVO B, ROG, JNJ, AMGN, AZN, NOVN and SAN. China Pharma includes 600276, 1093, 2186, BGNE, 000963, 600196, 000538, 600518, 002422, 000597, 3692 and ZLAB. India Pharma includes SUNPHARMA, 500257, AUROPHARMA, CIPLA, MANKIND, GLENMARK, 500124, ZYDUSLIFE. Europe Pharma includes Merck KGAA, IPN, HLUN A, BAYN, REC, SOBI, ALM, FRE, ORNBV, UCB, GRF. Japan Pharma includes Takeda, Daiichi-Sankyo, Chugai, Astellas, Eisai. Otsuka Holdings, Shionogi, Ono, Kyowa Kirin, Nippon Shinyaku, Santen and Sumitomo Pharma. Midcap biotech includes VRTX, ARGX, ALNY, BMRN, INCY, NBIX, OGN, IONS, EXEL, ALKS, ITCI, HRMY, INDV, BPMC, MRTX, SAGE, IDIA, APLS.

Life Sciences Sector Total Value Up Big Last Week

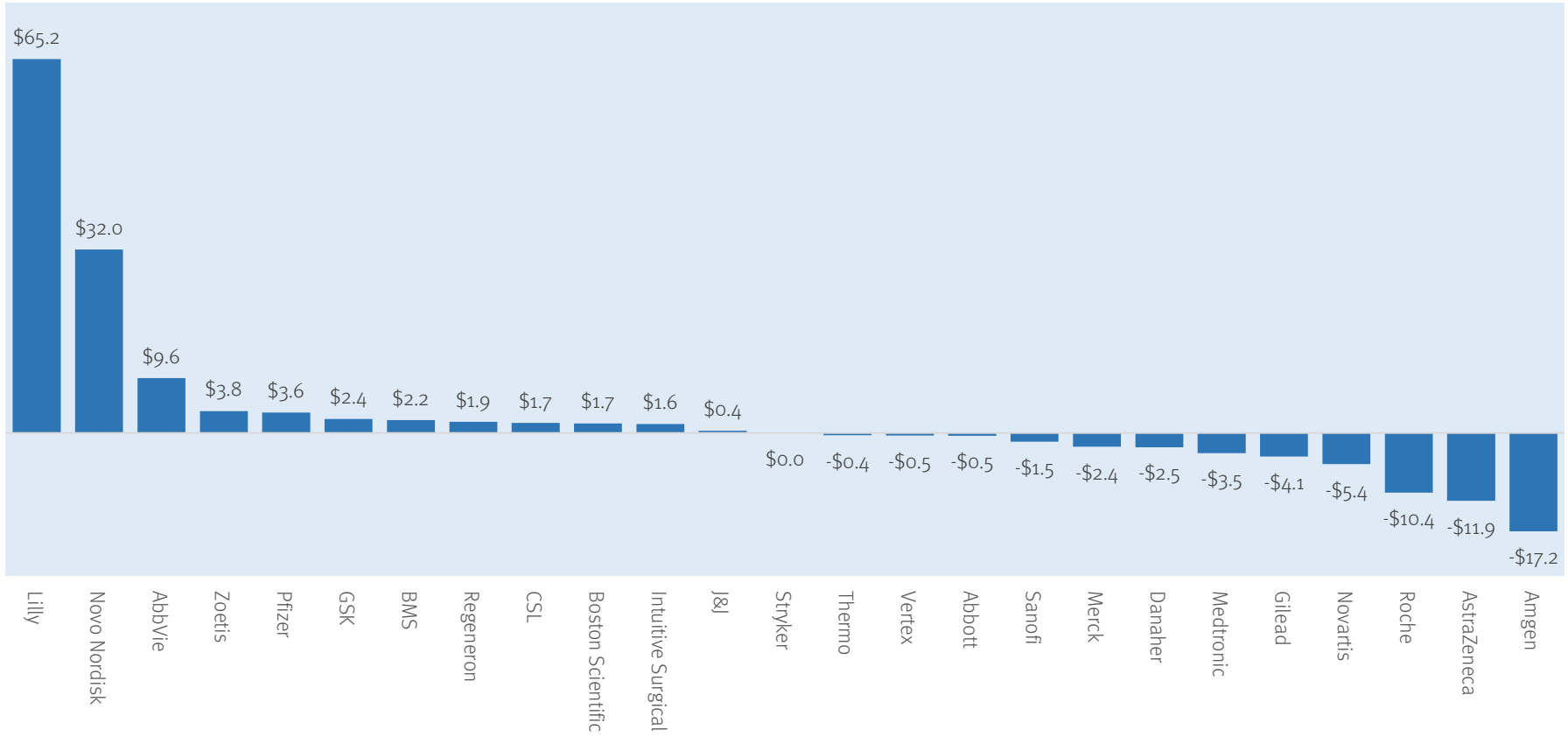
Last week saw the life sciences sector gain $213 billion in value. Subsectors that gained 4% or more included biotech, pharma services and HCIT. Life science tools was down a bit.

Sector	Firm Count	Enterprise Value (Feb 9, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$78,972	3.7%	-7.4%	-6.4%
Biotech	806	$265,295	8.5%	4.9%	-5.1%
CDMO	40	$146,646	1.1%	0.1%	-26.8%
Diagnostics	82	$270,826	3.7%	-2.6%	0.3%
OTC	30	$27,698	0.4%	-2.2%	-6.7%
Pharma	720	$6,098,988	2.6%	0.8%	8.1%
Pharma Services	39	$189,214	5.0%	-3.2%	-13.3%
LS Tools	51	$690,392	-0.4%	1.8%	-9.8%
Devices	181	$1,685,165	1.4%	1.6%	4.3%
HCIT	11	$21,131	5.9%	-2.1%	-25.3%
Total	**2041**	**$9,464,826**	**2.3%**	**0.8%**	**4.5%**

Source: CapitalIQ

Last Week Saw Lilly and Novo Gain $97 Billion in Enterprise Value While the Rest of Top 25 Players in Life Sciences Lost $37 Billion

Gain/Loss in Enterprise Value ($ Billions) Last Week (Feb 2 to Feb 9, 2024) of Top 25 Life Sciences Companies by Enterprise Value ($ Billions)



We're not sure we have ever seen two companies add nearly $100bn in EV in a **single week** in the history of the life sciences sector.

The market is highly focused on the obesity story with Amgen dropping $17 bn in value on side effect data for AMG133 (maridebart cafraglutide - MariTide) while Lilly and Novo skyrocketed on positive sales momentum for their GLP-1 franchises.

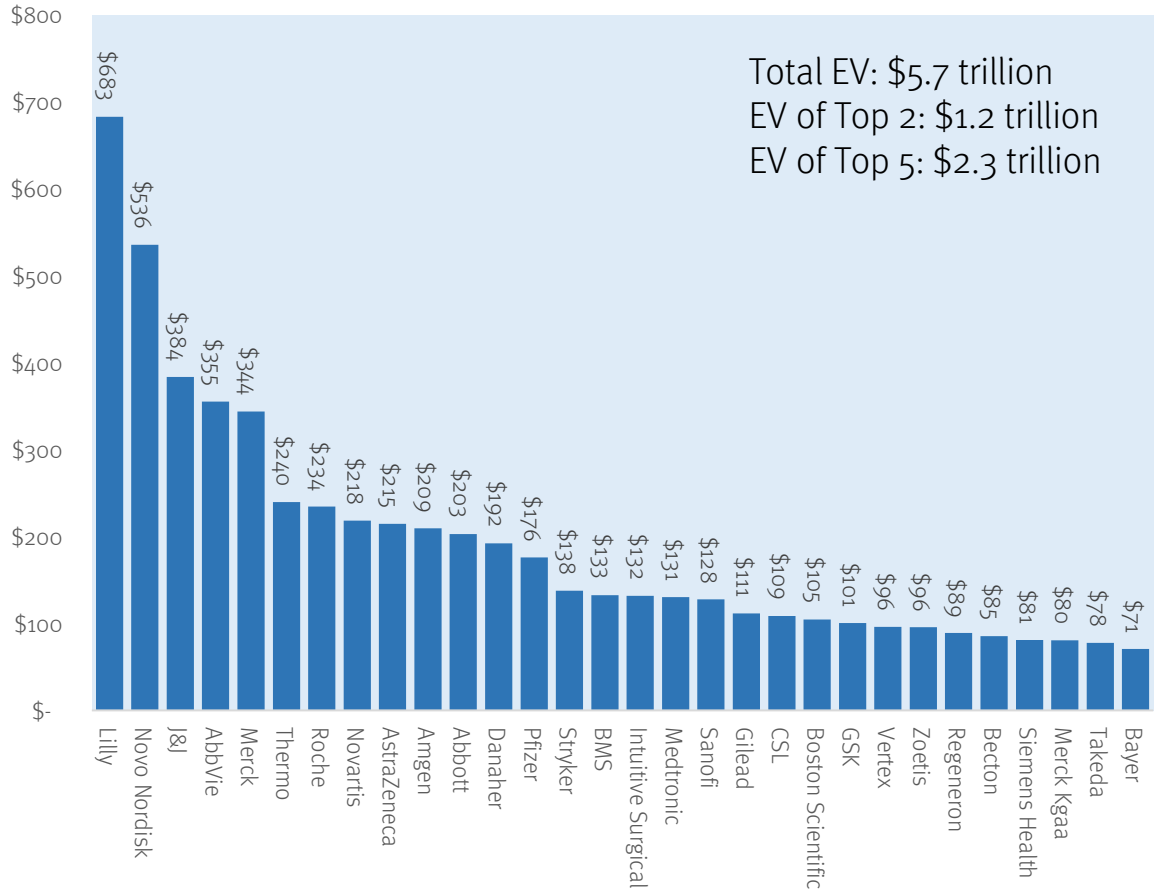
The combined EV of Lilly and Novo is now $1.2 trillion.

Source: CapitalIQ

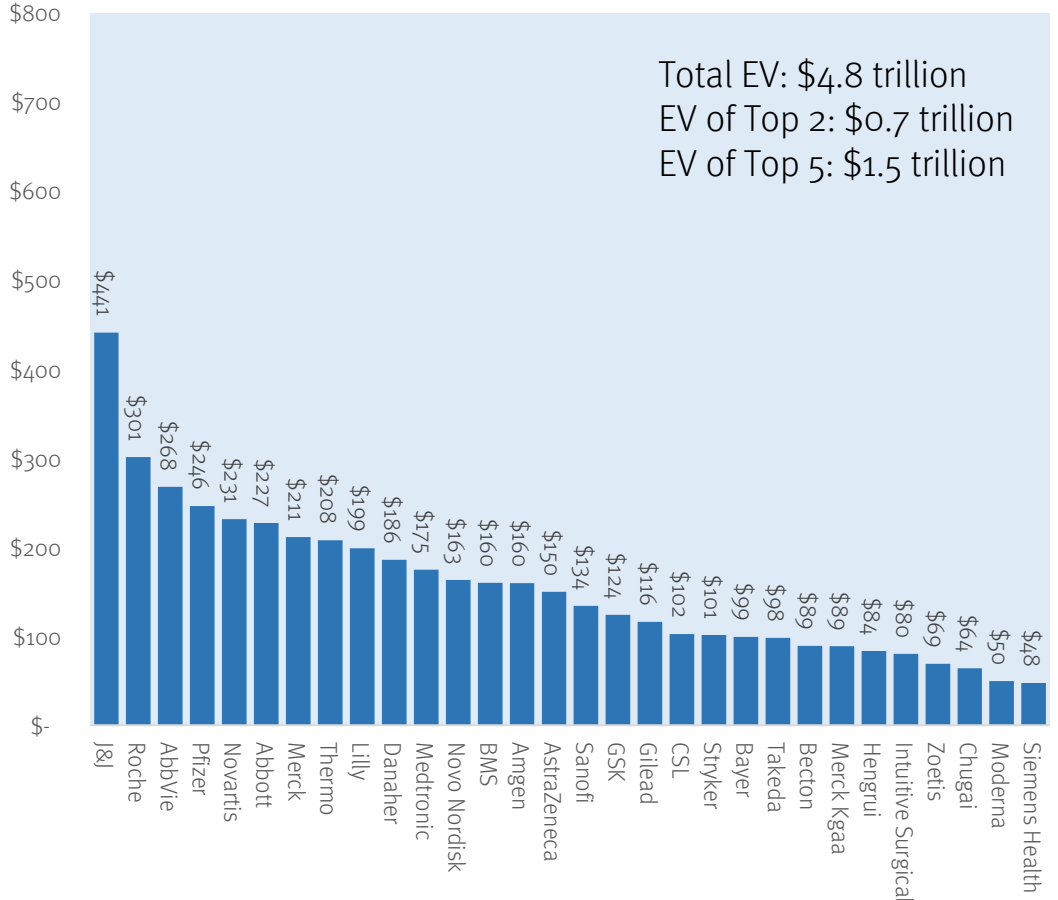
Comparison of EV of Top 30 Life Science Players Last Friday (Feb 9, 2024) Versus Same on Feb 8, 2021 (Pandemic Peak)

It doesn't look to us like the same industry. The top companies were clustered in value scale in Feb 2021 (Pandemic peak). Today, the top five companies are much larger and the top two stand out from the pack. Three years ago, J&J was somewhat bigger than the pack but not by such a massive margin.

Enterprise Value of Top 25 Companies in Life Sciences, Feb 9, 2024
($ billions)



Enterprise Value of Top 25 Companies in Life Sciences, Feb 8, 2021
($ billions)



Source: CapitalIQ

Could Novo, Lilly Become First Trillion-Dollar Healthcare Companies?

Meagan Parrish, PharmaVoice, Feb 2, 2024 (excerpt)

By every measure, weight loss drugs have quickly and dramatically transformed Novo Nordisk.

Fueled by the massive uptake of its GLP-1 agonists Ozempic and Wegovy in the last few years, Novo overtook luxury retailer LVMH as the most valuable company in Europe in September — a position maintained with a market cap of more than $500 billion, which is greater than the GDP of Novo's home country, Denmark.

And some Wall Street analysts now predict that GLP-1s will become the best-selling class of drugs in history.

Eli Lilly, whose rival GLP-1 Zepbound hit the scene in December, is on its own upswing. With a market cap at about $612 billion, Lilly is already the most valuable pharma company in the world and is expected to rake in Zepbound sales of $2.2 billion this year alone.

Earlier this week, Gemma Game, head of healthcare sector strategy at Norges Bank Investment Management, which owns a stake in both Novo and Lilly, said in a press conference that "fewer than a fraction of 1%" of patients living with obesity worldwide have been treated with weight loss drugs, and that the drugs' impact could stretch much further.

"The story is far from over," Game said. "Obesity is linked to around 200 different diseases and I'm looking forward to data on whether GLP-1 agonists can be effective treatments for chronic kidney disease, obstructive sleep apnea, Alzheimer's disease, and even test whether they extend human life spans."

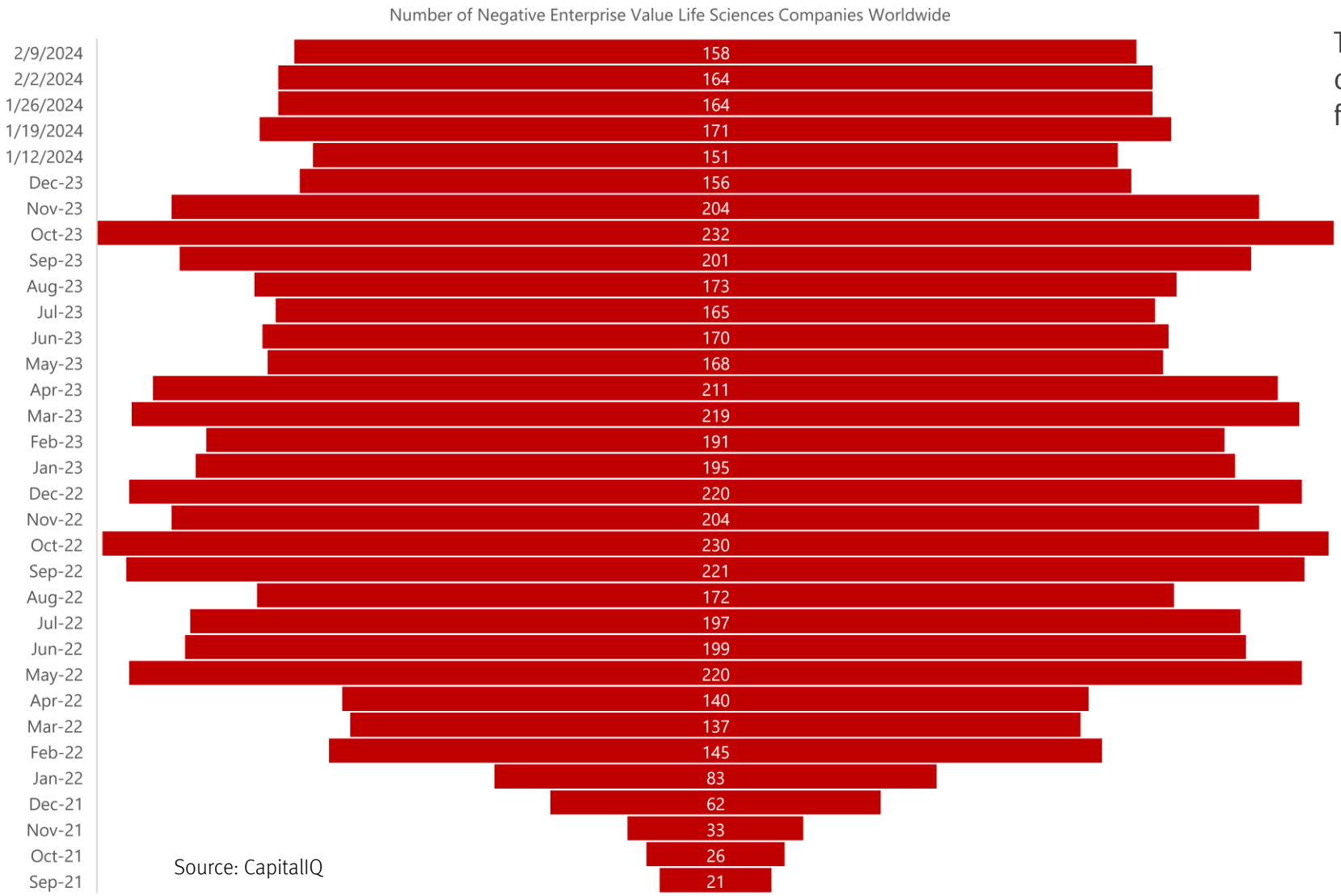
Game went on to speculate that perhaps in the future, "we'll be talking about Eli Lilly and Novo Nordisk as the world's first trillion-dollar healthcare companies."

With Lilly at a valuation of $700bn last week, this type of conversation is realistic.

Far from a foregone conclusion, it is nonetheless, likely, that either Lilly or Novo will hit a $1 trillion value in the years ahead.

Source: https://www.pharmavoice.com/news/novo-lilly-trillion-dollar-healthcare-ozempic-wegovy/706323/

Number of Negative Enterprise Value Life Sciences Companies Declined in Last Week



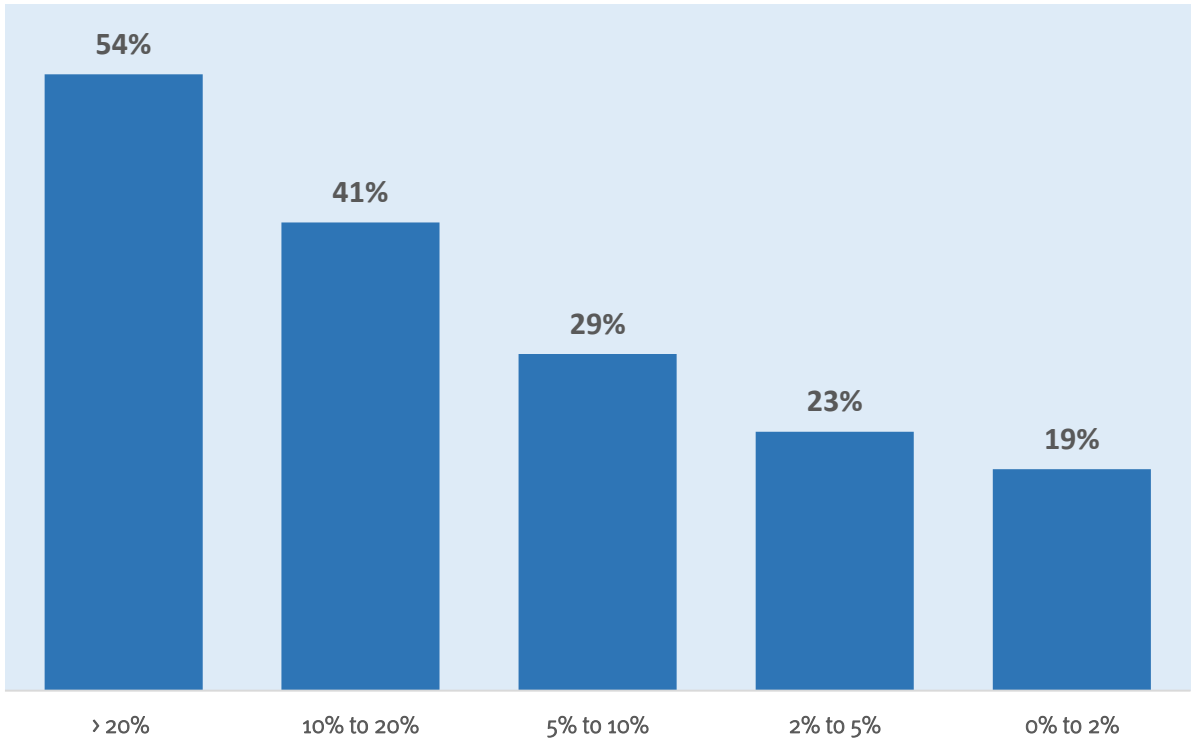
Source: CapitalIQ

The count of negative EV life sciences companies worldwide dropped to 158 from 164 last week.

Short Covering Less Important in First Six Weeks of 2024 than in Last Ten Weeks of 2023

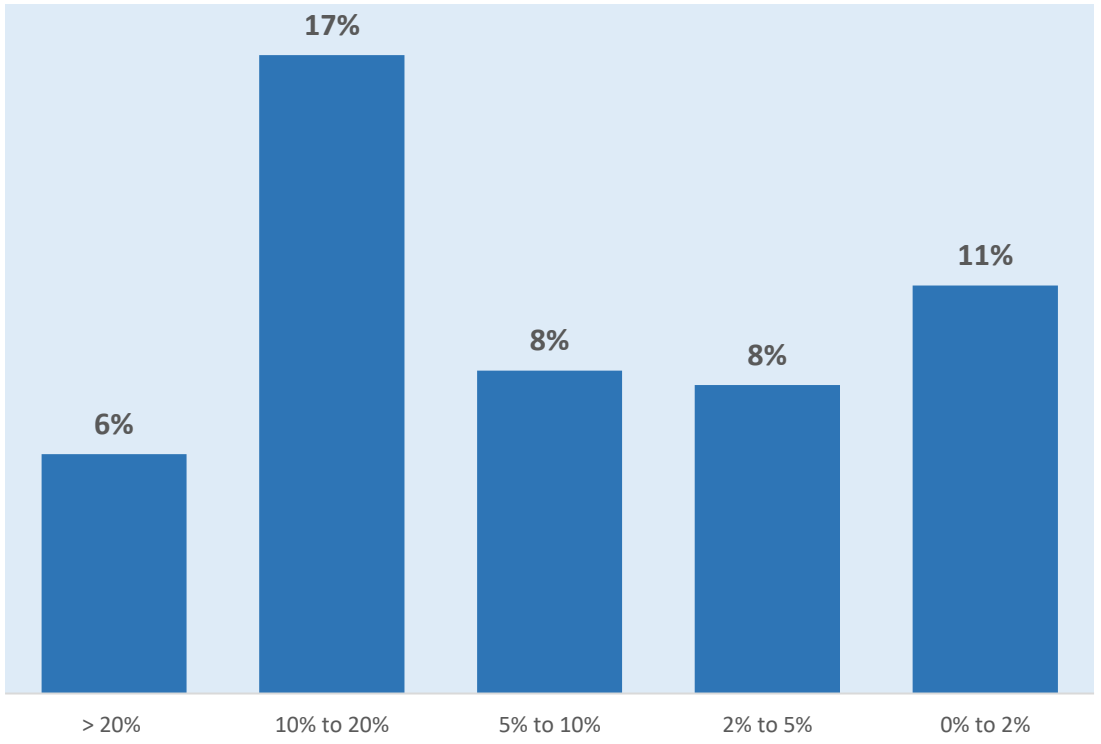
It was very clear to us that the rally of the last ten weeks of 2023 was influenced by short covering. This is evident in the chart at below left. There is no correlation between short interest at the start of 2024 and returns in the first six weeks of the year. This suggests that the rally we saw was driven by fundamental buying than in repositioning by hedge funds already in the market.

Percent of Stocks Up 50% or More in Last Ten Weeks by Short Category at Start of Period (Oct 27 to Dec 30, 2023)



Short Interest Level, Last Reporting Period in October 2023

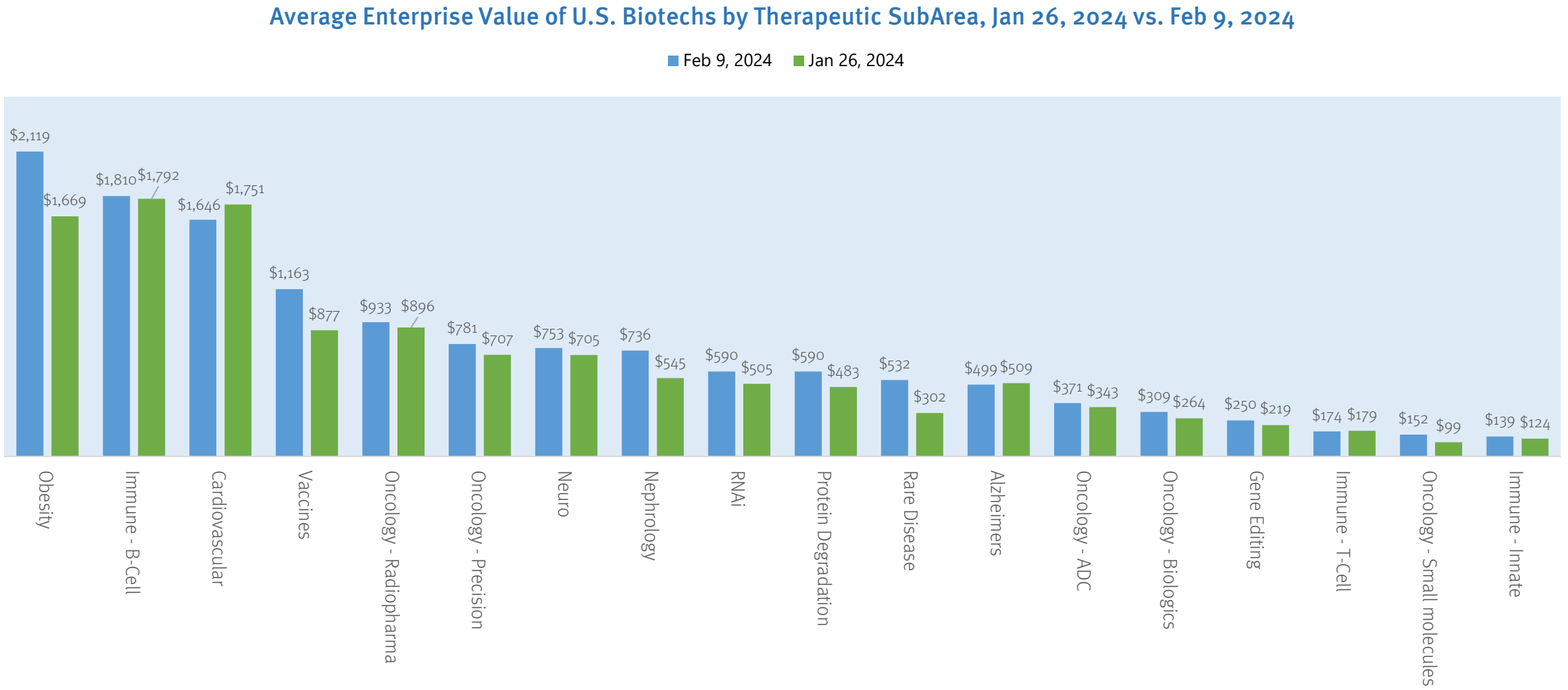
Percent of Stocks Up 50% or More in Last Six Weeks by Short Category at Start of Period (Dec 30, 2023 to Feb 9, 2024)



Short Interest Level, Last Reporting Period in December 2023

Source: CapitalIQ

Last Two Weeks Seeing Spiking in Value of Obesity, Vaccine and Rare Disease Biotechs



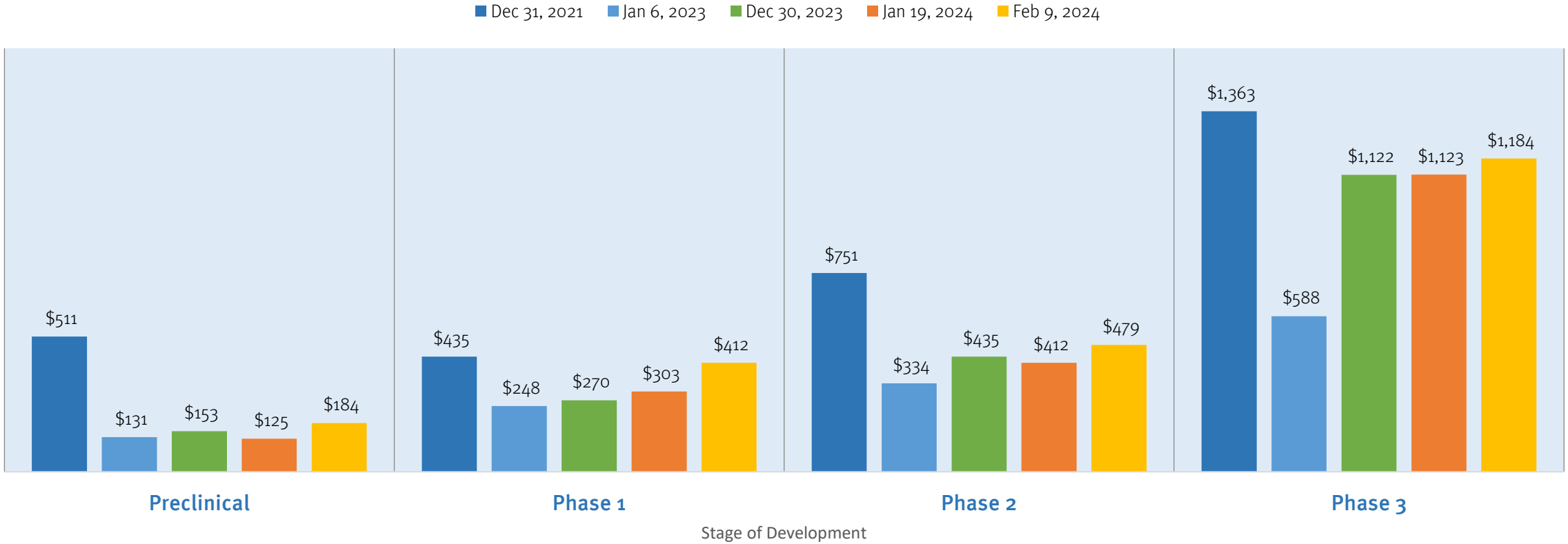
Source: CapitalIQ and Stifel analysis.

Market Showing Biggest Recovery in Phase 1 Valuations

At the start of 2024 the average enterprise value of a preclinical biotech was $153 million while, today, it's $184 million (up 20%). The average EV of a Phase 1 company was $270mm while, today, its $412 million (up 53%). The average EV of a Phase 2 company is up 10% and the average EV of a Phase 3 company is only up 5%. Interestingly, Phase 1 valuations today are close to where they were at the end of 2021.

Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development

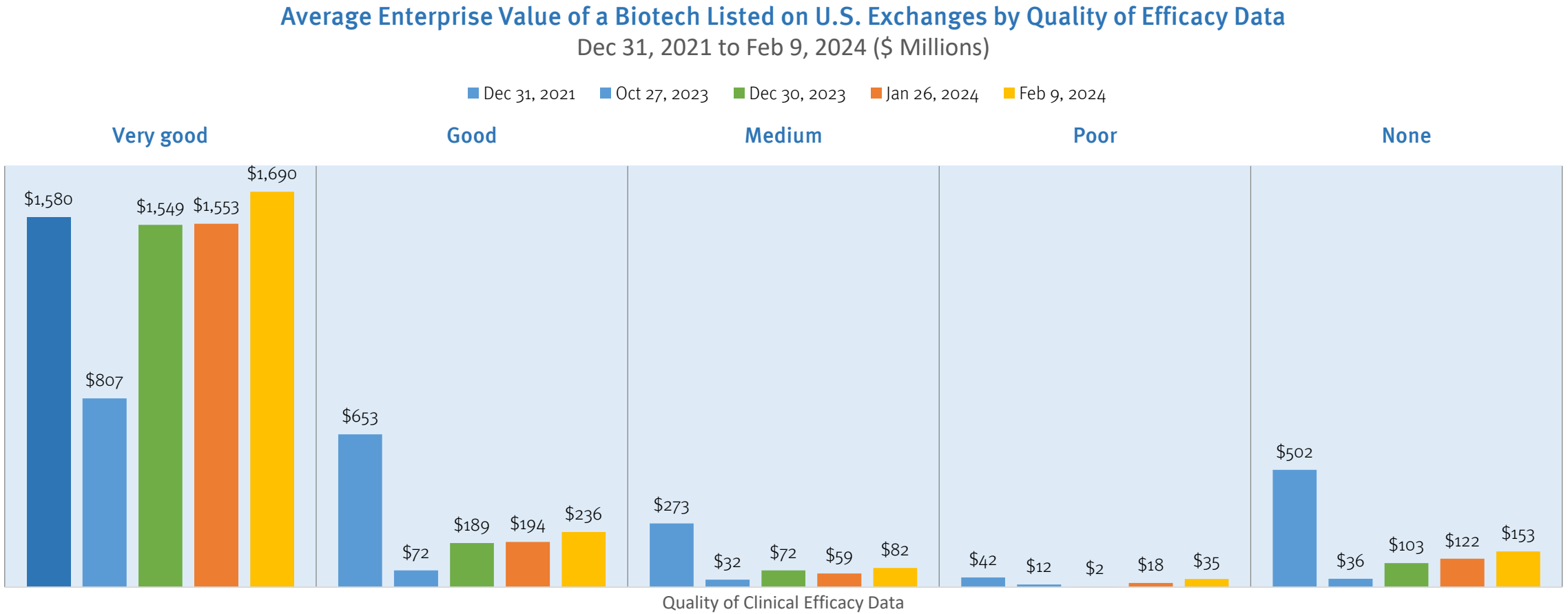
Dec 31, 2021 to Jan 19, 2023 ($ Millions)



Source: CapitalIQ and Stifel analysis. Phase of development is defined by release of at least some efficacy data from a given stage of clinical development. We define stage of development as the last completed stage of development rather than the current ongoing stage of development.

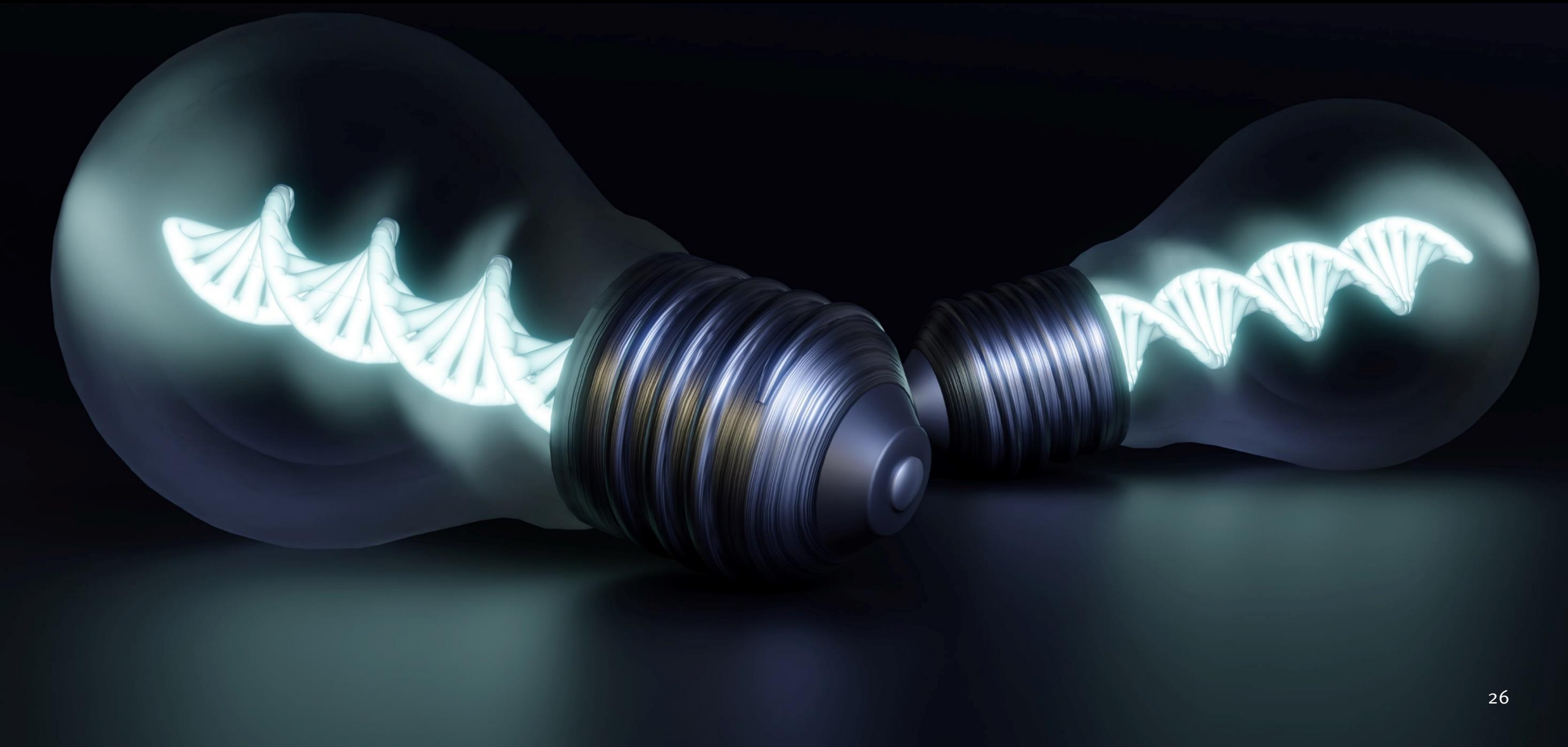
Market Showing Biggest Recovery in Pre-Data Companies

At the start of 2024 the average enterprise value of a company with a “very good” dataset was $1.55 billion while, today, the average is $1.7 billion (up 13%). The average EV of a company with a “good” dataset at start of the year was $189mm while, today, the average is up to $236 million (up 25%). The average EV of a company with a “medium” data set is up 14% and the average EV of a company with no data is up 49%. Many of these tend to be platform companies. We are starting to see a bit more interest in platform stories in the market.



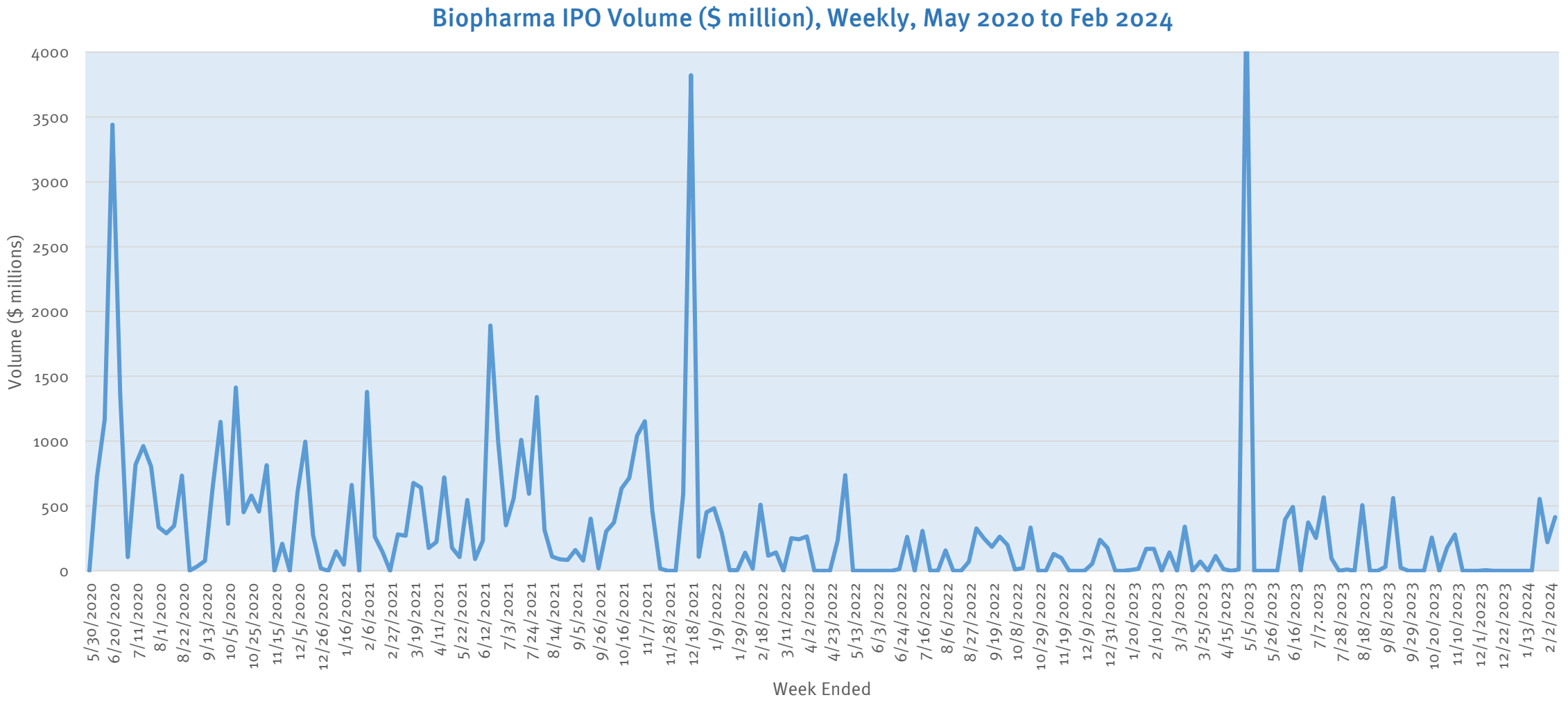
Source: CapitalIQ and Stifel Research. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as “very good”. We classified “good” data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial.

Capital Markets Update



IPO Market Active Last Week

This year has seen $1.2 billion in initial public offerings in the market. Last week saw Kyverna and Metagenomi go public.

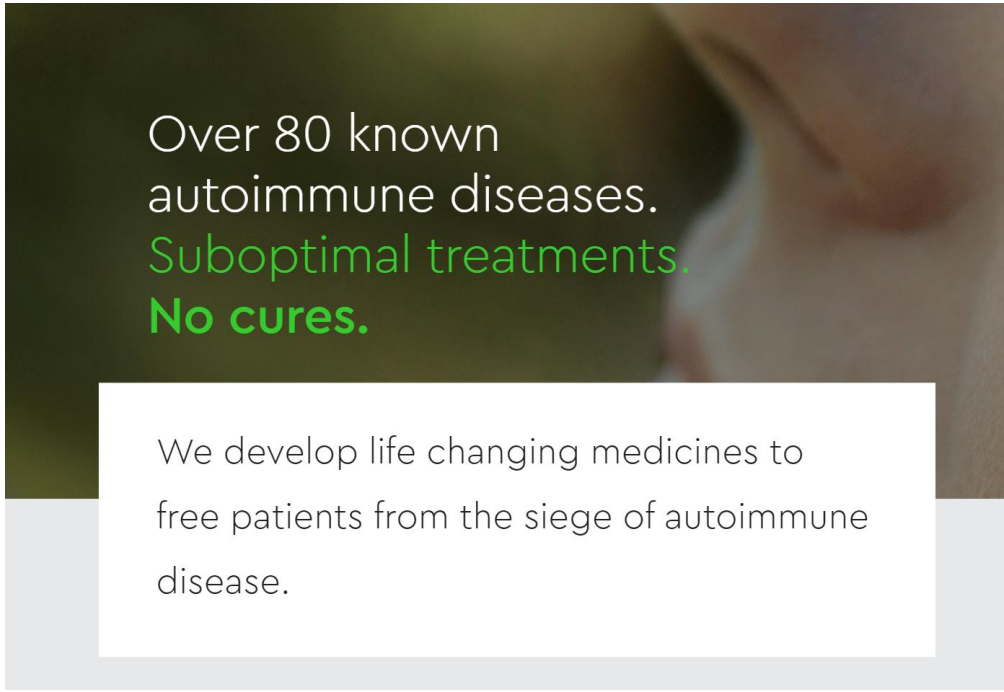


Source: Data from CapitalIQ and Stifel research.

Kyverna Therapeutics Announces Pricing of Upsized Initial Public Offering

Press Release, Feb 7, 2024 (excerpt)

Kyverna Therapeutics, Inc. (Kyverna), a patient-centered clinical-stage biopharmaceutical company focused on developing cell therapies for patients suffering from autoimmune diseases, today announced the pricing of its upsized initial public offering of 14,500,000 shares of its common stock at an initial public offering price of $22.00 per share. All of the shares are being offered by Kyverna. The gross proceeds from the offering, before deducting underwriting discounts and commissions and other offering expenses payable by Kyverna, are expected to be $319.0 million. Kyverna's common stock is expected to begin trading on the Nasdaq Global Select Market on February 8, 2024 under the ticker symbol "KYTX." The offering is expected to close on or about February 12, 2024, subject to the satisfaction of customary closing conditions.

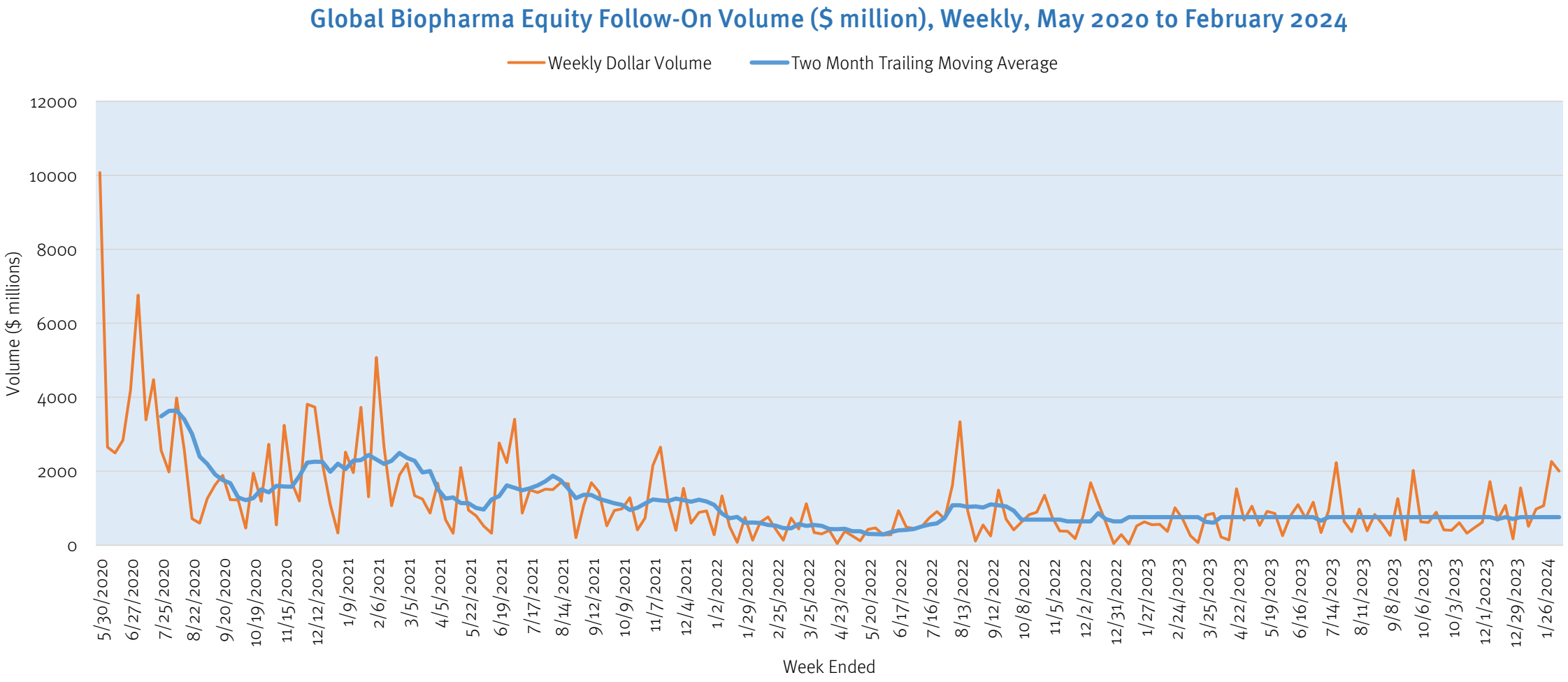


Kyverna shares ended the week up 36% over the IPO offer price.

Source: https://www.prnewswire.com/news-releases/kyverna-therapeutics-announces-pricing-of-upsized-initial-public-offering-302056924.html

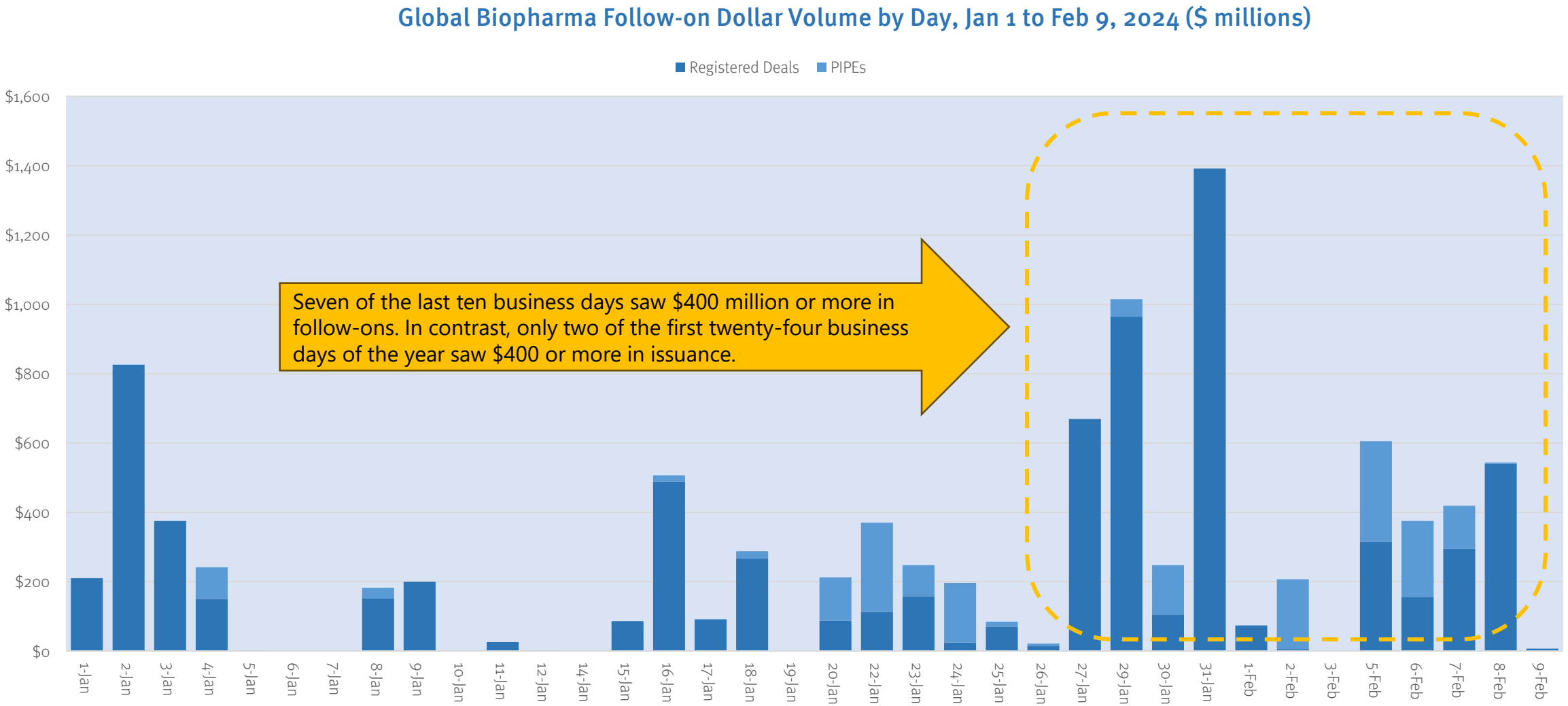
Follow-On Market Active Last Week

Last week saw $2bn in follow-on volume across 18 different offerings.



Source: Data from CapitalIQ and Stifel research.

Follow-On Issuance Volume of $4.6 Billion in the Last Two Weeks

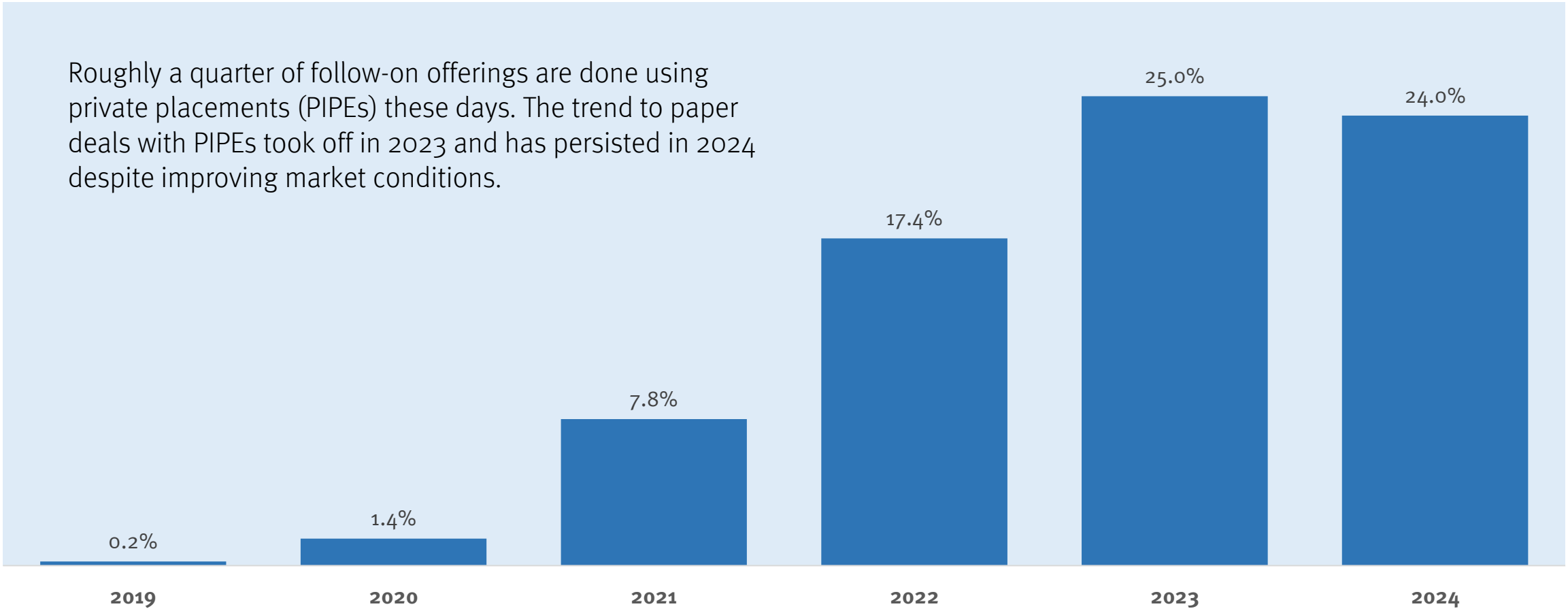


Source: Data from CapitalIQ and Stifel research.

PIPEs Much More Common in 2023 and 2024

Fraction of Global Biopharma Follow-On Offering Volume Done in the PIPE Format

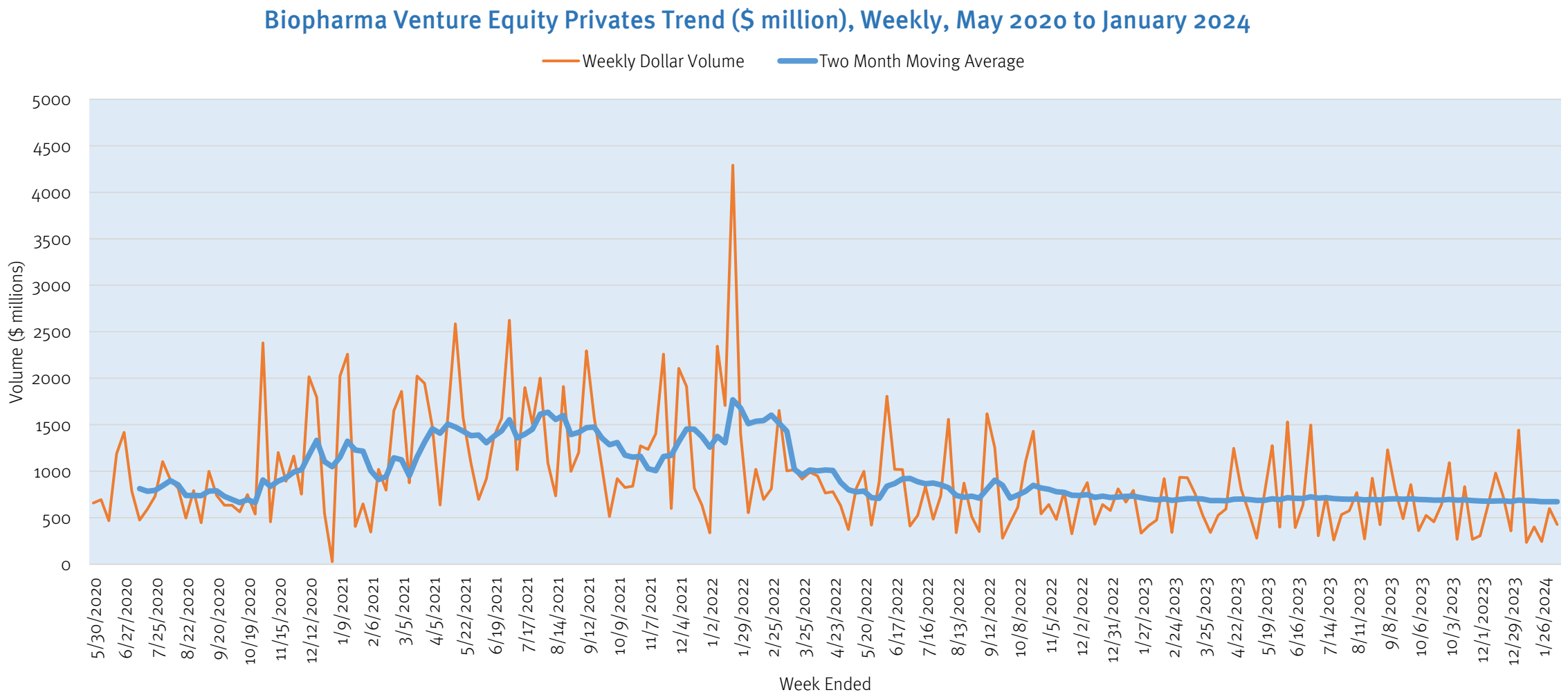
Roughly a quarter of follow-on offerings are done using private placements (PIPEs) these days. The trend to paper deals with PIPEs took off in 2023 and has persisted in 2024 despite improving market conditions.



Source: DealForma

Last Week's Venture Privates Volume Below Average

Last week saw a slow market for privates led by a $120 million issue from Neurona.



Source: Data from CapitalIQ, Crunchbase.

Neurona Therapeutics Raises $120M to Advance Groundbreaking Pipeline of Regenerative Cell Therapy Candidates for Chronic Neurological Disorders

San Francisco, CA, February 8, 2024 -- Neurona Therapeutics, a clinical-stage biotherapeutics company advancing regenerative cell therapy candidates for the treatment of neurological disorders, today announced the successful completion of a $120 million financing co-led by Viking Global Investors and Cormorant Asset Management with participation from new and existing investors, including The Column Group, LYFE Capital, Schroders Capital, Willett Advisors, Ysios Capital Partners, Euclidean Capital, SymBiosis, Alexandria Venture Investments, Berkeley Frontier Fund, Sphera Biotech Master Fund LP, Spur Capital Partners, UCB Ventures, and UC Investments. Proceeds from the financing will be used to advance the company's pipeline of wholly-owned, off-the-shelf cell therapies for multiple indications, including its lead investigational candidate, NRTX-1001. NRTX-1001 is being evaluated in an ongoing open-label, single-arm Phase I/II clinical trial for treatment of drug-resistant mesial temporal lobe epilepsy (MTLE) and has potential application in Alzheimer's disease and other disorders of the nervous system.

"We are excited to co-lead this financing with Viking and other committed investors to help advance Neurona's cell therapies to address unmet needs in chronic neurological disorders," said Raymond Kelleher, M.D., Ph.D., managing director of Cormorant and a neurologist at Massachusetts General Hospital, Harvard Medical School, who will be joining the Neurona Board of Directors. "Neurona has pioneered development of a fully-differentiated cell therapy for drug-resistant focal epilepsy that is designed to be disease-modifying, repairing the affected neural network, and is yielding very promising initial clinical data. As a neurologist, I am particularly encouraged by the data generated thus far, suggesting that NRTX-1001 has the potential to provide seizure control and preserve neurocognitive function, which would be a game-changer for the field."

Source: https://www.neuronatherapeutics.com/news/press-releases/020824/

"This financing is a testament to the hard work and dedication of the Neurona team, commitment of our collaborators, and encouraging preliminary data from the first patients in the ongoing clinical trial of NRTX-1001 cell therapy. We are grateful for the significant investment from this reputable syndicate of new and existing investors. It signifies the conviction that Neurona's cell therapies have the potential to transform the treatment of previously refractory, devastating neurological disorders."

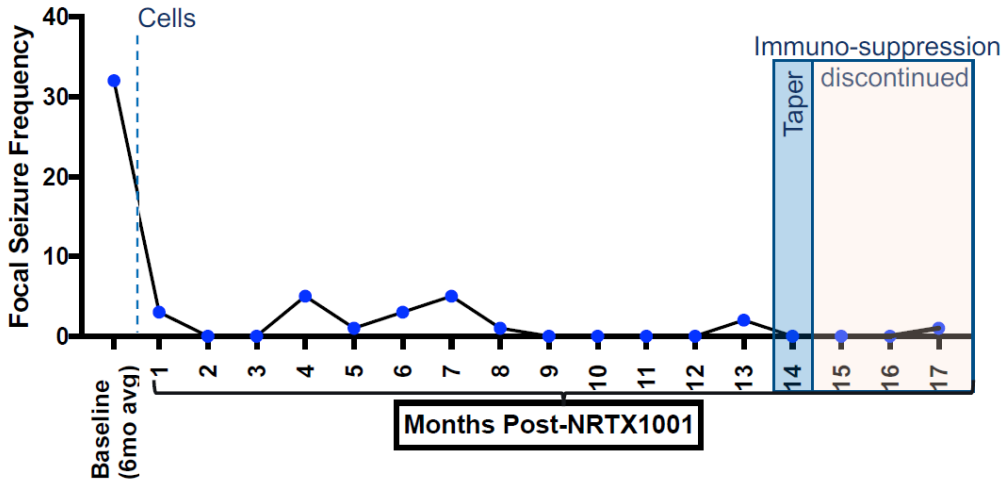
Cory Nicholas
Chief Executive Officer
Neurona Therapeutics

Neurona Has Shown Impressive Data in Control of Mesial Temporal Lobe Epilepsy with Cell Therapy

Seizure Counts after Single-dose Administration of NRTX-1001

Subject #1

All Seizure Events per Month

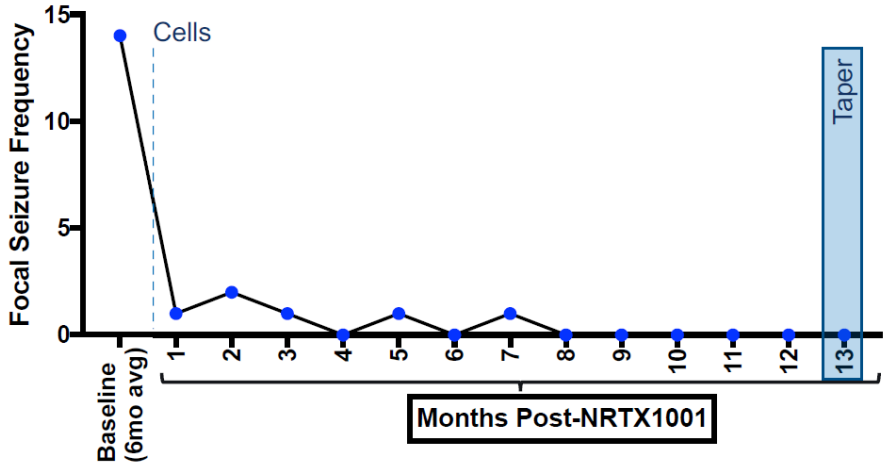


96% overall monthly seizure reduction post-NRTX1001:

- 96% reduction of focal aware
- 97% reduction of focal impaired awareness

Subject #2

All Seizure Events per Month



96% overall monthly seizure reduction post-NRTX1001:

- 100% reduction of focal aware
- 77% reduction of focal impaired awareness

Source: Neurona corporate presentation

Scion Life Sciences Launches with Oversubscribed $310 Million Fund to Create and Build Exceptional Biotech Companies

Press Release, Feb 7, 2024 (excerpt)

Scion Life Sciences, an affiliate of Petrichor, is a New York City-based life sciences venture capital firm dedicated to founding and building exceptional biotechnology companies that discover, develop, and seek to commercialize clinically transformational or curative new medicines, today announced the final close of its inaugural fund, which was oversubscribed with $310 million in capital commitments.

Scion was founded and is led by longstanding partners and experienced company-builders and investors Samuel W. Hall, PhD, and Aaron M. Kantoff, together with Tadd S. Wessel, founder, and Managing Partner of Petrichor. Scion's mission is to create medicines that cure or transform the clinical management of serious and life-threatening diseases and this overriding objective informs every aspect of the firm's strategy and approach. Scion forms and builds companies around translational innovations with the right bone structure to become clinically important medicines and is structured to support portfolio companies with the long-term capital and operational resources required to realize the mature clinical potential of the therapies they discover and develop. Scion is able to make initial investments as small as a few thousand dollars in early-stage incubation efforts but is resourced to cumulatively deploy $60 million or more over the life of each portfolio company investment and to support promising portfolio companies from pre-seed stage through to IPO and beyond.

Samuel Hall, PhD
Managing Partner

Aaron Kantoff
Managing Partner

Tadd Wessel
Managing Partner

Source: https://www.prnewswire.com/news-releases/scion-life-sciences-launches-with-oversubscribed-310-million-fund-to-create-and-build-exceptional-biotech-companies-302055568.html

Biotech Venture Firm Pitches Startups on Billboards

Brian Gormley, *Wall Street Journal*, Feb 5, 2024 (excerpt)

With startup investment sputtering and many entrepreneurs scrounging for cash, it would seem the last thing a venture-capital firm would need to do is advertise.

But that is what biotechnology investor Curie.Bio is doing—on orange billboards over highways running through Boston.

The Cambridge, Mass.-based firm has purchased space on billboards over Interstate 93 and the I-90 Massachusetts Turnpike. The ads went up in mid-January and will run for about two months, said Curie.Bio Chief Executive Zach Weinberg, adding that the firm might advertise on billboards elsewhere.

Venture capitalists typically get deals through personal networks. They prefer to be introduced to entrepreneurs over those making cold calls. Members of the Curie.Bio team source investments through their networks, but the firm also encourages startups to apply through its website.

Some applicants from the site have said they heard of Curie.Bio through the billboards, Weinberg said.

“We were not 100% sure exactly how effective they would be,” he said. “I would say, so far, so good.”

Curie.Bio, launched in 2022, aims to raise its profile among existing entrepreneurs and lure new ones who haven’t acted on their ideas. The firm placed the ads so biotech workers could see them while commuting. One billboard asks, “Have a therapeutic idea worthy of funding?”

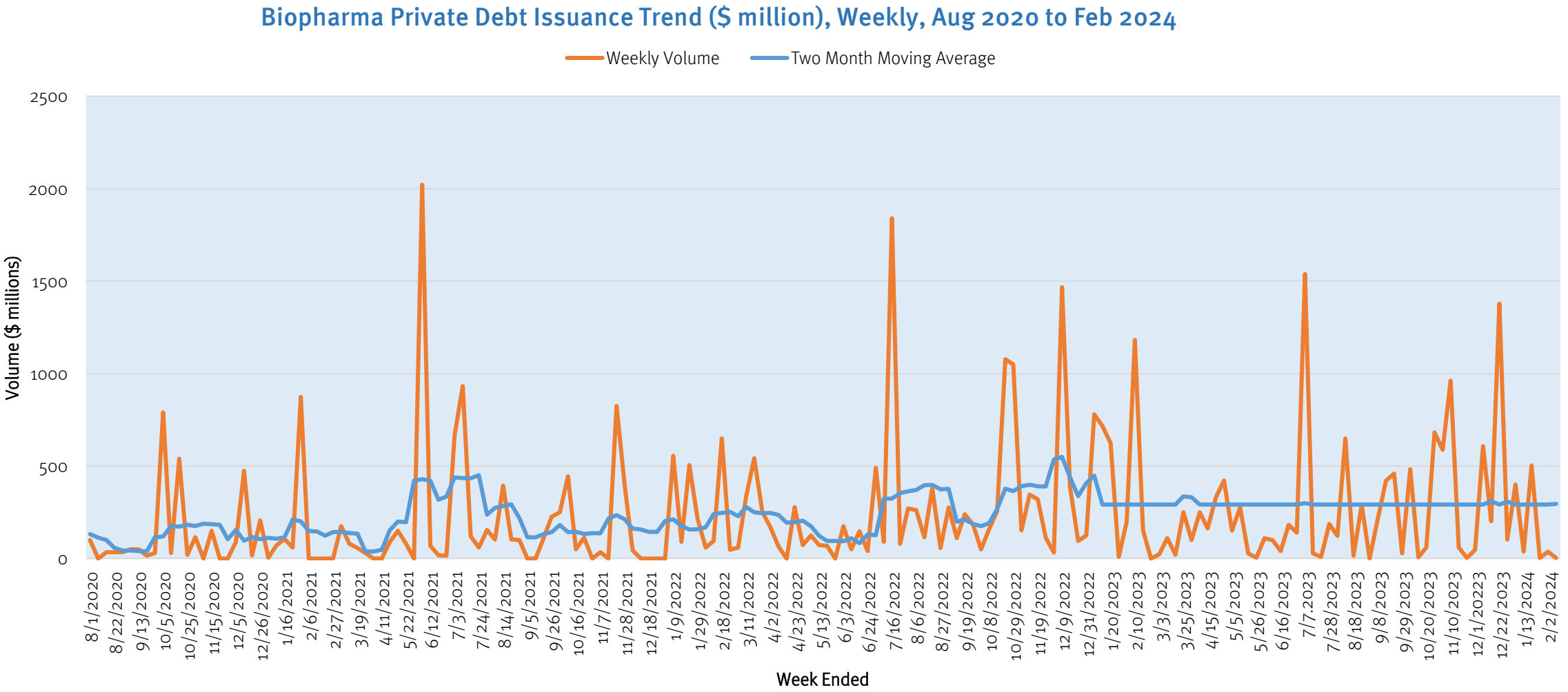
Wouldn’t resourceful entrepreneurs discover Curie.Bio on their own?

Not necessarily, said Weinberg, who co-founded oncology software company Flatiron Health—which was acquired in 2018 by life sciences company Roche—before co-founding Curie.Bio. Great biotech founders are usually excellent scientifically but aren’t always well-versed in other areas, such as who to call for funding, he said.

Source: https://www.wsj.com/articles/biotech-venture-firm-pitches-startups-on-billboards-d867d649

Biopharma Private Debt Placement Market Inactive

The debt privates market was quiet last week. The largest transaction was a $3mm debt deal. There has been little volume over the last three weeks.

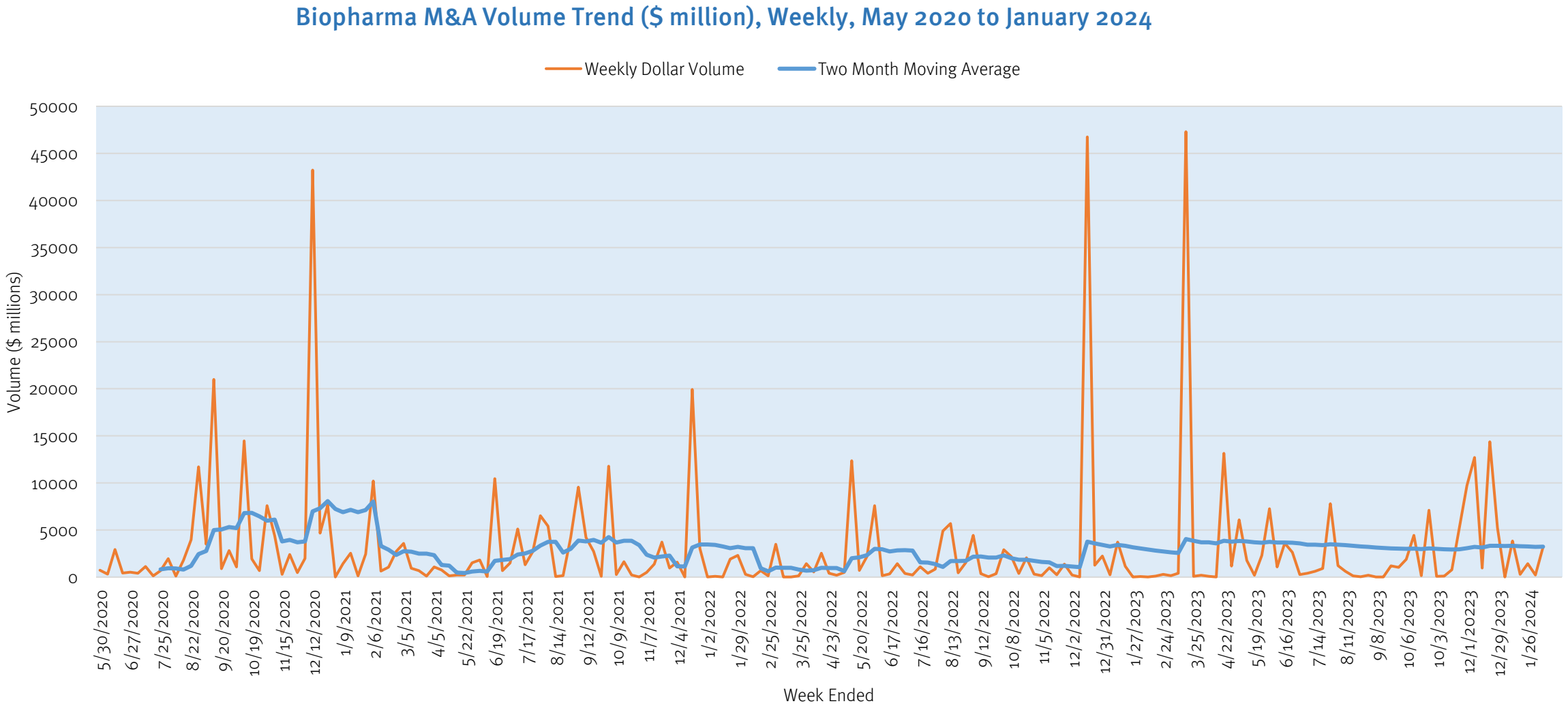


Source: Data from CapitalIQ, Crunchbase.

Deals Update

Last Week Saw $4.5 Billion in M&A / Asset Sale Volume

Last week saw Novartis buy Morphosys for €2.7 billion and Merck buy Elanco's Aqua business for $1.3 billion.



Source: S&P, CapitalIQ

Novartis to Strengthen Oncology Pipeline with Agreement to Acquire MorphoSys AG for €2.7bn

Basel – Feb 5, 2024-- Novartis today announced that it has entered into an agreement to make a voluntary public takeover offer to acquire MorphoSys AG (FSE: MOR; NASDAQ: MOR), a Germany-based, global biopharmaceutical company developing innovative medicines in oncology. The acquisition, which is subject to customary closing conditions, including a minimum acceptance threshold of 65% of outstanding shares tendered in the takeover offer and regulatory approvals, further expands and complements Novartis pipeline in oncology, one of its priority therapeutic areas, while also enhancing Novartis global footprint in hematology.

Upon completion of the acquisition, Novartis will own pelabresib (CPI-0610), a novel and potentially practice changing treatment option with a well-tolerated safety profile provided in combination with ruxolitinib for patients with myelofibrosis (MF). It will also include tulmimetostat (CPI-0209), an early-stage investigational dual inhibitor of enhancer of zeste homolog 1 and 2 (EZH1 and EZH2) proteins currently being tested in patients with solid tumors or lymphomas.

Pelabresib in combination with ruxolitinib recently met its primary endpoint of spleen volume reduction in the Phase 3 MANIFEST-2 study in JAK inhibitor-naive MF patients. The combination also demonstrated favorable trends in symptom improvement as evidenced by key secondary endpoints of absolute and 50% change in total symptom score (TSS) at week 24 compared to baseline. All four clinical hallmarks of disease in myelofibrosis – splenomegaly, disease-associated symptoms, anemia and bone marrow fibrosis – were improved with the pelabresib and ruxolitinib combination. In the earlier Phase 2 MANIFEST trial, the third arm of the study with a patient population comparable to MANIFEST-2, showed durable improvements in both spleen volume and total symptom score up to week 602. Regulatory filing with the U.S. FDA is planned for the second half of 2024.

“We are excited about the opportunity of bringing pelabresib, a potential next-generation treatment combined with ruxolitinib, to people living with myelofibrosis, a rare and debilitating form of blood cancer,” said Shreeram Aradhye, M.D., President, Development and Chief Medical Officer of Novartis. “With the planned acquisition of MorphoSys, we aim to further strengthen our leading pipeline and portfolio in oncology, adding to our capabilities and expertise. Building on our long-standing development partnership with MorphoSys, we look forward to continuing our work together to realize the full impact and value of their investigational medicines for patients with unmet needs.”

Source: https://www.novartis.com/news/media-releases/novartis-strengthen-oncology-pipeline-agreement-acquire-morphosys-ag-eur-68-share-or-aggregate-eur-27bn-cash

Merck Animal Health to Buy Elanco's Aqua Business for $1.3Bn

Rahway – Feb 5, 2024-- Merck Animal Health, known as MSD Animal Health outside of the United States and Canada, a division of Merck & Co., Inc., Rahway, N.J., USA (NYSE:MRK), today announced that it has signed a definitive agreement to acquire the aqua business of Elanco Animal Health Incorporated (NYSE: ELAN) for $1.3 billion in cash, consisting of an innovative portfolio of medicines and vaccines, nutritionals and supplements for aquatic species; two related aqua manufacturing facilities in Canada and Vietnam; as well as a research facility in Chile. The acquisition is expected to be completed by mid-year 2024, subject to approvals from regulatory authorities and other customary closing conditions.

Upon closing, the acquisition will broaden Merck Animal Health's aqua portfolio with products, such as CLYNAV®, a new generation DNA-based vaccine that protects Atlantic salmon against pancreas disease, and IMVIXA®, an anti-parasitic sea lice treatment. This acquisition also brings a portfolio of water treatment products for warm water production, complementing Merck Animal Health's warm water vaccine portfolio. In addition to these products, the DNA-based vaccine technology that is a part of the business has the potential to accelerate the development of novel vaccines to address the unmet needs of the aqua industry.

"We are excited for the acquisition of Elanco's aqua products, solutions as well as the capabilities and expertise the team brings to our business," said Rick DeLuca, president, Merck Animal Health. "We believe this acquisition, coupled with our commercial and scientific prowess, will deliver enhanced benefits for our aqua customers. The addition of this innovative portfolio of cold water and warm water aqua products across vaccines, anti-parasitic treatments, water supplements and nutrition, will establish Merck Animal Health as a leader in aqua."

Elanco Animal Health President and CEO Jeff Simmons said, "Following a robust process over the last year, Merck Animal Health emerged as the right strategic buyer for the aquaculture business. I am confident they will continue to deliver value to the aqua customers that rely on these products and create opportunities for our team to continue to grow. We are deeply grateful to our aqua organization's dedication to delivering for our customers and to our bigger purpose of enriching lives with animal protein."

MERCK Animal Health

Merck picked up a substantial aquaculture business through the purchase of Schering Plough. Last week it took a decisive step to grow this business by buying Elanco's Aqua business.

Source: https://www.merck.com/news/merck-animal-health-to-acquire-elancos-aqua-business/

Chanelle Pharma of Ireland Bought for €300 Million

Joseph Keenan, *FiercePharma*, Feb 8, 2024 (excerpt)

Human and animal generics manufacturer Chanelle Pharma, the largest domestic drugmaker in Ireland, was acquired by U.K. private equity firm Exponent.

Although financial details of the deal weren't disclosed, market analysts have previously speculated the maker of both generic human and animal drugs would likely reap around 300 million euros ($323 million), according to the Irish Independent.

Chanelle, which is located near Galway, Ireland, was founded almost 40 years ago and employs more than 700 workers in Ireland, the U.K., Europe and Jordan, according to a Feb. 7 press release.

The company offers services such as R&D and the registration and production of generic human and veterinary pharmaceuticals.

“The business has established itself as a leading pharmaceutical manufacturer of both veterinary and medical products with an extensive portfolio of licenses,” James Gunton, a partner at Exponent, said in the release. “We see tremendous opportunity in the development pipeline and look forward to bringing new products to market, as well as continuing to invest in Research and Development in the years to come.”

Source: https://www.fiercepharma.com/manufacturing/irelands-chanelle-pharma-acquired-private-equity-firm-estimated-eu300m

A $250 Million Pharma Sale Last Week in China

Feb 7, 2024 (Reuters) - Hong Kong-listed Sino Biopharmaceutical (1177.HK), opens new tab will sell a 67% stake in unit CP Pharmaceutical (Qingdao) for 1.82 billion yuan ($253.28 million) to entities controlled by state-owned Guoxin Group, the company said late on Tuesday.

Sino Biopharmaceutical will keep a 26% stake in CP Qingdao after the disposal, the pharmaceutical conglomerate said in a filing to the Hong Kong Stock Exchange. CP Qingdao, established in China, is mainly involved in research and development, production and sale of osteoporosis medicines and marine pharmaceuticals.

Through the deal, Guoxin Group plans to enter the life and health industry characterized with marine biological pharmaceuticals, Sino Biopharmaceutical said.

CP Qingdao Site in Shandong Province

Source: https://www.reuters.com/markets/deals/sino-biopharmaceutical-divest-67-stake-unit-cp-qingdao-253-mln-2024-02-07/

I-Mab Using an M&A Structure to Redomicile in the U.S.

I-Mab Signs Agreement to Divest its Assets and Business Operations in China

ROCKVILLE, Md., Feb. 7, 2024 /PRNewswire/- I-Mab (the "Company") (NASDAQ: IMAB), a global biotech company exclusively focused on bringing highly differentiated immunotherapies and biologics for cancer treatment to patients around the world, today announced that as part of its strategy to become a U.S.-based biotech, its Chinese subsidiaries have entered into definitive agreements with I-Mab Biopharma (Hangzhou) Co., Ltd. (the "Hangzhou Company"), an unconsolidated affiliate of the Company, and a group of China-based investors to divest the Company's assets and business operations in China.

"This agreement to divest our operations in China marks an important milestone for I-Mab in bringing a greater focus on the U.S. and ex-China markets," said Raj Kannan, Director and Chief Executive Officer of I-Mab. "Importantly, we believe that this transaction allows us to reduce significant operational costs and enables us to reallocate our capital on current key priorities and new potential opportunities in further strengthening our portfolio while maintaining a strong balance sheet."

Pursuant to the definitive agreements, the Company will transfer 100% of the outstanding equity interest in I-Mab Biopharma Co., Ltd. ("I-Mab Shanghai"), a wholly owned subsidiary of the Company that operates the Company's business in China, on a cash-free and debt-free basis, to the Hangzhou Company for an aggregate consideration of the RMB equivalent of up to US$80 million, contingent on the Hangzhou Company group's achievement of certain future regulatory and sales-based milestone events. The Company also retains a right of first negotiation outside of Greater China related to three future investigational new drug candidates.

Source: https://ir.i-mabbiopharma.com/news-releases/news-release-details/i-mab-signs-agreement-divest-its-assets-and-business-operations

Big Pharma Targets Smaller Companies With Megadeals Out of Favor

Ashleigh Furlong and Angela Feliciano, *Bloomberg*, Feb 6, 2024 (excerpt)

Pharmaceutical companies are racing to snap up innovative biotechs with a flurry of bolt-on purchases, shying away from the megadeals that once marked the sector as they attempt to fill looming gaps in their pipelines.

Novartis AG agreed to buy MorphoSys AG on Monday to gain an experimental medicine for blood cancer, which fits with its own. The deal is one of six worth over $1 billion that have been announced this year alone. Others include Sanofi's planned purchase of the US biotech Inhibrx Inc. and Johnson & Johnson's agreement for Ambrx Biopharma Inc.

The acquisitions often target a specific drug that either allows the company to enter into a new disease area or significantly bolster an existing focus — as was seen in GSK Plc's offer for asthma-drug maker Aiolos Bio Inc.

"We're seeing bolt-on acquisitions which are more product-centric," said Wouter Joustra, general partner at venture capital firm Forbion, one of the founding investors in Aiolos. The acquisitions often relate to products that are late stage, as companies "look to plug certain holes in revenue projections due to losses of patent exclusivity," he said.

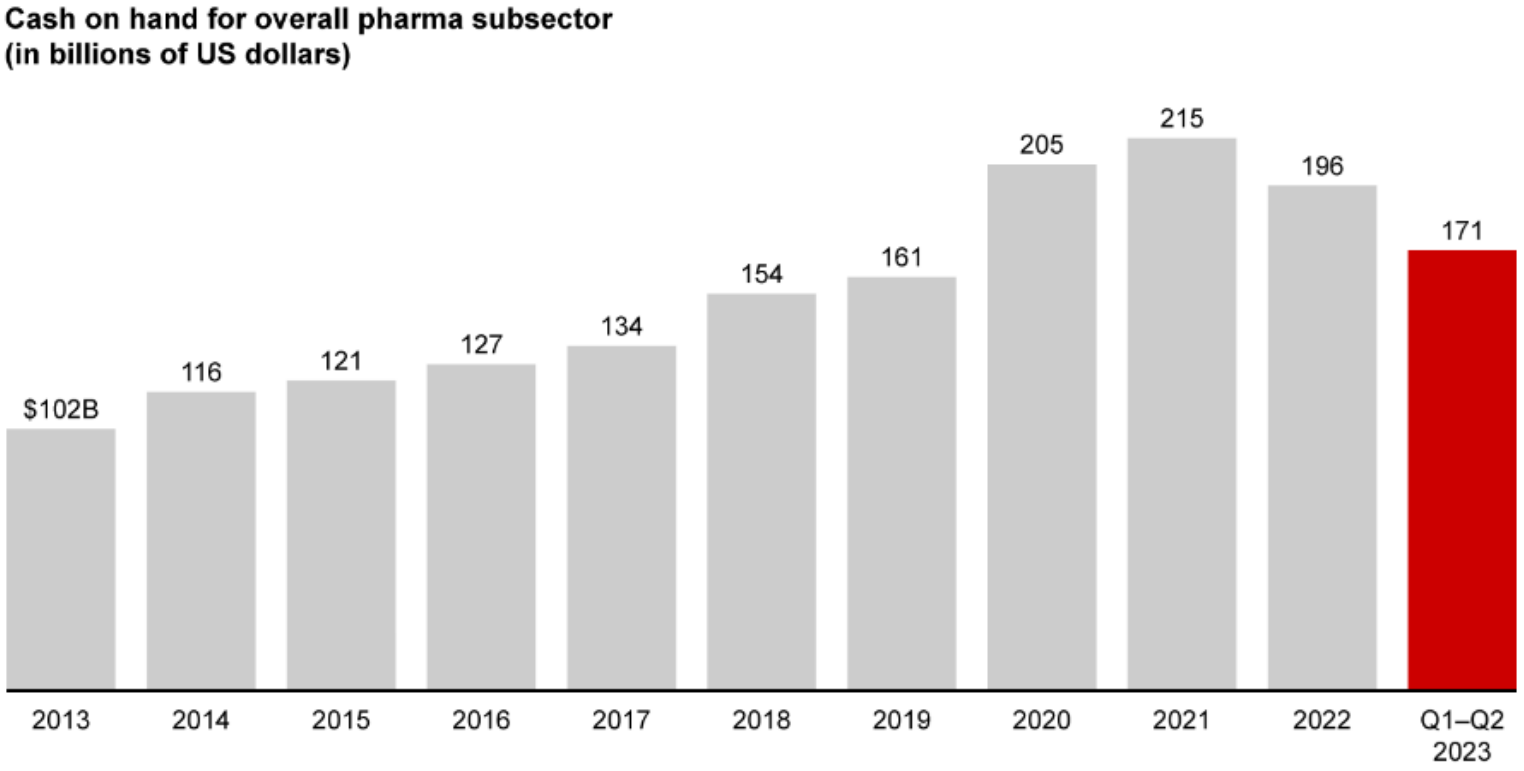
Big Pharma Targets Smaller Companies for the Past 12 Months

Company	Deal Count	Average (in USD)
Eli Lilly & Co	7	1.5B
Novartis	6	1.1B
Novo Nordisk	6	430M
Bristol-Myers Squibb	5	4.4B
Roche Holding	5	2.5B
Sanofi	5	1.7B

Source: https://www.bloomberg.com/news/articles/2024-02-06/big-pharma-targets-one-hit-wonders-with-megadeals-out-of-favor

Big Pharma Cash Balances Down Somewhat

Bain Report, "M&A in Healthcare and Life Sciences: A Shrinking Margin for Error in Deals," Jan 31, 2024 (excerpt)



Sources: S&P Capital IQ; Crunchbase

2023 demonstrated that despite high interest rates, regulatory scrutiny, and macroeconomic uncertainty, the healthcare and life sciences industry can't keep M&A on the back burner for too long. And we anticipate this trend to continue. The industry is sitting on high levels of cash—$171 billion across pharma companies (see Figure 1). Also, top-line growth has a disproportionate impact on total shareholder returns (TSRs) in this industry.

Source: https://www.bain.com/insights/healthcare-and-life-sciences-m-and-a-report-2024

Priority Review Voucher Market Remains Active

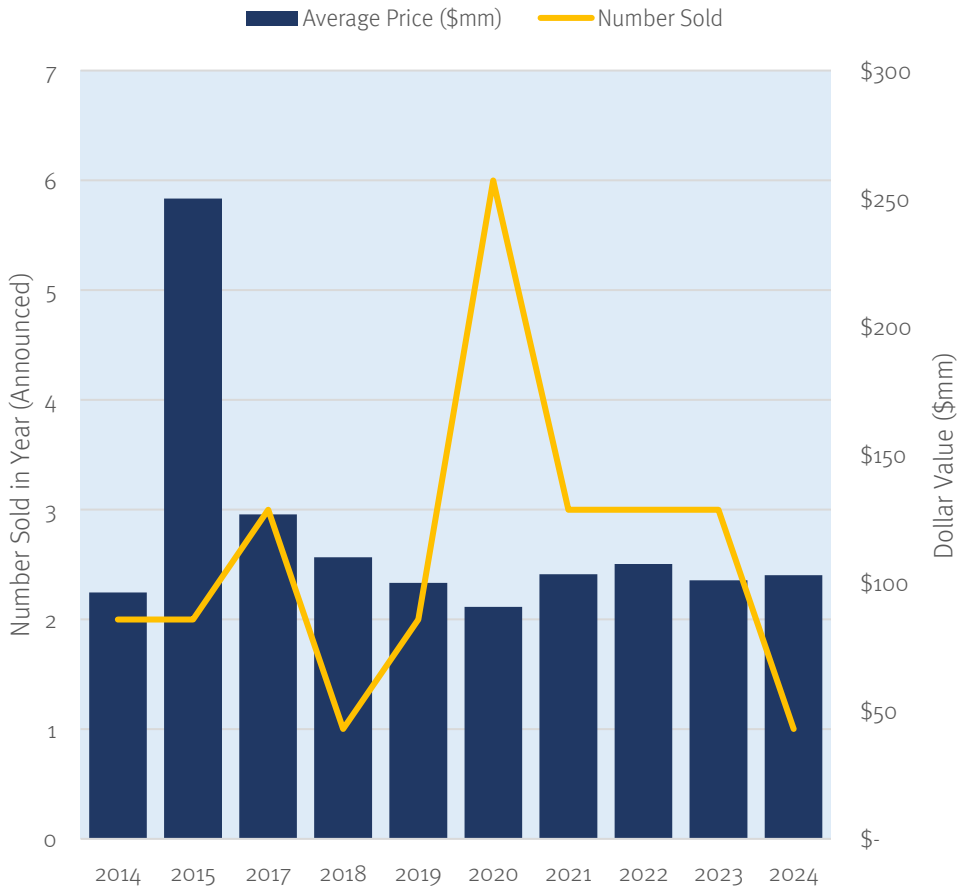
Valneva Announces Sale of Priority Review Voucher for $103 Million

Saint-Herblain (France), February 5, 2024 – Valneva SE (Nasdaq: VALN; Euronext Paris: VLA), a specialty vaccine company, today announced it sold the Priority Review Voucher (PRV) it received from the U.S. Food and Drug Administration (FDA) for $103 million (€95 million).

The Company was awarded a tropical disease PRV in November 2023 following U.S. FDA approval of IXCHIQ®, Valneva's single-dose, live-attenuated vaccine indicated for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 18 years of age and older who are at increased risk of exposure to CHIKV. With this approval, IXCHIQ® became the world's first licensed chikungunya vaccine available to address this unmet medical need.

Valneva will invest proceeds from the sale of the PRV into its R&D projects, including the co-development of its Phase 3 vaccine candidate against Lyme disease, additional clinical trials for its chikungunya vaccine IXCHIQ® and the expansion of the Company's clinical pipeline.

Average Price of a Priority Review Voucher ($mm), 2014 to 2024



Stifel has been active in brokering PRV sales. We have advised on three such transactions. Interestingly, none of the deals we have worked have had announced prices and, thus, do not appear on the chart at left.

Put another way, there is a significant part of this market that remains confidential as buyers and sellers prefer not to announce their identities and intentions.

Sources: https://valneva.com/press-release/valneva-announces-sale-of-priority-review-voucher-for-103-million/. Data are from Stifel's internal database and DealForma.

BioNTech / Autolus Collaboration

Strategic alliance leverages manufacturing and commercial infrastructure as well as technology with the aim to advance both companies' autologous CAR-T programs towards market, pending market authorization

MAINZ, Germany and LONDON, Feb. 08, 2024 (GLOBE NEWSWIRE) BioNTech SE (Nasdaq: BNTX, "BioNTech"), a next-generation immunotherapy company pioneering novel therapies for cancer and other serious diseases, and Autolus Therapeutics plc (Nasdaq: AUTL, "Autolus"), a clinical-stage biopharmaceutical company developing next-generation programmed T cell therapies, today announced a strategic collaboration aimed at advancing both companies' autologous CAR-T programs towards commercialization, pending regulatory authorizations. In connection with the strategic collaboration, the companies entered into a license and option agreement and a securities purchase agreement.

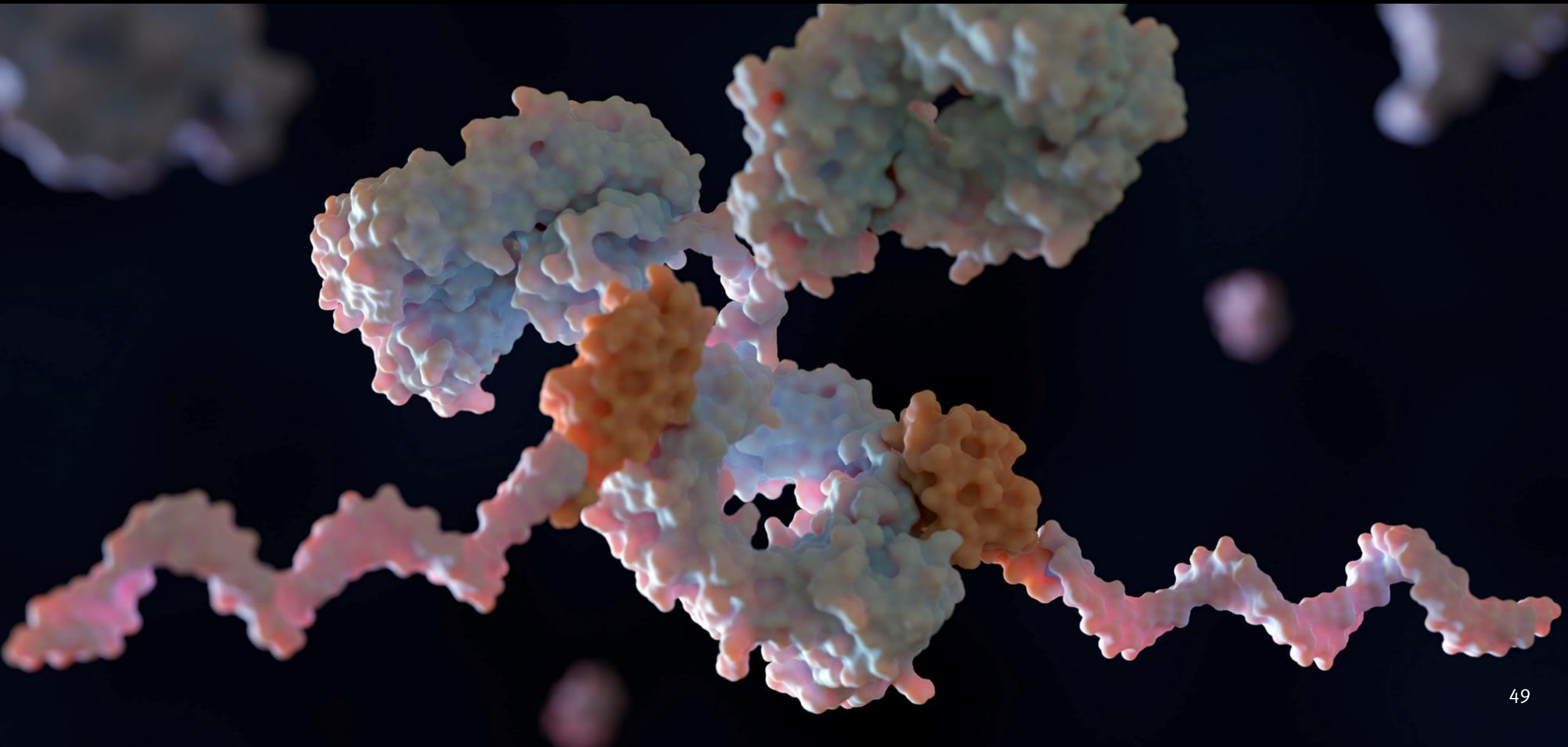
"The collaboration with Autolus enables us to expand our BNT211 program into trials for multiple cancer indications in a cost-efficient way. Autolus' state-of-the-art manufacturing facilities' set-up for clinical and commercial supply will enhance our own capacities in addition to our existing U.S. supply network and the ongoing expansion of our site in Gaithersburg, Maryland," said Prof. Ugur Sahin, M.D., CEO and Co-Founder of BioNTech. "Furthermore, this collaboration grants us access to Autolus' precise cell targeting tools to further support BioNTech's development of in vivo cell therapy and antibody-drug conjugate candidates." "We see a remarkable opportunity to leverage our core capabilities, accelerate pipeline programs, realize cost-efficiencies and expand opportunities beyond autologous cell therapies," said Dr. Christian Itin, Chief Executive Officer of Autolus. "We look forward to investing a portion of the capital raised on delivering on obe-cel's path in adult acute lymphoblastic leukaemia, potentially offering another treatment option for patients where there is still an unmet medical need. This collaboration creates a path for accelerating our respective oncology pipeline programs and broadening the use of Autolus' technology outside of autologous cell therapy applications." BioNTech has agreed to purchase $200 million of Autolus' American Depositary Shares in a private placement. BioNTech will have a right to appoint a director to the Board of Autolus.

Under the terms of the license and option agreement, BioNTech will make a cash payment of $50 million and is granted the following rights in exchange:

- BioNTech is eligible to receive an up to mid-single digit royalty on obe-cel net sales. Autolus will retain full rights to and control of the development and commercialization of obe-cel.
- BioNTech has the option to access Autolus' commercial and clinical site network, manufacturing capacities in the United Kingdom and commercial supply infrastructure in a cost-efficient set-up in order to accelerate the development of BNT211 in additional CLDN6+ tumor types. BioNTech plans to have 10 or more ongoing potentially registrational clinical trials in the pipeline by the end of 2024, including its fully owned CLDN6 CAR-T program BNT211 in relapsed or refractory germ cell tumors.

Source: https://autolus.gcs-web.com/news-releases/news-release-details/biontech-and-autolus-announce-strategic-car-t-cell-therapy

Industry News



Big Pharma CEOs Grilled on Capitol Hill Over Drug Prices

BMS CEO Chris Boerner Defends Pharma pricing practices on Capitol Hill. J&J indicated it gets 30% of Stelara price while Merck indicated it gets only 10% of Januvia list price.

Max Zahn, *ABC News*, Feb 8, 2024 (excerpt)

Senators grilled chief executives from three top pharmaceutical companies over prescription drug prices during an hourslong committee hearing Thursday on Capitol Hill. Members of both major political parties bemoaned drug prices they consider too high, but liberals and conservatives revealed differences in their views of the role played by the pharmaceutical companies.

The three CEOs -- Robert M. Davis of Merck, Joaquin Duato of Johnson & Johnson and Christopher Boerner of Bristol Myers Squibb -- said drug prices account for the considerable cost of research and development, as well as the ready availability of treatments in the United States.

Here are the biggest takeaways from the CEOs' testimony before the Senate Committee on Health, Education, Labor and Pensions:

Liberals confronted the pharmaceutical CEOs over prices, executive compensation

The testiest moments of the hearing came when liberal lawmakers challenged the pharmaceutical executives over what the senators said they viewed as high prices, invoking anecdotes of patients forced to choose between purchasing medicine or paying for essentials such as rent or food.

“We have to pay dividends because it’s the only way the company can remain operational and sustainable,” Duato added. “Otherwise, if we’re not operational and sustainable, we are not able to fulfill our mission of developing medicines for patients and making them affordable.”

Republicans shared the concern about prices but defended drugmakers

“Let’s just be clear, everybody in this panel cares about the high cost of prescription drugs and wants to work on real solutions to address this,” Republican Sen. Bill Cassidy of Louisiana said. “I don’t want the committee to delve into a CEO whack-a-mole that ends up with no serious legislation as a result.”

Senators grilled the CEOs on why the same drugs cost more in the U.S. than in other countries. Liberal lawmakers repeatedly criticized the relatively high cost of drugs in the U.S. compared to other wealthy countries such as Canada, France and Japan.

Pharmaceutical CEOs pointed to high research and development costs, middlemen

For their part, the chief executives acknowledged the elevated price of drugs in the U.S.

However, the CEOs placed the blame on cost-intensive research and development, as well as industry middlemen known as Pharmacy Benefit Managers, or PBMs. “Right now, we have nearly 20,000 researchers seeking breakthrough treatments,” said Davis, of Merck. The company has invested almost $160 billion in research and development since 2010, including $30 billion in 2023, Davis said.

All three CEOs aimed their ire at PBMs, third-party administrators hired by large employers and other institutions to set prices in negotiations with drugmakers.

Source: https://abcnews.go.com/Business/big-pharma-ceos-grilled-capitol-hill-takeaways/story?id=107057364

Are We Valuing Prescription Drugs Appropriately?

Peter Neumann and Joshua Cohen, Tufts University, *Health Affairs*, Feb 5, 2024 (excerpt)

With some new drug therapies priced like high-end condos, the question of whether prescription drugs are undervalued may seem misplaced. Still, there are compelling reasons to believe that the value of many drugs—and health care innovations broadly—is underestimated in conventional economic assessments. There are also important caveats to these arguments. These assessments matter because they seek to place a monetary value on a drug's therapeutic benefit and can inform negotiations over its price, including Medicare's drug price negotiations under the Inflation Reduction Act. Pricing drugs too high can divert health care resources away from better uses elsewhere. Pricing them too low can discourage worthwhile innovation.

We argue that methods for valuing drug therapies need updating. Such improvements would make the estimated value of some, although not all, prescription drugs more favorable in economic assessments. In the long run, these improvements will have the effect of promoting the continued development of drugs that produce health benefits that are worth more than what society must spend to invent those drugs in the first place.

Limitations Of Current Economic Analyses

One reason economic analyses may yield estimates that are too low is that they ignore the downstream declines in drug prices that occur when competitors enter the market and especially with the introduction of generic or biosimilar competition. Omitting such projections presumes that launch prices continue forever, akin to estimating the long-run cost of owning a house by pretending that its mortgage payments are everlasting.

Erroneously assuming that launch prices persist indefinitely mistakenly implies the need for lower launch prices to ensure that the aggregate amount paid for that drug over the long term is not too high. When combined with price declines that typically follow loss of market exclusivity, the lower recommended launch prices yield average drug life-cycle prices that are too low—that is, prices that understate the value of the drug's benefit. More realistic assumptions about drug price declines following the loss of market exclusivity would lead to higher recommended launch prices.

Consensus panels have endorsed the idea of accounting for life-cycle drug pricing, but most cost-effectiveness analyses exclude such assumptions because of uncertainty about the timing and consequences of generic entry, or presumably because such assumptions would support even higher drug prices. But while the path of genericization may be unpredictable, assuming brand-name prices will remain unchanged misrepresents—and often overstates—a drug's long-term costs.

Another reason drugs may be undervalued is that analyses use too high a discount rate when incorporating distant future costs and benefits. Discounting future costs and benefits, which scales down their value, is a long-standing and common practice in economics that recognizes that people tend to care more about events that happen sooner rather than later. However, an overstated discount rate reduces the apparent value of health benefits accrued in the distant future by too much

Traditional assessments also tend to exclude "spillover" effects conferred by drugs. An effective therapy also benefits the recipient's family and friends and can enhance worker productivity. However, most analyses ignore such consequences, either because the empirical basis is lacking or because health payers have little incentive to consider these factors in their budgets.

Finally, traditional metrics for valuing health benefits (for example, the quality-adjusted life-year (QALY) gained), while useful as benchmarks, do not adequately reflect people's preferences for health improvements. QALYs assume, for example, that people value a unit gain in health equally regardless of their starting point.

Source: https://www.healthaffairs.org/content/forefront/we-valuing-prescription-drugs-appropriately

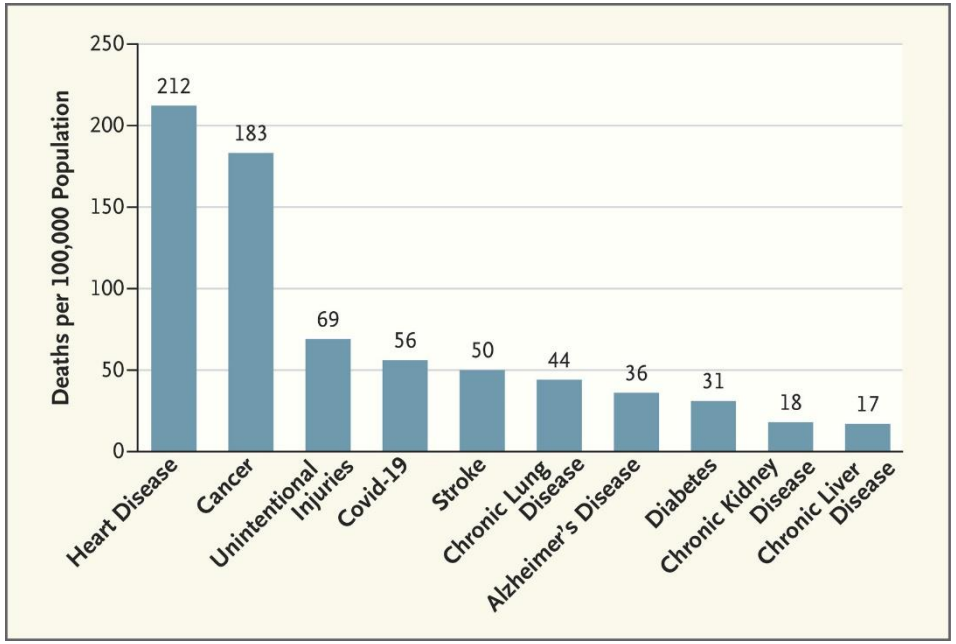
Addressing the Challenge of Common Chronic Diseases — A View from the FDA

Haider J. Warraich, M.D., Hilary D. Marston, M.D., M.P.H., and Robert M. Califf, M.D., *NEJM*, Feb 8, 2023 (excerpt)

Of the 10 most common causes of death in the United States, 7 are chronic diseases: heart disease, cancer, Alzheimer's disease, diabetes, and chronic lung, liver, and kidney diseases (see graph). These common chronic diseases are partly responsible for the recent startling decrease in life expectancy in the United States. Such diseases seldom occur in isolation: 58% of U.S. adults have two or more chronic diseases. Even among younger adults (those 20 to 29 years of age), more than one in five have multiple chronic diseases.

The position of the Food and Drug Administration (FDA) as a regulatory, scientific, and public health agency grants us opportunities to support the development of effective and accessible interventions for preventing and treating common chronic diseases and to promote the appropriate use of approved therapies. The FDA's remit spans drugs, biologic products, medical devices, food, and tobacco products. With collaboration among stakeholders, we can improve the way in which evidence is generated and interventions are developed and implemented to help address common chronic diseases.

One strategy involves transforming evidence-generation methods. The nature of common chronic diseases may require modification of the approaches used for studying the safety, efficacy, and clinical usefulness of treatments. These diseases often require lifelong treatment, which means that benefits may accrue or adverse events may occur over periods that exceed the length of traditional randomized, controlled trials. Lower event rates stemming from improvements in usual care may necessitate larger (and therefore more costly) trials or greater reliance on biomarkers and surrogate end points for assessing efficacy. To make randomized, controlled trials more generalizable, overly restrictive inclusion criteria should be avoided and innovative approaches to conducting research in populations that are more representative of the patients in whom therapies will be used should be developed. Pragmatic trials (including those incorporating decentralized elements, such as partnerships with local clinicians to perform routine trial-related procedures) may enable the study of larger, more representative populations that are tracked for longer periods at lower cost. These methods could provide a pathway for market entry for new products while preserving the important benefits of randomization for drawing causal inferences.



Source: https://www.nejm.org/doi/10.1056/NEJMp2313217

Major Change in European View of Gene Edited Agricultural Products

European Parliament Votes to Support Proposal for the Regulation of New Genomic Techniques

Cibus - Press release – Feb 7, 2024

The EU Parliament met 5-8 February in Strasbourg and, following a debate on Tuesday Feb 6th, the Parliament voted in favour of the NGT legislation the following day. Parliamentary negotiators now have a mandate to engage in 3-way discussions with the EU Council and the European Commission to agree on the final text of the legislation prior to formal adoption.

The legislation is part of a package of measures designed to ensure the sustainable use of natural resources and to strengthen the resilience of EU food systems. It describes a category of NGTs, classed as targeted mutagenesis and cisgenesis, producing modifications that could be obtained in nature or by conventional breeding. These are determined to be 'Conventional-like' and, once verified, would be regulated in the same way as conventional varieties.

In addition to enabling EU growers to benefit from improved varieties, the proposed regulation would also help facilitate international trade by bringing EU policy closer to that of trading partners in North and South America, UK, India, Australia, and Japan.

MEP and rapporteur Jessica Polfjärd said of the vote, "Historic step forward: the European Parliament supports my proposal for sustainable use of new genomic techniques (NGT). A game changer for sustainable agriculture and a clear signal that we embrace science and support our farmers."

"The parliamentary vote is a significant milestone in the EU legislative process providing a welcome boost to innovators particularly in academia and small and mid-sized enterprises developing NGT products that can contribute to a sustainable EU agri-food system," commented Tony Moran, Senior Vice President of International Development and Government Affairs at Cibus.

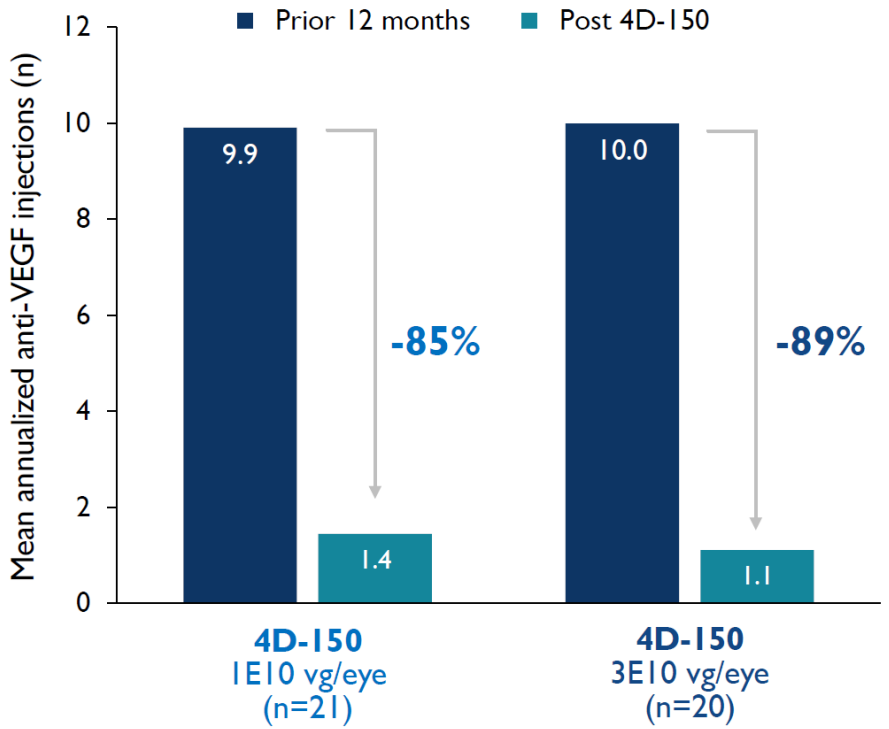
"This is a pivotal moment in the development of a sustainable global food supply system. The promise of gene editing is its ability to address major challenges of farming such as disease, insects and a globally changing environment with greater speed and precision with traits that are indistinguishable from conventional breeding. This vote continues a global alignment to regulate certain gene editing applications as conventional and to enable this revolution to help farmers," stated Rory Riggs CEO of Cibus.

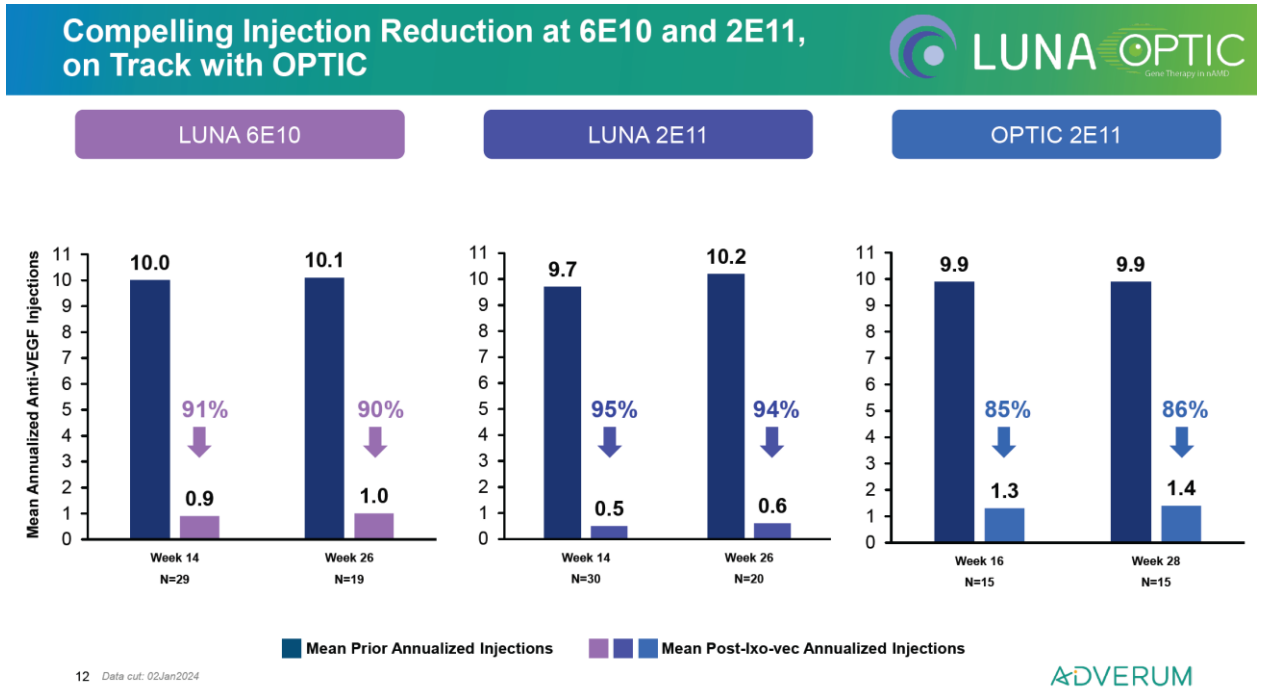
Source: https://investor.cibus.com/news-releases/news-release-details/european-parliament-votes-support-proposal-regulation-new

A Big Week for Gene Therapy for the Eye

4DMT ADVERUM

Gene Therapy for AMD Works Well for Both 4D Molecular and Adverum. Some Questions Remain But On Track





Novo Buys Three Plants for $11 Billion to Boost Wegovy Output

By Naomi Kresge and Christian Wienberg, *Bloomberg*, Feb 5, 2024 (excerpt)

Novo Nordisk A/S struck a deal that will allow the Danish drugmaker to respond to surging demand for its weight-loss drug Wegovy and diabetes treatment Ozempic.

Novo's biggest shareholder is buying Catalent Inc., one of the world's largest drug-manufacturing companies, for $16.5 billion, including debt. In a three-way arrangement, Novo will pay the holder $11 billion to get three of Catalent's factories acquired in the deal.

Novo is racing to build a more robust supply chain after facing shortages of both its Wegovy and Ozempic shots. Competition is heating up between Novo and Eli Lilly & Co., whose recently approved obesity shot Zepbound is predicted to become the best-selling drug in history. In patient trials, Lilly's drug led to more weight loss than anything Novo has put out to date.

The sale of Catalent has the backing of Elliott Investment Management, the activist investor, which has a stake in the US company. The agreement is worth $63.50 per share in cash, a 17% premium to Catalent's Friday close, the companies said Monday in a statement. Catalent's shares were trading around $140 apiece in September 2021 before a series of manufacturing issues with products it was making for several drugmakers, including Moderna Inc.'s Covid-19 vaccine and one of Regeneron Inc.'s best-selling drugs.

Production Woes

The acquisition of three factories in Italy, Belgium and Indiana isn't an immediate fix for Novo's production problems. It will gradually increase manufacturing capacity from 2026 and onward, according to a spokeswoman. Production has been a thorn in the Danish drugmaker's side even as it profits from the new class of obesity drugs it helped pioneer.

Source: https://www.bloomberg.com/news/articles/2024-02-05/novo-nordisk-spends-11-billion-on-meeting-obesity-drug-demand

Review

A break in mitochondrial endosymbiosis as a basis for inflammatory diseases

https://doi.org/10.1038/s41586-023-06866-z

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Accepted: 14 November 2023

Published online: 7 February 2024

Michael P. Murphy[1,2] & Luke A. J. O'Neill[3]

Mitochondria retain bacterial traits due to their endosymbiotic origin, but host cells do not recognize them as foreign because the organelles are sequestered. However, the regulated release of mitochondrial factors into the cytosol can trigger cell death, innate immunity and inflammation. This selective breakdown in the 2-billion-year-old endosymbiotic relationship enables mitochondria to act as intracellular signalling hubs. Mitochondrial signals include proteins, nucleic acids, phospholipids, metabolites and reactive oxygen species, which have many modes of release from mitochondria, and of decoding in the cytosol and nucleus. Because these mitochondrial signals probably contribute to the homeostatic role of inflammation, dysregulation of these processes may lead to autoimmune and inflammatory diseases. A potential reason for the increased incidence of these diseases may be changes in mitochondrial function and signalling in response to such recent phenomena as obesity, dietary changes and other environmental factors. Focusing on the mixed heritage of mitochondria therefore leads to predictions for future insights, research paths and therapeutic opportunities. Thus, whereas mitochondria can be considered 'the enemy within' the cell, evolution has used this strained relationship in intriguing ways, with increasing evidence pointing to the recent failure of endosymbiosis being critical for the pathogenesis of inflammatory diseases.

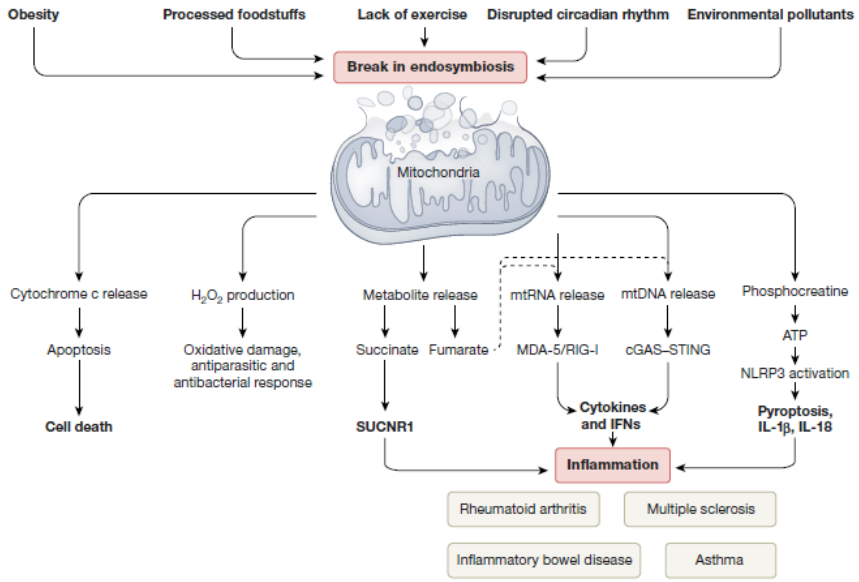


Fig. 2 | How breakdown in endosymbiosis can lead to inflammation. A large number of factors are implicated, including obesity and the impact of environmental pollutants on mitochondria, disrupting their integrity and driving the release of a range of factors that, via specific sensors, drive inflammation, notable examples being NLRP3 and nucleic acid sensors. Metabolites derived from mitochondria can also provoke inflammation and one, fumarate, when disrupted can drive release of mitochondrial dsRNA which, in turn, will drive type I IFN production. Could an increase in these various provoking factors be a reason for the rise in incidence of inflammation and autoimmune diseases?

Source: https://pubmed.ncbi.nlm.nih.gov/38326590/

nature cell biology

Article

https://doi.org/10.1038/s41556-023-01343-1

Mitochondrial DNA replication stress triggers a pro-inflammatory endosomal pathway of nucleoid disposal

Received: 17 October 2023

Accepted: 20 December 2023

Published online: 08 February 2024

Laura E. Newman, et al. Feb. 8, 2024

Mitochondrial DNA (mtDNA) encodes essential subunits of the oxidative phosphorylation system but is also a major damage-associated molecular pattern (DAMP) that engages innate immune sensors when released into the cytoplasm, outside of cells or into circulation. As a DAMP, mtDNA not only contributes to anti-viral resistance, but also causes pathogenic inflammation in many disease contexts. Cells experiencing mtDNA stress caused by depletion of the mtDNA-packaging protein, transcription factor A, mitochondrial (TFAM) or during herpes simplex virus-1 infection exhibit elongated mitochondria, enlargement of nucleoids (mtDNA–protein complexes) and activation of cGAS–STING innate immune signalling via mtDNA released into the cytoplasm. However, the relationship among aberrant mitochondria and nucleoid dynamics, mtDNA release and cGAS–STING activation remains unclear. Here we show that, under a variety of mtDNA replication stress conditions and during herpes simplex virus-1 infection, enlarged nucleoids that remain bound to TFAM exit mitochondria. Enlarged nucleoids arise from mtDNA experiencing replication stress, which causes nucleoid clustering via a block in mitochondrial fission at a stage when endoplasmic reticulum actin polymerization would normally commence, defining a fission checkpoint that ensures mtDNA has completed replication and is competent for segregation into daughter mitochondria. Chronic engagement of this checkpoint results in enlarged nucleoids trafficking into early and then late endosomes for disposal. Endosomal rupture during transit through this endosomal pathway ultimately causes mtDNA-mediated cGAS–STING activation.

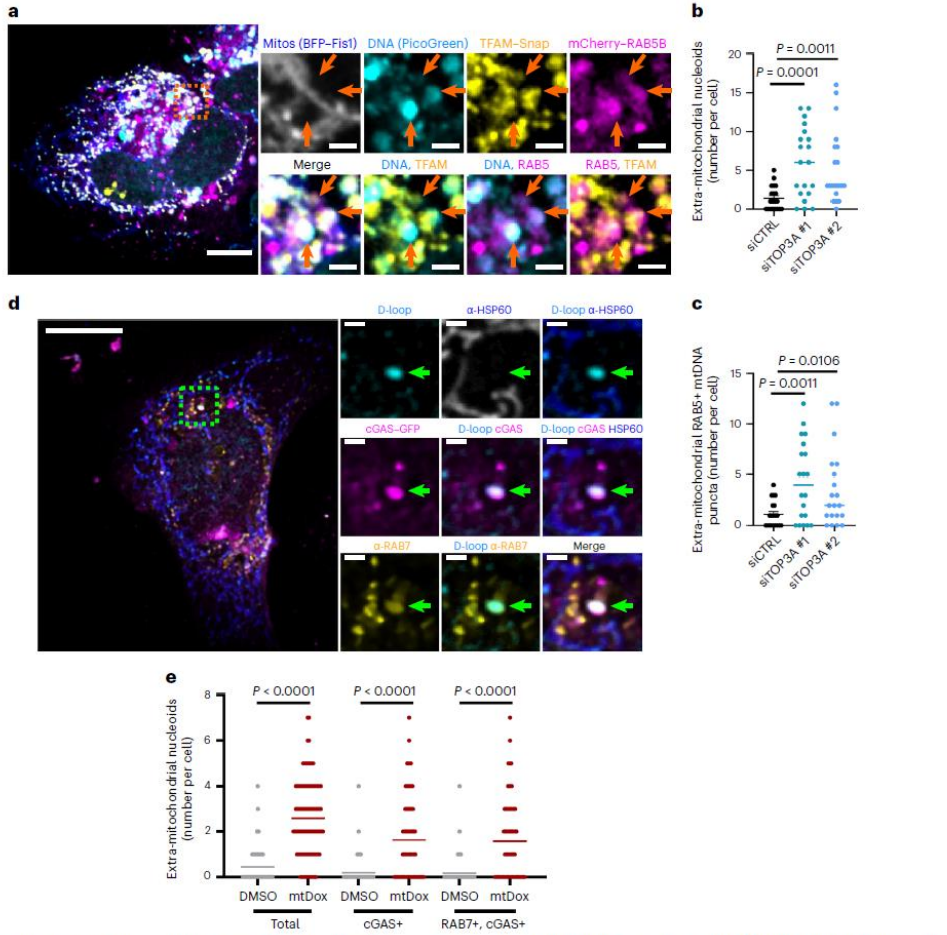


Fig. 8 | Loss of mtDNA segregation or mtDNA damage triggers endosomal trafficking of nucleoids. a, Confocal imaging of a live U2OS cell depleted of TOP3A (siRNA #1), labelled with PicoGreen, and expressing TFAM–SNAP, mCherry–RAB5B and BFP–Fis1. Scale bar, 10 µm and inset scale bars, 2 µm. **b**, The number of extra-mitochondrial nucleoids (non-mitochondrial PicoGreen also positive for TFAM–SNAP) per cell was scored. siCTRL was compared with TOP3A siRNAs #1 ($P = 0.0001$) or #2 ($P = 0.0011$). **c**, The number of extra-mitochondrial nucleoids also positive for mCherry–RAB5B was scored. siCTRL was compared to TOP3A siRNAs #1 ($P = 0.0011$) or #2 ($P = 0.0106$). For both **b** and **c**, $N = 20$ cells for all conditions. Data were pooled from three independent experiments. **d**, Spinning disk imaging of mtDNA FISH (D-loop probe), followed by immunofluorescence against HSP60 and GFP, in U2OS cells that were transfected with cGAS–GFP and then treated with either dimethylsulfoxide (DMSO) or mtDox (10 µM). Scale bars, 20 µm and inset scale bars, 2 µm. **e**, The number of extra-mitochondrial nucleoids that overlapped with cGAS–GFP and RAB7 was scored. DMSO was compared with mtDox ($P < 0.0001$). $N = 110$ cells for DMSO and $N = 101$ cells for mtDox. Data were pooled from three independent experiments. All differences were compared using an unpaired, two-tailed Student's *t*-test, and all plotted lines represent the mean. Source numerical data are available in Source data.

Source: https://www.nature.com/articles/s41556-023-01343-1

Amgen / Lilly Obesity Discussion

Eli Lilly site in South San Francisco.

Last Week's Back and Forth Between Amgen and Lilly

It's not every day that an earnings call gets taken over by a Phase 2 drug trial. But Amgen's earnings call last week saw just that happen. Investors asked a lot of questions about AMG133 / MariTide and by the time the week was out, Amgen stock had dropped $17 billion in value. We think that was due to newly released AMG133 data and negative comments from Lilly on the idea that GIP antagonism is a good way to go. They noted increase in lipids seen in Amgen's study (not seen with Tirzepatide). A senior Lilly executive called Amgen's results "a bit underwhelming".*

We are huge Lilly fans, in general. We love the company's culture, people, focus on excellence and commitment to science.

But, in this case, we think Amgen is on to something big. AMG133 has reported stunning weight loss data that clearly is better than what has been seen with tirzepatide. AMG133 weight loss matches what has been seen with bariatric surgery. To us, Amgen's recent data points to a drug that has potential to be one of the biggest in history. Further, there is a good argument to be made that Lilly's tirzepatide, while technically a GIPr *agonist*, is a *functional antagonist*. Many scientists believe this and there is strong evidence that agonism of GIPr can cause the receptor to internalize, thereby ablating its function. The fact that tirzepatide works well over an extended period is consistent with this view. Further, the underlying biology of GIP antagonism, highlighted in our obesity report last year, is well documented. GIPr is agonized in the gut by the passage of food which causes the expression of GIP that, in turn, signals insulin production from the pancreas. Insulin production instructs our fat cells to grab circulating glucose and store it. That's a main way in which we get fat. Antagonizing GIPr would prevent this from happening, hence Amgen's stunning results. There is a stealth biotech or two pursuing this idea with great effect presently. In this section, we dig a little bit more into Amgen's *Nature Metabolism* paper last week disclosing details of AMG133's Phase 1 study including some tolerability issues.

* See https://www.investors.com/news/technology/amgen-stock-amgen-earnings-q4-2023/

Amgen Disclosure in Feb 6, 2024 Earnings Presentation

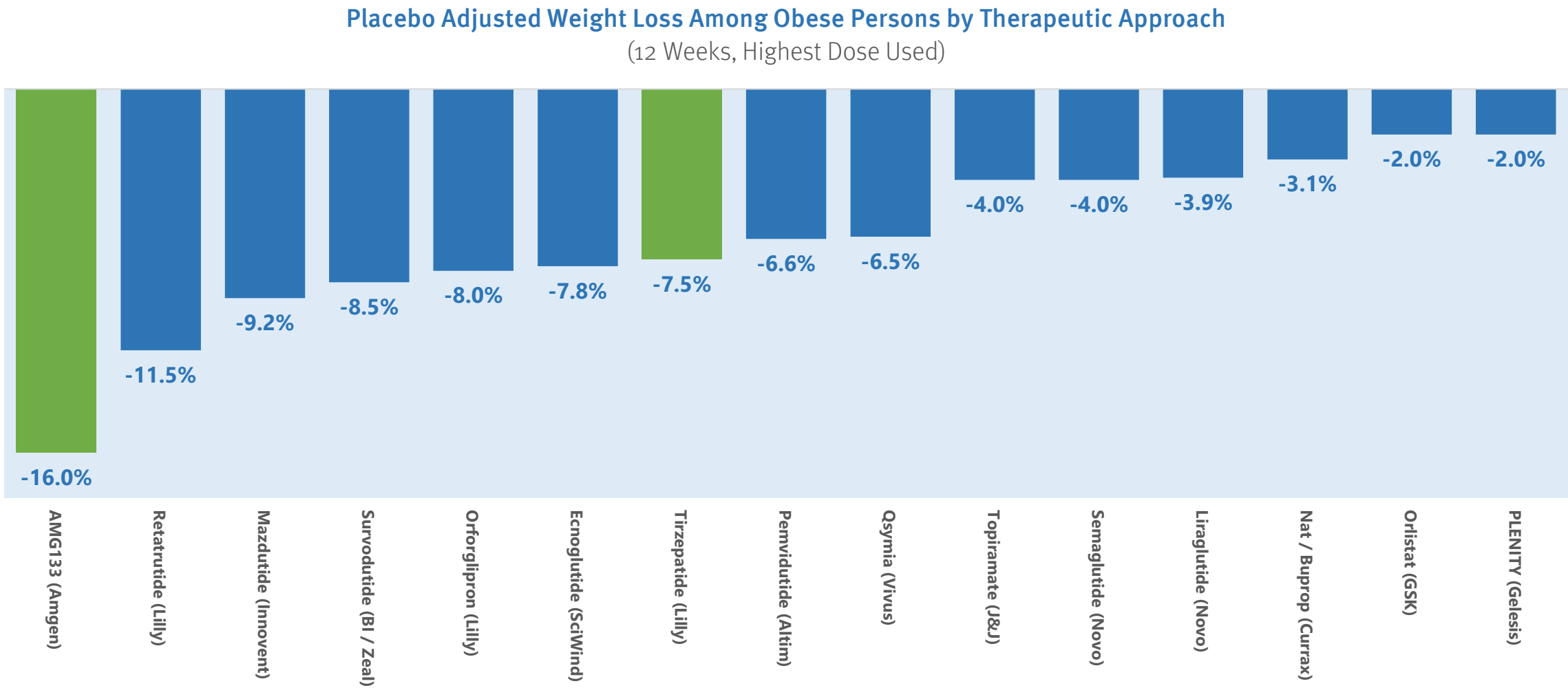
Maridebart cafraglutide (AMG 133) – multispecific GIPR inhibitor and GLP-1 receptor agonist

- **A Phase 2 study in overweight or obese adults with or without type 2 diabetes mellitus has completed enrollment, with topline data anticipated in late 2024. Recently added a Part 2 to this study which explores durable weight loss beyond 52 weeks.**
- **Planning for a comprehensive Phase 3 program across multiple indications remains on track.**
- **In Feb 2024, results of preclinical studies and the Phase 1 study of maridebart cafraglutide were published in *Nature Metabolism*.**

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

AMG133 Efficacy Data Best in Class

Lilly's Retatrutide is associated with 16% weight loss at 24 weeks. Amgen is seeing the *same* level of weight loss in half the time and is by far the leader at this point in terms of 12-week efficacy data.

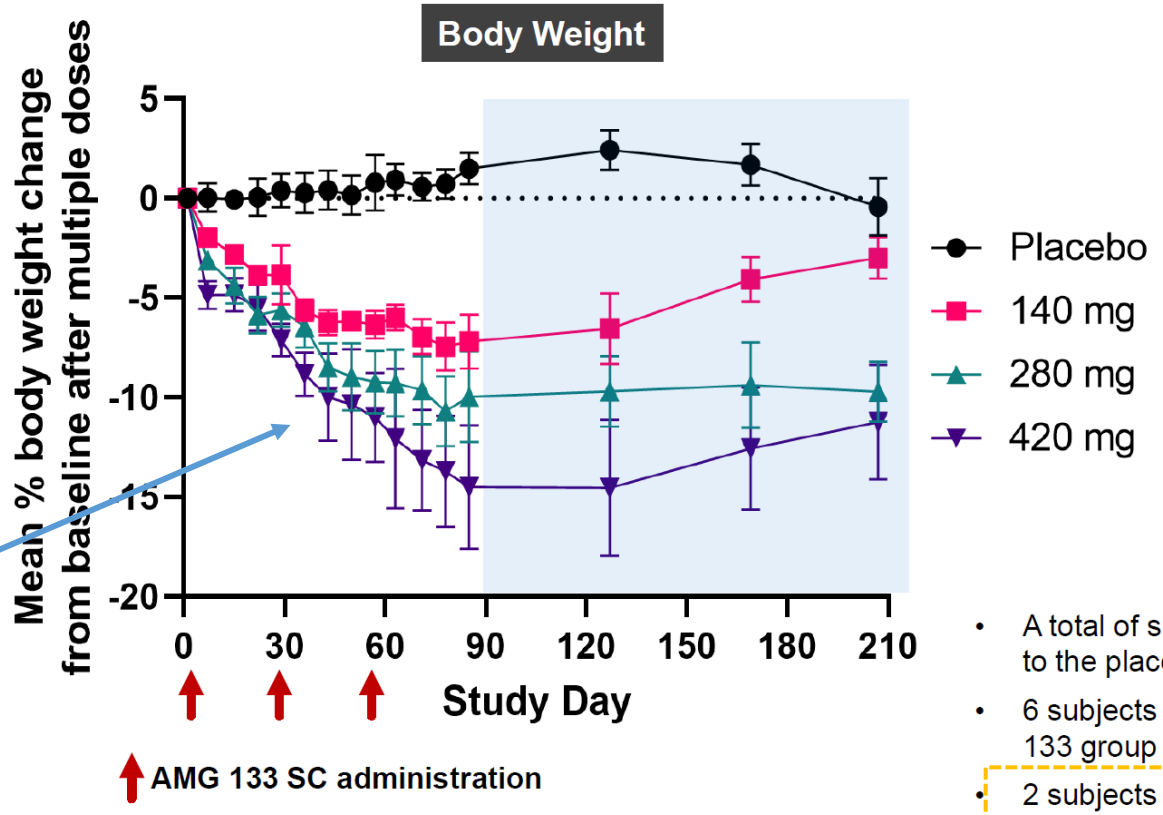


Source: Stifel analysis of study results for various agents.

The Scale of Weight Loss Seen with AMG133 Has Not Been Seen Before with a Pharmacological Agent

The observed weight loss with a GLP1 agonist and GIPr antagonist corresponds to going from 250 pounds to 215 pounds in three months.

The weight loss slope at the 420mg dose is quite high. Patients lost 1% of their body weight *every four* days.



- A total of six subjects were randomized to the placebo group across cohorts
- 6 subjects were randomized to the AMG 133 group at each dose level
- 2 subjects were replaced in the 420 mg dose group

SC = subcutaneous; mg = milligram.

12

Note that two subjects dropped out of the Phase 1b at the high dose. This discontinuation rate is not unusual for the GLP-1 class, however.

Amgen's Work on GIP Receptor Motivated by Rare Genetic Variants Seen in GWAS Studies at its deCODE Subsidiary

Obesity research at Amgen and Icelandic subsidiary deCODE Genetics began looking at the effects of rare genetic changes, called variants, on Body Mass Index (BMI), a measure of body fat based on height and weight. The Centers for Disease Control and Prevention (CDC) defines obesity as having a BMI of 30 or higher. deCODE looked for variants associated with low BMI in human data accumulated from hundreds of thousands of individuals across biobanks from several countries, with the idea that these could be valuable drug targets.

The deCODE work and other research uncovered variants in the GIPR (Gastric Inhibitory Polypeptide Receptor) gene that were particularly interesting. GIP and its receptor are involved in regulating insulin levels after eating. Individuals with specific variants in this gene that reduced its activity had lower BMIs. Further analysis by Amgen researchers confirmed this finding.

Source: https://www.amgen.com/stories/2022/12/targeting-obesity-using-biology-not-behavior

Amgen cites to GWAS work

1. Nature Genetics 2012; 44 (3):302-6
2. Nature Genetics 2010; 42 (11):937-48 (deCODEis collaborator)
3. Nature Genetics 2013; 45 (5):501-12 (deCODEis collaborator)
4. Science 2021; 373 (6550)

Mice With Loss-of-Function Mutations in GIPR Gain Only a Third of Weight of Normal Mice When Fed High Fat Diets

Normal mouse 3x heavier at 36 weeks

GIPr KO mouse gains weight but only modestly despite HF diet

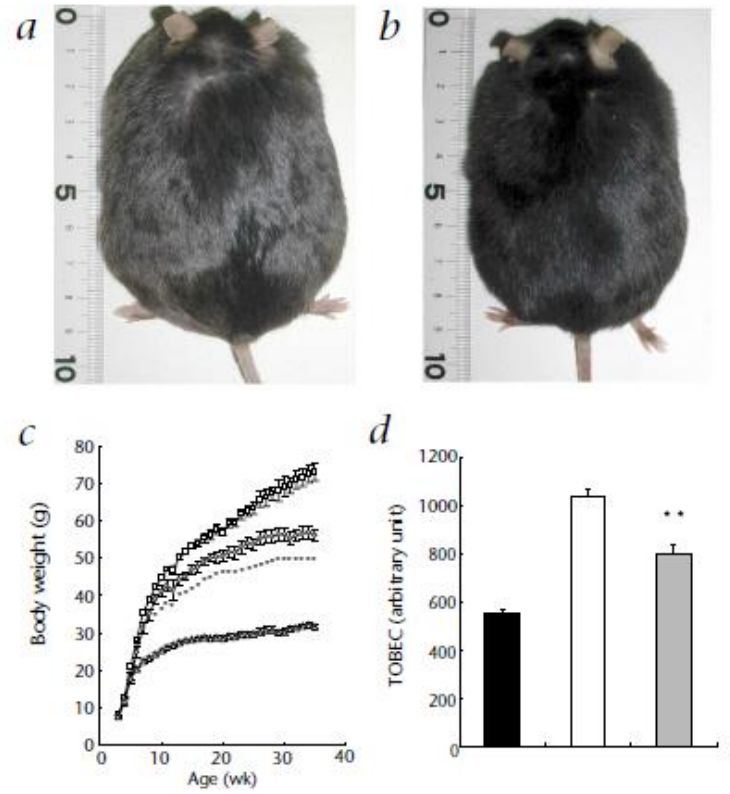


Fig. 2 Inhibition of GIP signal prevents hyperphagia-induced obesity. ***a*** and ***b***, Gross appearance of *Lepob*/*Lepob* (*a*) and *Gipr*–/– *Lepob*/*Lepob* (*b*) mice. ***c***, Body weight of WT (), *Lepob*/*Lepob* () and *Gipr*–/– *Lepob*/*Lepob* mice () at 35 wk of age. *n* = 4; *, *P* < 0.05, compared with *Lepob*/*Lepob* mice. ***d***, TOBEC of WT (), *Lepob*/*Lepob* () and *Gipr*–/– *Lepob*/*Lepob* () mice at 35 wk. *n* = 4; **, *P* < 0.01, compared with *Lepob*/*Lepob* mice.

Secretion of gastric inhibitory polypeptide (GIP), a duodenal hormone, is primarily induced by absorption of ingested fat. Here we describe a novel pathway of obesity promotion via GIP.

Wild-type mice fed a high-fat diet exhibited both hypersecretion of GIP and extreme visceral and subcutaneous fat deposition with insulin resistance.

In contrast, mice lacking the GIP receptor (Gipr(-/-)) fed a high-fat diet were clearly protected from both the obesity and the insulin resistance. Moreover, double-homozygous mice (Gipr(-/-), Lep(ob)/Lep(ob)) generated by crossbreeding Gipr(-/-) and obese ob/ob (Lep(ob)/Lep(ob)) mice gained less weight and had lower adiposity than Lep(ob)/Lep(ob) mice. The Gipr(-/-) mice had a lower respiratory quotient and used fat as the preferred energy substrate, and were thus resistant to obesity. **Therefore, GIP directly links overnutrition to obesity and it is a potential target for anti-obesity drugs.**

Source: https://pubmed.ncbi.nlm.nih.gov/12068290/

GIP Levels are an Independent Mortality Risk Factor

Diabetologia (2020) 63:1043–1054
https://doi.org/10.1007/s00125-020-05093-9

ARTICLE

Glucose-dependent insulinotropic peptide and risk of cardiovascular events and mortality: a prospective study

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In meta-analyses, higher fasting levels of GIP were associated with risk of higher total mortality (HR[95% CI] = 1.22 [1.11, 1.35]; p = 4.5 × 10−5) and death from CVD (HR[95% CI] 1.30 [1.11, 1.52]; p = 0.001). In accordance, 2SMR analysis revealed that increasing GIP concentrations were associate with CAD and myocardial infarction, and an additional reverse 2SMR revealed no significant effect of CAD on GIP levels, thus confirming a possible effect solely of GIP on CAD.

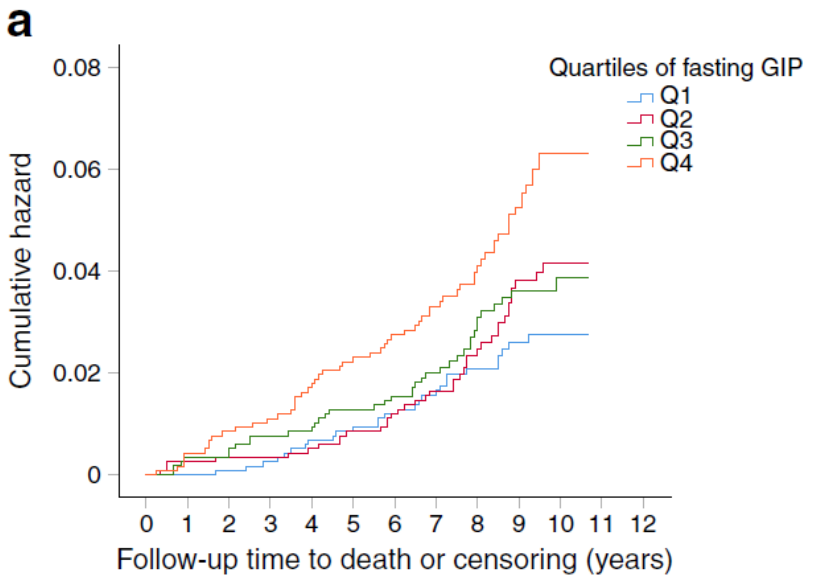


Fig. 1 Total mortality risk in quartiles of fasting GIP. (**a**) Cumulative hazard for total mortality over a mean follow-up of 8.8 years for fasting GIP quartiles in PPP-Botnia ($p = 0.001$). (**b**) Cumulative hazard for total

Source: https://link.springer.com/article/10.1007/s00125-020-05093-9

Evidence Indicates that Both GIP Agonism and Antagonism Can Work

Review

MOLECULAR METABOLISM

Targeting the GIPR for obesity: To agonize or antagonize? Potential mechanisms

Jonathan E. Campbell [1,2,3,*]

ABSTRACT

Background: Glucose-dependent insulinotropic peptide (GIP) is one of two incretin hormones that communicate nutrient intake with systemic metabolism. Although GIP was the first incretin hormone to be discovered, the understanding of GIP's biology was quickly outpaced by research focusing on the other incretin hormone, glucagon-like peptide 1 (GLP-1). Early work on GIP produced the theory that GIP is obesogenic, limiting interest in developing GIPR agonists to treat type 2 diabetes. A resurgence of GIP research has occurred in the last five years, reinvigorating interest in this peptide. Two independent approaches have emerged for treating obesity, one promoting GIPR agonism and the other antagonism. In this report, evidence supporting both cases is discussed and hypotheses are presented to reconcile this apparent paradox.

Scope of the review: This review presents evidence to support targeting GIPR to reduce obesity. Most of the focus is on the effect of singly targeting the GIPR using both a gain- and loss-of-function approach, with additional sections that discuss co-targeting of the GIPR and GLP-1R.

Major conclusions: There is substantial evidence to support that GIPR agonism and antagonism can positively impact body weight. The long-standing theory that GIP drives weight gain is exclusively derived from loss-of-function studies, with no evidence to support that GIPR agonisms increases adiposity or body weight. There is insufficient evidence to reconcile the paradoxical observations that both GIPR agonism and antagonism can reduce body weight; however, two independent hypotheses centered on GIPR antagonism are presented based on new data in an effort to address this question. The first discusses the compensatory relationship between incretin receptors and how antagonism of the GIPR may enhance GLP-1R activity. The second discusses how chronic GIPR agonism may produce desensitization and ultimately loss of GIPR activity that mimics antagonism. Overall, it is clear that a deeper understanding of GIP biology is required to understand how modulating this system impacts metabolic homeostasis.

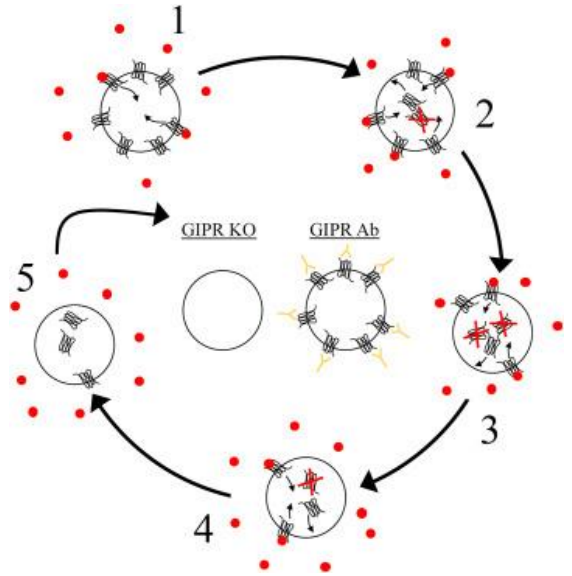
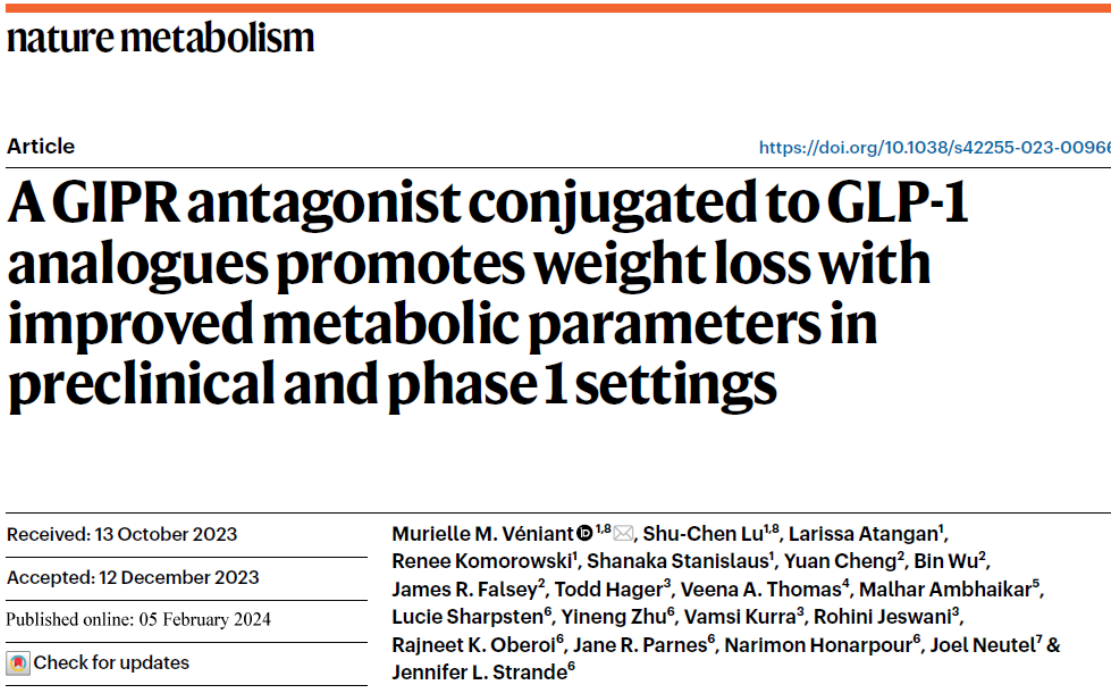


Figure 2. Chronic Agonism Equals Antagonism: A Hypothesis. 1) Agonism of the GIPR leads to internalization of the number of receptors that is proportional to the concentrations of agonists. 2) Some receptors will recycle back to the membrane, while others will degrade. 3–5) Chronic agonism eventually decreases the number of receptors present on the membrane to effectively resemble loss of function caused by either Gipr knockout or GIPR antagonism (GIPR Ab).

Source: https://www.sciencedirect.com/science/article/pii/S2212877820302131

Paper on AMG133 Phase 1 Out Last Week in *Nature Metabolism*



nature metabolism

Article

https://doi.org/10.1038/s42255-023-00966

A GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings

Received: 13 October 2023

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Check for updates

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In the MAD setting, participants receiving AMG 133 demonstrated sustained weight loss after 12 weeks of treatment. AMG 133 treatment was also associated with changes in glucose homeostasis markers as well as a dose-dependent reduction in levels of the inflammation marker hs-CRP.

Even though there was a reduction in cholesterol, LDL and triglycerides level associated with AMG 133 treatment in cynomolgus monkeys, the AMG 133 effects on lowering lipid parameters were inconclusive in the first-in-human (FIH) study due to the large variability associated with the small sample size of each cohort coupled with the observation that the placebo group also had reductions in cholesterol, LDL-C and triglycerides.

Source: https://www.nature.com/articles/s42255-023-00966-w

Significant Tolerability Issues with AMG133 in MAD Study

Table 2 | Gastrointestinal-related treatment-emergent adverse events in humans after a single dose (a) or multiple ascending doses (b) of placebo and AMG 133

b				
	Placebo (*n*=6)	140 mg (*n*=6)	280 mg (*n*=6)	420 mg (*n*=8)
Number of individuals reporting TEAEs	3 (50.0)	6 (100.0)	6 (100.0)	8 (100.0)
GI disorders				
Diarrhoea	0 (0.0)	1 (16.7)	0 (0.0)	2 (25.0)
Dyspepsia	0 (0.0)	1 (16.7)	0 (0.0)	1 (12.5)
Abdominal distension	0 (0.0)	1 (16.7)	0 (0.0)	1 (12.5)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Constipation	0 (0.0)	2 (33.3)	1 (16.7)	0 (0.0)
Nausea	1 (16.7)	5 (83.3)	4 (66.7)	8 (100.0)
Vomiting	0 (0.0)	4 (66.7)	5 (83.3)	6 (75.0)
GI safety laboratory				
Amylase elevation	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Lipase elevation	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)

Data show number (%) of participants with the event of interest.

Counterpoints

1. These tolerability issues should be manageable with tapered run-in dosing strategies (which Amgen is testing now in Phase 2).
2. Amgen found tolerability issues in less than 10% of subjects after the first two doses of drug.
3. Further, doses can be broken down from monthly to smaller amounts on a weekly basis to manage drug CMAX.
4. Importantly, few subjects dropped out of the study, and we think patients should be motivated to take the drug given the scale of the weight loss achievable with the drug.

Source: https://www.nature.com/articles/s42255-023-00966-w

Tolerability Issues Also Seen with High Dose Tirzepatide

It's important to note that Tirzepatide faced Phase 1 tolerability issues at higher doses that were eventually sorted out (75% vomiting rate at 15mg dose). What's interesting is that the high vomiting/nausea rate at the 15 mg dose was seen after run in with a 5mg dose. On the other hand, nausea and vomiting at the 10mg dose was quite modest.

Original Article

MOLECULAR METABOLISM

LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept

Tamer Coskun [1], Kyle W. Sloop [1], Corina Loghin [1], Jorge Alsina-Fernandez [1], Shweta Urva [1], Krister B. Bokvist [1], Xuewei Cui [1], Daniel A. Briere [1], Over Cabrera [1], William C. Roell [1], Uma Kuchibhotla [1], Julie S. Moyers [1], Charles T. Benson [1], Ruth E. Gimeno [1], David A. D'Alessio [2], Axel Haupt [1,*]

Table 3 — Adverse events in Patients with T2DM.

	LY3298176 0.5 mg N = 9	LY3298176 5 mg N = 9	LY3298176 5/5/10/10 mg N = 12	LY3298176 5/5/10/15 mg N = 12	Placebo N = 11	All N = 53
Any TEAE	5 (55.6)	7 (77.8)	10 (83.3)	11 (91.7)	3 (27.3)	36 (67.9)
Mild, events	15	17	54	87	6	179
Moderate, events	0	0	1	9	0	10
Severe, events	0	0	0	0	0	0
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study discontinuation due to adverse events	0 (0.0)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAEs in order of frequency						
Vomiting	1 (11.1)	0 (0.0)	1 (8.3)	9 (75.0)	0 (0.0)	11 (20.8)
Decreased appetite	2 (22.2)	6 (66.7)	5 (41.7)	11 (91.7)	1 (9.1)	25 (47.2)
Diarrhoea	1 (11.1)	1 (11.1)	3 (25.0)	5 (41.7)	1 (9.1)	11 (20.8)
Abdominal distension	0 (0.0)	1 (11.1)	2 (16.7)	7 (58.3)	0 (0.0)	10 (18.9)
Nausea	1 (11.1)	1 (11.1)	1 (8.3)	6 (50.0)	0 (0.0)	9 (17.0)
Gastrooesophageal reflux disease	0 (0.0)	1 (11.1)	1 (8.3)	5 (41.7)	0 (0.0)	7 (13.2)
Eructation	0 (0.0)	0 (0.0)	1 (8.3)	4 (33.3)	0 (0.0)	5 (9.4)
Weight decrease	0 (0.0)	0 (0.0)	2 (16.7)	2 (16.7)	0 (0.0)	4 (7.5)
Dyspepsia	0 (0.0)	0 (0.0)	3 (25.0)	0 (0.0)	0 (0.0)	3 (5.7)
Headache	1 (11.1)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	3 (5.7)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	2 (3.8)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	2 (3.8)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)	0 (0.0)	2 (3.8)
Pancreatic enzyme increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (9.1)	2 (3.8)
Other adverse events						
Total hypoglycaemia (≤70 mg/dL)	0 (0.0)	0 (0.0)	2 (16.7)	1 (8.3)	1 (9.1)	4 (7.5)
Severe hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

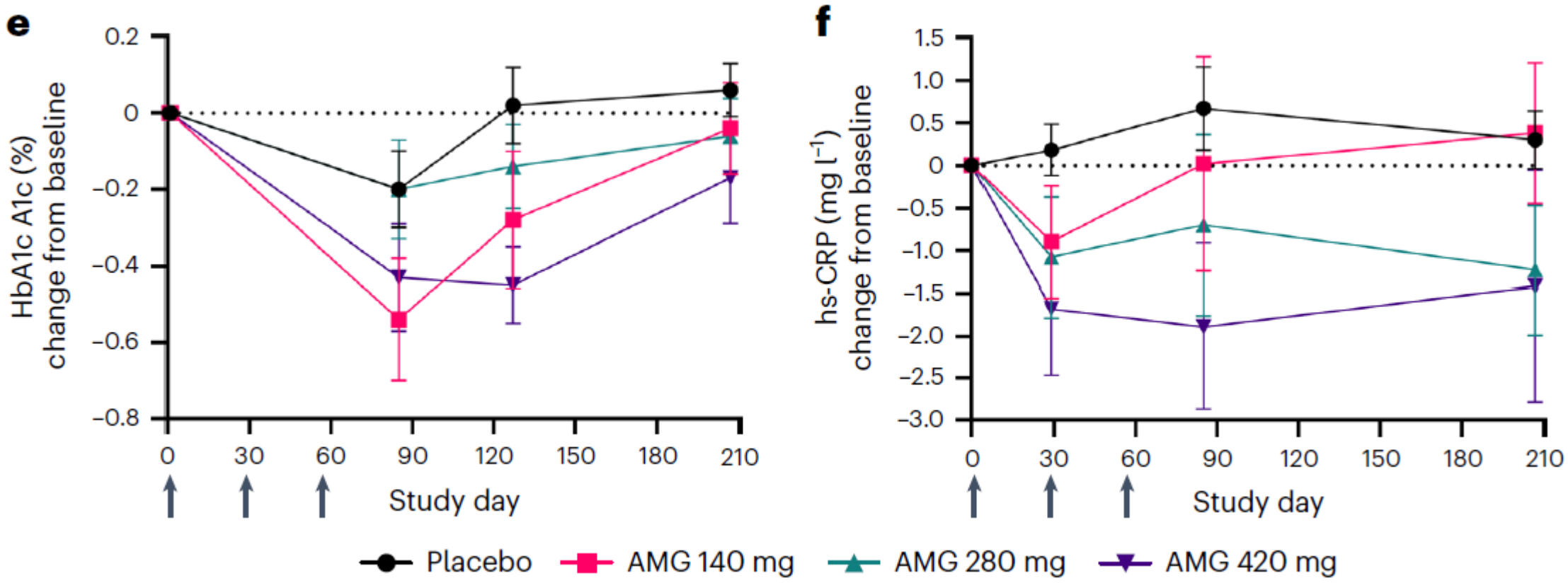
Data presented as n (%), unless otherwise noted. TEAE = treatment-emergent adverse event.

Source: https://www.sciencedirect.com/science/article/pii/S2212877818309001

Impressive Changes in Glucose and Inflammation with AMG133

The use of AMG133 was associated with impressive reductions in glucose levels relative to placebo and strong reductions in CRP versus placebo.

These changes bode well for long-term potential effects of the drug.



Source: https://www.nature.com/articles/s42255-023-00966-w

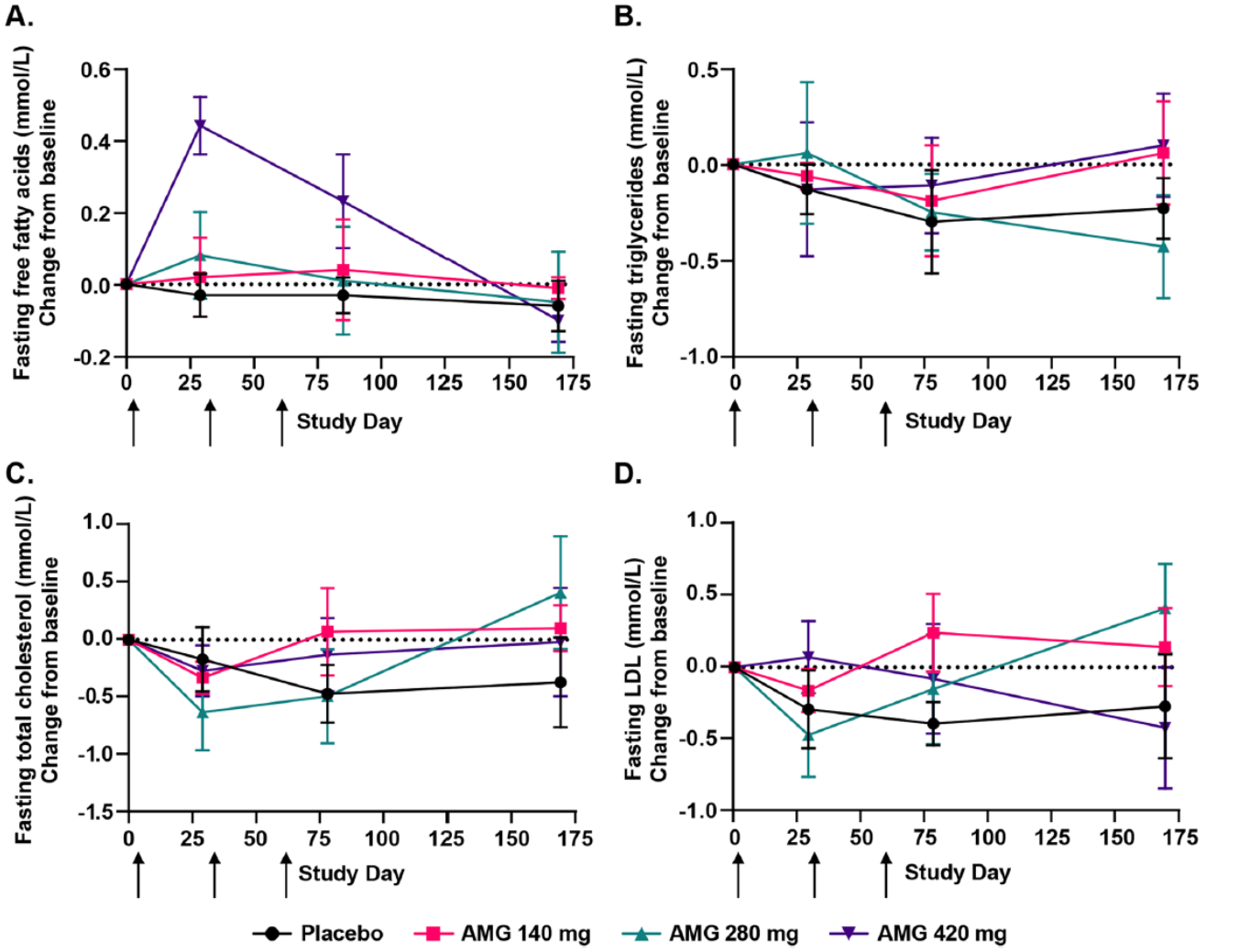
AMG133 Lipid Concern Seems Overblown

Lilly executives pointed to the data at right in their conference call last week.

The point is that TZP did not exhibit increases in free fatty acids after treatment in Phase 1.

This true but it's important to note that Amgen saw this only in one dose group and the change was transient.

Further, there is no adverse signal seen with triglycerides, cholesterol or LDL.



Extended Data Fig. 4 | Changes in free fatty acids and lipid parameters in humans with multiple ascending doses of AMG 133. (a–d) Mean (SE) change from baseline in fasting free fatty acids, n = 6–8 for AMG 133 and n = 6 for placebo at Day 1 (A), fasting triglycerides, n = 6 for AMG 133 and n = 6 for placebo at Day 1 (B), fasting total cholesterol, n = 6–8 for AMG 133 and n = 6 for placebo at Day 1 (C), fasting LDL, n = 6 for AMG 133 and n = 6 for placebo at Day 1 (D) after multiple ascending doses of AMG 133 or placebo. Arrows indicate when the investigational product was administrated: at day 1, 29, and 57.

Source: https://www.nature.com/articles/s42255-023-00966-w

AMG 786 Data Due in Q2 2024

Separately, Amgen's AMG 786 is in a Phase 1 study, and we should be seeing data in H1 2024 based on last week's announcements from Amgen.

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

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

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

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

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

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

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

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

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

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

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

Related U.S. Application Data

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

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

Publication Classification

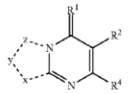
(51) **Int. Cl.**
C07D 513/04 (2006.01)
A61P 3/04 (2006.01)
C07D 487/04 (2006.01)
C07D 498/04 (2006.01)

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

(57) **ABSTRACT**

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

I

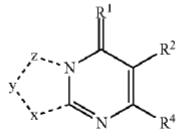


wherein the variables of Formula I are defined herein. This disclosure also provides pharmaceutical compositions comprising the compounds, uses of the compounds, and compositions for treatment of, for example, a metabolic or cardiovascular disorder. Further, the disclosure provides intermediates useful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

What is claimed is:

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

I



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

About D5D and Amgen's Potential New Drug

Amgen filed a provision patent on Nov 25, 2019 for a group of delta-5 desaturase inhibitors for the treatment of obesity.

Their DIO mouse data are disclosed and are highly impressive. There is strong GWAS rationale for hitting this target. And the target is clearly linked to obesity and the formation of cardiac plaque.

The big unmet needs in obesity drugs are for an oral, a drug that avoids nausea, a drug that is lower cost, a source of lasting weight loss and a drug that avoids muscle loss. The D5D inhibitor in example 2 was associated with a 39.2% weight loss vs placebo (vehicle) in 84 days. Almost all the weight loss was in fat rather than lean mass.

Yet food consumption dropped little when comparing those on drug to placebo. Insulin levels were massively decreased (91%) as were levels of leptin (down 85%).

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

In general DIO mouse data replicate in humans but with a lessened effect. We think that the AMG 786 trial has a good chance of showing strong efficacy, particularly for an oral. The key unknown will be safety. There are no major known safety issues with the relevant FADS1 knockout mouse.

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

TABLE 17

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

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

It would be remarkable if Amgen can get anywhere close to this with a pill in humans. You don't eat much less but drop huge amounts of fatty weight while sacrificing little lean mass. Your trigs, cholesterol, insulin, leptin and blood glucose all drop. A lot. We may have the first-in-human D5D data in Q2 of this year.

D5D: Greenlandic Inuit Show Genetic Signatures of Diet and Climate Adaptation

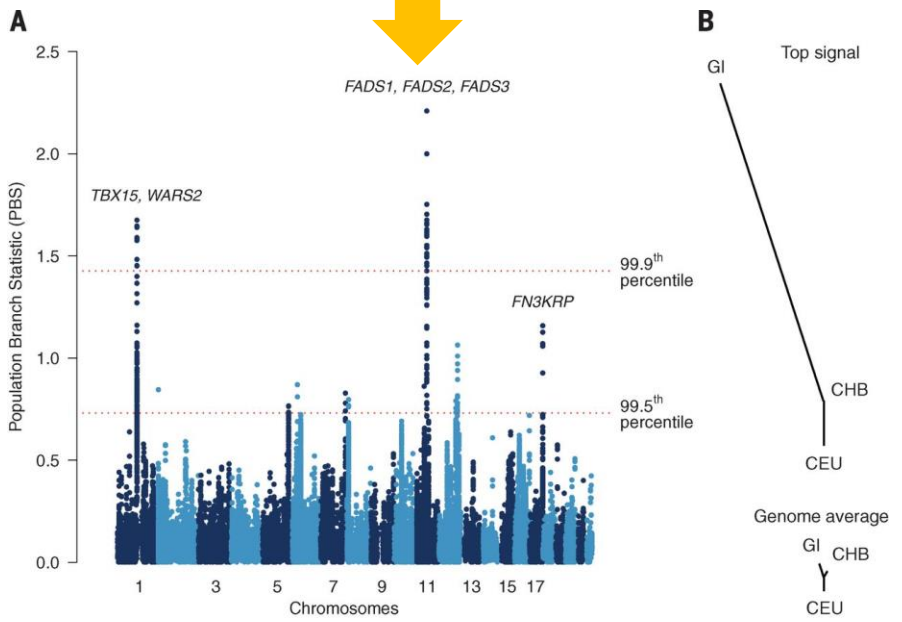
The Inuit People are Largely Metabolically Healthy Despite a Fatty Diet

Fumagalli M, et.al., "Greenlandic Inuit show genetic signatures of diet and climate adaptation," *Science*. 2015 Sep 18;349(6254):1343-7.

The indigenous people of Greenland, the Inuit, have lived for a long time in the extreme conditions of the Arctic, including low annual temperatures, and with a specialized diet rich in protein and fatty acids, particularly omega-3 polyunsaturated fatty acids (PUFAs).

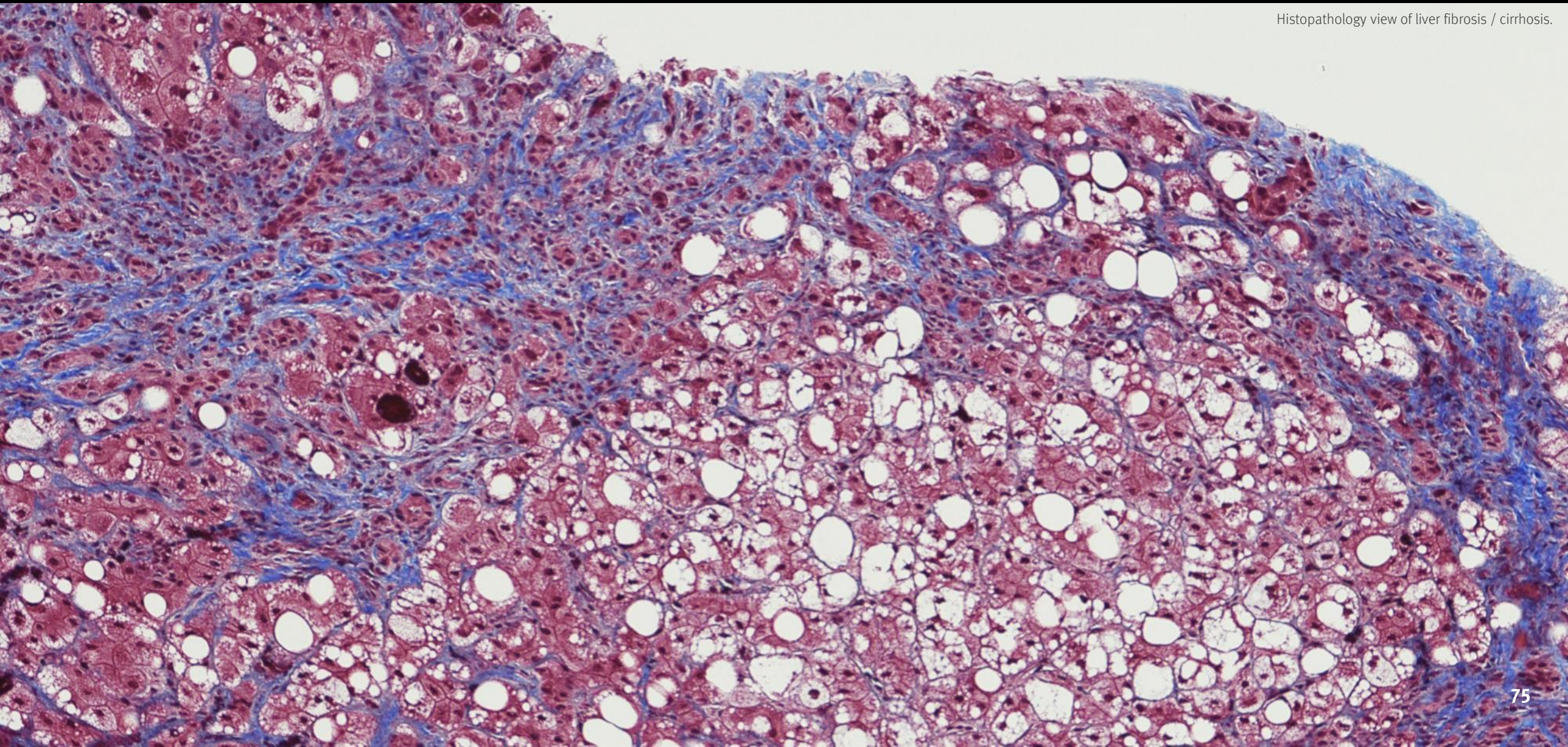
A scan of Inuit genomes for signatures of adaptation revealed signals at several loci, with the strongest signal located in a cluster of fatty acid desaturases that determine PUFA levels. The selected alleles are associated with multiple metabolic and anthropometric phenotypes and have large effect sizes for weight and height, with the effect on height replicated in Europeans. By analyzing membrane lipids, we found that the selected alleles modulate fatty acid composition, which may affect the regulation of growth hormones. Thus, the Inuit have genetic and physiological adaptations to a diet rich in PUFAs.

D5D, D6D polymorphisms / mutations (also known as FADS1/2/3) help to explain why the Inuits can eat a fatty diet but have low CV disease, less obesity and less T2DM. Amgen appears to be putting this idea to work with a pill.



Source: https://pubmed.ncbi.nlm.nih.gov/26383953/. Also see an article summary at https://phys.org/news/2015-09-high-fat-diet-inuits-healthier-shorter.html. Photo from Getty Images.

Update on Fibrosis and NASH



Histopathology view of liver fibrosis / cirrhosis.

Madrigal's Phase 3 NASH Data Published Last Week

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Harrison SA et al. DOI: 10.1056/NEJMoa2309000

CLINICAL TRIAL

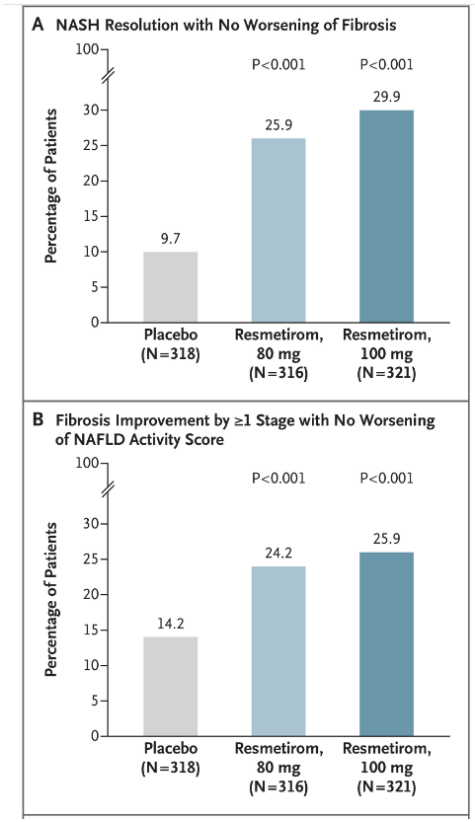
Design: An ongoing, phase 3, multinational, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and liver fibrosis.

Intervention: 966 patients with NASH and fibrosis of stage F1B, F2, or F3 were assigned in a 1:1:1 ratio to receive once-daily resmetirom (80 mg or 100 mg) or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by ≥1 stage with no worsening of the NAFLD activity score.

RESULTS

Efficacy: Among evaluable patients, both doses of resmetirom were superior to placebo with respect to the two primary end points.

Safety: More than 90% of the patients in each group had adverse events, most of which were mild or moderate in severity. Diarrhea and nausea occurred more often with resmetirom than with placebo. The incidence of serious adverse events was similar among the groups.



The two primary end points at week 52 were resolution of nonalcoholic steatohepatitis (NASH) with no worsening of fibrosis (Panel A), and an improvement (reduction) in fibrosis by at least one stage with no worsening of the nonalcoholic fatty liver disease (NAFLD) activity score (Panel B).

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2309000

Accompanying Editorial Cautious on Resmetirom

Kenneth Cusi MD, "Selective Agonists of Thyroid Hormone Receptor Beta for the Treatment of NASH," *NEJM*, Feb 8, 2023 (excerpted)

In this issue of the Journal, Harrison et al. report the week 52 results of the ongoing phase 3 MAESTRO-NASH trial.

Among the patients with available data, resmetirom markedly increased sex hormone–binding globulin levels and increased levels of total estradiol and testosterone. Elevations in sex hormone–binding globulin levels indicate THR-β engagement and are associated with treatment response.

Taken together, these results are encouraging to the field. Both NASH resolution and fibrosis improvement were more likely with resmetirom than with placebo. If conditional approval is given by the Food and Drug Administration, it may boost guideline recommendations to screen in primary care persons at high risk for NASH, especially to identify those with stage F2 or higher fibrosis (known as "at risk" NASH). However, the trial also highlights the challenging nature of the disease. **Although resmetirom treatment was successful, the placebo-subtracted effect of resmetirom was overall modest (16.4 to 20.7 percentage points for NASH resolution and 10.2 to 11.8 percentage points for fibrosis), which means that approximately 2 of 10 patients treated will have NASH resolution and approximately 1 of 10 patients treated will have fibrosis improvement.** Thus, most patients will need combination therapy with agents for obesity and type 2 diabetes recommended in guidelines (GLP-1 receptor agonists or pioglitazone).1-3 If resmetirom is approved to treat F2 to F3 (moderate to advanced)) fibrosis, it is speculated that it will be a costly medication.

Source: https://www.nejm.org/doi/full/10.1056/NEJMe2314365

Eli Lilly Says Weight Loss Drug Shows Promise as Treatment for Fatty Liver Disease

Annika Kim Constantino, *CNBC*, Feb 6, 2024 (excerpt)

Eli Lilly on Tuesday said its highly popular drug used for weight loss and diabetes showed promise as a treatment for fatty liver disease in a midstage trial.

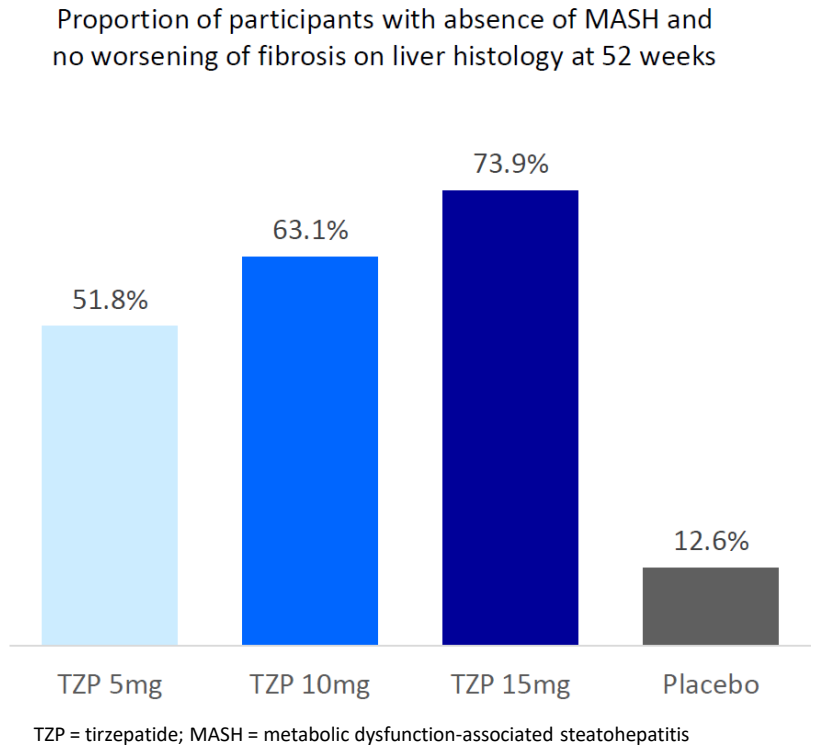
The initial study results add to a long list of potential health benefits of the treatment, known as tirzepatide, besides helping patients shed significant pounds and regulate blood sugar under the drug's brand names, Zepbound and Mounjaro, respectively. Those additional benefits could potentially expand the limited insurance coverage for weight loss drugs, most of which cost close to $1,000 per month.

The pharmaceutical giant said in its fourth-quarter earnings release that tirzepatide showed positive results in a phase two trial as a treatment for a serious form of liver disease called metabolic dysfunction-associated steatohepatitis, or MASH.

There are currently no cures or medicines available to directly treat MASH. The condition is characterized by excess fat buildup and inflammation in the liver and can lead to liver scarring, also known as fibrosis. An estimated 3% to 5% of adults in the U.S. are affected by MASH, according to some studies.

The trial followed around 190 adults with MASH with severe stages of liver scarring, Eli Lilly executives said on an earnings call Tuesday.

Sources: https://www.cnbc.com/2024/02/06/eli-lilly-weight-loss-drug-may-treat-fatty-liver-disease.html, https://investor.lilly.com/static-files/ecfe166b-dd40-45df-afd7-ddb81fe2cb33

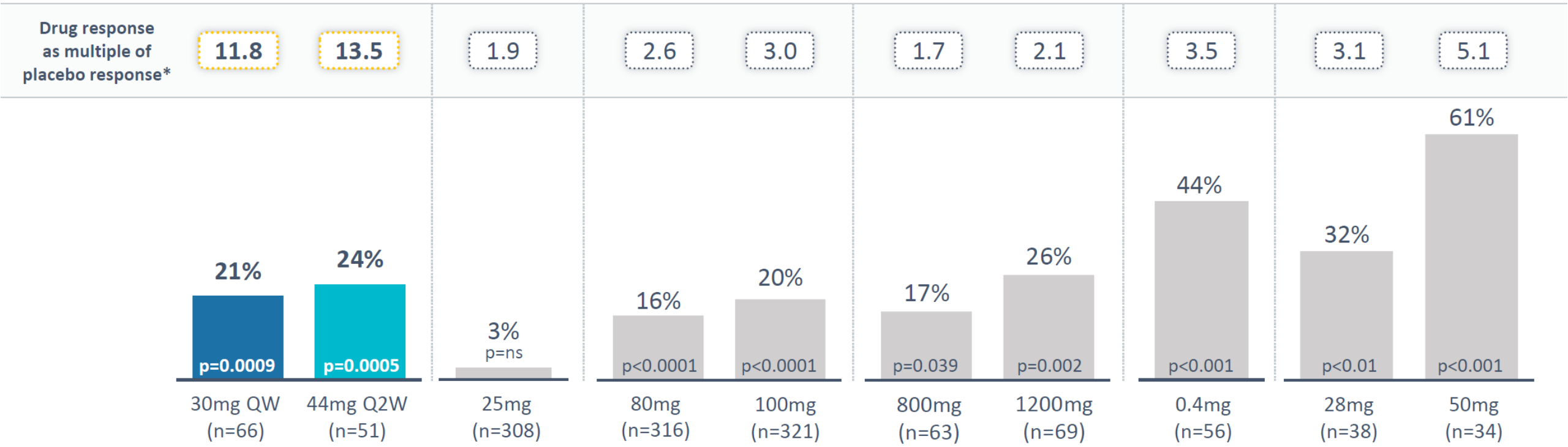


Lilly: "Phase 2 study in adults with biopsy-proven MASH with stage 2 or 3 fibrosis. All doses met primary endpoint of absence of MASH with no worsening of liver histology. Secondary endpoint of decrease in fibrosis by at least one stage with no worsening of MASH on liver histology was clinically meaningful across doses."

Comparative Clinical Data in Non-Cirrhotic Patients

NASH Resolution with No Worsening of Fibrosis

Stifel note: At first blush, the Lilly TZP data look far better than what is seen with these agents. Indirect antifibrotics appear to us to have met their match.



* Drug response as multiple of placebo response is calculated by dividing drug response by placebo response

[1] Results same for Completer Analysis Set; [2] NASH resolution with ≥2 point reduction in NAS and no worsening of fibrosis

[†]Program discontinued

Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

Source: 89Bio Corporate Pres., Jan 2024

89bio

Liver Disease Biotechs' Stocks Crash on Eli Lilly's Mounjaro Data

Jonathan Nathan-Kazis, *Barrons*, Feb 8, 2024 (excerpt)

A clinical trial result presented almost as an aside in Eli Lilly's latest earnings report dropped like a bomb this week on the biotechs developing treatments for the liver condition known as MASH.

MASH, an advanced liver disorder that can lead to cancer or liver failure, is thought to be widespread, though little-known, and drug companies see the potential for a large market. Biotechs have hustled for years to introduce treatments for it. The new data released Tuesday suggest that Lilly's weight-loss drug could upend that incipient market.

Once known as NASH, doctors and drugmakers have recently shifted to calling the condition MASH, short for metabolic dysfunction-associated steatohepatitis. After a wave of hype peaked around 2019, the MASH field has seen a long list of disappointments. Many of the biotechs that focused on the condition have fallen by the wayside.

Last May, a Food and Drug Administration advisory panel slammed an application for approval for a MASH drug from Intercept Pharmaceuticals, a stalwart in the field; the company was bought shortly thereafter for a fraction of its 2019-era market value. Today, a handful of biotechs still remain in the race for MASH treatments. But on Tuesday, their stocks suffered massive selloffs, on fears that Lilly's Type 2 diabetes and obesity drug, tirzepatide, could swipe the MASH market out from under their feet.

On Thursday, 89bio and Akero shares were up, while Madrigal continue to fall. By Thursday afternoon, Madrigal shares had fallen 22.9% since the release of the Lilly data, 89bio had fallen 12.2%, and Akero had fallen 6%. On an investor call Tuesday, Lilly's chief scientific officer, Daniel Skovronsky, said the study had not been statistically powered to measure a decrease in fibrosis. Still, he said, "the study results showed a clinically meaningful treatment effect across all doses on the proportion of participants achieving a decrease of at least one fibrosis stage with no worsening of MASH to placebo."

That question of how good tirzepatide is at actually improving fibrosis is an important one, and may be cleared up when the company releases the full results from the study. In the meantime, however, the data announced Tuesday seem to bear out the worry that tirzepatide and Novo's semaglutide might obviate the need for specific molecules to treat MASH. Both drugs are powerful treatments for weight loss and Type 2 diabetes, key risk factors for MASH.

Madrigal is testing a drug called resmetirom in NASH in Phase 3 studies, while Akero is testing a drug called efruxifermin, and 89bio is testing a drug called pegozafermin. Another biotech, Viking Therapeutics, has a NASH and obesity drug that works similarly to the Lilly drug in its pipeline; Viking shares were roughly flat Tuesday and Wednesday.

Sources: https://www.barrons.com/articles/eli-lilly-stock-mounjaro-liver-disease-mash-63d06fc1

Comment on the Tirzepatide “MASH-UP” From Last Week

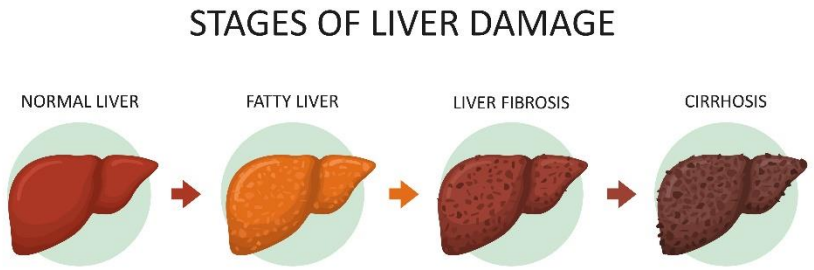
Lilly’s data highlight an essential truth which is that the liver is a place where the body stores fat. If you lose weight, you are going to have less fat in your liver. And, if you have less liver fat, it turns out that there will be less stress on liver tissue and hence buildup of tissue scarring – otherwise known as liver fibrosis.

There has been a proliferation of interest in agents that slow down, reverse or at least prevent liver fibrosis. Big pharma and biotech alike have been chasing the goal and we may be close to seeing a first FDA approval from Madrigal’s Resmetirom.

We wish to note the obvious which is that the medical priority is to deal with more advanced disease. This is where hospitalizations, medical cost and premature mortality all come from.

There has been some really promising data from the likes of Akero, Madrigal and Viking. Yet, there has also been a paucity of hard evidence of clinically meaningful reversal of advanced fibrosis at a molecular level.

Essentially, what we are seeing is the effect of “debridement of foie gras” with delipidating agents on fibrosis. The antifibrotic effect is there but is unlikely to be profound once the disease progresses from fatty liver to full-blown cirrhosis / advanced fibrosis. That is, many agents currently in development are promising for the *prevention* of liver fibrosis but are not likely to be helpful in treating advanced disease.



This section of our weekly report dives a little deeper into the space of fibrosis therapies and looks for agents that are more direct acting.

It turns out that there are agents in development that can actively break up fibrotic tissue or directly prevent the deposition of cross-linked collagen from fibroblasts or stellate cells (in the case of liver fibrosis).

It’s been conspicuous that for all of the pharma M&A in recent years, there has not been a take-out of one of the mid-clinical NASH/MASH players such as Akero, 89Bio or Madrigal. We are not seers so, for all we know, Akero gets bought tomorrow morning. But we think that is unlikely. The reason is that big pharma largely does not view liver fat debridement as sufficiently disease modifying. Pharma is looking for direct acting antifibrotics (e.g., agents that reduce collagen excretion from fibroblasts). In this section we identify exciting therapeutics in development which have that promise and are good potential targets for pharma. Companies that have caught our attention include names like Agomab, Alentis, Endeavor, Mission Therapeutics, Pliant and Thirona. Today’s crop of fibrosis biotechs is the best we have ever had.

Fibrosis – Huge Area of Unmet Medical Need

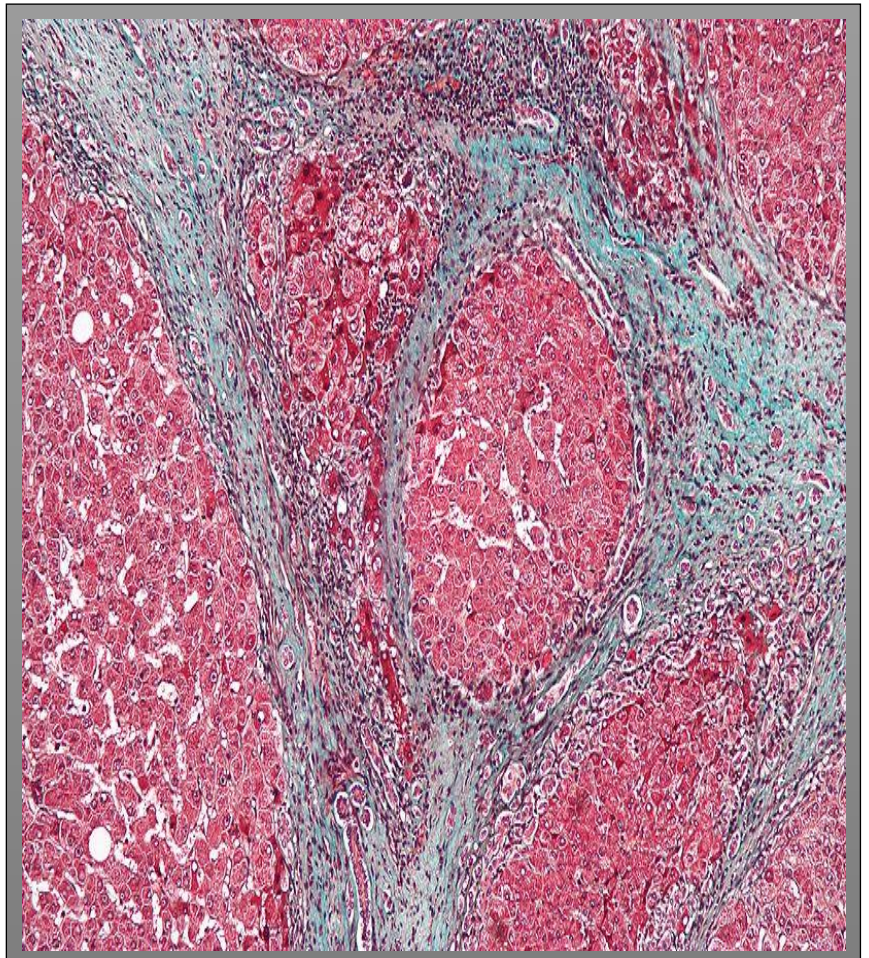
Fibrosis is healing gone wrong. Too much build up of scar tissue.

Hallmark of congestive heart failure, liver cirrhosis, diabetes, chronic asthma, etc.

20mm+ patients suffer from organ failure due to fibrosis.

There is a view that fibrosis pathology is common across tissues.

A successful anti-fibrosis drug could see sales over $20 billion.



Micrograph of Liver Fibrosis

Massive Market Opportunities for a Disease-Modifying Fibrosis Drug

Indication	Total Addresable Market ($ billion)
Diabetic Retinopathy	$5 billion+
Diabetic Nephropathy	$15 billion+
Scleroderma	$3 billion+
Pulmonary Fibrosis	$5 billion+
Liver Fibrosis / Cirrhosis	$10 billion+
Cardiac / Artheriosclerosis	$10 billion+

Source: Stifel Estimates

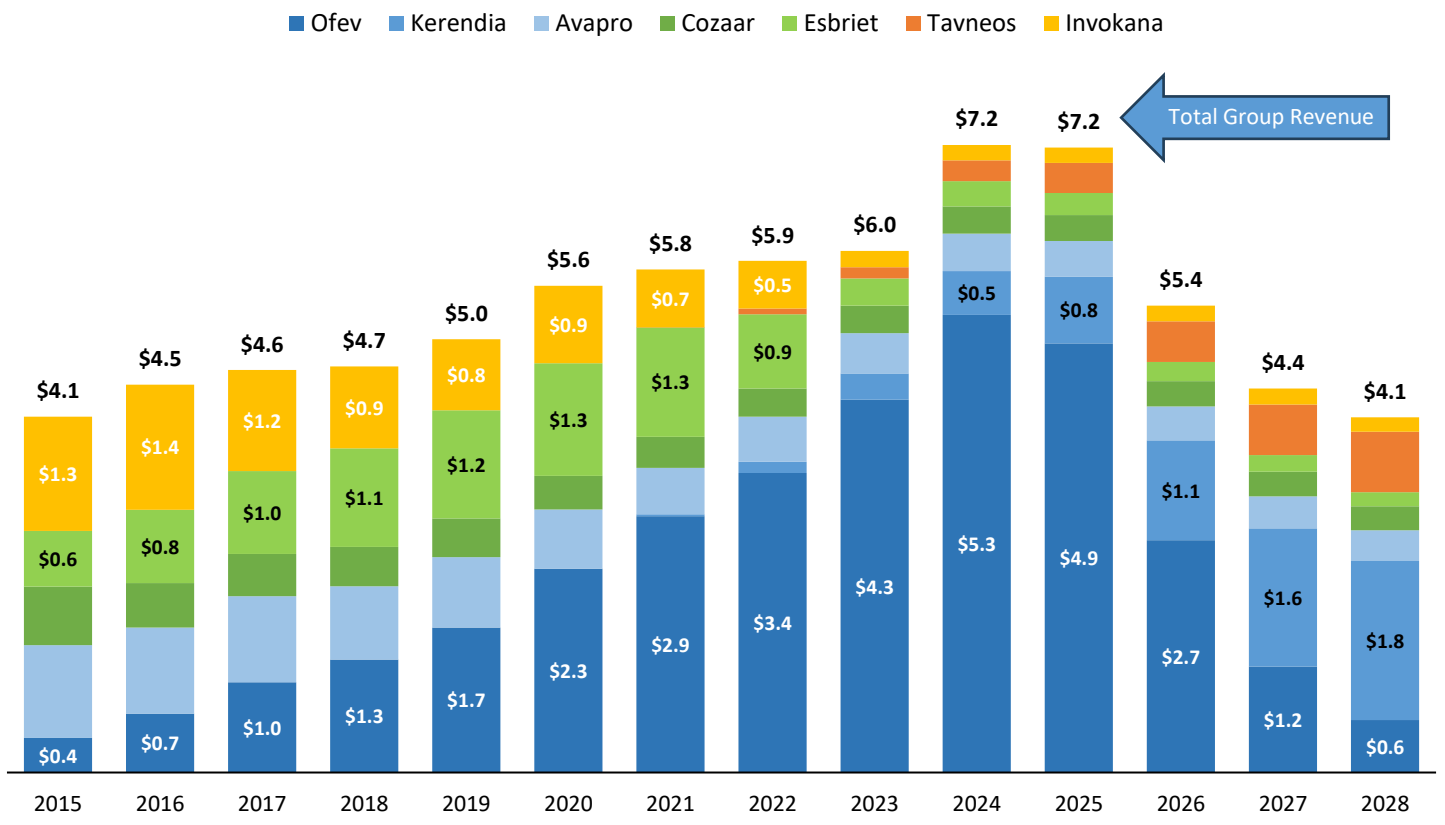
Revenue Profile of In-Line Products in Fibrosis

Historical and projected revenue demonstrates blockbuster potential in fibrosis, but also highlights the lack of available treatments given the underlying market potential.

Product Profiles of Major Fibrosis Products

Product	Marketer	1st Launch	Indication	2024E Sales
OFEV (nintedanib)	Boehringer Ingelheim	2014	IPF ILDs, incl. SSc-ILD	$5.26bn
Kerendia (finerenone) tablets	BAYER	2021	CKD associated with T2D	$0.50mm
Avapro (irbesartan) Tablets	sanofi	1997	Hypertension Diabetic Nephropathy	$0.43mm
COZAAR (losartan potassium tablets)	ORGANON	1995	Hypertension Diabetic Nephropathy	$0.31mm
Esbriet (pirfenidone) tablets	Roche	2008	IPF	$0.29mm
TAVNEOS (avacopan)	AMGEN	2021	AAV	$0.24mm
Invokana (canagliflozin) tablets	Johnson & Johnson	2013	Diabetic Nephropathy	$0.18mm

Historical and Projected Revenue (in $bn)

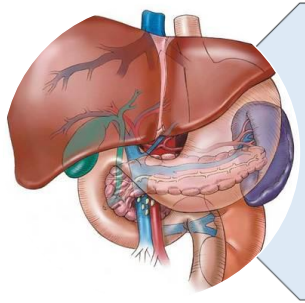


Sources: Evaluate Pharma, FDA, company and product websites

Examples of Fibrosis Products in Clinical Development

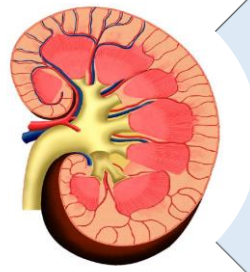
Idiopathic Pulmonary Fibrosis

- Roche's Esbriet / Pirfenidone is approved
- Boehringer's nintedanib Ofev (TKI inhibitor) is approved
- BMS in Phase 3 with BMS-986278 an LPA1 antagonist
- Pliant is in Phase 2 with Bexotegrast, a dual selective inhibitor of αvβ6/αvβ1



NASH / Liver Fibrosis

- Madrigal has a pending NDA for Resmetirom a THR-ß antagonist
- Akero and 89Bio are developing FGF21 modulators for NASH
- Eli Lilly in Phase 2 development with Tirzepatide (GLP-1 agonist)
- Viking is in Phase 2 with VK2809, a TRß antagonist



Kidney Fibrosis

- Bayer is approved with Kerendia for CKD
- Travere is Approved for Sparsentan for IGA Nephropathy
- Alentis is in Phase 2 with lixudebart for Rapidly Progressive Glomerulonephritis
- Certa is in Phase 1 development with OCX063 for CKD and FSGS

Fibrosis Pipeline by Specific Targeted Disease

Lead Phase[1]	Lung Fibrosis / IPF	Liver Fibrosis / NASH	Kidney Fibrosis / CKD	Scleroderma / Sclerosis
Marketed	Esbriet (pirfenidone) tablets; OFEV (nintedanib)		Avapro (irbesartan) Tablets; Cozaar (Losartan Potassium Tablets); Invokana (canagliflozin) tablets; Kerendia (finerenone) tablets; TARPEYO (budesonide) delayed release capsules; TAVNEOS (avacopan)	Mitchga Syringes; Saphnelo (anifrolumab-fnia) Intravenous Use 300 mg/vial; UPLIZNA (inebilizumab-cdon) INJECTION
Phase 3	Boehringer Ingelheim; Bristol Myers Squibb; 正大天晴 CHIATAI TIANQING; United Therapeutics	akero; CymaBay; Galectin Therapeutics; inventiva; Madrigal Pharmaceuticals	CSL; Lilly Retatrutide; TRAVERE THERAPEUTICS	
Phase 2	BLADE THERAPEUTICS; calliditas THERAPEUTICS; MEDICINOVA; PLIANT; PURETECH HEALTH; Redx; sanofi Belumosudil	89bio; calliditas THERAPEUTICS; GENFIT Towards Better Medicine; Lilly Tirzepatide; PLIANT; VIKING THERAPEUTICS	Alentis THERAPEUTICS; GLYCADIA PHARMACEUTICALS; Lilly Tirzepatide	CERTA THERAPEUTICS; OliX Pharmaceuticals; sanofi Romilkimab
Phase 1	AGOMAB THERAPEUTICS; Alentis THERAPEUTICS; IMMUNOMET; mission therapeutics; Lassen THERAPEUTICS	Alentis THERAPEUTICS; ALIGOS THERAPEUTICS; Lilly PNPLA3, SCAP siRNA; OliX Pharmaceuticals	CERTA THERAPEUTICS; mission therapeutics; skye	THIRONA BIO

Note: (1) Last initiated phase shown for lead phase, i.e. a Phase 3 ready asset will be shown as Phase 2

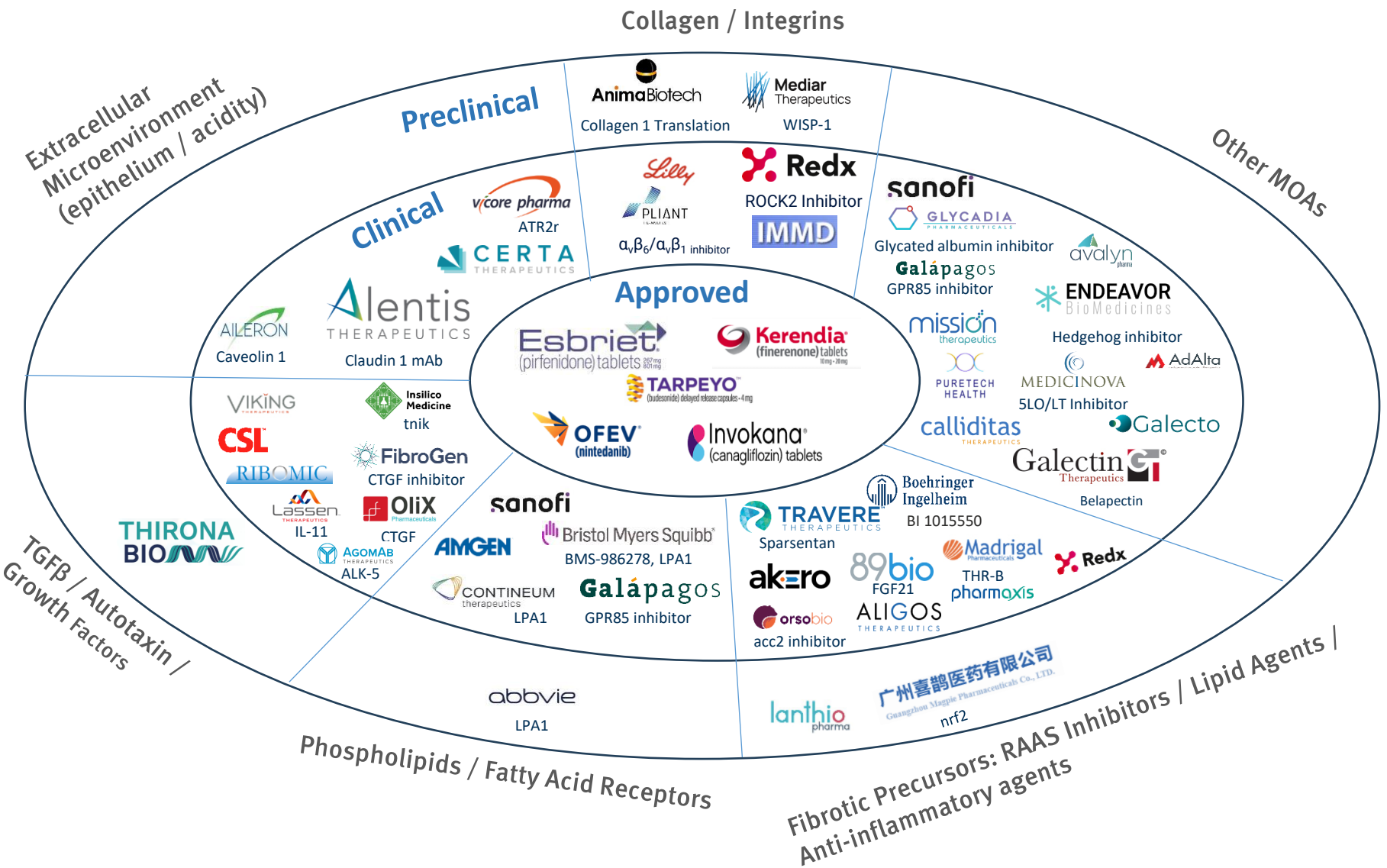
Source: Stifel Research and DealForma

The fibrosis development field is somewhat crowded.

However, data showing dramatic efficacy of antifibrotic agents is largely absent, perhaps with the exception of collagenase which is used for Dupuytren's Syndrome.

Further, few of these players are developing drugs that can reverse disease. The general exception is in liver disease where a regenerative liver means that a slowdown in buildup of fibrosis can eventually be disease modifying.

Fibrosis Pipeline by Mechanism of Action



This chart classifies drugs in development in broad sense by mechanism of action.

Many drugs in development work through the classic TGFß pathway, while others attempt to interfere directly with cross-linked collagens or associated integrins involved in laying down collagen.

Yet other agents are designed to slow down environmental pressures leading to fibrosis including lipid buildup, inflammation, epithelial-to-mesenchymal transition or even acidity.

Source: Stifel Research and DealForma

Public Company Valuations in Fibrosis

Company	Lead Asset	MOA	Lead Indication	Current Status	Latest Data	Market Cap	Enterprise Value
Madrigal	Resmetirom	THR-β	NASH	Ph3	Ph3 Topline	$4,349	$4,231
CymaBay	Seladelpar	PPARδ Agonist	PBC	Filed	Ph3 Pivotal	$2,701	$2,367
Viking	VK2809	TRβ Agonist	NASH	Ph2b	Ph2a	$2,346	$1,969
Akero	Efruxifermin	FGF21 Analogue	NASH	Ph3	Ph2b	$1,159	$627
Pliant	PLN-74809	α1β6/αvβ1 Inhibitor	IPF	Ph2b	Ph2a	$1,042	$529
89bio	Pegozafermin	FGF21 Analogue	NASH	Ph3 Ready	Ph2b	$926	$502
PureTech	LYT-100	TNFα Inhibitor	IPF	Ph2b	Ph2	$649	$402
Travere	Filspari	Angiotensin II Receptor	IgAN	Marketed	Approval	$638	$380
Calliditas	Tarpeyo	NOX Inhibitor	IgAN	Marketed	Approval	$570	$565
Vicore	C21	ATR2r	IPF	Ph2b Ready	Ph2a	$140	$90
Galectin	Belapectin	GAL3 Inhibitor	NASH	Ph3	Ph2b	$109	$151
Redx	EXC007	ROCK2 Inhibitor	IPF	Ph2a	Ph1	$98	$92
MediciNova	MN-001	5LO/LT Inhibitor	NASH	Ph2	Ph1	$69	$17
Aligos	ALG-055009	THR-β	NASH	Ph2a Ready	Ph1	$56	-$14
Aileron	LTI-03	Caveolin 1	IPF	Ph1b	Ph1a	$23	$11
Galecto	GB1211	GAL3 Inhibitor	Liver Fibrosis	Ph2	Ph1b/2a	$17	-$27
AdAlta	AD-214	CXCR4 Inhibitor	IPF	Ph1	Ph1 Interim	$8	$8

The median Phase 1 company in fibrosis has a public market today of $56 million. The mean value is similar. EV's are much lower. Values go up quickly once positive datasets are achieved.

Overall	**1st Q**	**$69**	**$17**
	Mean	**$876**	**$700**
	Median	**$570**	**$380**
	3rd Q	**$1,042**	**$565**
Phase 1 Data Reported	**1st Q**	**$23**	**$8**
	Mean	**$51**	**$23**
	Median	**$56**	**$11**
	3rd Q	**$69**	**$17**
Phase 2 Data Reported	**1st Q**	**$132**	**$136**
	Mean	**$799**	**$530**
	Median	**$787**	**$452**
	3rd Q	**$1,071**	**$553**
Phase 3 Data Reported (Excl. Commercial)	**1st Q**	**$3,113**	**$2,833**
	Mean	**$3,525**	**$3,299**
	Median	**$3,525**	**$3,299**
	3rd Q	**$3,937**	**$3,765**

Source: Stifel Research and CapitalIQ

Historical Licensing Deals in Fibrosis, 2015 to 2023

The median upfront payment in these deals was $30 million (clinical or pre-clinical). The mean upfront was $58 million.

Ann. Date	In-licensor	Out-Licensor	Lead Asset	Status on Deal Date	Lead Indication	Upfront Cash	Total Deal Value	Upfront / Total	Max Royalty[1]
May-23	GENFIT	Seal Rock	SRT-015	Ph2a	Liver Diseases	Und	$107	N/A	Tiered
Sep-22	Novo Nordisk	Ventus	VENT-01	PC	NASH, CKD	$70	$703	10%	Tiered
Aug-22	Roche	Kiniksa	Vixarelimab	Ph2b	Fibrosis-related Diseases	$100	$700	14%	Und.
Dec-21	Lilly	Regor	Metabolic Disorders Program	PC	Diabetes	$50	$1,550	3%	Low DD
Nov-21	GSK	Arrowhead	ARO-HSD	Ph1/2	NASH	$120	$1,030	12%	Tiered
Nov-21	Ironwood	Cour Pharma	CNP-104	Ph1 Ready	PBC	$20	$495	4%	Low DD
Sep-21	Incyte	Syndax	Axatilimab	Ph2	cGVHD, IPF	$152	$602	25%	DD
Feb-21	SarcoMed	Protalix	PRX–110	Ph2	IPF	$4	Und.	N/A	Tiered
Nov-20	AstraZeneca	Ionis	ION-455	PC	NASH	$30	$330	9%	Und.
Nov-20	Galapagos	OncoArendi	OATD-01	Ph2 Ready	IPF	$30	$377	8%	Low DD
Aug-20	Takeda	Engitix	Fibrotic Research Project	PC	Liver Fibrosis	Und.	$500	N/A	Und.
Aug-20	Merck	Hanmi Pharma	Efinopegdutide	Ph2	NASH	$10	$870	1%	DD
Jul-19	Boehringer Ingelheim	Bridge Bio	BBT-887	Ph1	IPF	$51	$1,301	4%	Und.
Jul-19	Boehringer Ingelheim	Yuhan	FGF21/GLP1 Agonist	PC	NASH	$40	$870	5%	Tiered
Apr-19	Gilead	Insitro	NASH targets	PC	NASH	$15	$1,050	1%	Und.
Jan-19	Gilead	Yuhan	NASH Program	PC	NASH	$15	$785	2%	Und.
Sep-18	United Tx	Biosplice	SM04646	Ph1	IPF	$10	$350	3%	DD
May-18	Novo Nordisk	Epigen	LPA1 Receptor Program	PC	Diabetic & Chronic Kidney Disease	Und.	$200	N/A	Tiered
Aug-18	Poxel	DeuteRx	DRX-065	Ph1	NASH	$8	Und.	N/A	Low SD
Apr-18	AstraZeneca	Ionis	AZD2693	PC	NASH	$30	$330	9%	Und.
Jan-18	NeuroBo	Dong-A ST	DA-9801	Ph2	Diabetic Neuropathy	$2	$180	1%	Und.
Oct-17	Boehringer Ingelheim	Dicerna	GalXC RNAi Program	PC	CLD	$10	$201	5%	Low DD
Dec-16	Novartis	Conatus	Emricasan	Ph2	NASH, CLD	$50	Und.	N/A	Und.
Nov-16	Bristol Myers Squibb	Nitto Denko	ND-L02-s0201	Ph1b	Liver Fibrosis	$100	Und.	N/A	Und
Apr-16	Gilead Sciences	Nimbus	ACC Program	Ph1	NASH	$400	$1,200	33%	Und.
Apr-16	Dong-A	Tobira	Suganon	Ph2	NASH	$2	$75	3%	Tiered
Jan-15	Gilead	Phenex	FXR Program	PC	NASH	$100	$470	21%	Und.

Overall	1st quartile	$10	$330	3%
	Mean	$58	$626	8%
	Median	$30	$551	5%
	3rd quartile	$70	$870	10%

Source: Stifel Research, internal deal database and DealForma.

Historical M&A Deals in Fibrosis, 2010 to 2023

The median upfront payment in these fibrosis M&A was $150mm. Median total deal package of $255 million. Obviously, M&A deals draw higher upfronts than license transactions.

Date	Seller	Buyer	Stage Signed	Indication	Upfront Cash	Total Value
10/31/2023	Lung Therapeutics	Aileron Therapeutics	Phase 2	IPF	$29	$47
08/21/2023	Bird Rock Bio	Skye Bioscience	Phase 1	CKD	NA	$20
10/20/2022	DJS Antibodies	AbbVie Inc.	Preclinical	IPF	$255	$255
10/28/2021	Origo Biopharma	AgomAb Therapeutics	Preclinical	IPF	NA	NA
09/07/2021	Metys Pharmaceuticals	Novaremed AG	Phase 2	CKD	NA	NA
04/02/2020	Curzion Pharma	Horizon Therapeutics	Phase 2	Scleroderma	$45	$45
11/15/2019	Promedior	Roche	Phase 2	IPF	$390	$1,390
08/31/2015	Promedior	Bristol Myers Squibb	Phase 2	IPF	$150	$1,250
05/07/2015	Lanthio Pharma	MorphoSys	Preclinical	CKD	$23	$23
08/24/2014	InterMune	Roche	Approved	IPF	$8,300	$8,300
5/12/2014	Lumena	Shire	Phase 1	NASH	260	NA
05/05/2014	Fibrotech	Shire	Phase 1	CKD	$75	$558
2/14/2012	Stromedix	Biogen	Phase 1	CKD	$75	$488
11/21/2011	Excalliard Pharma	Pfizer	Phase 1	Scleroderma	$45	$135
7/21/2011	Amira	Bristol Myers Squibb	Phase 1	IPF	$325	$475
12/20/2010	Arresto	Gilead	Preclinical	General Fibrosis	$225	$225

First Quartile	$45	$47
Mean	$784	$1,016
Median	$150	$255
Third Quartile	$260	$558

Source: Stifel Research, internal deal database and DealForma.

Significant Value Can be Associated with Deals Involving Early-Stage Fibrosis Compounds

Buyer	Target	Year	Key Indication	Mechanism	Validated Target?	Last Completed Phase	Upfront	Total Package
Gilead	Phenex	2015	Liver Fibrosis	FXR Agonist	Yes	Discovery	$100	$470
Gilead	Arresto	2010	Fibrosis	LOXL2 Agonist	No	Preclinical	$225	$225
Shire	Fibrotech	2014	FSGS	Undisclosed	No	Preclinical	$75	$650
Merck	NGM	2015	NASH	β-Klotho/FGFR1c	No	Preclinical	$95	$450
Boehringer-Ingelheim	Inventiva	2016	IPF	Undisclosed	No	Preclinical	NA	$175
Shire	Lumena	2014	NASH	Undisclosed	No	Phase 1	$260	na
Biogen	Stromedix	2012	IPF	Integrin Target	No	Phase 1	$75	488
BMS	Amira	2011	IPF	LPA1r Agonist	No	Phase 1	$325	$475
BMS	Nitto Medic	2016	Liver Fibrosis	HSP47	No	Phase 1b	$100	NA
Pfizer	Excaliard Pharma	2011	Scleroderma	CTGF Blockage	No	Phase 2a	NA	NA
Novartis	Conatus Pharma	2017	Cirrhosis	Pan Caspase Inhibitor	No	Phase 2a	$50	$450
Roche	Promedior	2019	IPF	Pentraxin-2	No	Phase 2b	$390	$1,450
BMS	Promedior	2015	IPF	Pentraxin-2	No	Phase 2a	$150	$1,250
Roche	Intermune	2011	IPF	TGF-ß	No	Marketed	$8,300	$8,300
						Median Overall	$125	$475
						Preclinical/P1	$100	$470

This table shows upfront payments made in fibrosis licensing and M&A deals in the 2011 to 2019 period. Interestingly, upfront payments, on average, are a little higher for earlier stage compounds. Fibrosis compounds are sold based on science rather than on clinical data. This is because there has only been one compound (Pirfenidone) that got approved for a mainstream indication in fibrosis.

Stifel has been involved as an advisor with three deals listed in this table (Phenex, Fibrotech and Conatus). We have observed that the quality of the preclinical packages were key in generating attractive deal economics.

Source: Stifel Research, Stifel internal fibrosis deal database and DealForma.

Factors to Consider in Developing Fibrosis Drugs

Slow Moving Disease

- Kidney, lung and liver fibrosis involve the gradual excess deposition of extracellular matrix
- This disease progresses over a period of decades rather than months which one typically looks at in trials
- Clinically meaningful therapeutic changes can take 3-5 years to manifest
- There are some settings such as NASH, RPGN and chronic allograft nephropathy where the disease moves faster

Reaching Meaningful Efficacy in Man is Key

- There are few resounding POC success stories in man. Approved drugs have modest efficacy and/or significant AEs
- Failure rates in fibrosis clinical trials have been all too high
- Success stories to date include collagenase in Dupuytren's, BMS with its LPA1r and Lilly with Tirzepatide
- Multi-billion plus market valuations are available after reaching meaningful efficacy

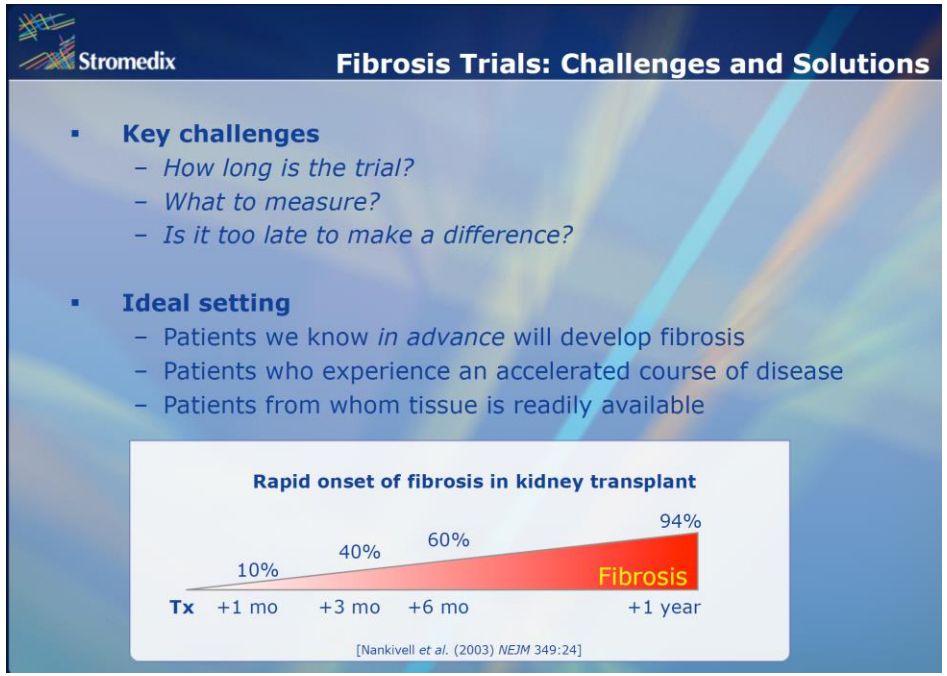
Disease Reversal is a Priority

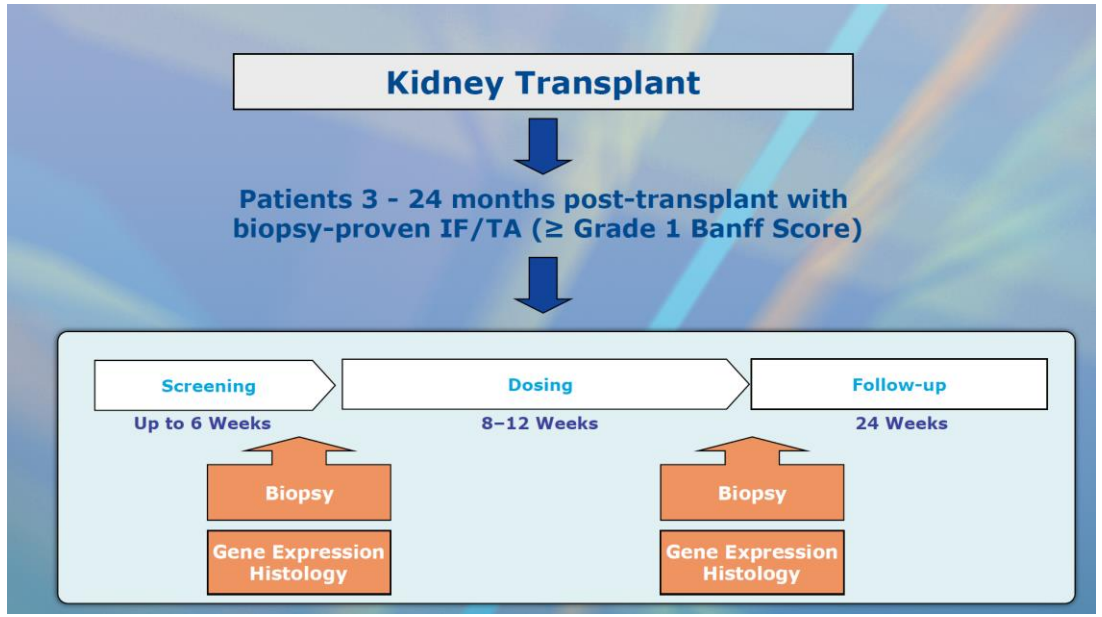
- A particular need is for drugs that can degrade cross-linked collagen and reverse fibrosis vs slowdown of progress
- We are seeing progress in this area in liver fibrosis because the liver remodels quickly. There has been some progress as well IPF where some agents are showing improvements in FVC
- A major current medical priority is to find ways to reverse fibrosis in kidney and cardiac tissue

Source: Stifel Research and industry conversations

Stromedix Attacked a Fast-Moving Form of Kidney Fibrosis

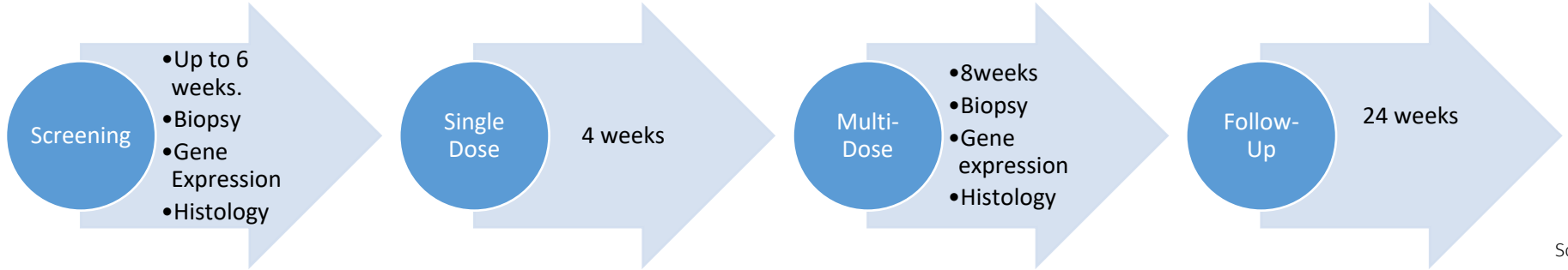
Even though Stromedix's integrin drug candidate did not get approved after its acquisition by Biogen, the company was quite clever in clinical trial design. They recognized that kidney fibrosis will develop quickly after a transplant with high likelihood and therefore represent an ideal setting in which to achieve a clinical POC.





The standard protocol after a kidney transplant is to assess success with periodic biopsies, Stromedix was able to obtain biopsy level data including histological evidence of regression of fibrosis and gene expression information.

Stromedix Phase 2 Study Design:



Source: Stromedix, Nonconfidential Deck, Dec 2008

Another Approach to Fibrotic Kidney Disease

The Swiss company Alentis is developing an antibody against Claudin-1 in kidney fibrosis. While this disease normally moves very slowly, Alentis has identified a rapidly moving form of the disease in patients with ANCA-Associated Vasculitis. This strategy appears to have high promise.

Basel, Switzerland – Dec 5, 2023, Alentis Therapeutics ("Alentis"), a clinical-stage biotechnology company developing treatments for Claudin-1 positive (CLDN1+) tumors and organ fibrosis, announced today the first patient dosed in a Phase 2 clinical trial of lixudebart (formerly named ALE.F02), a Claudin-1 (CLDN1) targeting investigational antibody for the treatment of organ fibrosis.

The randomized, double-blind, placebo-controlled Phase 2 study (NCT06047171) of lixudebart evaluates the drug's safety, tolerability, pharmacokinetics, and how well it protects against the loss of kidney function. The study plans to recruit patients with Antineutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis with Rapidly Progressive Glomerulonephritis (RPGN). This disease typically causes a rapid and dramatic loss of kidney function and can result in kidney loss with patients requiring dialysis or a transplant. While current treatments can eventually stabilize the underlying disease ('vasculitis'), there's a need to specifically protect against the severe and dramatic kidney loss that occurs while awaiting stabilization.

"*With lixudebart (ALE.F02) we explore a truly novel approach in ANCA-RPGN patients. It is the second clinical trial investigating lixudebart in patients after the initiation of a clinical study in advanced liver fibrosis patients earlier this year,*" said Luigi Manenti, MD, Chief Medical Officer of Alentis. "*The ANCA-RPGN trial is a steppingstone to develop lixudebart for other more common renal indications that are characterized by high CLDN1 expression such as lupus nephritis, IgA nephropathy and diabetic nephropathy.*"

Per Ivarsen, Clinical Professor and Principal Investigator of the trial at Aarhus University Hospital in Denmark added, "*Dosing the first patient in the study at our hospital brings us a step closer to understanding the potential of lixudebart (ALE.F02) to treat patients with this very severe renal disease. I am looking forward to the study progressing as more patients are enrolled, and to seeing the results of the study.*"

David Jayne, Professor of Clinical Autoimmunity at Cambridge University said, "*This is an important study into the potential of lixudebart (ALE.F02) to recover kidney function in patients with severe nephritis due to ANCA-associated vasculitis. Chronic and end-stage kidney disease remain common outcomes for patients, and this study will give us our first indication on the safety and efficacy of lixudebart in this population.*"

Source: https://alentis.ch/alentis-therapeutics-doses-first-anca-associated-vasculitis-rapidly-progressive-glomerulonephritis-patient-in-phase-2-clinical-trial-of-lixudebart-ale-f02/

Update on Endometriosis Research

Endometriosis

Affects

30,000,000+

Women in G8 countries.

Affects female life course in profound ways.

Associated with severe pain, stigma and shame.

Sufferers widely neglected and often go undiagnosed.

Only specialists in the market focus on surgery which is not a great long-term fix.

Scientific explanations for the disease have been advancing in recent years, opening up the potential for novel therapeutic approaches.

Surge in Endometriosis Research After Decades of Underfunding Could Herald New Era for Women's Health

Clare Watson, *Nature Medicine*, Feb 6, 2024

Advances in organoids and the role of the microbiome and diet are leading to new diagnostics and treatments for endometriosis, motivating a precision health approach to this long-neglected disease.

In the 7 to 10 years it takes, on average, for someone to be diagnosed with endometriosis, the disease can be dismissed by doctors as all manner of things. Even after a diagnosis is confirmed by surgery or, in some cases, by imaging, there are few lasting pain therapies and most other treatments interfere with fertility.

Hormone treatments can come with unwanted side effects, such as menopausal-like bone loss, and surgically removing lesions that grow throughout the pelvic cavity in endometriosis can sometimes make the pain worse. "Most of our approaches are pretty blunt," admits Jason Abbott, a gynecologist at the Royal Hospital for Women in Sydney, Australia.

But now, after years of tireless advocacy from people with the condition, endometriosis is slowly coming into sharper focus, with a surge in research that could radically change our understanding of the condition, and how to treat it.

In the past year, the largest genetic study of endometriosis and a range of single-cell sequencing studies have started teasing apart distinct subtypes of the disease that could explain symptoms or treatment responses. Researchers have also shown how bacteria can promote the growth of endometriosis lesions in mice and found an anti-inflammatory drug that shrinks these lesions in monkeys.

Source: https://www.nature.com/articles/s41591-024-02795-0

Teams have succeeded in culturing all known types of endometriosis lesions in the lab and refined their methods for growing organoids from menstrual fluid and biopsy tissues, which could expedite translational research. Plus, a French group released interim data from an industry-sponsored trial on the first-ever salivary diagnostic test for endometriosis that could slash diagnosis times, if validated.

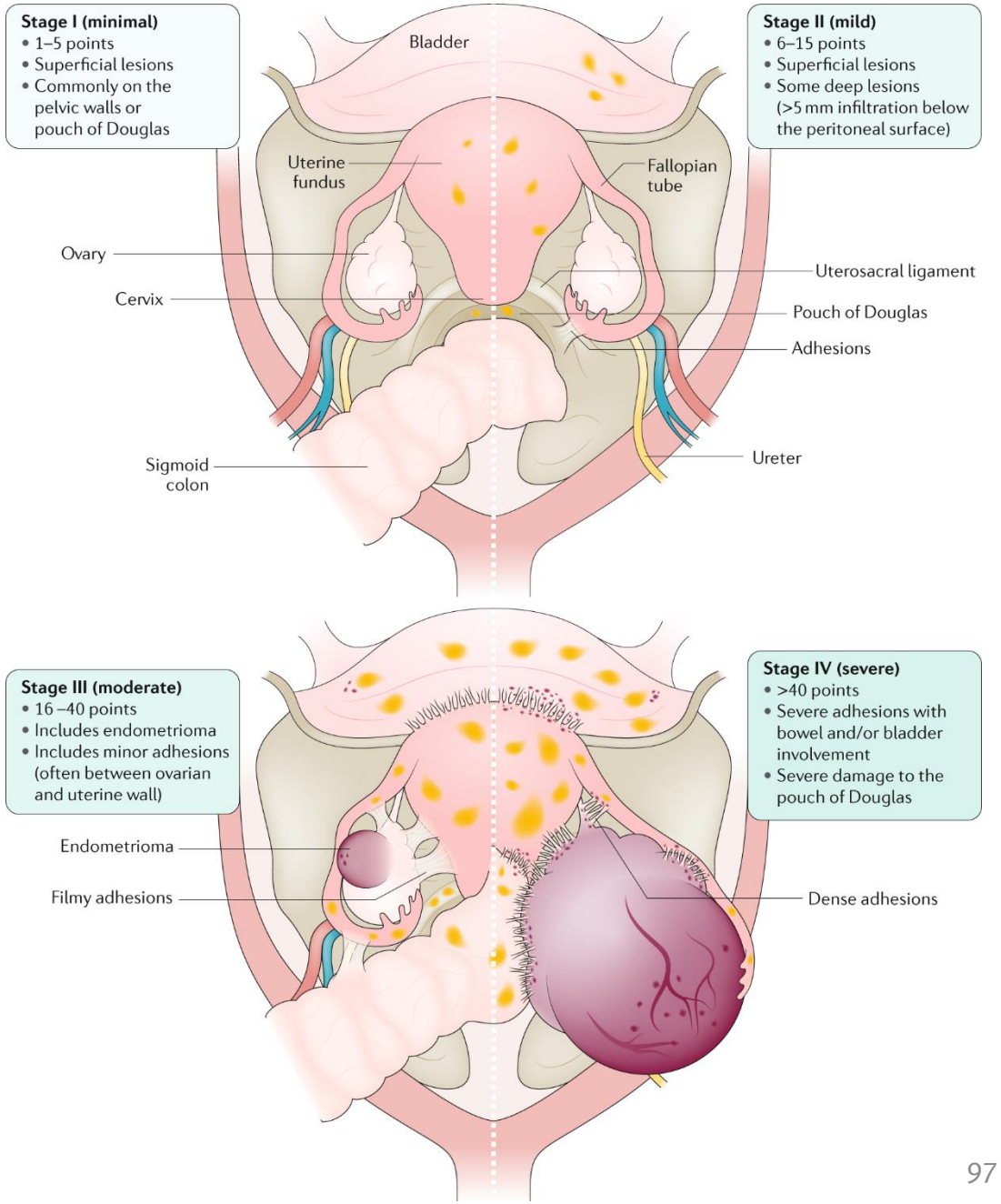
"A lot has happened in the last year, but it's just the beginning," says Caroline Gargett, a cell biologist at Hudson Institute of Medical Research in Melbourne, Australia. With the technologies researchers now have at their disposal, "we are really on the cusp of discovering much more" about endometriosis and the endometrium itself, she says.

Scottish and UK governments have introduced women's health plans in which endometriosis features highly; Connecticut passed a historic bill to create a state-wide endometriosis research program; and US federal funding for endometriosis research has also increased. But there is still an awfully long way to go before funding reflects the true burden of the disease, which parallels type 2 diabetes, Zondervan says. As one patient describes it, endometriosis is still "not talked about because it is about women's bodies and blood".

Stages of Endometriosis

The American Society for Reproductive Medicine (ASRM) stages or grades Endometriosis according to the number of lesions and depth of infiltration that doctors would assign points for. Based on the results, the condition is then ranked in one of four stages: minimal (Stage I), mild (Stage II), moderate (Stage III), and severe (Stage IV).

However, the stage does not correlate with pain or infertility. Having Stage 4 does not equate to having a lower quality of life compared to other stages. Some patients are graded with Stage 2 but face paralyzing pain too.



Novel Tests in Development to Test for Endometriosis

Test	Description	Sensitivity	Specificity	AUC
Ziwig Endotest®[1]	miRNAs saliva test	97%	100%	0.983
DotEndo® Test[2]	miRNAs blood and saliva test	83%	96%	0.939
Mitomic® Endometriosis Test[3]	8.7kb mtDNA blood test	81%	65%	0.801

Source: 1. Bendifallah, S., Suisse, S., Puchar, A., Delbos, L., Poilblanc, M., Descamps, P., Golfier, F., Jornea, L., Bouteiller, D., Touboul, C., Dabi, Y., & Daraï, E. (2022). Salivary MicroRNA Signature for Diagnosis of Endometriosis. Journal of Clinical Medicine, 11(3), 612; 2. Moustafa, S., Burn, M., Mamillapalli, R., Nematian, S., Flores, V., & Taylor, H. S. (2020). Accurate diagnosis of endometriosis using serum microRNAs. American journal of obstetrics and gynecology, 223(4), 557.e1–557.e11; 3. Harbottle, A., Maggrah, A., Usher, R., Desa, E., & Creed, J. M. (2020). A novel 8.7-kb mitochondrial genome deletion accurately detects endometriosis in the plasma of symptomatic women. Biomarkers in medicine, 14(2), 97–107.

Ziwig Endotest®

- Price: $1255[1]
- Available in Switzerland (reimbursed), UK, Germany and Austria[2]
- Won Prix Galien 2022 in the Medical Devices category[3]
- An ongoing trial of 1,000 patients in five medical centers across France[3]

Sources: 1. https://home2lab.co.uk/products/ziwig-endotest-the-revolutionary-new-saliva-test-for-endometriosis-diagnosis; 2. https://femtechinsider.com/zivig-saliva-based-endometriosis-test/; 3. https://sifted.eu/articles/femtechs-france-healthcare.

Ziwig External Validation Study

Inclusion Criteria:

- Patient aged between 18 and 43 years,
- Patient having dated and signed the consent form,
- Patient affiliated to the French health system,
- Patient with pelvic MRI and/or pelvic ultrasound,
- Patient from one of the 3 study populations:
  - Patient with a formal endometriosis diagnosed by clinical examination and imaging AND an indication for specialised endometriosis follow-up or medically assisted procreation (MAP) or surgery validated by RCP (in routine care);
  - Patient with suspected endometriosis for whom the diagnosis is the source of a discrepancy between clinical and radiological data AND a surgical indication validated by RCP (in routine care);
  - Patient with a gynaecological indication for surgery of the small pelvis by laparoscopy or laparoscopy validated in RCP (in routine care) AND symptoms suggestive of endometriosis (dysmenorrhoea, ...)(1).

Exclusion Criteria:

- Patient with recurrence of deep endometriosis (excluding endometrioma),
- Patient with endometriosis of the torus and/or utero-sacral ligaments without indication for surgery,
- Patient with parietal endometriosis alone without indication for surgery,
- Patient with adenomyosis alone on imaging without indication for surgery,
- Patient with gynaecological infection requiring surgical management,
- Pregnant patient,
- Patient infected with the human immunodeficiency virus (HIV),
- Patient with significant difficulties in reading or writing the French language,
- Patient with a personal history of cancer,
- Patient unable to comply with study and/or follow-up procedures,
- Patient who has objected to the collection of her data.
- Patient participating in another clinical research study.

- Prospective cohort study
- Enrollment: 1150 patients
- Estimated completion: Dec. 2023
- Inclusion: formally diagnosed or suspected endometriosis who are already receiving either medical (MAP) or surgical treatment
- Interim data
  - ✓ Sensitivity = 96.2%
  - ✓ Specificity = 95.1%
  - ✓ AUC = 0.96

Source: 1. Bendifallah, S., Dabi, Y., Suisse, S., Delbos, L., Spiers, A., Poilblanc, M., ... & Descamps, P. (2023). Validation of a Salivary miRNA Signature of Endometriosis—Interim Data. NEJM Evidence, EVIDoa2200282; 2. https://clinicaltrials.gov/study/NCT05244668.

DotLab EMPOWER Study Reasonable in Picking up Endometriosis

TABLE 1
Patient demographics and clinical characteristics

Variables	Endometriosis (n = 41)	Control (n = 59)
Age	34.1 ± 7.1	36.9 ± 8.2
Body mass index	28.1 ± 7.5	30.4 ± 7.5
Race, n %		
White	28 (68)	24 (40)
Black/African American	4 (10)	18 (31)
Hispanic	7 (17)	12 (20)
Asian	2 (5)	2 (3)
Other	0 (0)	3 (5)
rASRM endometriosis stage		
I	11 (27)	—
II	7 (17)	—
III	15 (36)	—
IV	8 (19)	—
Control diagnoses		
No abnormality	—	18 (31)
Leiomyoma	—	23 (39)
Cystadenoma	—	4 (7)
Chronic infection	—	5 (8)
Teratoma	—	3 (5)
Paratubal cyst	—	6 (10)
Hormonal treatment		
Combined OCP	10 (24)	10 (17)
Progesterone	5 (12)	16 (27)
Estrogen	0 (0)	1 (2)
GnRH agonist	6 (14)	5 (8)
Aromatase inhibitor	1 (2)	1 (2)
No treatment	19 (46)	26 (44)
Phase of menstrual cycle		
Proliferative	8 (19)	14 (24)
Secretory	15 (36)	13 (22)
Unable to determine	18 (44)	32 (54)

GnRH, gonadotropin-releasing hormone; *OCP*, oral contraceptive pill; *rASRM*, revised American Society of Reproductive Medicine.

Moustafa et al. Endometriosis diagnosis by microRNA biomarkers. Am J Obstet Gynecol 2020.

TABLE 2
ROC analysis of individual miRNAs

ROC model	Area	SE	95% Wald confidence limits	Optimal cutoff	Correct, %	Sensitivity, %	Specificity, %
miR_125b	0.73	0.05	0.63–0.83	0.084	68.0	56.1	78.0
miR_150	0.68	0.06	0.57–0.78	0.44	63.9	20.0	94.7
miR_342	0.92	0.04	0.86–0.99	0.085	90.8	90.0	91.2
miR_451a	0.84	0.04	0.76–0.92	0.35	79.8	90.0	72.9
miR_3613	0.76	0.05	0.66–0.85	0.014[a]	74.0	92.7	61.0
let_7b	0.78	0.05	0.69–0.87	0.012[a]	73.7	82.5	67.8

miRNA, microRNA; *ROC*, receiver-p[erating characteristic.

[a] Greater than cutoff indicates lower odds of being in the endometriosis group.

Moustafa et al. Endometriosis diagnosis by microRNA biomarkers. Am J Obstet Gynecol 2020.

- Description: Performance of a microRNA (miRNA)-based assay compared to visual inspection during surgery for the diagnosis of active endometriosis
- Outcome: Clinical validity

Source: Moustafa, S., Burn, M., Mamillapalli, R., Nematian, S., Flores, V., & Taylor, H. S. (2020). Accurate diagnosis of endometriosis using serum microRNAs. *American Journal of Obstetrics and Gynecology*, 223(4), 557.e1–557.e11.

Endometriosis Prevalence is Surprisingly High

ENDOMETRIOSIS | VOLUME 96, ISSUE 2, P360-365, AUGUST 2011

ENDOMETRIOSIS

Incidence of endometriosis by study population and diagnostic method: the ENDO study

Germaine M. Buck Louis, Ph.D.,[a] Mary L. Hediger, Ph.D.,[a] C. Matthew Peterson, M.D.,[b] Mary Croughan, Ph.D.,[d,e] Rajeshwari Sundaram, Ph.D.,[a] Joseph Stanford, M.D.,[c] Zhen Chen, Ph.D.,[a] Victor Y. Fujimoto, M.D.,[d] Michael W. Varner, M.D.,[b] Ann Trumble, Ph.D.,[a] and Linda C. Giudice, M.D., Ph.D.,[d] on behalf of the ENDO Study Working Group

[a] Division of Epidemiology, Statistics, and Prevention Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Rockville, Maryland; [b] Department of Obstetrics and Gynecology and [c] Department of Family and Preventive Medicine, University of Utah, Salt Lake City, Utah; and [d] Department of Obstetrics, Gynecology, and Reproductive Sciences and [e] Department of Epidemiology and Biostatistics, University of California, San Francisco, California

Objective: To estimate the incidence of endometriosis in an operative cohort of women seeking clinical care and in a matched population cohort to delineate more fully the scope and magnitude of endometriosis in the context of and beyond clinical care.
Design: Matched-exposure cohort design.
Setting: Surgical centers in the Salt Lake City, Utah, and San Francisco, California, areas.
Patient(s): The operative cohort comprised 495 women undergoing laparoscopy/laparotomy between 2007 and 2009, and the population cohort comprised 131 women from the surgical centers' catchment areas.
Intervention(s): None.
Main Outcome Measure(s): Incidence of endometriosis by diagnostic method in the operative cohort and by pelvic magnetic resonance imaged (MRI) disease in the population cohort.
Result(s): Endometriosis incidence in the operative cohort ranged by two orders of magnitude by diagnostic method: 0.7% for only histology, 7% for only MRI, and 41% for visualized disease. Endometriosis staging was skewed toward minimal (58%) and mild disease (15%). The incidence of MRI-diagnosed endometriosis was 11% in the population cohort.
Conclusion(s): Endometriosis incidence is dependent on the diagnostic method and choice of sampling framework. Conservatively, 11% of women have undiagnosed endometriosis at the population level, with implications for the design and interpretation of etiologic research. (Fertil Steril® 2011;96:360–5. ©2011 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, epidemiology, histology, incidence, laparoscopy, magnetic resonance imaging

The NIH estimates that 11% of the population of child-bearing age women in America have endometriosis.

They estimate the population at 6 million women.

Roughly 60% of these have minimal disease and 15% have mild disease. The other 25% have more severe disease.

Source: https://www.fertstert.org/article/S0015-0282(11)00873-9

See https://www.womenshealth.gov/a-z-topics/endometriosis

Endometriosis in America Survey in 2020

The 3rd Annual Endometriosis In America survey was conducted online from January through March of 2020. Of the 1,234 people who completed the survey, 85% had been diagnosed with endometriosis and 7% were in the process of being diagnosed.

Endometriosis is typically associated with pelvic pain, bloating, heavy bleeding, and painful periods. While these experiences are very really, the impacts of endometriosis go beyond the pelvis. In fact, this year's survey found that the most common endometriosis symptom was fatigue - affecting 96% of women. Similarly, 9 in 10 have experienced endo-related complications, with bowel and bladder problems being the most common.

70% of persons with endometriosis received a laparoscopy and over half of them received more than one. With an average out of pocket cost for a surgery of $4,923, out-of-pocket expenses can create a huge burden, especially after repeated surgeries.

While the symptoms and complications of endometriosis can impact many aspects of life, *relationships* are one area where endo can really take its toll. When faced with constant fatigue, debilitating pain, and unexpected flares, it can be difficult to maintain relationships with loved ones, family, and friends. 47% of women shared that endometriosis has negatively impacted their marriage/romantic relationships. Similarly, 44% cited a negative impact on their non-romantic relationships.

Endometriosis symptoms can be unpredictable and difficult to control. And, while surgery is the gold standard for endometriosis treatment, even after surgery, endo symptoms are likely to recur (or come back). Survey respondents rated the effectiveness of past surgeries as low, and 1 in 4 experienced complications from their endo surgery.

For many endo warriors, one of the most frustrating parts about endometriosis is being dismissed, ignored, or belittled. Sadly, many of our community members have faced this kind of discrimination. One member shared, "I have had endo symptoms since I was 15, and have just been brushed off by physicians and told that my complaints were normal". Another shared, "My endometriosis was not validated… my pain was written off as just being dramatic!".

When asked what they regret, our community members shared many different experiences. Many have regrets about using specific hormones or treatments, such as Lupron and Depo-Provera.

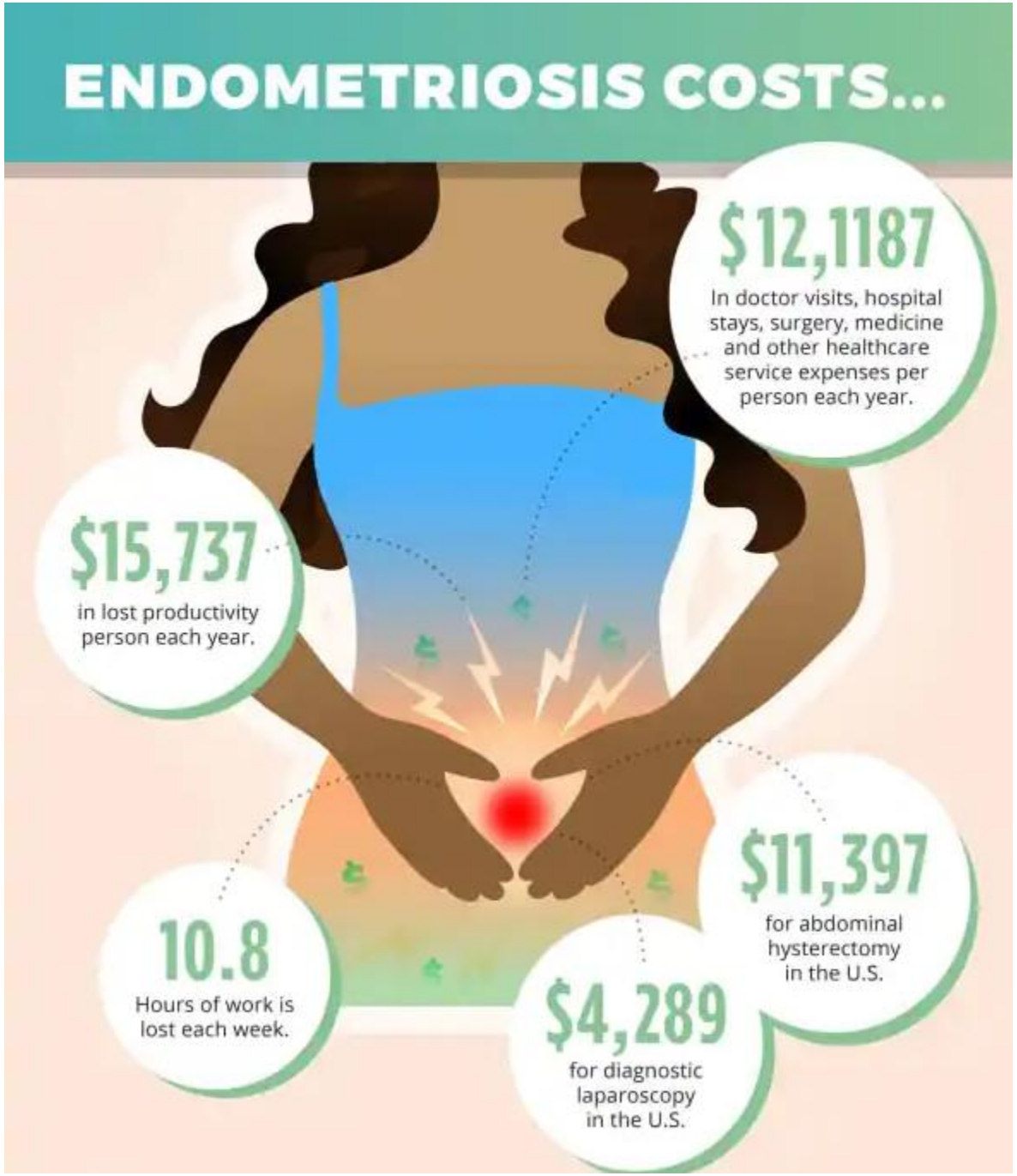
Source: https://endometriosis.net/infographic/speak-truth

Endometriosis is Costly

Endometriosis is expensive. Direct and indirect costs are difficult to approximate because the treatment is so holistic, and it impacts women in very different ways. First there are the diagnostic and excision surgery fees; often in the four-digit figures you'd think these were the biggest expenses. But people with chronic pain and associated symptoms like fatigue are often less productive than their physically fit counterparts.

Absences from work and reduced hours in the office can setback an annual household income by thousands. Then there are the difficult-to-budget-for lifestyle changes: expensive diets, physiotherapy appointments, painkillers, supplements, travel to-and-from appointments with specialists, period products and daycare costs for those with children.

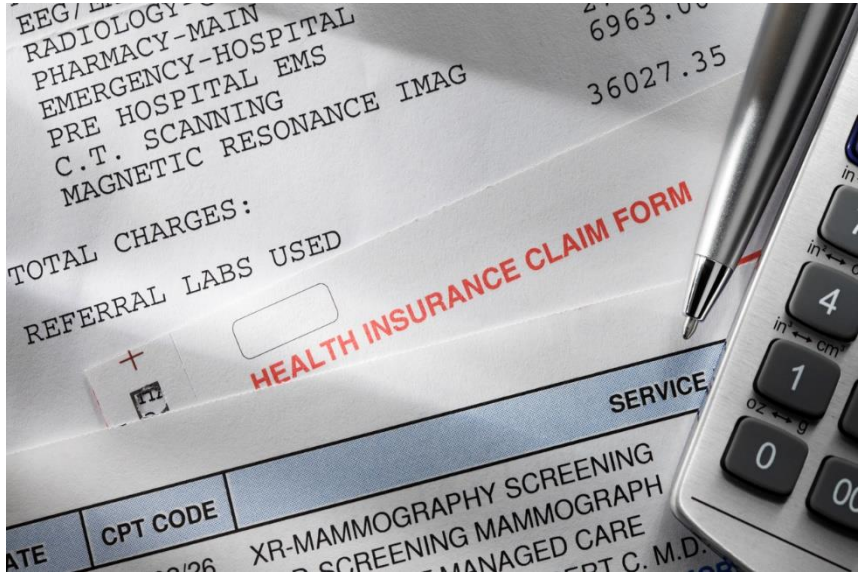
The economic burden of endometriosis in the U.S. is difficult to measure, though several large-scale studies have attempted to do so, and we've pulled out some of the main findings in the infograph at right. We also asked 22 women, ages 19-47 (with an average age of 30), to approximate the cost of living with endometriosis.



Source: https://www.sheknows.com/health-and-wellness/articles/1141872/what-endometriosis-costs/

Endometriosis Patients Are Expensive to Payors

Fuldeore M, Yang H, Du EX, Soliman AM, Wu EQ, Winkel C. Healthcare utilization and costs in women diagnosed with endometriosis before and after diagnosis: a longitudinal analysis of claims databases. *Fertil Steril.* 2015 Jan;103(1):163-71.



A total of 37,570 matched pairs of women with and without (controls) endometriosis were identified from the Truven Health MarketScan claims database (2000-2010).

Mean patient age at index (first diagnosis) date was 36.4 years for endometriosis patients and controls. Endometriosis patients had a higher utilization of outpatient and emergency room services during each pre- and post-index year, and a higher utilization of inpatient services during the last pre-index year and all 5 post-index years. Total costs were highest in the first post-index year for endometriosis patients, reaching $13,199, compared with $3,747 for controls. Annual costs were significantly higher for patients than controls during each pre- and post-index year; overall, the cost difference was $26,305 over 10 years: $7,028 in the 5 years before diagnosis and $19,277 in the 5 years after diagnosis.

Source: https://pubmed.ncbi.nlm.nih.gov/25455535/

Current Treatments for Endometriosis Are Far from Ideal

Chen LH, Lo WC, Huang HY, Wu HM. A Lifelong Impact on Endometriosis: Pathophysiology and Pharmacological Treatment. *Int J Mol Sci.* 2023 Apr 19;24(8):7503.

Endometriosis is defined by the presence of endometrial-like tissue (“lesions”) outside the uterine cavity confirmed during surgery, where the diagnosis is often delayed after the onset of symptoms and mistaken because of its nonspecific complaints.

Nowadays, the diagnosis of endometriosis can be accelerated by advanced imaging techniques and associated serum biomarkers. The conventional treatment includes surgical removal of endometriotic lesions followed by hormonal suppression.

Current pharmacological treatments have limited efficacy and unwanted side effects. Half of the women undergoing surgery without long-term medication control may have another procedure in 5 years, resulting in organ damage complicated with loss of function. Current therapeutic strategies highlight enduring symptom relief and fertility preservation.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10139092/

Kondo Paper: Fusobacterium Infection Found in 64% of Endometriosis Cases in Japanese Sample versus 7% in Controls

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ENDOMETRIOSIS

Fusobacterium infection facilitates the development of endometriosis through the phenotypic transition of endometrial fibroblasts

Ayako Muraoka[1,2], Miho Suzuki[1], Tomonari Hamaguchi[3], Shinya Watanabe[1], Kenta Iijima[1], Yoshiteru Murofushi[1], Keiko Shinjo[1], Satoko Osuka[2], Yumi Hariyama[4], Mikako Ito[3], Kinji Ohno[3], Tohru Kiyono[5], Satoru Kyo[6], Akira Iwase[7], Fumitaka Kikkawa[2], Hiroaki Kajiyama[2], Yutaka Kondo[1,8]*

Retrograde menstruation is a widely accepted cause of endometriosis. However, not all women who experience retrograde menstruation develop endometriosis, and the mechanisms underlying these observations are not yet understood. Here, we demonstrated a pathogenic role of *Fusobacterium* in the formation of ovarian endometriosis. In a cohort of women, 64% of patients with endometriosis but <10% of controls were found to have *Fusobacterium* infiltration in the endometrium. Immunohistochemical and biochemical analyses revealed that activated transforming growth factor–β (TGF-β) signaling resulting from *Fusobacterium* infection of endometrial cells led to the transition from quiescent fibroblasts to transgelin (TAGLN)–positive myofibroblasts, which gained the ability to proliferate, adhere, and migrate in vitro. *Fusobacterium* inoculation in a syngeneic mouse model of endometriosis resulted in a marked increase in TAGLN-positive myofibroblasts and increased number and weight of endometriotic lesions. Furthermore, antibiotic treatment largely prevented establishment of endometriosis and reduced the number and weight of established endometriotic lesions in the mouse model. Our data support a mechanism for the pathogenesis of endometriosis via *Fusobacterium* infection and suggest that eradication of this bacterium could be an approach to treat endometriosis.

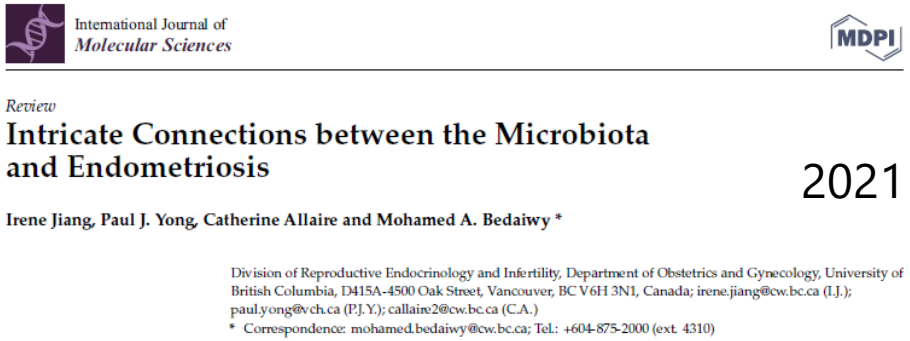
Source: https://www.science.org/doi/abs/10.1126/scitranslmed.add1531

Yutaka Kondo, Nagoya School of Medicine:

"Our findings suggest that *Fusobacterium* infection may contribute to the pathogenesis of endometriosis and that antibiotic treatment to eradicate endometrial infection should be further studied. Therefore, the next important requirement is clinical trials of antibiotic treatment for endometriosis patients in a big cohort."

The Lancet Microbe, July 18, 2023

Today, A Variety of Reviews Identify Bacterial Differences Associated with Endometriosis



International Journal of *Molecular Sciences*

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Review

Intricate Connections between the Microbiota and Endometriosis

2021

Irene Jiang, Paul J. Yong, Catherine Allaire and Mohamed A. Bedaiwy *

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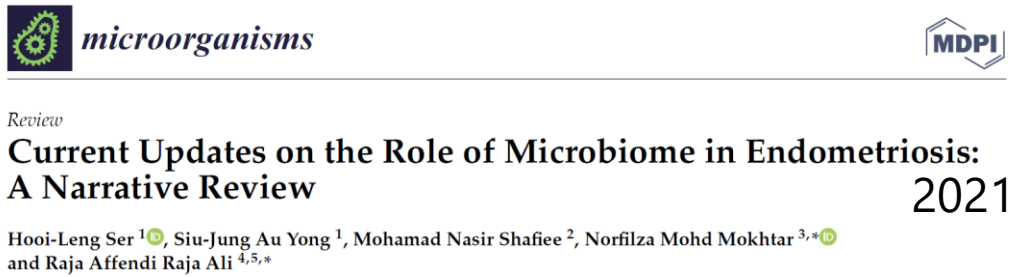

microorganisms

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Review

Current Updates on the Role of Microbiome in Endometriosis: A Narrative Review

2021

Hooi-Leng Ser [1], Siu-Jung Au Yong [1], Mohamad Nasir Shafiee [2], Norfilza Mohd Mokhtar [3,*] and Raja Affendi Raja Ali [4,5,*]

Reproductive Sciences (2021) 28:2367–2377
https://doi.org/10.1007/s43032-021-00506-5

ENDOMETRIOSIS: ORIGINAL ARTICLE

Associations Between Endometriosis and Gut Microbiota

Agnes Svensson [1] · Louise Brunkwall [2] · Bodil Roth [1] · Marju Orho-Melander [2] · Bodil Ohlsson [1]

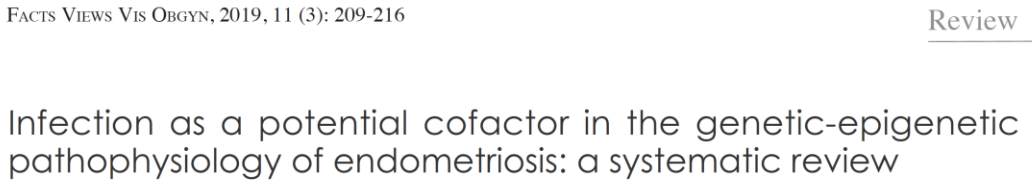
frontiers | Frontiers in Cellular and Infection Microbiology

Gut and genital tract microbiomes: Dysbiosis and link to gynecological disorders

2022

Hoda Elkafas[1], Melinique Walls[2], Ayman Al-Hendy[3] and Nahed Ismail[4*]

[1]Department of Pharmacology and Toxicology, Egyptian Drug Authority (EDA; formerly The National Organization for Drug Control and Research (NODCAR)), Cairo, Egypt, [2]Pritzker School of Medicine, University of Chicago, Chicago, IL, United States, [3]Department of Obstetrics and Gynecology, University of Chicago, Chicago, IL, United States, [4]Department of Pathology, University of Illinois at Chicago, Chicago, IL, United States



FACTS VIEWS VIS OBGYN, 2019, 11 (3): 209-216

Review

Infection as a potential cofactor in the genetic-epigenetic pathophysiology of endometriosis: a systematic review

P.R. KONINCKX[1,2,3,4], A. USSIA[3,5], M. TAHLAK[1], L. ADAMYAN[6,7], A. WATTIEZ[1,8], D.C. MARTIN[9,10,11], V. GOMEL[11]

For Example, Cregger Study Identified Bacterial Differences Between Those With and Without Endometriosis in 2017

Cregger MA, Braundmeier A, Lenz K, Leary E, Leach R et al. Reproductive microbiomes: using the microbiome as a novel diagnostic tool for endometriosis. Reprod Immunol 2017;2:36.

Background: Endometriosis is a chronic inflammatory disease which results in significant pain and long term reproductive consequences for up to 50% of infertile women. This study was focused to understand how endometriosis altered the uterine and cervical bacterial community.

Methods and findings: Urogenital swabs and uterine washes were collected from 19 pre-menopausal women undergoing laparoscopic surgery for pelvic pain, suspected endometriosis (experimental n=10), and women undergoing laparoscopic surgery for benign ovarian/uterine conditions (control n=9). Patients were followed for the next year and repeat cervical swabs were obtained. Bacterial community composition was assessed from these samples using Illumina next generation 16S rRNA amplicon sequencing. Bacterial communities were significantly different between sample sites, the uterus and cervix, and stage III endometriosis resulted in significant alterations in the cervical bacterial community. Both bacterial richness and phylogenetic diversity increased in association with stage III endometriosis. Surgical intervention resulted in a stabilized cervical bacterial community for a short period of time.

Conclusion: Bacterial community profiling may provide a useful diagnostic tool for identifying endometriosis in asymptomatic, infertile women in a clinical setting.

Source: https://reproductive-immunology.imedpub.com/reproductive-microbiomes-using-the-microbiome-as-a-novel-diagnostic-tool-for-endometriosis.php

Kahn Study Finds Convincing Evidence that Today's Hormonal Treatments May *Worsen* Endometriosis Given Bacterial Origin

Khan KN, Fujishita A, Hiraki K, Kitajima M, Nakashima M, Fushiki S, Kitawaki J. Bacterial contamination hypothesis: a new concept in endometriosis. *Reprod Med Biol*. 2018 Jan 18;17(2):125-133.

The authors examined the pattern of bacterial growth in the endometrial samples that had been derived from the GnRHa-treated and -untreated women with and without endometriosis, using the bacterial culture method. Among the colony formations of nine different microbial species, according to the treatment status of GnRHa, a significantly increased colony formation was found of Gardnerella and E. coli ($P < 0.05$ for each) in the GnRHa-treated control women and Gardnerella, Enterococci, and E. coli ($P < 0.05$ for each) was found in the GnRHa-treated women with endometriosis, compared to the GnRHa-untreated women.59 A Kruskal–Wallis test still indicated a higher growth of these microbial species after GnRHa treatment than other microbes. The microbial growth of lactic acid-producing protective bacteria (Lactobacillus spp.) was decreased in the endometrial samples that had been derived from the women with endometriosis and after GnRHa treatment. Most recently, the authors confirmed the bacterial culture-based findings by the molecular method. The authors' finding of IUMC was consequently associated with the occurrence of both acute and chronic endometritis in the women with endometriosis. The occurrence of endometritis was significantly higher in the GnRHa-treated women than in the GnRHa-untreated women, with and without endometriosis (control, 68.4% vs 26.5%, $P = 0.003$; endometriosis, 85.7% vs 37.2%, $P = 0.001$, both by X 2-test).59 From these recent findings, it is presumed that a worsening of IUMC and a higher occurrence of endometritis could occur in women with endometriosis after GnRHa treatment. These findings of the association between endometriosis and chronic endometriosis were supported by two recently published reports.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5902457/

Kahn Study Suggests Big Positive Effects of Antibiotics in Endometriosis

Khan KN, Fujishita A, Muto H, Masumoto H, Ogawa K, Koshiba A, Mori T, Itoh K, Teramukai S, Matsuda K, Nakashima M, Kitawaki J. Levofloxacin or gonadotropin releasing hormone agonist treatment decreases intrauterine microbial colonization in human endometriosis. *Eur J Obstet Gynecol Reprod Biol.* 2021 Sep;264:103-116.

In this prospective non-randomized observational study, we demonstrated for the first time that treatment with a single dose of broad-spectrum antibiotic (levofloxacin, LVFX) with or without GnRHa was able to significantly decrease a proportion of bacterial genera in endometrial samples collected from women with and without endometriosis. These findings were coincided with decreased tissue inflammation, cell proliferation and angiogenesis in endometria and endometriotic lesions with remarkable histological improvement of ovarian endometrioma. These findings were based on our serial study for the last 10 years that bacterial contamination indeed occurs in menstrual blood/endometrial samples collected from women with endometriosis associated with increased occurrence of chronic endometritis [5, 8, 11]. Using bacteria culture method and 16S rDNA metagenome assay, we previously demonstrated significantly increased intrauterine bacterial colonization in women with endometriosis comparing to control women. While we previously analyzed bacterial family [[11]], here we analyzed bacterial genera by 16S rDNA metagenome assay in both control women and women with endometriosis. In addition to individual effect of LVFX on some target bacteria, addition of LVFX with GnRHa was able to significantly decrease the prevalence rate of Acidibactor and Bradyrhizobium in control women and Acidibactor, Atopobium, Bradyrhizobium in women with endometriosis. The differential response of LVFX and GnRHa to suppress a proportion of analyzed microbiota, and not all, may be due to the difference in their efficacy. Another new finding in this study is that occurrence rate of chronic endometritis was significantly decreased after combined treatment with GnRHa and LVFX.

These findings are clinically important, because decrease in IUMC with consequent reduction in the risk of chronic endometritis may improve the adverse reproductive outcome in women suffering from endometriosis. Current treatment strategies, including hormonal therapy and surgery, have significant side effects and do not prevent recurrence. Treatment with an antimicrobial agent either alone or in combination with GnRHa in human endometriosis could be a promising therapeutic approach in ameliorating the occurrence or recurrence of endometriosis. Our findings in human study are supported by a recent elegant study in mice [[15]]. In this animal study, the authors found that in mice treated with broad-spectrum antibiotics particularly with metronidazole, endometriotic lesions were significantly smaller with fewer proliferating cells and reduction of inflammatory response than those in vehicle-treated mice [[15]]. We have clinically replicated these findings in human endometriosis by our current findings with both antibiotic and hormonal treatment.

Source: https://pubmed.ncbi.nlm.nih.gov/34298448/

Endometriosis is Impacted by TGFβ

Young VJ, Ahmad SF, Duncan WC, Horne AW. The role of TGF-β in the pathophysiology of peritoneal endometriosis. Hum Reprod Update. 2017 Sep 1;23(5):548-559.

Search methods: We searched the Pubmed database using the terms 'transforming growth factor beta' and 'endometriosis' for studies published between 1995 and 2016. The initial search identified 99 studies and these were used as the basic material for this review. We also extended our remit for important older publications. In addition, we searched the reference lists of studies used in this review for additional studies we judged as relevant. Studies which were included in the review focused on peritoneal endometriosis only as increasing evidence suggests that ovarian and deep endometriosis may have a differing pathophysiology. Thus, a final 95 studies were included in the review.

Outcomes: TGF-β1 is reported to be increased in the peritoneal fluid, serum, ectopic endometrium and peritoneum of women with endometriosis compared to women without endometriosis, and TGF-β1-null mice have reduced endometriosis lesion growth when compared to their wild-type controls. Studies in mice and women have indicated that increasing levels of TGF-β ligands are associated with decreased immune cell activity within the peritoneum, together with an increase in ectopic endometrial cell survival, attachment, invasion and proliferation, during endometriosis lesion development. TGF-β1 has been associated with changes in ectopic endometrial and peritoneal cell metabolism and the initiation of neoangiogenesis, further fuelling endometriosis lesion development.

Wider implications: Together these studies suggest that TGF-β1 plays a major role in the development of peritoneal endometriosis lesions and that targeting this pathway may be of therapeutic potential.

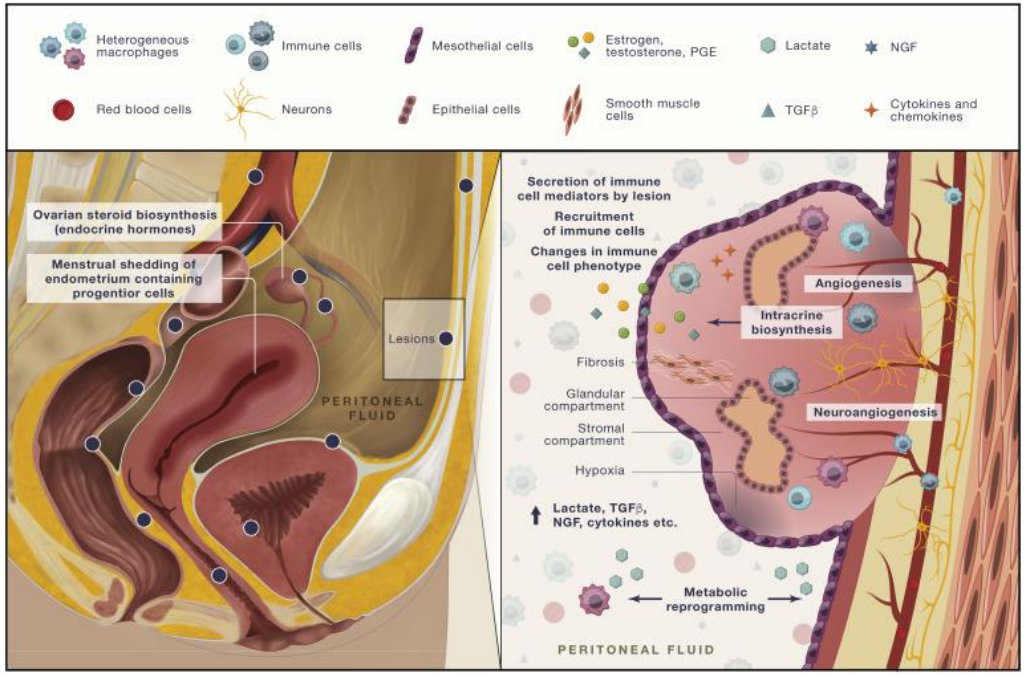
Souce: https://pubmed.ncbi.nlm.nih.gov/28903471/

Endometriosis is an Inflammatory Disorder

Saunders PTK, Horne AW. Endometriosis: Etiology, pathobiology, and therapeutic prospects. *Cell*. 2021 May 27;184(11):2807-2824.

The classification of endometriosis as an inflammatory disorder is based on multiple lines of evidence including reports that the peritoneal environment in women with endometriosis is altered, that endometriosis lesions recruit a large number of immune cells, and that aberrant production of pro-inflammatory regulatory proteins and cytokines (see figuer) (Horne and Saunders, 2019; Riccio et al., 2018; Zondervan et al., 2020).

New insights including evidence of crosstalk between immune cells, nerves, and central pain pathways are also providing opportunities to develop more targeted therapies.



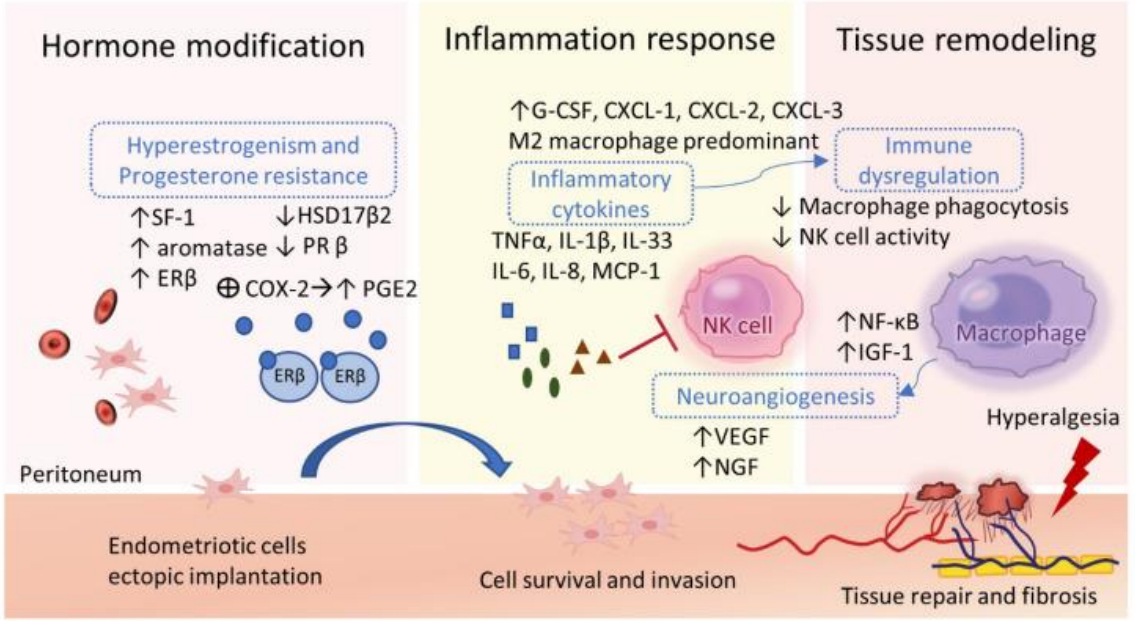
Endometriosis lesions contain a complex mixture of cells and represent a unique specialized microenvironment
(Left) Locations of lesions within the pelvis and other key organs including the bowel, uterus, and bladder. Note the pelvic cavity is lined by mesothelial cells, and the organs are bathed in peritoneal fluid, the constituents of which are altered in women with endometriosis.
(Right) Diagram of a superficial lesion attached to the wall of the peritoneal cavity. Lesions are complex multi-cellular structures with stromal (pink) and epithelial (dotted) compartments, with the former containing fibroblasts, multiple subtypes of immune cells, newly developed blood vessels (angiogenesis), nerves, and regions of fibrosis and hypoxia. Immune cells are recruited to the lesions both from the blood and also from the peritoneal fluid, and their phenotype is influenced by locally high concentrations of steroids and prostaglandins (intracrine synthesis) as well as production of cytokines. Blood vessels and nerves that invade the lesions are found in close proximity (neuroangiogenesis). Mesothelial cells lining the cavity and some macrophage populations produce lactate as a byproduct of metabolism (metabolic reprograming).

Souce: https://pubmed.ncbi.nlm.nih.gov/34048704/

Endometriosis Formation is a Complex Process Involving Inflammation

Chen LH, Lo WC, Huang HY, Wu HM. A Lifelong Impact on Endometriosis: Pathophysiology and Pharmacological Treatment. Int J Mol Sci. 2023 Apr 19;24(8):7503.

Endometriotic implants are complex multicellular structures that ectopic endometrial cells migrate, adhere, and evade through a serial process of tissue remodeling, followed by the influx of pro-inflammatory cytokines and the growth of new blood vessels (angiogenesis) [66] (Figure 2). Peritoneal fluid in affected patients is also found to contain increased pro-inflammatory cytokines [67,68,69]. The aberrantly increased concentrations of interleukins (IL-1β, IL-6, IL-8, IL-33), tumor necrosis factor-alpha (TNF-α), insulin-like growth facto-1 (IGF-1), monocyte chemoattractant protein/C-C motif chemokine ligand (MCP-1 CCL2, CCL5), and vascular endothelial growth factor (VEGF) activate the inflammatory response by upregulating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in affected women [70,71,72,73,74,75,76,77]. Circulating cytokines and immune cells further create a widespread inflammatory environment which drives the systemic effect of endometriosis on immunologic, cardiovascular, neurological, and metabolic function [64,71,76,78,79]. VEGF/tyrosine kinase signaling pathway has been upregulated and involved in numerous mechanisms of vascularization, including de novo growth (angiogenesis), vasculogenesis, and the formation of interconnected networks. Furthermore, the link between the growth of new blood vessels and nerve fibers contributes to the “neuro-angiogenesis”, ectopic endometriotic lesions, and pain pathways [80,81].



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10139092/

Celecoxib Effective in Reducing Endothelial Cell Proliferation in Human Endometriosis Samples

Olivares C, Bilotas M, Buquet R, Borghi M, Sueldo C, Tesone M, Meresman G. Effects of a selective cyclooxygenase-2 inhibitor on endometrial epithelial cells from patients with endometriosis. Hum Reprod. 2008 Dec;23(12):2701-8.

Celecoxib, a selective cyclooxygenase (COX)-2 inhibitor, also has anti-proliferative properties and pro-apoptotic effects on different in vivo and in vitro models, two actions that may be efficacious in therapy for endometriosis. We evaluated the effects of celecoxib on apoptosis and proliferation, and vascular endothelial growth factor (VEGF) production and COX-2 expression and activity in endometrial epithelial cells (EECs).

Thirty-two endometriosis and 13 control women were included in the study. EECs from eutopic endometrium and control biopsies were cultured with different doses of celecoxib. Celecoxib at 50, 75 and 100 μM (versus vehicle control) inhibited EEC proliferation in cultures from controls ($P < 0.05$, $P < 0.01$ and $P < 0.01$, respectively) and patients with endometriosis ($P < 0.05$, $P < 0.01$ and $P < 0.01$), as assessed by 3H-thymidine uptake. Celecoxib at 50, 75 and 100 μM induced apoptosis in EEC from controls ($P < 0.05$, $P < 0.001$ and $P < 0.001$) and patients with endometriosis ($P < 0.001$, $P < 0.001$ and $P < 0.01$), as revealed by the Acridine Orange–Ethidium Bromide technique. Western blot analysis showed that celecoxib was effective at increasing COX-2 protein at 100 μM in EEC from endometriosis patients ($P < 0.05$). In EEC from endometriosis patients, celecoxib at 25, 50 and 100 μM was also effective in reducing COX-2 activity, reflected in the reduction of prostaglandin E2 (PGE2) synthesis ($P < 0.001$), and VEGF secretion ($P < 0.001$; $P < 0.05$ and $P < 0.001$), assessed by enzyme-linked immunosorbent assay. Exogenous PGE2 did not reverse celecoxib-induced growth inhibition.

Source: https://pubmed.ncbi.nlm.nih.gov/18716040/

Kahn Study Shows Antibiotics Can Reduce Expression of Inflammatory Markers in Endometriosis

Khan KN, Fujishita A, Muto H, Masumoto H, Ogawa K, Koshiba A, Mori T, Itoh K, Teramukai S, Matsuda K, Nakashima M, Kitawaki J. Levofloxacin or gonadotropin releasing hormone agonist treatment decreases intrauterine microbial colonization in human endometriosis. *Eur J Obstet Gynecol Reprod Biol.* 2021 Sep;264:103-116.

Immunohistochemical expressions of CD68, Ki-67, CD31, COX2, and fibronectin in endometria.

We speculated that differential intrauterine microbial colonization and their variable response to GnRHa, LVFX and GnRHa + LVFX treatment might reduce inflammatory response in endometrium with consequent decrease of cell proliferation, angiogenesis, and expressions of COX2 and fibronectin. We found that tissue infiltration of CD68 + macrophages were significantly decreased after either of GnRHa, LVFX, and GnRHa + LVFX treatment comparing to non-treatment. This was equally observed in control women and women with endometriosis (Fig. 5A). Comparing to untreated group, LVFX and GnRHa + LVFX treatment significantly decreased Ki-67-stained gland cells and stromal cells (Fig. 5B, C) derived from endometria of both control and endometriosis women. This effect was not observed after GnRHa treatment. The micro-vessel density

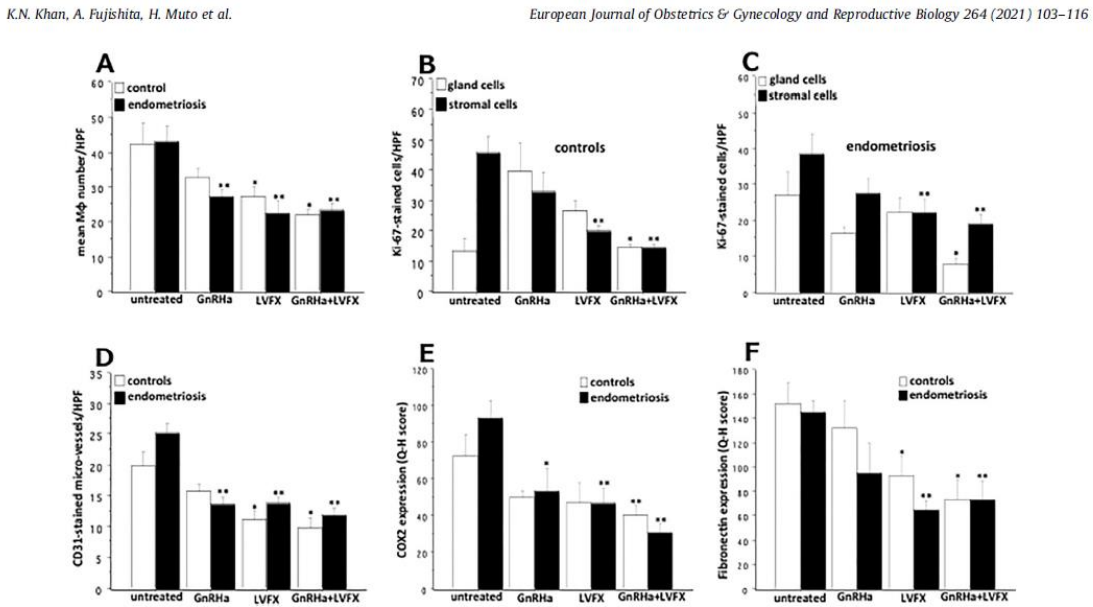


Fig. 5. Immunohistochemical staining levels of CD68 (macrophage marker, **A**), Ki-67 (cell proliferation marker, **B**, **C**), CD31 (vascular cell marker, **D**), COX2 (rate limiting enzyme for prostaglandin production, **E**), and fibronectin (cell adhesion marker, **F**) in endometrial biopsy samples collected from untreated- and GnRHa-treated, LVFX-treated, and GnRHa + LVFX-treated control women (white bar, **A**, **D**, **E**, **F**) and women with endometriosis (black bar, **A**, **D**, **E**, **F**). Comparing to untreated group, treatment with either of GnRHa, LVFX, and GnRHa + LVFX significantly decreased tissue infiltration of macrophages, Ki-67-stained gland cells (white bar, **B**, **C**) or stromal cells (black bar, **B**, **C**), CD31-stained micro-vessels, and quantitative histogram (Q-H) scores of COX2 and fibronectin expression. The results are expressed as mean ± SEM. (**A**) CD68-stained macrophages: $^{**}p < 0.05$ (for each) vs. untreated group. $^{*}p < 0.05$ vs. untreated group. (**B**) Ki-67-stained cells (controls): $^{**}p < 0.01$ (for each) vs. untreated group, $^{*}p < 0.01$ vs. untreated group. (**C**) Ki-67-stained cells (endometriosis): $^{**}p < 0.05$ (for each) vs. untreated group, $^{*}p < 0.05$ vs. untreated group. (**D**) CD31-stained micro-vessels: $^{**}p < 0.05$ (for each) vs. untreated group, $^{*}p < 0.05$ vs. untreated group. (**E**) Q-H scores of COX2 expression: $^{**}p < 0.05$ (for each) vs. untreated group, $^{*}p < 0.05$ vs. untreated group. (**F**) Q-H scores of fibronectin expression: $^{**}p < 0.05$ (for each) vs. untreated group, $^{*}p < 0.05$ (for each) vs. untreated group.

Source: https://pubmed.ncbi.nlm.nih.gov/34298448/

Disclosure

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