Biopharmaceutical Sector

Weekly Update – Feb 19, 2024

STIFEL | Healthcare

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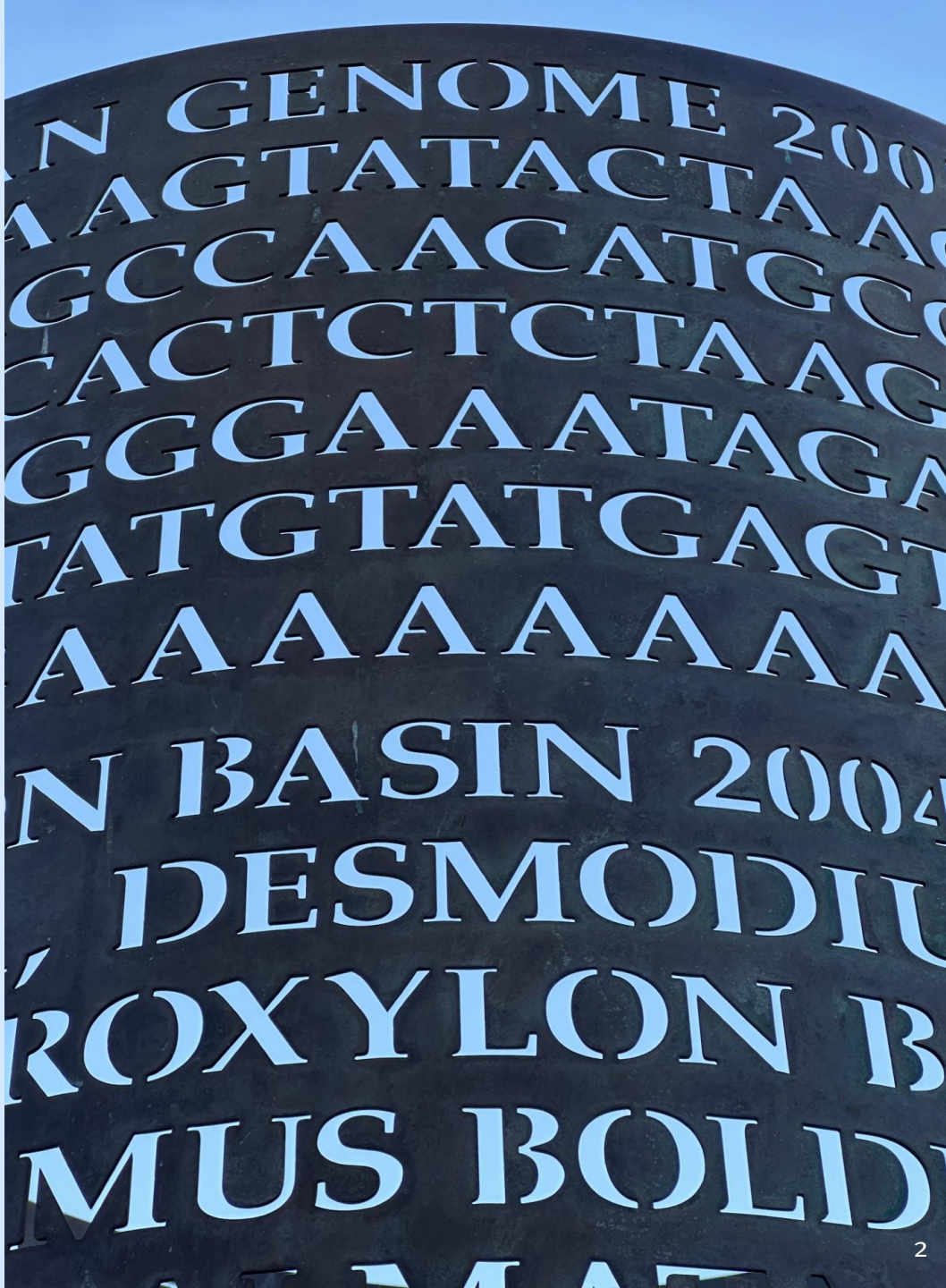


Accessing Past Issues

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 12, 2024 (Fibrosis, Endometriosis)
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 16, 2024.

The next event will be on February 23, 2024.

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

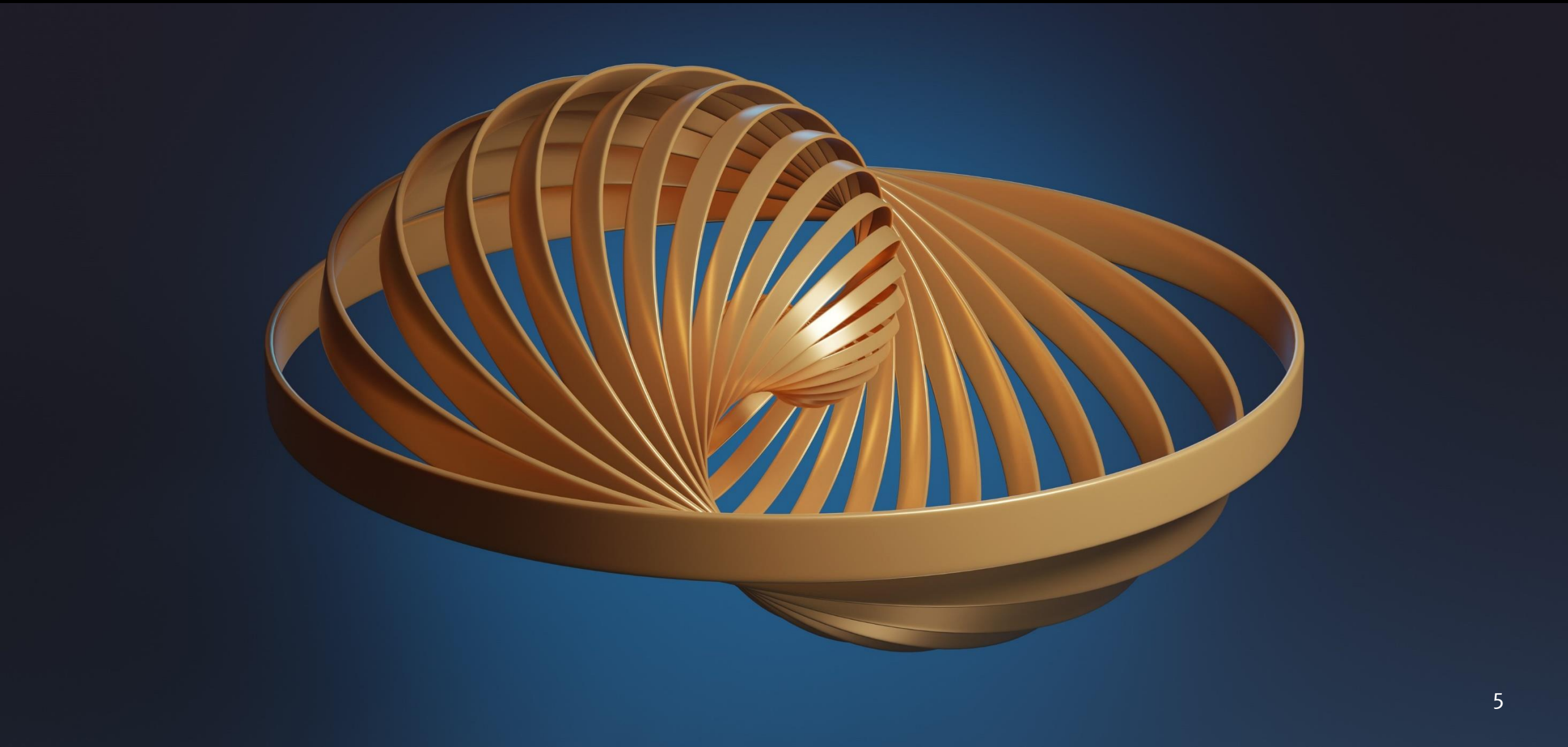
Please join us.

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

Macroeconomics Update



Strong Services Price Increases Lift US Producer Inflation in January

Lucia Mutikani, *Reuters*, Feb 16, 2024 (excerpt)

Producer price index increases 0.3% in January
PPI rises 0.9% year-on-year

WASHINGTON, Feb 16 (Reuters) - U.S. producer prices increased more than expected in January amid strong gains in the costs of services such as hospital outpatient care and portfolio management, stoking financial market fears inflation was picking up after months of cooling.

The increase reported by the Labor Department on Friday was the largest in five months. The report followed on the heels of an above-expectations rise in consumer prices in January and prompted financial markets to dial back expectations that the Federal Reserve would start cutting interest rates in June.

Data on Thursday also showed prices of imported goods surging in January. But some economists cautioned against concluding that inflation was re-accelerating noting that businesses typically raise prices at the start of the year. These price hikes probably were larger this year as businesses tried to make up for higher labor costs in the past year.

Economists also suspected that the model used by the government to strip out seasonal fluctuations from the data could be falling short. Nevertheless, the reports this week raised the risk of higher readings in the personal consumption expenditures (PCE) price indexes, the measures tracked by the U.S. central bank for its 2% inflation target, when the government publishes January's data later this month.

Source: https://www.reuters.com/markets/us/us-producer-prices-rise-more-than-expected-january-2024-02-16/

Fed's Bostic Says May Take 'Some Time' to Hit Rate-Cut Threshold

Steve Matthews and Alex Harris, *Bloomberg*, Feb 15, 2024 (excerpt)

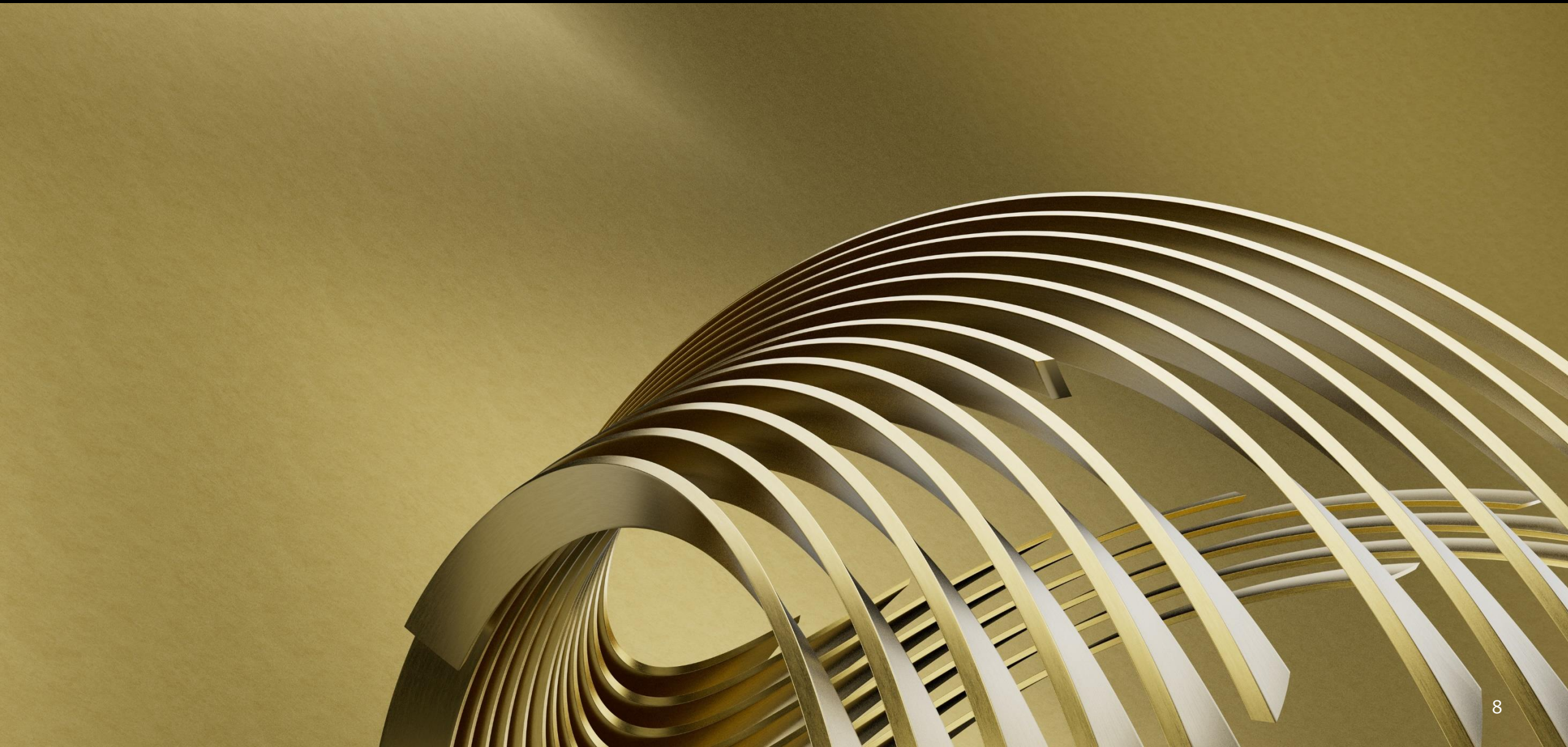
Federal Reserve Bank of Atlanta President Raphael Bostic said there's no rush to cut interest rates with the US labor market and economy still strong, and cautioned it's not yet clear that inflation is heading sustainably to the central bank's 2% target.

"The evidence from data, our surveys, and our outreach says that victory is not clearly in hand, and leaves me not yet comfortable that inflation is inexorably declining to our 2% objective," Bostic said in a speech Thursday in New York. "That may be true for some time, even if the January CPI report turns out to be an aberration."

Raphael Bostic
President
Atlanta Fed

Source: https://www.bloomberg.com/news/articles/2024-02-15/bostic-says-may-take-some-time-to-know-inflation-heading-to-2

Biopharma Market Update



The XBI Closed at 93.15 Last Friday (Feb 16), Up 2.3% for the Week

The XBI is up 4.3% since the year began. The biotech market's momentum continued despite rising Treasury rates. The 10-year U.S. Treasury yield is now up 42 basis points YTD – quite a large move.

Biotech Stocks Up Last Week

Return: Feb 10 to Feb 16, 2024

Nasdaq Biotech Index: +0.8%
Arca XBI ETF: +2.3%
Stifel Global Biotech EV (adjusted): +5.4%*
S&P 500: -0.4%

Return: Jan 1 to Feb 16, 2024

Nasdaq Biotech Index: +0.9%
Arca XBI ETF: +4.3%
Stifel Global Biotech EV (adjusted): 19.8%*
S&P 500: +4.9%

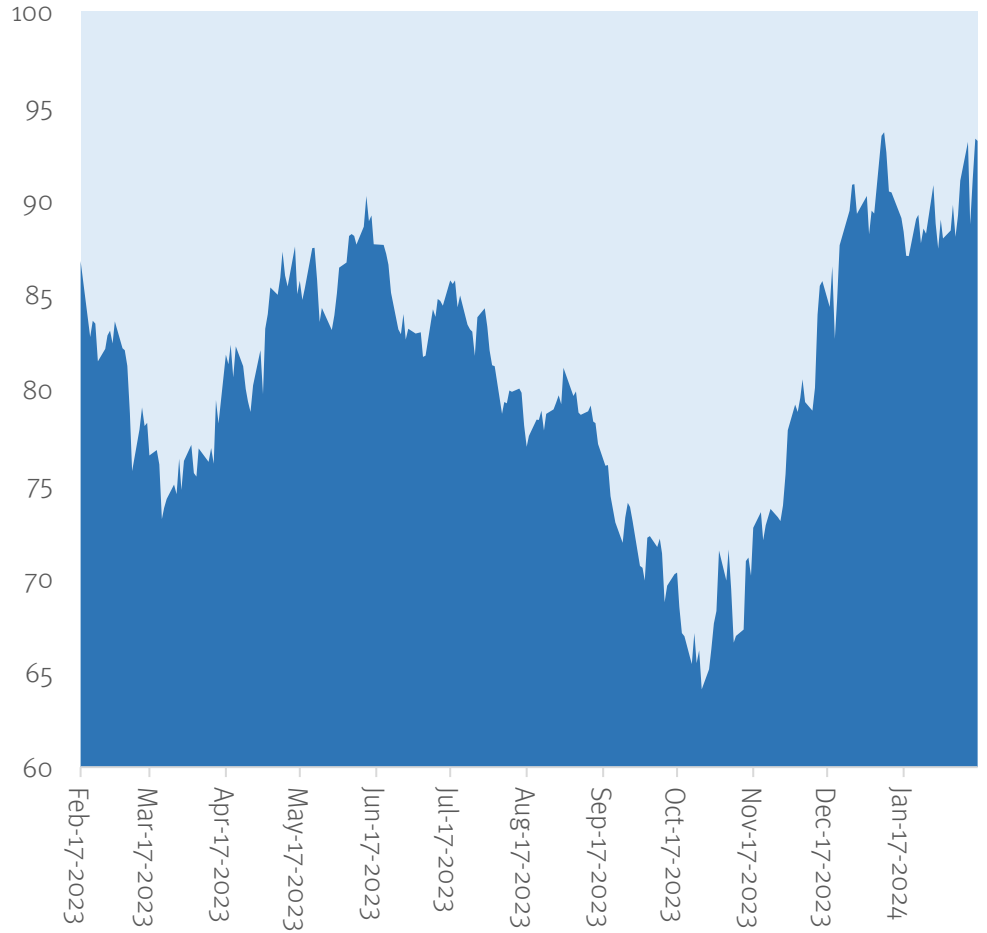
VIX Up

Jan 20, 2023: 19.9%
May 26, 2023: 18.0%
July 21, 2023: 13.6%
Sep 29, 2023: 17.3%
Oct 27, 2023: 21.2%
Dec 29, 2023: 12.45%
Jan 26, 2024: 13.26%
Feb 9, 2024: 12.9%
Feb 16, 2024: 14.2%

10-Year Treasury Yield Up

Jan 20, 2023: 3.48%
May 26, 2023: 3.8%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Oct 27, 2023: 4.86%
Dec 29, 2023: 3.88%
Jan 26, 2024: 4.15%
Feb 9, 2024: 4.17%
Feb 16, 2024: 4.3%

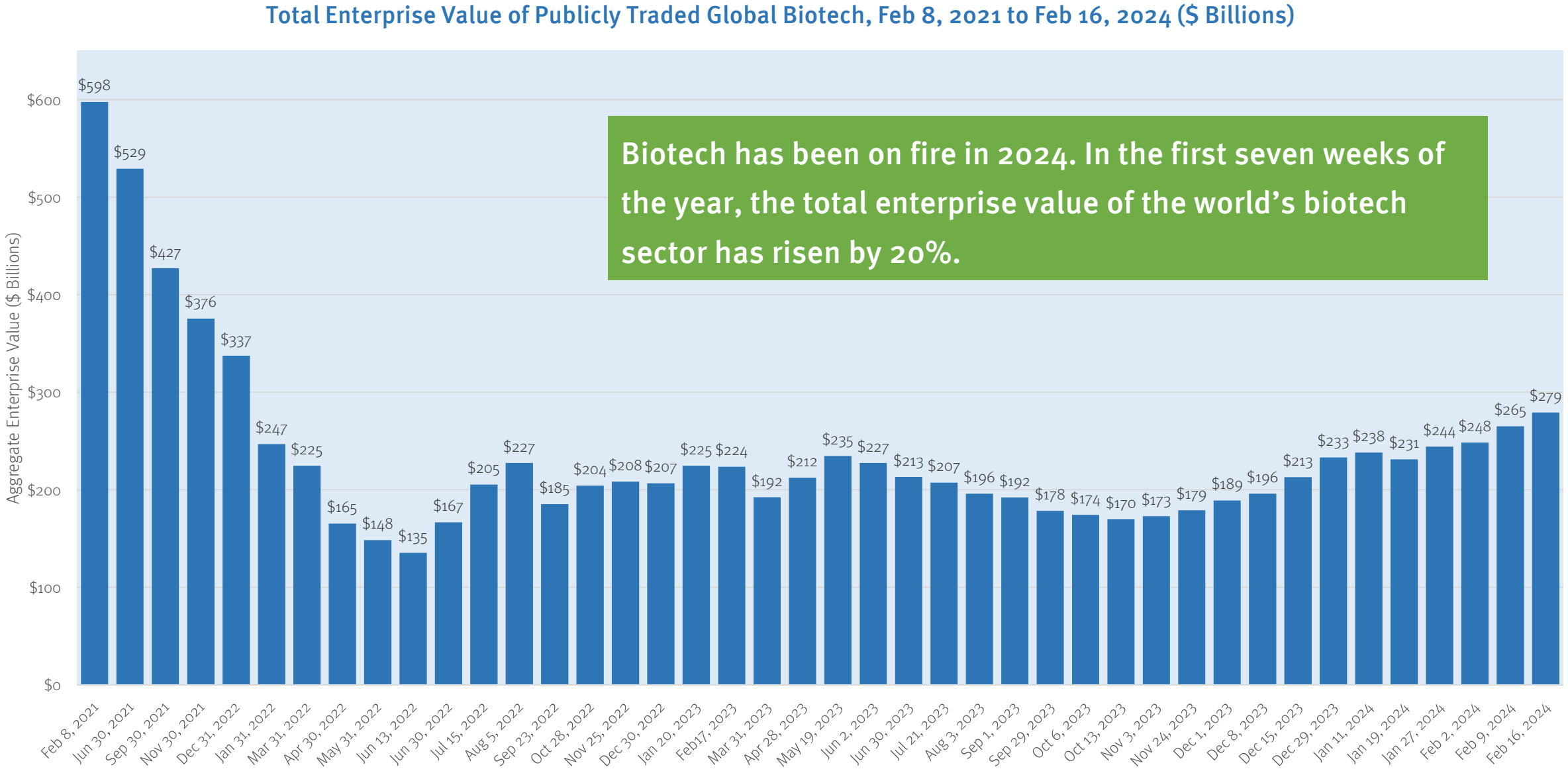
XBI, Feb 17, 2023 to Feb 16, 2024



* 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 5.4% Last Week



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

Understanding the XBI Vs. Our Measure of Biotech Value

We are showing a 19.8% increase in biotech sector EV so far in 2024 but the XBI is showing only a 4.3% rise. Why the wide discrepancy? The figures below provide insight into the question. First, we look at *enterprise value* not market cap and we look at R&D stage companies only rather than a mix of R&D stage and commercial stage companies. The reason is that we are trying to look at an economic sense of what the pre-commercial sector is worth rather than providing an investment benchmark *per se*. The total global biotech EV increase of 19.8% this year compares to a 10.8% increase in market cap of the same biotech group. Further, the median increase in value of an R&D-stage company in the XBI rose only 5.65% this year. While not a value-weighted index, the XBI overweights mid and large caps and these have not performed as well as small cap biotechs. Further, nearly half of the XBI comprises commercial pharma. These companies have a median return this year of -2.3%. If one is interested in how a U.S.-centric portfolio of popular mid and large cap biotech and specialty pharmas are doing then the XBI is a great benchmark. Otherwise, it's not a great benchmark.

Commercial Pharma in XBI	R&D Stage Biotech in XBI	Diagnostics Companies in XBI
39% of companies 45% of weights	55% of companies 50% of weights	65 of companies 5% of weights
Median Return YTD: -2.33%	Median Return YTD: 5.65%	Median Return YTD: 11.2%

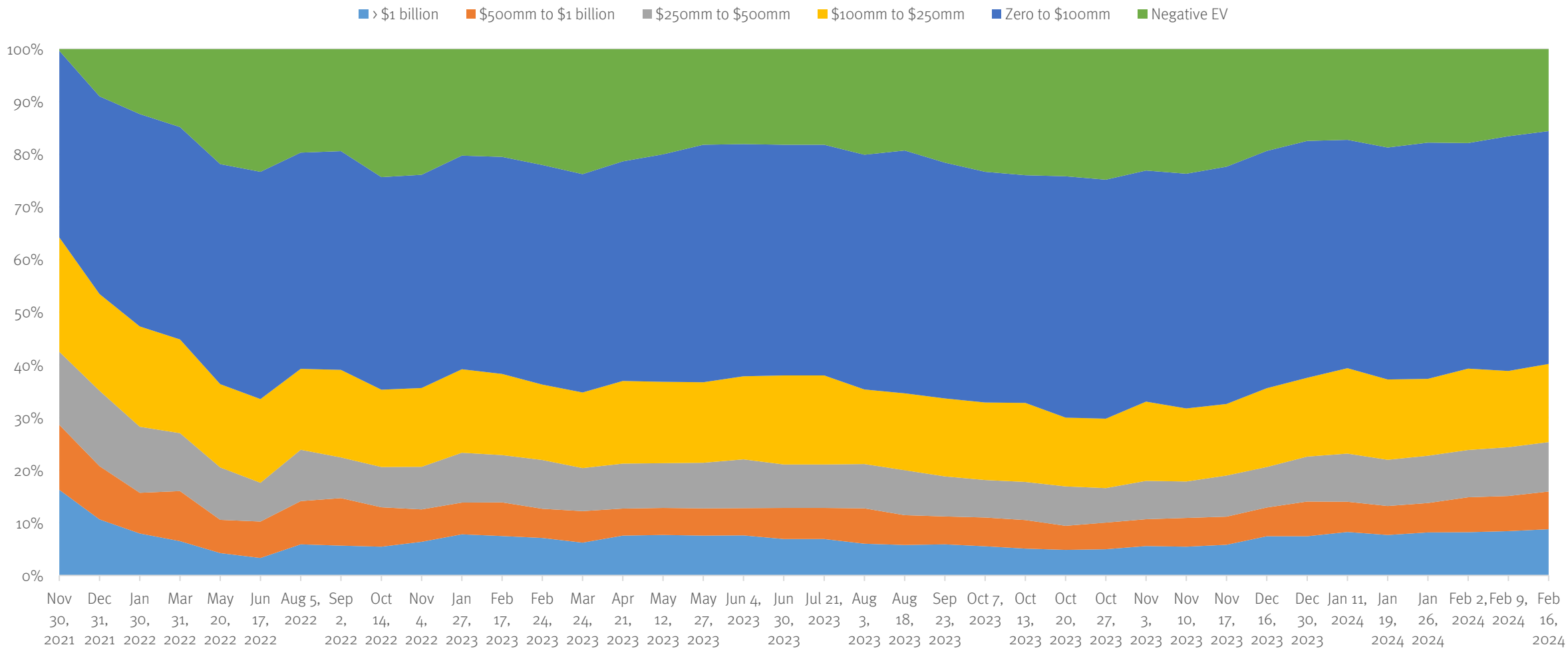
Total Global Biotech Change in Enterprise Value YTD:	19.8%
Total Global Biotech Change in Market Cap YTD:	10.8%

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 continued rapid shrinkage of the negative EV population sector in biotech.

Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Feb 16, 2024



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

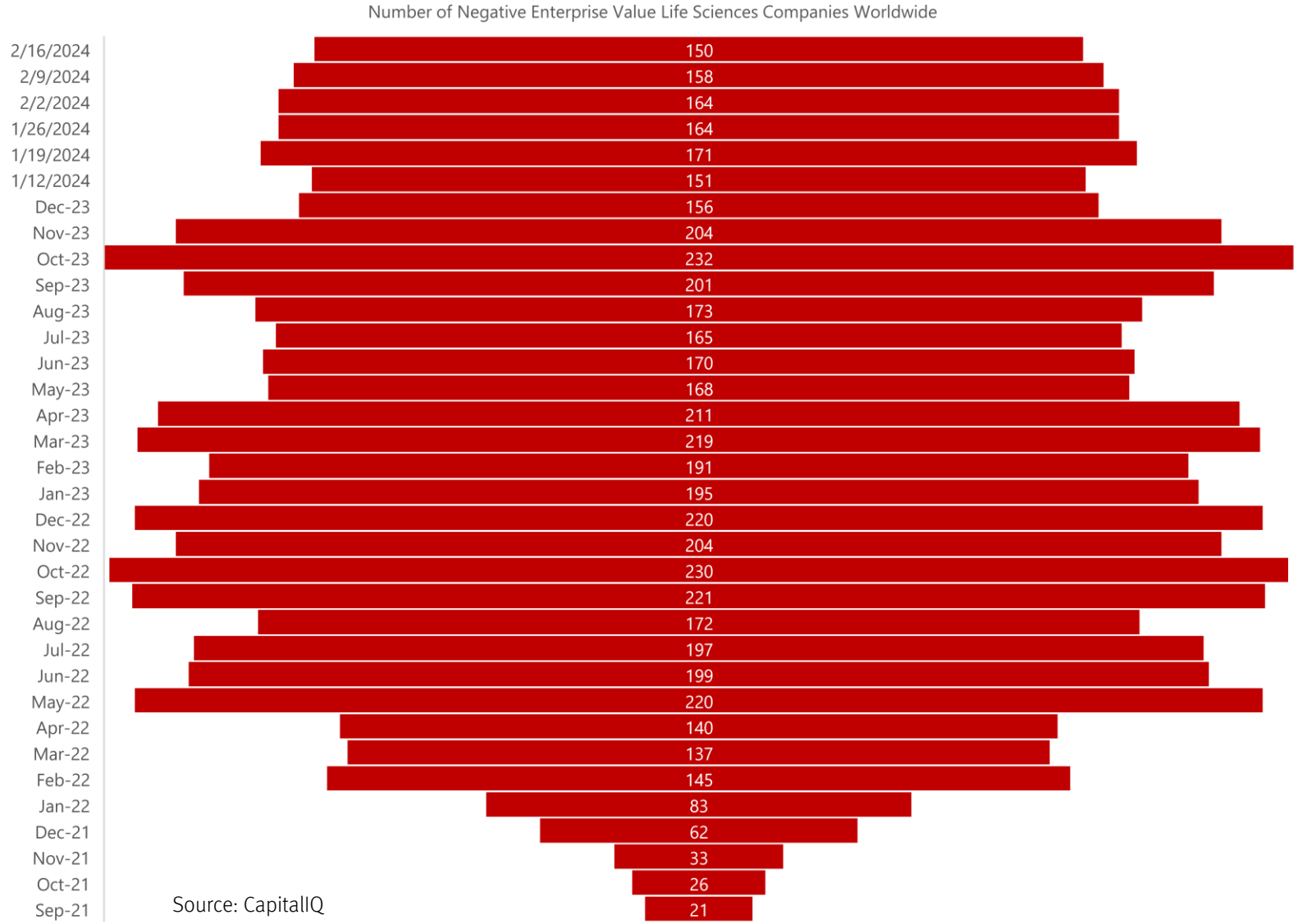
Life Sciences Sector Total Value Up Last Week by 1.2%

Last week saw the life sciences sector gain $111 billion in value. Subsectors that gained 4% or more included biotech and HCIT. The diagnostics sector lost some value.

Sector	Firm Count	Enterprise Value (Feb 16, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$80,088	1.2%	-2.3%	-5.0%
Biotech	806	$278,620	5.4%	15.7%	-5.1%
CDMO	40	$149,314	1.8%	5.1%	-23.5%
Diagnostics	81	$267,231	-1.3%	-1.2%	-0.6%
OTC	30	$27,970	1.0%	1.0%	-7.3%
Pharma	719	$6,161,792	1.2%	3.4%	9.5%
Services	39	$193,074	2.1%	0.3%	-10.3%
Tools	51	$702,437	1.6%	4.9%	-7.4%
Devices	181	$1,699,533	0.8%	3.0%	5.8%
HCIT	11	$22,133	4.7%	3.2%	-23.2%
Total	2039	$9,572,191	1.2%	3.5%	6.2%

Source: CapitalIQ

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



Source: CapitalIQ

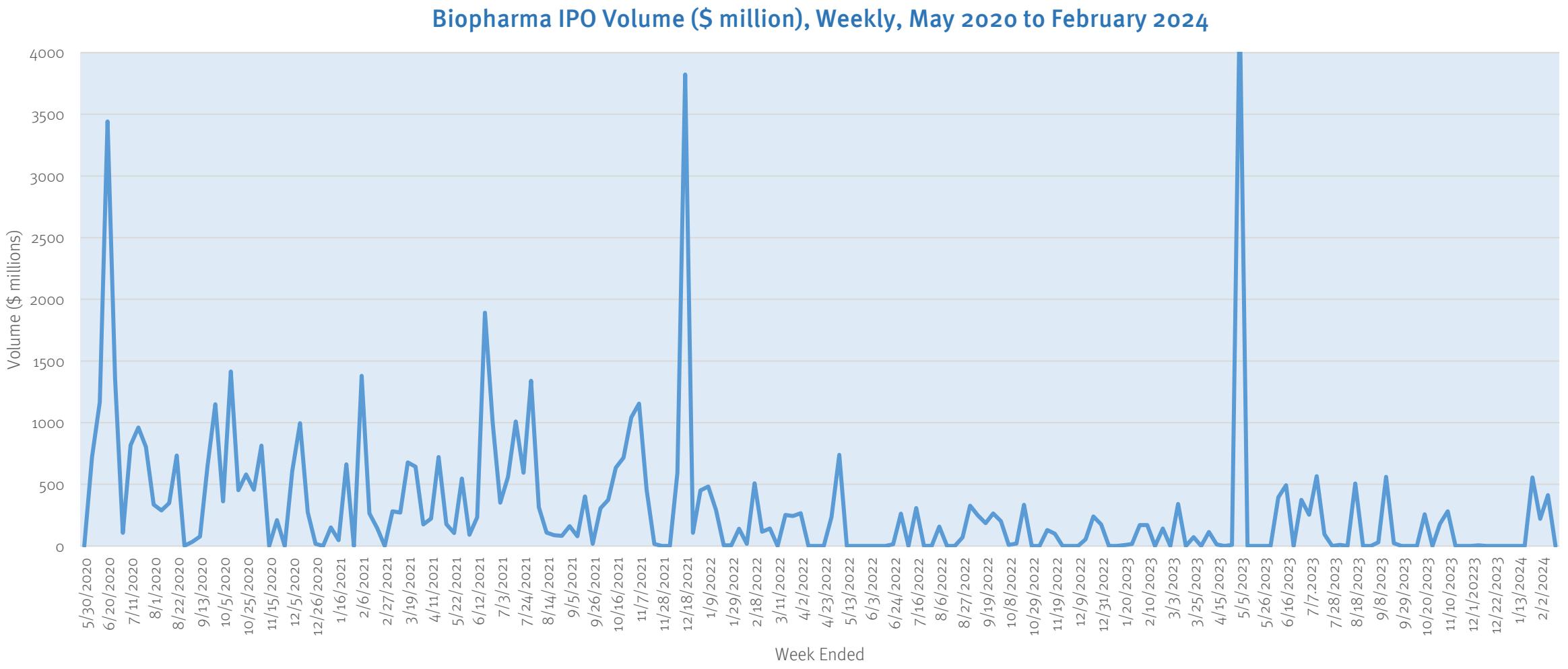
The count of negative EV life sciences companies worldwide dropped to 150 from 158 last week.

We haven't seen this few negative EV companies since April 2022.

Capital Markets Update

IPO Market Took a Breather Last Week

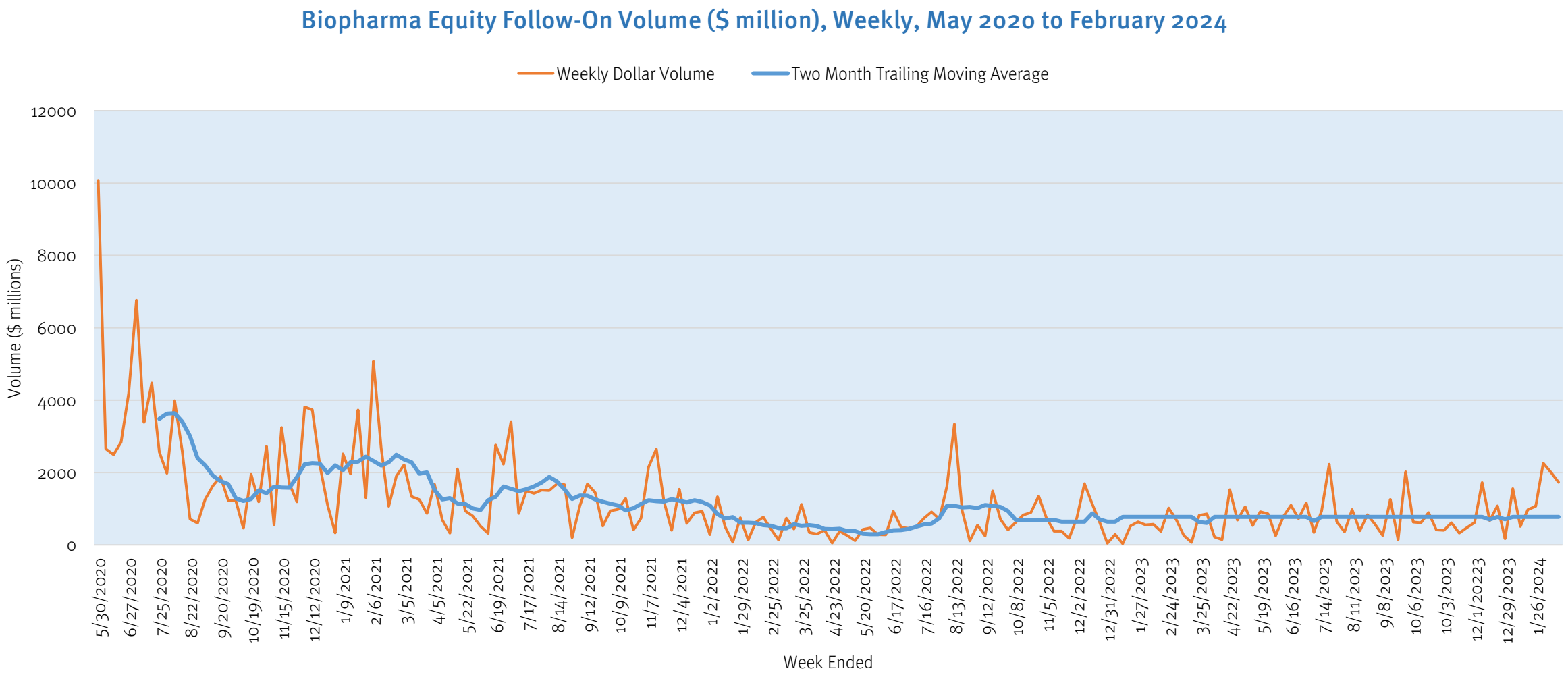
After an active six weeks, the IPO market took a break last week.



Source: Data from CapitalIQ and Stifel research.

Follow-On Market Active Last Week

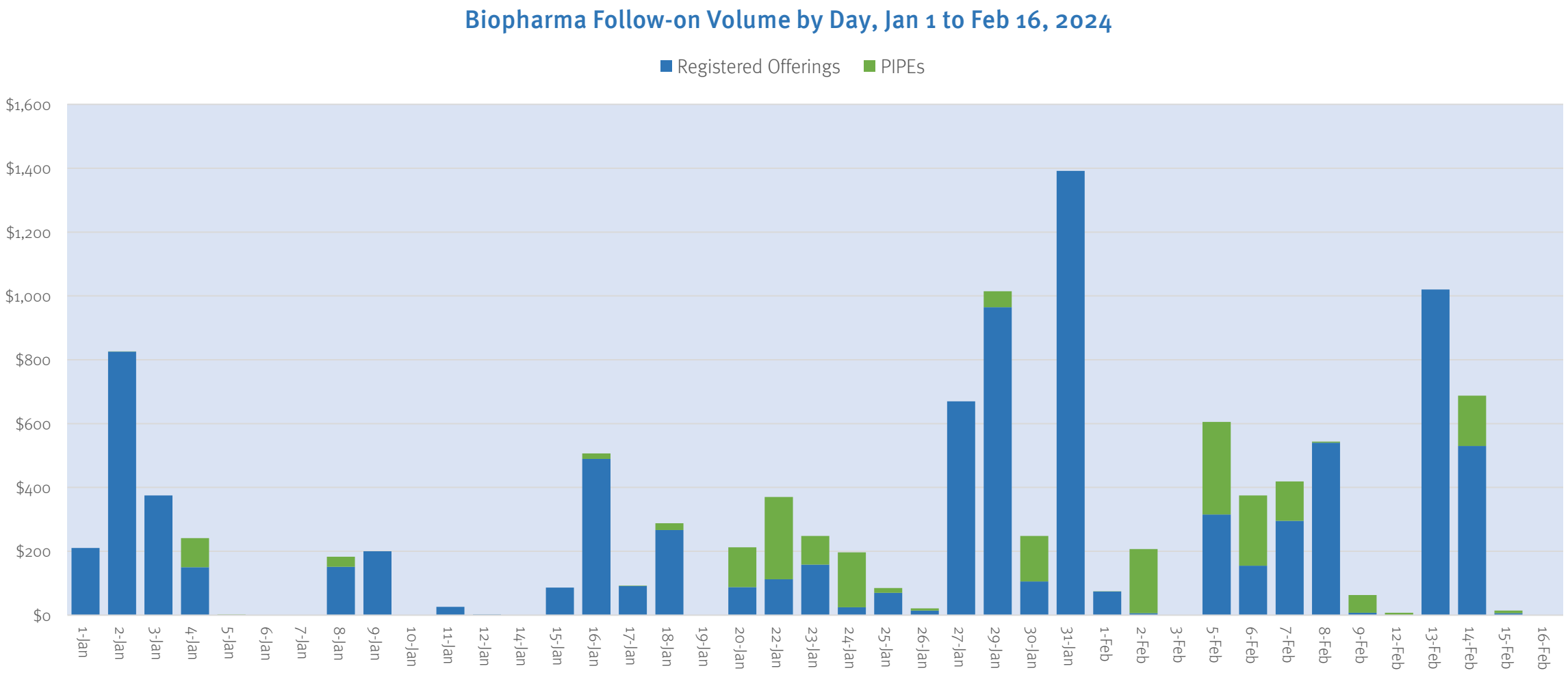
Last week saw $1.7bn in follow-on volume across 18 different offerings. The pace of issuance matched the last two prior weeks.



Source: Data from CapitalIQ and Stifel research.

Follow-On Issuance Volume of $3 Billion Since February Began

We saw over $4bn in follow-on volume in January. Now, February is on the same or a higher pace. Issuers are very focused on taking down capital while the market is open, knowing that 2024 is an election year in the U.S.



Source: Data from CapitalIQ and Stifel research.

US Biotech Fundraising Boom Ends 2-Year Deal Drought

Nicholas Magaw, *Financial Times*, Feb 12, 2024 (excerpt)

Biotech companies are rushing to raise money in US equity markets at the fastest rate since the peak of the mid-pandemic market boom.

Drug developers raised $6.2bn in equity capital markets in January.

The funding surge marks a sharp turnaround after a two-year deal drought that forced many companies to cut jobs and shelve projects to save costs, and forced some out of business.

Fundraising has been encouraged by a rebound in stock prices, expectations that the Federal Reserve will soon start cutting interest rates, and a boom in mergers and acquisitions activity in the sector.

The closely followed SPDR S&P Biotech ETF tumbled almost two-thirds from its 2021 high, weighed down by rising interest rates and a backlash to pandemic-era over-optimism about new drugs.

But the ETF has rebounded about 40 per cent since late October as investors bet that interest rates had peaked.

The bulk of the recent fundraising, $5.6bn, was raised by already listed companies, but initial public offerings have also been picking up pace, and the strong performance of recent deals was expected to encourage a further increase.

“There’s a good backlog of biotechs who didn’t go public over the past year or so who are sharpening their pencils again,” said Yasin Keshvargar, a capital markets partner at Davis Polk, the law firm.

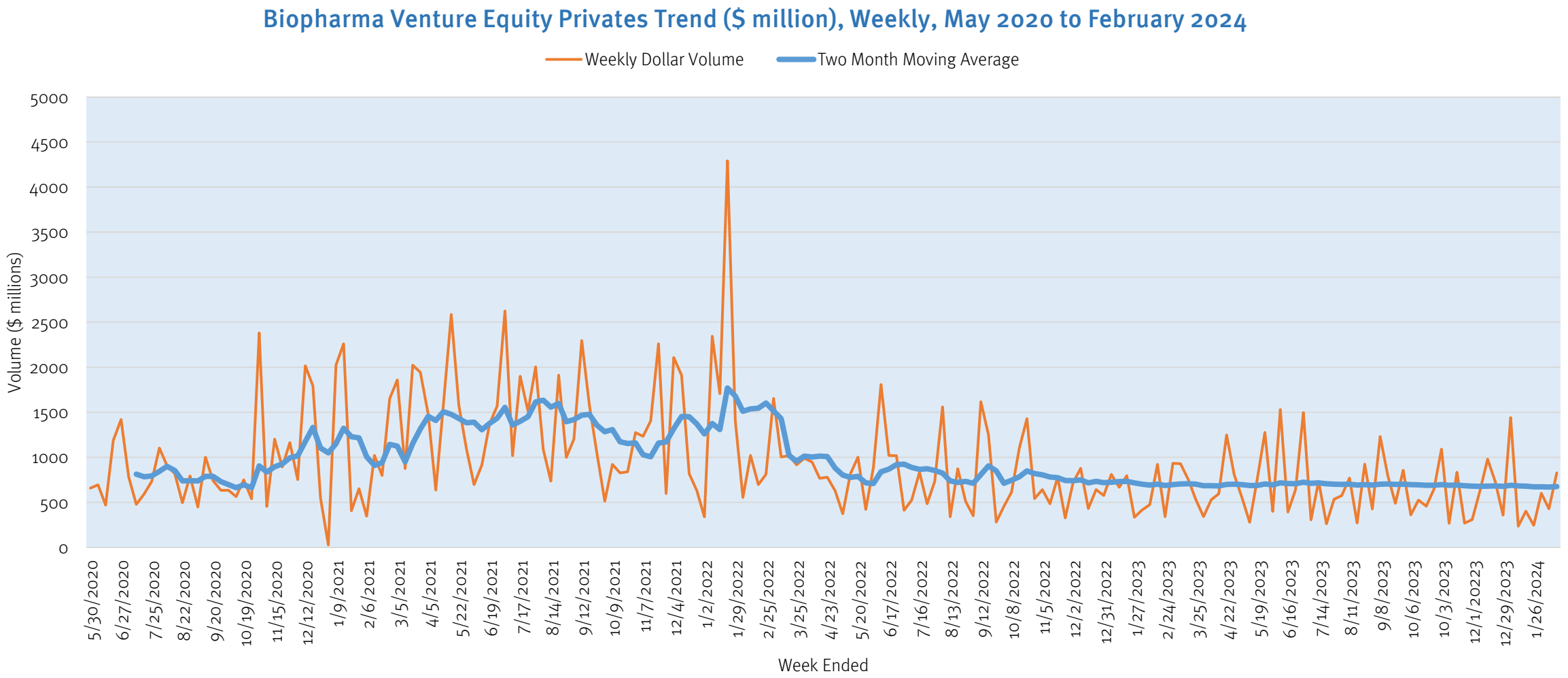
Shares in US-based CG Oncology jumped 96 per cent to close at $37.17 on their first day of trading in late January, while Arrivent Biopharma raised $175mn in an initial public offering during the same week. Its share price has risen just over 5 per cent since listing.

Peter Maag, CEO of Kyverna, said it may take longer for fundraising to rebound for the riskiest companies, but added: “If you have good clinical data and know what you’re doing, I think companies are financeable right now.” Biotechs are particularly reliant on equity markets because they often need large amounts of capital to fund drug development before they generate enough revenue to repay debt.

Source: https://www.ft.com/content/5c45f23b-9b43-4a95-8dcc-44587317bodd

Last Week's Venture Private Volume Picked Up

Last week saw $827 million in privates deal volume led by a $170 million raise by BioAge.



Source: Data from CapitalIQ, Crunchbase.

BioAge Announces $170 Million Series D Financing to Accelerate Development of Obesity and Metabolic Disease Therapeutics

RICHMOND, Calif.--(BUSINESS WIRE) – Feb 13, 2024 -- BioAge Labs ("BioAge"), a clinical-stage biotechnology company developing novel therapies for obesity and metabolic diseases by harnessing the biology of aging, announced today the completion of an oversubscribed Series D financing round of $170 million led by Sofinnova Investments. New investors including Longitude Capital, RA Capital, Cormorant Asset Management, RTW Investments, SV Health Investors, OrbiMed Advisors, Sands Capital, Pivotal bioVenture Partners, Osage University Partners, Lilly Ventures, and Amgen Ventures also participated in the round alongside existing investors including Andreessen Horowitz (a16z) Bio + Health.

In connection with the financing, James Healy, M.D., Ph.D., managing partner at Sofinnova Investments, will join BioAge as Chairman of the Board, and Patrick Enright, managing director at Longitude Capital, will join as Board Director.

The funding will be used to support Phase 2 clinical development of BioAge's lead compound azelaprag, an oral apelin receptor agonist, in combination with Lilly's Zepbound (tirzepatide) and other incretins for treatment of obesity. The studies with Zepbound are expected to begin in mid-2024, in collaboration with Eli Lilly's Chorus organization. Azelaprag is an oral drug with the potential to significantly increase weight loss and improve body composition when combined with any incretin. In a Phase 1b trial, azelaprag promoted muscle metabolism, increased energy expenditure, and prevented muscle atrophy in healthy older volunteers at bedrest. In preclinical studies, azelaprag doubled the weight loss achieved on incretin drugs with improvements in body composition and muscle function.

"We're thrilled to partner with a top-tier syndicate of investors and pharma companies at the forefront of developing novel therapeutics for metabolic diseases. This funding will support us through key clinical milestones and data readouts for our lead compound azelaprag in obesity, as well as advance our earlier-stage metabolic aging pipeline. The azelaprag program highlights our discovery platform's ability to identify novel approaches to treating metabolic disease"

Kristen Fortney
Chief Executive Officer
BioAge Labs

Source: https://www.businesswire.com/news/home/20240213546755/en/

Hunting a Non-opioid Painkiller, a Biotech Reveals Plans to Chase Vertex

Ned Pagliarulo, *Biopharma Dive*, Feb 14, 2024 (excerpt)

A little over four years ago, biotechnology giant Amgen retreated from neuroscience research, halting much of its work developing treatments for diseases of the brain and trimming associated staff.

Amgen's pivot proved a boon for a small startup that was then just getting started in the big drugmaker's backyard. Latigo Biotherapeutics, which, like Amgen, is based in Thousand Oaks, California, quickly hired some of those former Amgen scientists to jump-start its own neuroscience plans.

"We were fortunate that, just at that moment, Amgen strategically exited neuroscience and laid off a lot of really good people into the local community here, including folks I knew quite well from my days as head of R&D at Amgen," said Sean Harper, who after leaving Amgen in 2018 became co-founding managing director of venture firm Westlake Village Biopartners.

Westlake created Latigo and later led a $135 million fundraising that gave the startup the resources to build a pipeline of painkillers it hopes could yield a non-addictive alternative to opioids like Vicodin. On Wednesday, the company debuted publicly, revealing the Series A financing as well as its lead drug candidate.

Latigo's target is the same as Vertex's: a kind of molecular "gate" found in certain nerve cells that relays pain signals to the brain. This gate, a sodium channel known as NaV1.8, is only found in peripheral nerve cells, meaning drugs that block it could avoid the kind of brain-involved side effects that make opioids dangerous.

Source: https://www.biopharmadive.com/news/latigo-launch-biotech-pain-nav-18-non-opioid/707433/

Two GV Investors on Biotech's Reset and Building Their Next Drug Startups

Gwendolyn Wu, *Biopharma Dive*, Feb 13, 2024 (excerpt)

As the venture arm of Alphabet, GV can be thought of as a technology investor. But over the last 15 years, the firm has become one of the biotechnology sector's most prolific startup creators, too.

Since being spun out of the tech giant in 2009, GV has backed diagnostics developers, health tech companies and drug startups. GV was an investor in Flatiron Health and One Medical before their acquisitions by larger companies, and has supported several gene editing startups, among them Editas Medicine, Prime Medicine and Verve Therapeutics. Last year, it participated in nine funding deals, making it one of the most active biotech investors, according to a report from HSBC. On Tuesday, Anthony Philippakis, a cardiologist and formerly chief data officer at the Broad Institute of MIT and Harvard, officially joined them. Phillippakis has worked with the firm in a part-time role for more than a decade, during which time he helped form startups like Verve and healthcare AI company Layer Health. He's now a general partner with the firm, having left his post at the Broad in September.

What do you make of the newfound optimism surrounding biotech right now?

KRISHNA YESHWANT (Managing Partner, GV): It feels much more calibrated to where the science is and how things are going. During the bubble, we didn't change too much of what we did. But we saw a lot of things happening that we couldn't quite make sense of in terms of very large or high-priced rounds. Things seem to be back toward where we expect them.

There were many rounds that happened during the bubble where we would talk to a company and they would tell us that we had a week to decide, or needed to decide right there on the call. We weren't able to do that and still be good fiduciaries of capital.

Now it feels like we can learn the science and get to know the team. That's healthier for everybody, because all these companies go through ups and downs. If we know what we're getting into and who we're doing this with, then we can completely weather that. That's what we're built to do. But if these things are happening overnight, and nobody quite knows who they're making these deals or what the partnerships look like, that's all getting strained.

ANTHONY PHILIPPAKIS (Partner, GV): This is a time when good ideas really can get the support they need, and you can build a company. At the same time, there isn't this feeling of needing to get more capital out the door for the sake of doing so.

Source: https://www.biopharmadive.com/news/gv-anthony-philippakis-krishna-yeshwant-biotech/707139/

Sofinnova's Maha Katabi on Recent M&A and IPO Success

Maha Katabi, Partner, Sofinnova Investments

Kyle LaHucik, *Endpoints News*, Feb 16, 2024 (excerpt)

Maha Katabi has had a great three months. The Sofinnova general partner has been in the boardroom of two recent M&A exits: radiopharmaceuticals maker RayzeBio, sold to Bristol Myers Squibb, and asthma startup Aiolos Bio, to GSK.

Kyle LaHucik: Start with your general reflections on 2023.

Maha Katabi: A lot of private companies that were in the clinic that would have gone public in prior years were now willing to consider private financings — either to strengthen their syndicates so they'd be in a better position when public markets were ready again or simply a larger availability of clinical-stage assets. [Now,] valuations are a lot more rational. Clinical-stage is valued higher than preclinical, which wasn't the case in previous years.

LaHucik: You mentioned more companies forming around clinical-stage assets. Do you see this becoming mainstream?

Katabi: There's a lot more of that for a couple of reasons. [Pharma's] pipeline prioritization exercises are ongoing in addition to everything that's available from Chinese companies. We capitalized on that in building up Aiolos, but there are numerous other opportunities, whether it's in the inflammation space, metabolic, oncology. That, to us, has been a business model that we really like. We don't shy away from taking single-asset risk.

LaHucik: Talk more about what the RayzeBio experience was like, going from an IPO in the fall to an M&A exit just a few months later.

Katabi: If you look at how RayzeBio was set up, it was to build a pipeline of radiopharmaceutical assets that was focused on actinium as a radioisotope. The management team did a terrific job in not only just building the pipeline and having essentially a differentiated value proposition with a new radioisotope compared to lutetium, but also securing manufacturing and supply of actinium and being able to do that more effectively than their competitors.

LaHucik: In terms of the deal flow that you're looking at every year, has that level changed at all with where biotech has been the past two years?

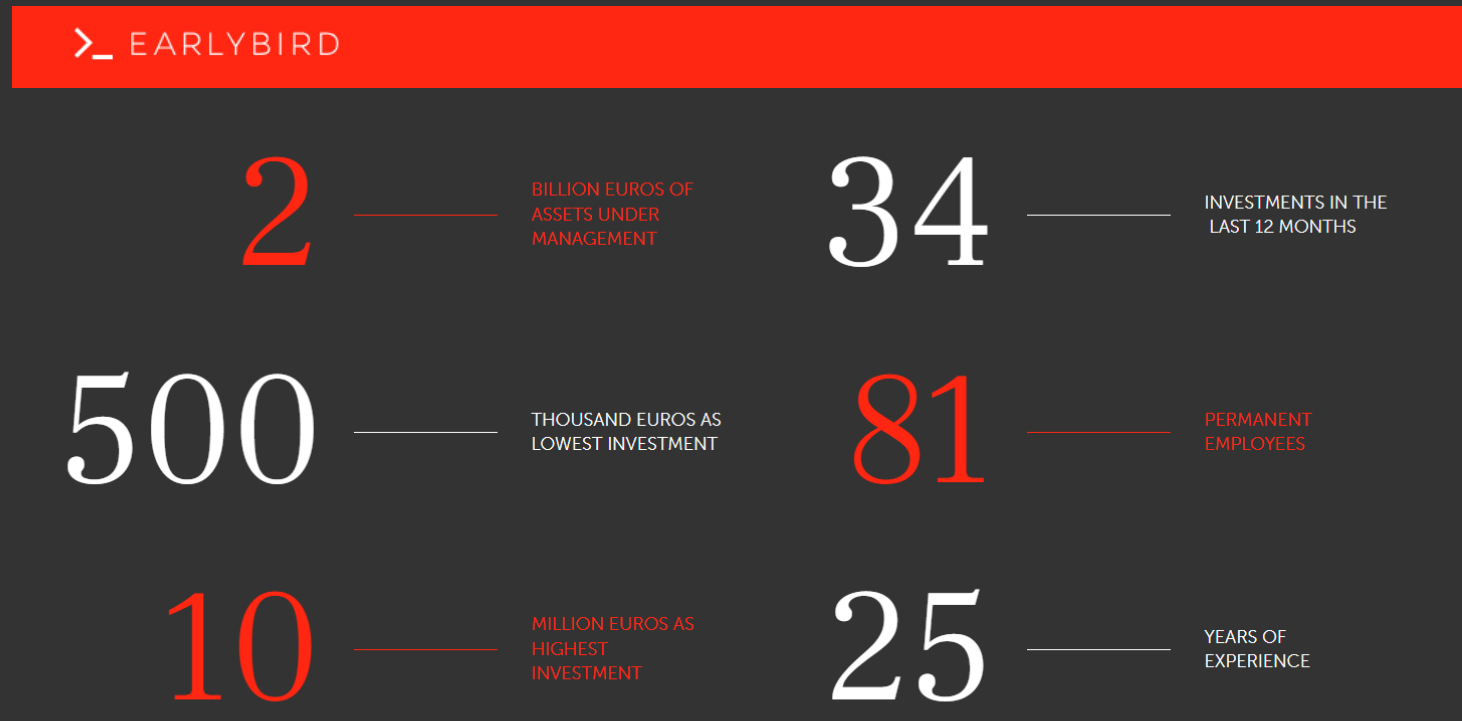
Katabi: The deal flow — it's never been any better. Probably that's a function of how public markets have corrected. A lot more companies are interested in exploring more fully the availability of capital in private markets before going down the IPO path.

Source: https://endpts.com/sofinnovas-maha-katabi-on-recent-ma-and-ipo-success-and-how-deal-flow-has-never-been-any-better/

Earlybird Health Closes €173 Million Fund

Berlin/Cologne, February 14, 2024

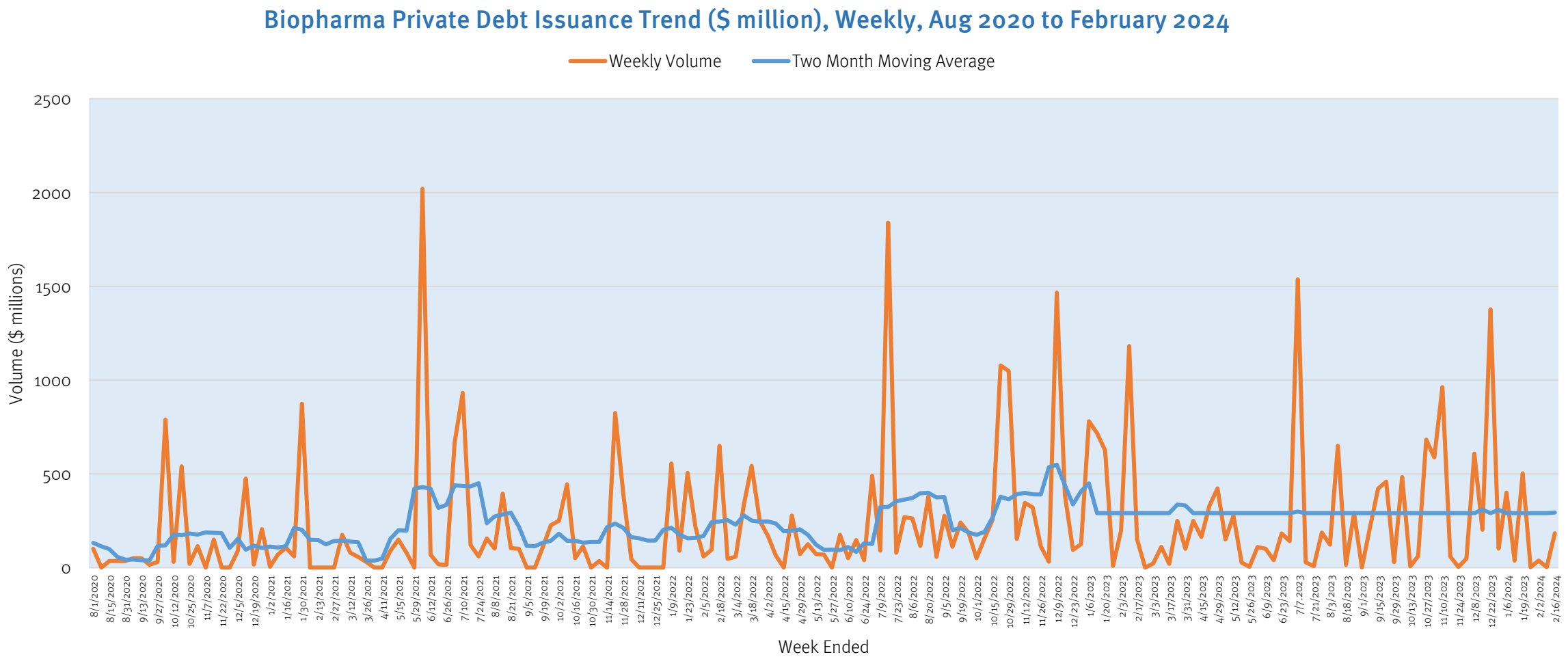
Earlybird Health announces the final closing of its latest healthcare fund of EUR 173M. The independently managed Fund is significantly larger than the previous Fund, demonstrating increased investor interest in healthcare. Earlybird Health Fund will predominantly invest in European companies from the early development stage to advanced technologies nearing regulatory approval and commercialisation. The Fund aims to invest in companies across healthcare sectors including digital health, diagnostics, medical devices, R&D tools, and biopharma – delivering robust and positive patient outcomes, regardless of the technology applied. It also complies with the Article 8 Fund criteria, per the EU's Sustainable Finance Disclosure Regulation (SFDR). With a team of more than 10 professionals, Earlybird Health brings a wealth of investment expertise to identify investment opportunities and provide financial and strategic support to its portfolio companies. Newly-appointed Partner Florent Gros comments: "Joining Earlybird Health felt like a natural evolution, given that we have a shared commitment to revolutionise patient care. Earlybird's prior investment in my company Priothera, coupled with my previous role with the Novartis Venture Fund helps us leverage our experience in strengthening Earlybird's impact, especially in biotech and biopharma."



Source: https://earlybird.com/press/

Biopharma Private Debt Placement Back in Business

The debt privates market picked up after several quiet weeks. The biggest issuers in the market were Codexis and Impulse Dynamics.



Source: Data from CapitalIQ, Crunchbase.

Codexis Secures $40 Million in Strategic Financing Deal with Innovatus Capital Partners to Further Strengthen Cash Position

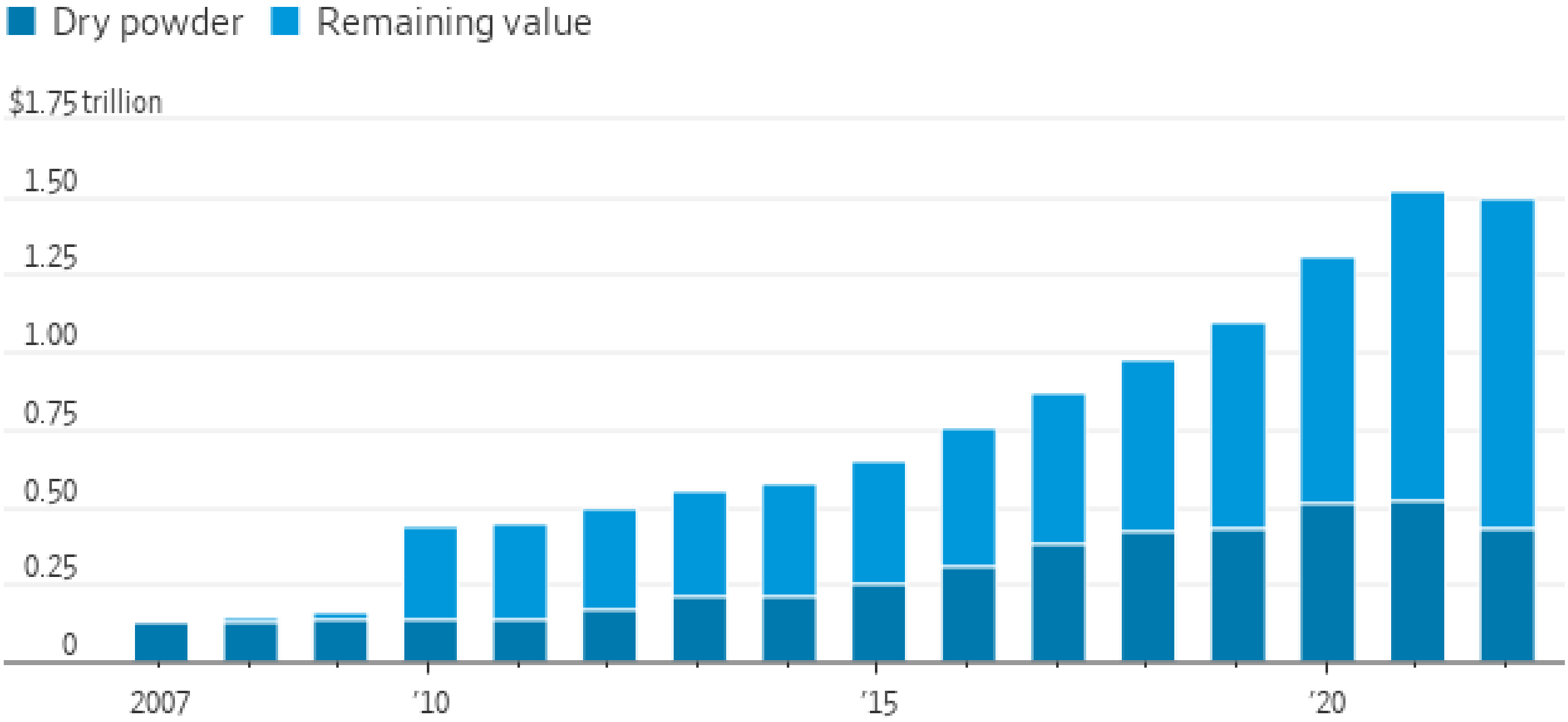
REDWOOD CITY, Calif., Feb. 13, 2024 -- Codexis, Inc. (NASDAQ: CDXS), a leading enzyme engineering company, today announced it has entered into a loan facility agreement with an affiliate of Innovatus Capital Partners, LLC (Innovatus) for up to $40 million, including $30 million upfront and access to an additional $10 million upon achieving certain prespecified revenue thresholds. This loan facility reinforces the strength of Codexis' cash position, provides additional flexibility to its projected runway through cash-flow positive around the end of 2026 and will support the ongoing development and commercialization of the Company's Enzyme-Catalyzed Oligonucleotide (ECO) Synthesis™ manufacturing platform.

"The rapid technical progress we have made with our ECO Synthesis™ manufacturing platform has exceeded our expectations and opened the door for us to make targeted investments in accelerating our technology's value creation. After a competitive process, we are excited to partner with a leading financier like Innovatus, who truly understand the incredible opportunity that RNAi therapeutics represents," said Stephen Dilly, MBBS, PhD, Chief Executive Officer of Codexis. "By opening this line of non-dilutive capital, we can prudently deploy a portion of the funds to support our ambitions of growing up the value chain by building out a small-scale facility for making siRNA at the lab level—our planned ECO Synthesis™ Innovation Lab. This financing, combined with the anticipated return to growth of our Pharmaceutical Manufacturing business this year, gives Codexis the time and financial cushion to realize the full potential of our ECO Synthesis™ manufacturing platform."

The planned ECO Synthesis™ Innovation Lab will support both technical advancement and commercialization efforts related to the Company's ECO Synthesis™ manufacturing platform. Notably, in addition to providing a strong basis for partnering discussions and early access customer testing, this facility will enable the Company to develop new RNAi constructs, test new nucleotide modifications and conjugation modalities, develop tech transfer protocols and ensure flexibility with a small-scale footprint before potentially embarking on a full-scale GMP facility.

Source: https://www.codexis.com/investors/news-events/press-releases/detail/380/codexis-secures-40-million-in-strategic-financing-deal

Global Private Debt Assets Under Management



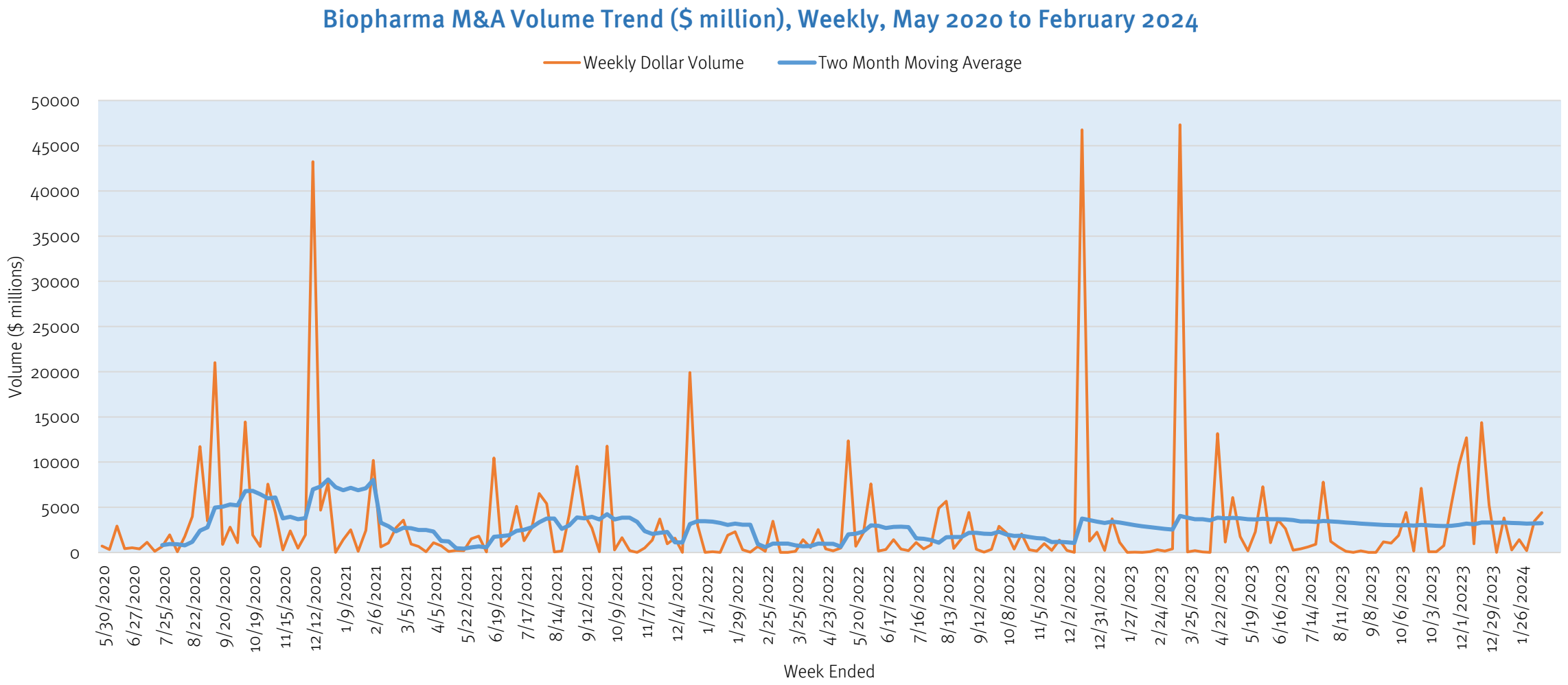
Source: PitchBook

Source: https://createsend.com/t/d-458F9AC48C5190EC2540EF23F30FEDED

M&A Update

Last Week Saw $4.4 Billion in M&A / Asset Sale Volume

Last week saw Gilead buy CymaBay for $4.3 billion and Kinnate agree to be acquired by Xoma for $113 million.



Source: S&P, CapitalIQ

Gilead Sciences Expands Liver Portfolio With Acquisition of CymaBay Therapeutics

FOSTER CITY, Calif. & NEWARK, Calif.--(BUSINESS WIRE) – Feb 12, 2024 - Gilead Sciences, Inc. (Nasdaq: GILD) and CymaBay Therapeutics, Inc. (Nasdaq: CBAY) announced today a definitive agreement under which Gilead will acquire CymaBay for $32.50 per share in cash or a total equity value of $4.3 billion. The addition of CymaBay's investigational lead product candidate, seladelpar for the treatment of primary biliary cholangitis (PBC) including pruritus, complements Gilead's existing liver portfolio and aligns with its long-standing commitment to bringing transformational medicines to patients.

"We are looking forward to advancing seladelpar by leveraging Gilead's long-standing expertise in treating and curing liver diseases," said Daniel O'Day, Chairman and Chief Executive Officer, Gilead Sciences. "Building on the strong research and development work by the CymaBay team to date, we have the potential to address a significant unmet need for people living with PBC and expand on our existing broad range of transformational therapies."

PBC is a rare, chronic, cholestatic liver disease mainly affecting women (1 in 1,000 women over the age of 40 or about 130,000 total people in the U.S.) that impairs liver function and quality of life. The most common early symptoms of PBC are pruritus (itching) and fatigue, which can be debilitating for some patients. Progression of PBC is associated with an increased risk of liver-related mortality.

Under the terms of the merger agreement entered into in connection with the transaction, a wholly-owned subsidiary of Gilead will promptly commence a tender offer to acquire all of the outstanding shares of CymaBay's common stock at a price of $32.50 per share in cash, which offer price represents a 27 percent premium to CymaBay's closing share price on February 9, 2024. Following successful completion of the tender offer, Gilead will acquire all remaining shares not tendered in the offer through a second step merger at the same price as in the tender offer. Upon FDA approval of seladelpar, the proposed transaction is expected to enhance Gilead's revenue growth, and it is also expected that the transaction will be approximately neutral to earnings per share in 2025 and significantly accretive thereafter.

Source: https://www.gilead.com/news-and-press/press-room/press-releases/2024/2/gilead-sciences-expands-liver-portfolio-with-acquisition-of-cymabay-therapeutics

Kinnate Biopharma Inc. Enters into Agreement to be Acquired by XOMA

SAN FRANCISCO and SAN DIEGO, Feb. 16, 2024 (GLOBE NEWSWIRE)- Kinnate Biopharma Inc. (Nasdaq: KNTE) ("Kinnate" or the "Company"), a clinical-stage precision oncology company, today announced it has entered into a definitive merger agreement (the "Merger Agreement") whereby XOMA Corporation ("XOMA") will acquire Kinnate for a price per share of Kinnate common stock ("Kinnate common stock") of between $2.3352 and $2.5879 in cash, consisting of (i) a base cash price of $2.3352 per share and (ii) an additional cash amount of up to $0.2527 per share, plus one non-transferable contingent value right per share, representing the right to receive (a) 100% of the net proceeds payable from any disposition of the Company's investigational pan-RAF inhibitor, exarafenib, and/or any other pan-RAF inhibitors prior to the closing of the merger transaction and (b) 85% of the net proceeds payable from any disposition of other Kinnate assets entered into prior to, or within one year from, closing and received within five years of closing pursuant to a definitive contingent value rights agreement.

Following a thorough review process conducted by a special committee of disinterested and independent members (the "Special Committee") of Kinnate's Board of Directors (the "Board"), with the assistance of the Special Committee's legal and financial advisors, all disinterested and independent members of the Board unanimously determined that the acquisition by XOMA is in the best interests of all Kinnate shareholders, and has, following the unanimous recommendation of the Special Committee, approved the Merger Agreement and related transactions.

Pursuant and subject to the terms of the Merger Agreement, a wholly owned subsidiary of XOMA will commence a tender offer (the "Offer") by March 4, 2024 to acquire all outstanding shares of Kinnate common stock. Closing of the Offer is subject to certain conditions, including the tender of Kinnate common stock representing at least a majority of the total number of outstanding shares, the availability of at least $120 million of cash (net of transaction costs, wind-down costs and other liabilities) at closing, and other customary closing conditions. Kinnate officers, directors and shareholders holding approximately 46% of Kinnate common stock have signed support agreements under which such parties have agreed to tender their shares in the Offer and support the merger transaction. The merger transaction is expected to close in the first half of 2024.

Source: https://www.globenewswire.com/news-release/2024/02/16/2830725/0/en/Kinnate-Biopharma-Inc-Enters-into-Agreement-to-be-Acquired-by-XOMA-Corporation-for-Between-2-3352-and-2-5879-Per-Share-in-Cash-Plus-One-Contingent-Value-Right-per-Share.html

Eris Buys Majority Stake in Swiss Parenterals for $77 Million

The Economic Times (of India), Feb 13, 2024 (excerpt)

New Delhi, Eris Lifesciences on Tuesday said it has acquired a 51 per cent stake in Swiss Parenterals for Rs 637.5 crore. Ahmedabad-based Swiss Parenterals is a leading player in the sterile injectables business in over 80 emerging markets across Africa, the Asia Pacific and Latin America.

It has two facilities in Gujarat, which produce a wide range of sterile injectable formulations.

"The acquisition of Swiss Parenterals will help us strengthen our India footprint through the launch of a domestic Injectables-focused Branded Formulations business," Eris Lifesciences Chairman and MD Amit Bakshi said in a statement.

Source: https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/eris-acquires-51-pc-stake-in-swiss-parenterals-for-rs-637-5-cr/articleshow/107665426.cms

Invitae Files for Chapter 11 Bankruptcy

INVITAE

Invitae, Form 8-K, Feb 13, 2024

On February 13, 2024 (the "Petition Date"), Invitae Corporation (the "Company") and certain of its direct and indirect subsidiaries (together with the Company, the "Company Parties") filed voluntary petitions to commence proceedings under chapter 11 (the "Chapter 11 Cases") of title 11 of the United States Code (the "Bankruptcy Code") in the United States Bankruptcy Court for the District of New Jersey (the "Bankruptcy Court"). The Company Parties have requested that the Chapter 11 Cases be jointly administered under the caption In re Invitae Corporation, et al.

The Company Parties will continue to operate their business and manage their properties as "debtors in possession" under the jurisdiction of the Bankruptcy Court and in accordance with the applicable provisions of the Bankruptcy Code and the orders of the Bankruptcy Court. In order to ensure their ability to continue operating in the ordinary course of business and minimize the effect of bankruptcy on the Company Parties' customers, patients, employees, vendors and other stakeholders, the Company Parties filed with the Bankruptcy Court certain motions seeking a variety of "first day" motions, including a motion seeking authority to pay employee wages and benefits, to pay certain vendors and suppliers for goods and services provided both before and after the Petition Date, and to continue honoring insurance and tax obligations as they come due. In addition, the Company filed motions with the Bankruptcy Court seeking approval for the consensual use of cash collateral and other customary operational and administrative relief. The Company Parties expect that the Bankruptcy Court will approve the relief sought in these motions on an interim basis.
Additional information about the Chapter 11 Cases, including access to Bankruptcy Court documents, is available online at www.kccllc.net/invitae, a website administered by Kurtzman Carson Consultants LLC, a third-party bankruptcy claims and noticing agent. The documents and other information on this website are not part of this Current Report and shall not be incorporated by reference herein.

Invitae had about $535 million in assets and about $1.62 billion in debts as of Sept. 30, according to a filing with the U.S. Bankruptcy Court.

Source: https://www.sec.gov/ixviewer/ix.html?doc=/Archives/edgar/data/0001501134/000150113424000016/nvta-20240213.htm

Aurinia Announces Actions to Enhance Shareholder Value

ROCKVILLE, Maryland & EDMONTON, Alberta--(BUSINESS WIRE), Feb. 15, 2024

Aurinia Pharmaceuticals Inc. (NASDAQ: AUPH) (Aurinia or the Company) today provided an update on its 2023 fourth quarter and full year business performance, as well as a corporate update regarding the Company's strategic review. This includes corporate actions designed to enhance shareholder value, including an exclusive focus on driving commercial execution of the LUPKYNIS® (voclosporin) business, and a significant share repurchase program.

Effective immediately, Aurinia will discontinue its future development of AUR200 and AUR300 research and development programs and prioritize resource allocation. This will result in a one-time charge in the first quarter of 2024 of approximately $11 - $15 million and expected operational cost savings of approximately $50 - $55 million annually, with approximately 75% of the savings being recognized in 2024 excluding the one-time restructuring charge in the first quarter of 2024.

The Board initiated a robust strategic review at the end of June 2023 to review all strategic options for the Company. Together with management, JP Morgan, the Company's financial advisor in the strategic review process, engaged with more than 60 parties, **receiving only one non-binding expression of interest, which included a due diligence process, but did not result in a formal offer.**

Aurinia also explored potentially acquiring or licensing other entities or assets during this time. After assessing a range of alternatives over the last seven months, the Board elected to conclude Aurinia's strategic review process. The Board ultimately determined that none of the explored opportunities that were available to it to pursue were in the best near-term interests of the Company to execute on, and that the best path forward is for management to streamline its operations as it announced today and focus on the Company's commercial execution.

Additionally, in 2018, the Company under previous management and at the Board's discretion, engaged a leading investment bank to conduct a confidential strategic review process. During the 2018 process, the Company received only one non-binding expression of interest to acquire the Company, which included a due diligence process, but did not result in a formal offer.

Outside of these two expressions of interest, the Company has never received an offer of any kind to acquire the Company. The Board and management remain open to exploring opportunities that are in the best interests of the Company and are open to considering any bona fide offers that the Company receives.

Source: https://www.auriniapharma.com/investors-and-media/news-events/press-releases/detail/314/aurinia-discloses-2023-year-end-financial-and-operational

LianBio To Return Cash and Shut Down

SHANGHAI, China and PRINCETON, N.J., Feb. 13, 2024 (GLOBE NEWSWIRE)

-- LianBio (Nasdaq: LIAN) ("LianBio" or the "Company"), a biotechnology company dedicated to bringing innovative medicines to patients in China and other major Asian markets, today announced that the Company's Board of Directors (the "Board") had completed its comprehensive strategic review of the Company and determined to initiate the wind down of its operations, including the sale of remaining pipeline assets, the delisting of its American Depositary Shares ("ADSs"), each representing the right to receive one ordinary share, from the Nasdaq Global Market ("Nasdaq") and deregistration under Section 12(b) of the Securities Exchange Act of 1934 (the "Exchange Act") and workforce reductions. The Company currently anticipates a substantial portion of the wind down activities, including fulfillment of transition service obligations under its existing agreements and gradual cessation of currently active clinical trials, will be completed by the end of 2024. In parallel with the wind down of operations, the Board has declared a special cash dividend in the amount of $4.80 per ordinary share, including ordinary shares represented by ADSs, for an aggregate cash dividend amount of approximately $528 million.

"In October 2023, the Board of Directors initiated a comprehensive strategic review of the Company, including numerous options for the future of the Company, as our commitment to represent the best interests of LianBio and shareholders," said Konstantin Poukalov, Founder and Executive Chairman of LianBio's Board. "Following the shift in focus away from mavacamten commercialization and the licensing of rights to NBTXR3 to Janssen, the Board unanimously decided that winding down operations is the way to realize maximum shareholder value in the current biotech market."

Source: https://investors.lianbio.com/news-releases/news-release-details/lianbio-announces-completion-strategic-review

Industry News

China-US Tensions are Spilling Into the Biotech Sector

Isaac Hanson, Pharmaceutical Technology, February 15, 2024 (excerpt)

The ongoing US-China trade war has already affected sectors from AI to agriculture and shows few signs of slowing. Now the conflict is spilling into medicine, leaving some Chinese biotechnology companies in the cold. Whilst the sector's collaborative nature has generally protected subsidiaries operating in the US, two recent legislative moves suggest that this is changing.

The first is a bill introduced on 25 January by two leading members of the US' Select Committee on the CCP (Chinese Communist Party) that hopes to ban federally funded medical providers from using the services of any Chinese biotechs, particularly BGI Group, MGI and WuXi AppTec. This would effectively ban the companies from the US market. The bill argues that due to the CCP's legal ability to view private data held by any companies based in its territory, handing over genetic data to them constitutes a national security risk.

A Reuters investigation from 2021 shows that these fears are not entirely unfounded. BGI – formerly Beijing Genomics Institute – has been shown to work with the People's Liberation Army (PLA) of China in gene sequencing, as well as storing data from millions of prenatal tests globally in China's gene database. However, Reuters found no evidence of this data being misused, and the company has stated that it has never provided or been asked to provide genomic data to Chinese authorities.

The question of what exactly China would do with US genomic data is open, though the bill's proponents have some ideas. Chairman of the group Mike Gallagher suggested it could "potentially even [be used] to develop a bioweapon used to target the American people."

This bill was followed up on 12 February by a letter from members of the Select Committee arguing for specific sanctions against WuXi AppTec, a multinational biotech and medical devices company headquartered in Shanghai. The letter claims that the company has ties to the PLA and as such represents a threat to national security, a claim it strongly denies. A statement on its website states that "WuXi AppTec has a strong track record of upholding the highest intellectual property, data and privacy protection standards, as well as maintaining the trust of our customers." The company has in the past worked with Pfizer, AstraZeneca and GSK, amongst others.

Source: https://www.pharmaceutical-technology.com/features/china-us-tensions-are-spilling-into-the-biotech-sector/

How the Push to Limit Chinese Biotech Could Threaten U.S. Edge

Alison Snyder, *Axios*, Feb 12, 2024 (excerpt)

Efforts in Congress to restrict U.S. market access for Chinese biotech companies and investors face a central dilemma: They could disrupt key relationships and supply chains U.S. life sciences companies rely on.

Why it matters: Bipartisan consensus for action is growing amid deteriorated U.S.-China relations, but it's running into the reality that they'll have to balance moves to address U.S. national security concerns with the risk of setting back companies that underpin the country's competitive edge.

The "geopolitics and trade and investment parts of the U.S.-China relationship are on totally different planes," says Scott Michael Moore, director of China Programs and Strategic Initiatives at the University of Pennsylvania.

Driving the news: The House Select Committee on the Chinese Communist Party was scheduled to hold a field hearing on U.S-China biotech competition and national security risks in the sector Tuesday in Boston, but it was postponed due to weather.

The panel is expected to discuss possible actions to ban certain Chinese biotech companies from operating in the U.S., to stop China from acquiring U.S. biotech companies and to support the U.S. biotech sector.

Witnesses include Jason Kelly, CEO of Ginkgo Bioworks, a Boston-based synthetic biology company, and Tara O'Toole, executive vice president of In-Q-Tel, a not-for-profit venture-capital firm established by the Central Intelligence Agency, and former homeland security official during the Obama administration.

Source: https://www.axios.com/2024/02/12/us-china-biotech-restriction

We are sympathetic with the message of this article.

It's hard to figure out how restricting access to companies like Wuxi is in the interest of the United States in any way.

Healthcare, in general, is not an area where national security interests are at stake. Chinese and American people die from the same diseases and there should be a common interest between the countries to help each other in efforts to combat disease and to disseminate technologies for doing so.

As noted at left, limiting access to China biotech could prove to be self-destructive.

We wonder if lobbying efforts of companies that compete against the likes of Wuxi may be behind recent congressional interest in this area.

Iovance's AMTAGVI™ (lifileucel) Receives U.S. FDA Accelerated Approval for Advanced Melanoma

SAN CARLOS, Calif., Feb. 16, 2024 (GLOBE NEWSWIRE)

Iovance Biotherapeutics, Inc. (NASDAQ: IOVA), a biotechnology company focused on innovating, developing and delivering novel polyclonal tumor infiltrating lymphocyte (TIL) cell therapies for patients with cancer, today announced that the U.S. Food and Drug Administration (FDA) has approved AMTAGVI™ (lifileucel) suspension for intravenous infusion. AMTAGVI is a tumor-derived autologous T cell immunotherapy indicated for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. This indication is approved under an accelerated approval based on overall response rate (ORR) and duration of response. Iovance is also conducting TILVANCE-301, a Phase 3 trial to confirm clinical benefit.

AMTAGVI is the first and the only one-time, individualized T cell therapy to receive FDA approval for a solid tumor cancer. The proposed mechanism for AMTAGVI offers a new cell therapy approach that deploys patient-specific T cells called TIL cells. When cancer is detected, the immune system creates TIL cells to locate, attack, and destroy cancer. TIL cells recognize distinctive tumor markers on the cell surface of each person's cancer. When cancer develops and prevails, the body's natural TIL cells can no longer perform their intended function to fight cancer.

AMTAGVI is manufactured using a proprietary process to collect and expand a patient's unique T cells from a portion of their tumor. AMTAGVI returns billions of the patient's T cells back to the body to fight their cancer.* Authorized Treatment Centers (ATCs) will administer AMTAGVI to patients as part of a treatment regimen that includes lymphodepletion and a short course of high-dose PROLEUKIN® (aldesleukin).

Source: https://ir.iovance.com/news-releases/news-release-details/iovances-amtagvitm-lifileucel-receives-us-fda-accelerated

Move Over, CRISPR: RNA-Editing Therapies Pick Up Steam

Mariana Lenharo, *Nature*, Feb. 16, 2024 (excerpt)

RNA editing is gaining momentum. After decades of basic research into how to manipulate this complex molecule, at least three therapies based on RNA editing have either entered clinical trials or received approval to do so. They are the first to reach this milestone.

Proponents of RNA editing have long argued that it could be a safer and more flexible alternative to genome-editing techniques such as CRISPR, but it poses substantial technical problems. The launch of human trials signals the growing maturity and acceptance of the field, scientists say. “There’s a much greater understanding of RNA technology, and that’s been partially enhanced by the RNA vaccine and the COVID pandemic,” says Andrew Lever, a biologist at the University of Cambridge, UK. “RNA is now seen as a very important therapeutic molecule.”

One common RNA-editing approach, single-base editing, harnesses an enzyme that is already found in cells: adenosine deaminase acting on RNA (ADAR). This enzyme swaps a base called adenine in the RNA sequence for a base called an inosine.

Wave Life Sciences in Cambridge, Massachusetts, is exploring single-base editing to treat a genetic disorder called alpha-1 antitrypsin deficiency (AATD), which can damage the lungs and the liver. The disease reduces the production of AAT, a protein made in liver cells that protects lungs from damage caused by inhaling polluted air or other irritants.

Another approach, called RNA exon editing, changes thousands of genetic letters in an RNA molecule at once, as opposed to changing just one letter. Exon editing is akin to editing a whole paragraph instead of correcting one typo, says Lever. This technology is particularly important for disorders caused by multiple mutations in a person’s genome; such arrays of mutations are difficult to address with single-base changes, he adds.

Rznomics’s approach involves mRNA splicing — but, unlike Ascidian’s method (leveraging the RNA-splicing process to remove mutation-containing exons and replace them with healthy ones), it doesn’t use the cell’s own splicing machinery. Instead, the company co-opted a naturally occurring ribozyme, an RNA molecule that can induce splicing in target regions of mRNA. Researchers engineered the ribozymes to cut open mRNAs in tumour cells and insert a lethal cargo: an RNA sequence that is translated into a protein that generates a toxin that induces cell death. When surrounding cancer cells come into contact with these cells, the toxin spreads, promoting their death as well. This therapeutic molecule replaces an RNA sequence that is associated with tumour growth.

The use of the splicing approach against more than one disease is very exciting, says Lever, who is also the chief medical officer of Spliceor in Cambridge, UK, a firm that is working on RNA-splicing therapies. “It opens up a whole new range of possibilities of treatment for things which otherwise can't be treated.”

Source: https://www.nature.com/articles/d41586-024-00275-6

Over 5% of U.S. Population Has Immunosuppression

Martinson ML, Lapham J., "Prevalence of Immunosuppression Among US Adults," *JAMA*, Feb 15, 2024:e2328019 (excerpt)

The prevalence of immunosuppression from health conditions and medication use among US adults is often reported to be about 3%, which is based on an estimate of 2.7% from nationally representative data from 2013 and an estimate of 2.8% for the prevalence of immunosuppressive drug use among commercially insured adults younger than 65 years of age.

Immunosuppression prevalence is an important consideration for public health in the US given this population's increased risk from viral and bacterial infections. These estimates were of particular concern during the COVID-19 pandemic because people with immunosuppression are less likely to have an adequate response to vaccines and are more likely to experience severe COVID-19 symptoms even after vaccination. This population has also been advised to continue with COVID-19 precautions to avoid infection.

In addition, immunocompromised conditions and medication use may have changed over the last decade. We present population prevalence estimates of immunosuppression among US adults using nationally representative data from 2021.

Table. Self-Reported Status of Immunosuppression for 2021

	Unweighted data, No. (%)		Weighted prevalence per 100 US population, % (95% CI)
	Total sample (N = 29 164)	Had immunosuppression (n = 2123)	
Had immunosuppression		2123 (7.2)[a]	6.6 (6.2-6.9)
Sex			
Male	13 246 (45.4)	737 (35.3)	5.2 (4.8-5.7)
Female	15 918 (54.6)	1351 (64.7)	7.9 (7.4-8.4)
Race and ethnicity[b]			
Hispanic	4044 (13.9)	229 (11.0)	5.0 (4.3-5.8)
Non-Hispanic			
African American or Black	3126 (10.7)	222 (10.6)	6.1 (5.2-7.2)
American Indian or Alaska Native	401 (1.4)	43 (2.1)	8.4 (6.0-11.7)
Asian	1774 (6.1)	70 (3.3)	3.7 (2.8-4.8)
White	19 458 (66.7)	1508 (72.2)	7.4 (6.9-7.8)
Other[c]	361 (1.2)	16 (0.8)	4.2 (2.3-7.3)
Age group, y			
18-29	3836 (13.2)	141 (6.8)	3.3 (2.8-4.0)
30-39	4713 (16.2)	224 (10.7)	4.5 (3.8-5.2)
40-49	4341 (14.9)	300 (14.4)	6.6 (5.8-7.4)
50-59	4731 (16.2)	422 (20.2)	8.7 (7.8-9.6)
60-69	5341 (18.3)	514 (24.6)	9.5 (8.6-10.5)
70-79	4059 (13.9)	355 (17.0)	8.9 (7.9-10.0)
≥80	2143 (7.3)	132 (6.3)	6.6 (5.4-8.1)
Health insurance status			
Insured	27 210 (93.3)	2018 (96.6)	6.9 (6.6-7.3)
Uninsured	1954 (6.7)	70 (3.4)	3.0 (2.2-3.9)

[a] Based on responses to the 5 survey questions presented in the Box. Immunosuppression was present if the participant responded "yes" to question 1 or question 2 or if the participant reported having hematologic cancer within the past 2 years (based on question 4 and date calculations from question 5). Those not meeting this definition were categorized as not having immunosuppression.

[b] Hispanic or non-Hispanic ethnicity was asked separately from race in the NHIS.

[c] The NHIS includes a choice for "some other race" in the questionnaire for respondents who do not identify with the racial and ethnic categories provided.

Source: https://jamanetwork.com/journals/jama/fullarticle/2815274

Unlocking Infinite Biotech Breakthroughs: The Power of Creativity

University of Bristol, *SciTech Daily*, Feb 15, 2024 (excerpt)

New research suggests that scientists engaged in biological design should prioritize understanding the unique characteristics of biological systems rather than striving for over-optimization.

In a study, published in *Science Advances*, researchers from the Universities of Bristol and Ghent have shown how exploring the unknown may be the crucial step needed to realize the continual innovation needed for the biotechnologies of the future.

Recognising the role of open-endedness in achieving this goal and its growing importance in fields like computer science and evolutionary biology, the team mapped out how open-mindedness is linked to bioengineering practice today and what would be required to achieve it in the lab.

For success, algorithms used for biological design should not solely focus on moving toward a specific goal – such as better yield – but also consider the creation and maintenance of novelty and diversity in the solutions that have been found.

Dr Thomas Gorochowski, co-author and Royal Society University Research Fellow in the School of Biological Sciences at Bristol, explained: "When we try to design a complex biological process, it's often tempting to just tweak something that partially works rather than take the risk of trying something completely new.

"In this work we highlight that in these situations the best solutions often come from unexpected directions because we don't always fully understand how everything works. With biology, there are lots of unknowns and so we need a vast and diverse toolkit of building blocks to ensure we have the best chance of finding the solution we need."

Professor Michiel Stock, lead author from Ghent University, added: "Biological systems have a natural capacity for innovation that has led to the overwhelming biodiversity we see in nature today.

"Our own attempts to engineer biology, in contrast, lack this creativity – they are far more rigid, less imaginative, and often don't make the best use of what biology is capable of.

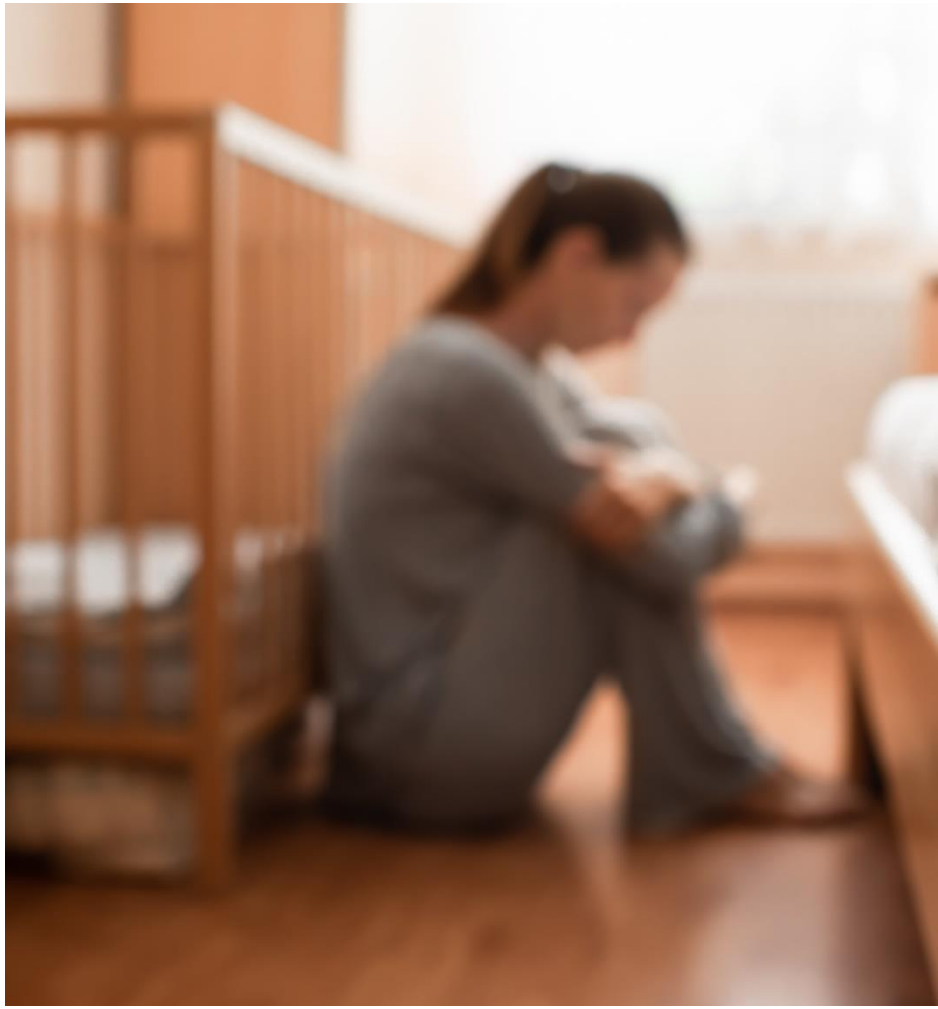
"With all life around us originating from the open-ended process of evolution, wouldn't it be awesome if we could harness some of that power for our own biological designs."

Source: https://scitechdaily.com/unlocking-infinite-biotech-breakthroughs-the-power-of-creativity/

Anxiety-Focused Cognitive Behavioral Therapy Delivered by Non-Specialists to Prevent Postnatal Depression

Pamela Surkan et.al., *Nature Medicine*, Feb. 16, 2024 (Abstract)

Anxiety experienced by women during pregnancy is highly prevalent, especially in resource-poor settings and strongly predicts postnatal common mental disorders (CMDs), anxiety and depression. We evaluated the effectiveness of an anxiety-focused early prenatal intervention on preventing postnatal CMDs. This study was a phase 3, two-arm, single-blind, randomized controlled trial conducted in Pakistan with women who were ≤22 weeks pregnant and had at least mild anxiety without clinical depression. Participants were randomized to the Happy Mother–Healthy Baby program, based on cognitive behavioral therapy, consisting of six one-on-one intervention sessions in pregnancy delivered by non-specialist providers, or to enhanced care alone. The primary outcome was major depression, generalized anxiety disorder or both at 6 weeks after delivery. Overall, 755 women completed postnatal assessments (380 (50.3%), intervention arm; 375 (49.7%) enhanced-care arm). The primary outcomes were met. Examined jointly, we found 81% reduced odds of having either a major depressive episode (MDE) or moderate-to-severe anxiety for women randomized to the intervention (adjusted odds ratio (aOR) = 0.19, 95% CI 0.14–0.28). **Overall, 12% of women in the intervention group developed MDE at 6 weeks postpartum, versus 41% in the control group.** We found reductions of 81% and 74% in the odds of postnatal MDE (aOR = 0.19, 95% CI 0.13–0.28) and of moderate-to-severe anxiety (aOR = 0.26, 95% CI 0.17–0.40), respectively. The Happy Mother–Healthy Baby program early prenatal intervention focusing on anxiety symptoms reduced postpartum CMDs.



Source: https://www.nature.com/articles/s41591-024-02809-x

The Future of Precision Cancer Therapy Might be to Try Everything

Elie Dolgin, *Nature*, Feb. 15, 2024 (excerpt)

The blood cancer had returned, and Kevin Sander was running out of treatment options. A stem-cell transplant would offer the best chance for long-term survival, but to qualify for the procedure he would first need to reduce the extent of his tumour — a seemingly insurmountable goal, because successive treatments had all failed to keep the disease in check.

As a last throw of the dice, he joined a landmark clinical trial. Led by haematologist Philipp Staber at the Medical University of Vienna, the study is exploring an innovative treatment strategy in which drugs are tested on the patient's own cancer cells, cultured outside the body. In February 2022, researchers tried 130 compounds on cells grown from Sander's cancer — essentially trying everything at their disposal to see what might work.

One option looked promising. It was a type of kinase inhibitor that is approved to treat thyroid cancer, but it is seldom, if ever, used for the rare subtype of lymphoma that Sander had. Physicians prescribed him a treatment regimen that included the drug, and it worked. The cancer receded, enabling him to undergo the stem-cell transplant. He has been in remission ever since. "I'm a bit more free now," says Sander, a 38-year-old procurement manager living in Podersdorf am See, Austria. "I do not fear death any more," he adds. "I try to enjoy my life."

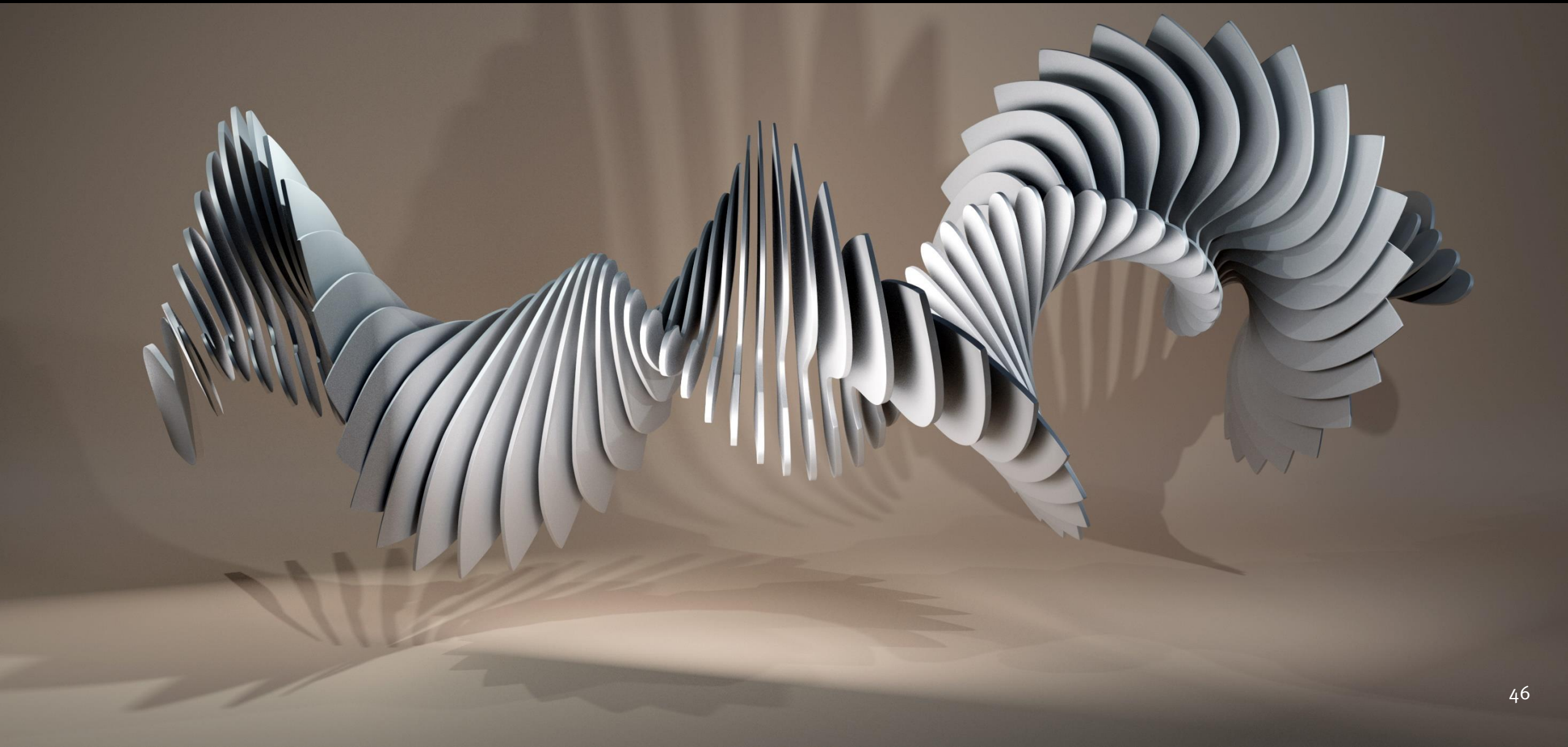
His story is a testament to this kind of intensive and highly personalized drug-screening method, referred to as functional precision medicine. Like all precision medicine, it aims to match treatments to patients, but it differs from the genomics-guided paradigm that has come to dominate the field. Instead of relying on genetic data and the best available understanding of tumour biology to select a treatment, clinicians throw everything they've got at cancer cells in the laboratory and see what sticks.

But what it sometimes lacks in elegance, it could make up for in results: in pilot studies, Staber and his colleagues found that more than half of people with blood cancer whose treatment was guided by functional drug testing enjoyed longer periods of remission compared with their experiences of standard treatments. Large-scale testing of genome-directed approaches suggests that the techniques are very effective against some cancers, yet they benefit, at most, only around 10% of patients overall. Staber and his group's latest trial is the first to compare functional- and genome-guided approaches head-to-head alongside treatments directed by standard pathology and physician intuition.

"That'll be a very powerful study, and it will probably vindicate the utility of these functional assays," says Anthony Letai, a haematologist at the Dana-Farber Cancer Institute in Boston, Massachusetts, and president of the Society for Functional Precision Medicine, a professional organization founded in 2017 to advance the field. And, if anecdotal reports serve as any indication, the try-everything tactic seems to bring about meaningful improvements, even when the genetic sequence of a tumour provides no actionable information, as was the case for Sander.

Source: https://www.nature.com/articles/d41586-024-00392-2

The Big Drugs for Big Diseases Industry Theme

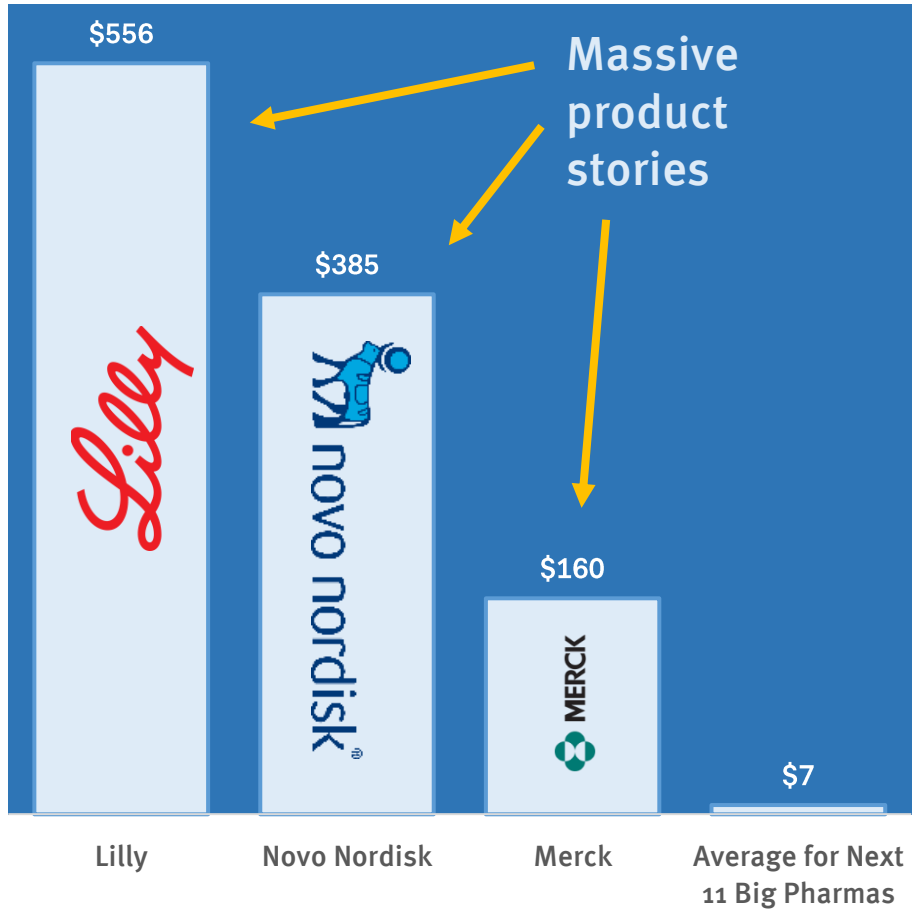


The Rules of the Game for Big Pharma Changed After 2020

The rules of the pharma game changed after the Pandemic. The new thought process: "Go Big or Go Home"

- Real drugs for big diseases with real data are now in vogue.
- The big moves have been in obesity drugs where there is massive scale possible due to many indications and widespread need.
- "Big efficacy on big markets" is the new mantra.
- Precision on narrow markets was the old mantra.
- Payors and patients want to see drugs that really work for major diseases.
- Investors have also understood this message. Hence deals like BioAge this week.
- Most pharmas instead are showing large pipelines of mid-sized drugs ($1bn to $10bn in size). The economics of buying, building and launching these products are not terribly favorable. This is visible in the chart at right in value accretion in the last four years.
- We are starting to see much more emphasis by most pharmas on larger disease categories than before.

Change in Enterprise Value of Big Pharmas, Feb 7, 2020 to Feb 16, 2024 ($ Billions)



Source: CapitalIQ

Big Drug Theme Will Continue and Grow in Next Decade

1. **Payors will pay for these drugs (non-competitive markets)**
    a) Payor tolerance for $15,000 to $30,000 per annum pricing for drugs that make a big difference in fairly common diseases
    b) For example, Dupilumab is priced between $20,000 to $40,000 per year for atopic derm, asthma and COPD
2. **Even in competitive market segments there is solid pricing for "big disease" drugs**
    a) Repatha priced at around $6,000 per year after discounts and rebates
    b) GLP-1's priced at around $6,000 per year after discounts and rebates
    c) SGLT2 reimbursed at $6,000 per year after discounts and rebates
    d) With this pricing at 5mm patients, there is a $30bn revenue opportunity – the economics work
3. **Commercial payors and governments highly incentivized to pay for drugs that take down costs of care**
    a) Direct costs of care are borne in value-based environments
    b) Value-based care is spreading in the U.S. rapidly. More than 50% of Medicare is value-based now
    c) Integrated "payvidors" increasingly own PBMs and are directly incentivized to pay for diseases that fill emergency rooms and drive care costs
    d) The spread of value-based care will massively fuel the growth of the "big drug" theme for years to come.

Cost of Common Chronic Diseases

$3.7 tn

Total (including indirect) costs of chronic disease in U.S. each year

$1.5 tn

Amount spent in treating chronic disease in US yearly

68%

of Medicare members have more than one chronic disease

95%

Amount of Medicare dollars allocated to managing long-term chronic conditions

Source: CDC, Institute of Medicine

FDA is Highly Focused on Common Chronic Disease

Rob Califf
FDA Commissioner

The approximately 5-year shorter life expectancy in the US, compared with other high-income countries, must be addressed by improving outcomes for **common chronic diseases**."

JAMA
Feb 2022

Patrizia Cavazzoni
Director, CDER, January 2022

Challenges for Drug Development for Common Diseases With Unmet Need

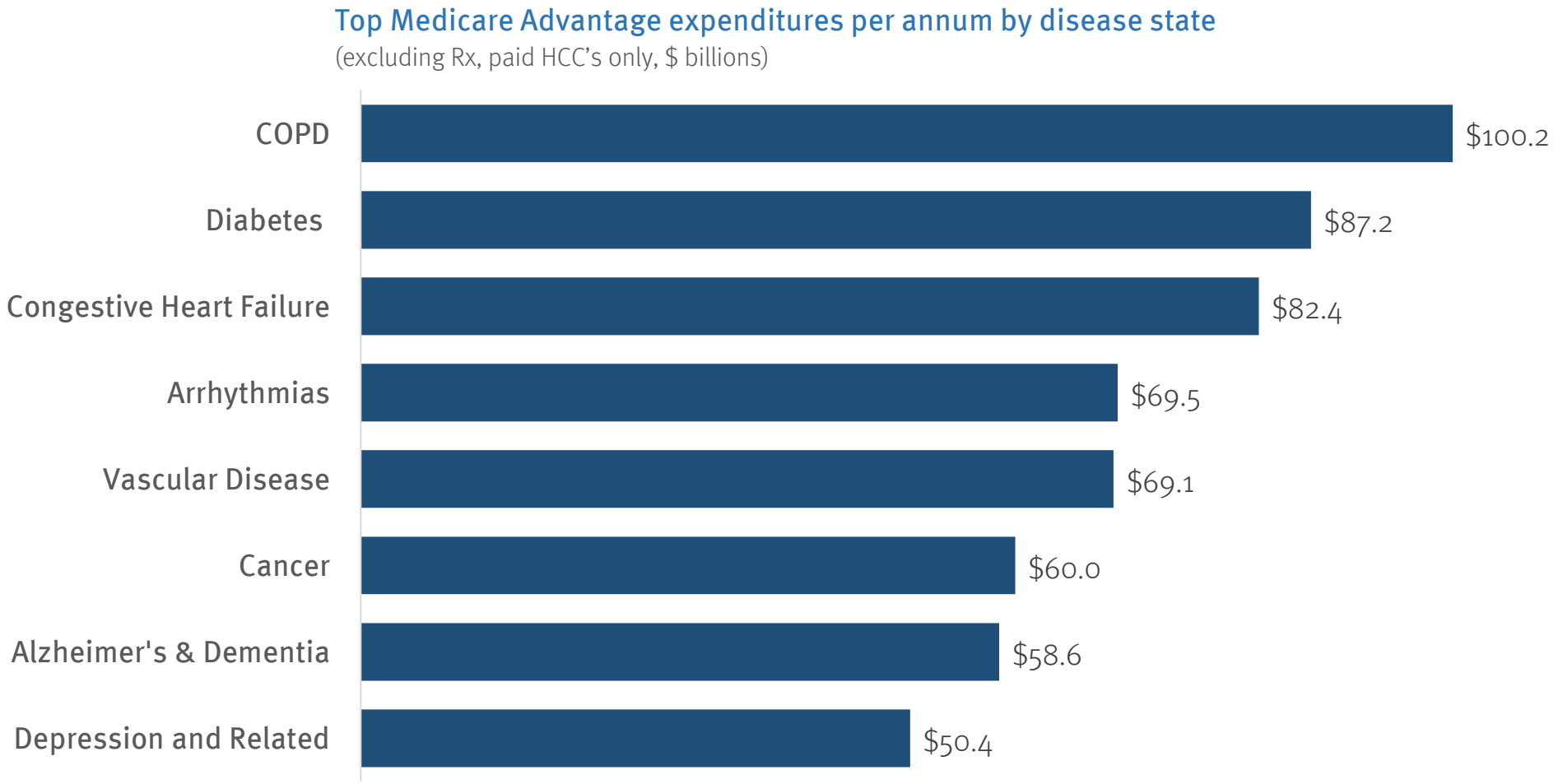
FDA

- Unmet needs may be in **defined subpopulations** of common disease
  - Resistant disease (e.g., resistant depression)
  - "Subsets" with unmet needs such as heart failure with normal ejection fraction
  - Patients who remain inadequately controlled (e.g., T2DM) despite current SOC
  - Diseases with new options, but residual substantial unmet need such as obesity
  - Residual increased mortality despite many treatments such as in coronary disease
- Presents **unique challenges**
  - Trial recruitment – identifying "subset" of overall population, may require extensive screening
  - Trial designs may require superiority to SOC or add-on to SOC therapies
  - Identification of "resistant" patients may be challenging
- **Flexible and innovative approaches** *must be considered*
  - Range of less common designs must be considered: run-in treatment, randomized withdrawal, superiority to SOC, add-on to SOC
  - Master protocols and platform trials to study range of treatments
  - Adaptive designed trials to improve trial efficiency
  - Novel endpoint development – that may enhance trial efficiency

6

See https://jamanetwork.com/journals/jama/fullarticle/2795742 and https://www.science.org/doi/10.1126/science.ade5003.

Medicare Advantage Spending by Selected Chronic Diseases



Note: These figures are estimated by multiplying prevalence estimates from MedPac for key HCC's by average spend per disease state obtained from the literature. Most spend is on individuals with multiple chronic conditions. The numbers shown here overcount actual spend because they are not specific to spend attributable to the single disease. On the hand, note that we have not included atherosclerosis as a disease state as it is not, in general, reimbursed in Medicare Advantage.

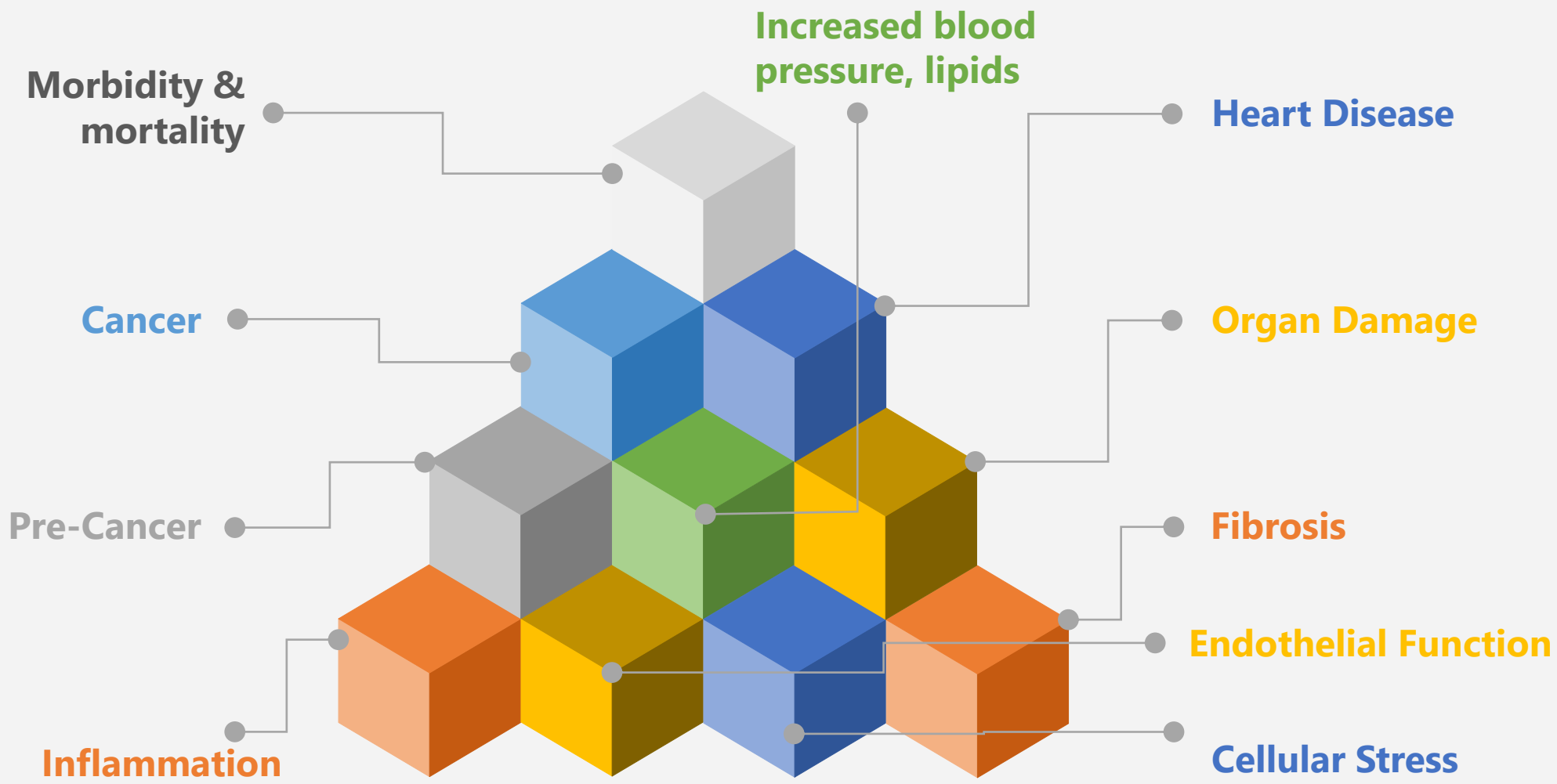
Huge Opportunity in Addressing Subclinical Pathologies

Traditional medicine spends little time analyzing the underlying causes of disease including inflammation, cellular stress, fibrosis, epithelial disease and somatic mutations.

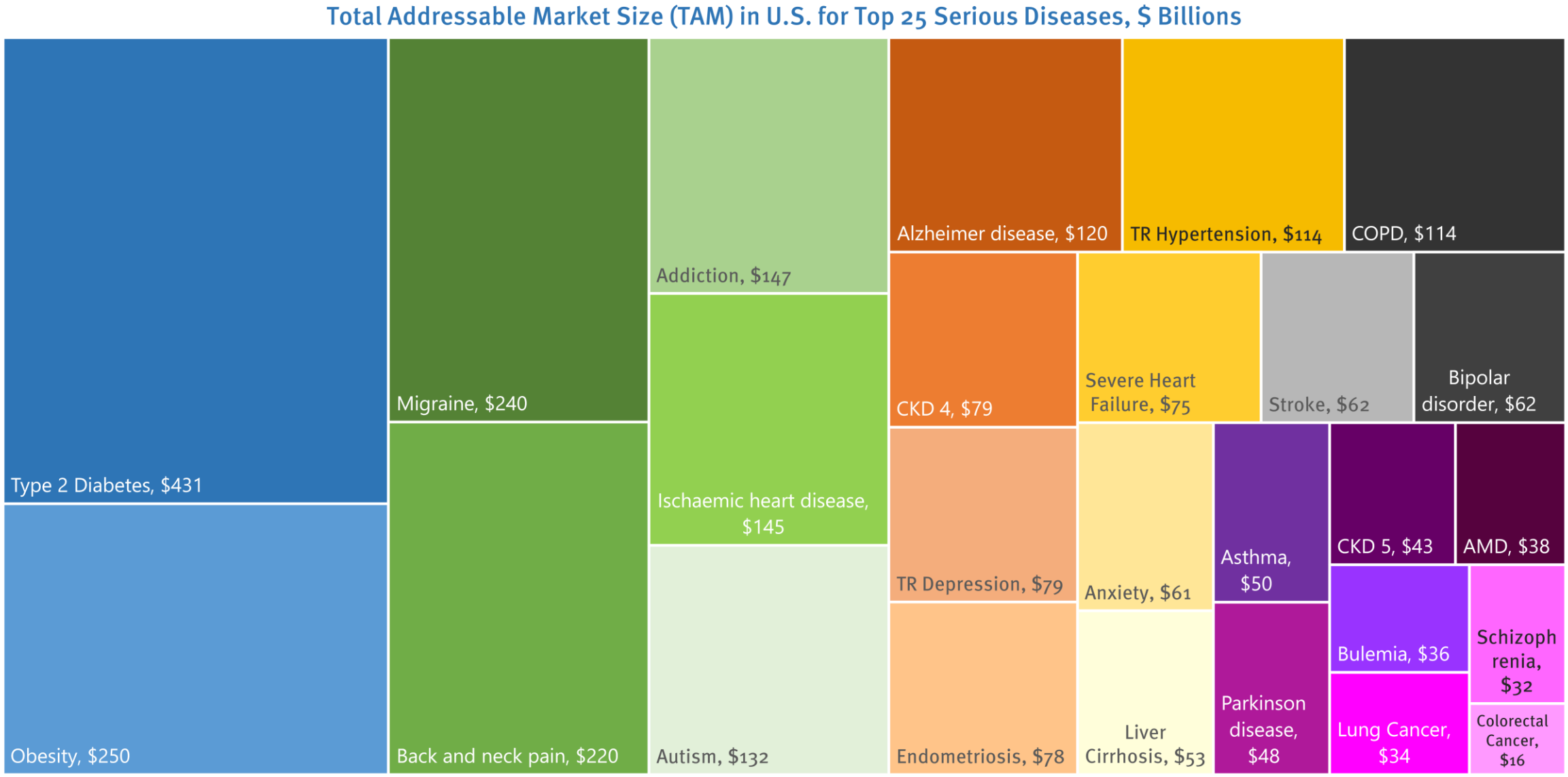
Consequences

Overt disease
Mid-stage phenotypic disease

Underlying Causes of Overt Disease
Subclinical disease

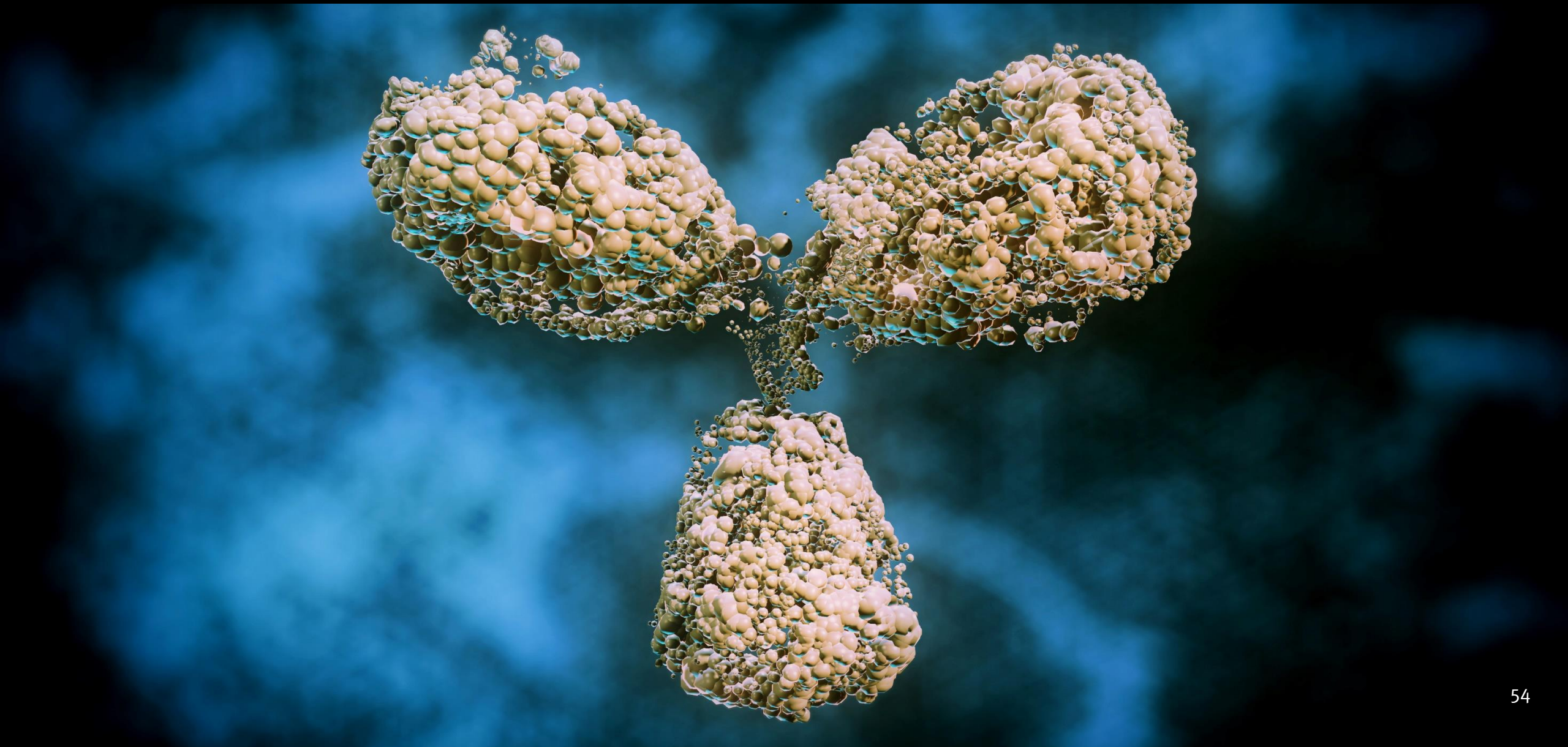


Gigantic Markets for Game-Changing Treatments for Large Disease States



Source: Stifel analysis based on U.S. prevalence and incidence data versus market pricing tolerance using existing benchmarks in the same or similar disease states.

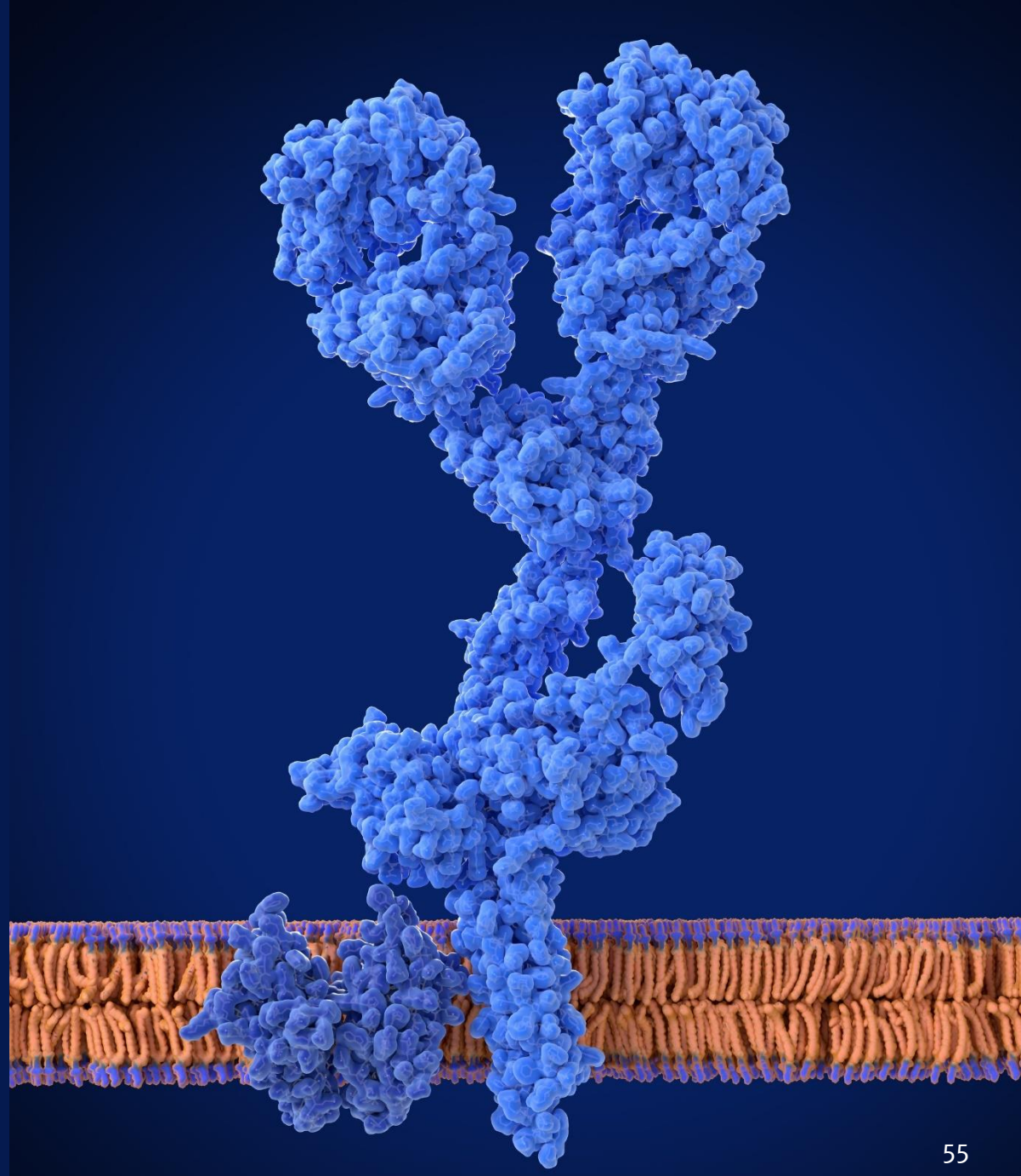
Research on Autoantibodies



Autoantibodies Characteristic of B-Cell Autoimmune Disease

B cells play an important role in regulating the immune response in both physiological and pathological conditions. Dysregulation of B-cell function can lead to severe consequences for the host. A primary feature of autoimmune diseases is the loss of B-cell tolerance and the inappropriate production of autoantibodies. More than 80 distinct autoimmune diseases have been described which are caused by autoantibodies. This include myasthenia gravis (MG), and systemic lupus erythematosus (SLE).

Clonally silent B cells can escape cell death then proliferate and secrete self-reactive antibodies in otherwise healthy individuals in the setting of a random event, such as a virus that induces strong activation signals (e.g., cytokines).



Article in *Science* Last Week Highlights Autoantibodies

Jaycox JR, Dai Y, Ring AM., "Decoding the autoantibody reactome," *Science*, Feb 16, 2024; 383 (6684): pp. 705-707.

Investigating the causes of individual variation in health outcomes has led to transformative insights into human biology and advances in nearly every branch of medicine. Historically, emphasis has been placed on how genetic factors contribute to phenotypic variation within populations. However, an emerging concept is that self-reactive antibodies (autoantibodies) represent a critical yet largely underexplored factor that influences human health and disease. Investigating autoantibodies and their protective as well as pathological roles in disease may unlock new treatment paradigms, much like the prior study of genetics.

Generated by the humoral immune system, antibodies are capable of specifically binding to virtually any biomolecule target (broadly termed "antigens"). Although the primary function of antibodies is to provide adaptive immunity against pathogens, invariably some antibodies arise that bind to self-antigens. These autoantibodies elicit a wide range of biological effects, including altering the activity of their targets and immunomodulation (see the figure). Every person carries a distinct array of autoantibodies—an "autoantibody reactome"—offering a potential avenue for trait diversity that mirrors the way genetic differences influence phenotypes.

Autoantibodies are usually known for their etiologic role in mediating autoimmune diseases. Canonically, autoantibodies can drive pathological inflammation within nearly any tissue, notably affecting the skin, joints, muscles, and central nervous system as well as organs such as the thyroid and pancreas.

Similarly, **autoantibodies can trigger distinctive syndromes marked by highly specific biological effects, akin to the distinct impact observed with Mendelian single-gene mutations, because they interfere with essential pathways in the body.** Notable examples include myasthenia gravis, a neuromuscular disease caused by autoantibodies that inhibit the acetylcholine receptor, and the hyperthyroidism in Grave's disease that is driven by autoantibodies that activate the thyrotropin receptor.

Source: https://www.science.org/doi/10.1126/science.abn1034

Autoantibodies Can Also be Protective

Jaycox JR, Dai Y, Ring AM., "Decoding the autoantibody reactome," *Science*, Feb 16, 2024; 383 (6684): pp. 705-707.

However, autoantibodies are not uniformly deleterious, and in some instances, they may provide protective effects that ameliorate or prevent disease. IFN-I autoantibodies are again instructive. Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by elevated IFN-I signaling in >50% of patients. Intriguingly, ~5% of SLE patients have autoantibodies that neutralize IFN-I signaling. In contrast to COVID-19, these autoantibodies are associated with substantially lower disease activity, presumably by attenuating pathological IFN-I pathway function. This counterintuitive observation emphasizes the dualistic nature of autoantibodies, demonstrating their ability to confer protective benefits in the very diseases they are typically implicated in causing.

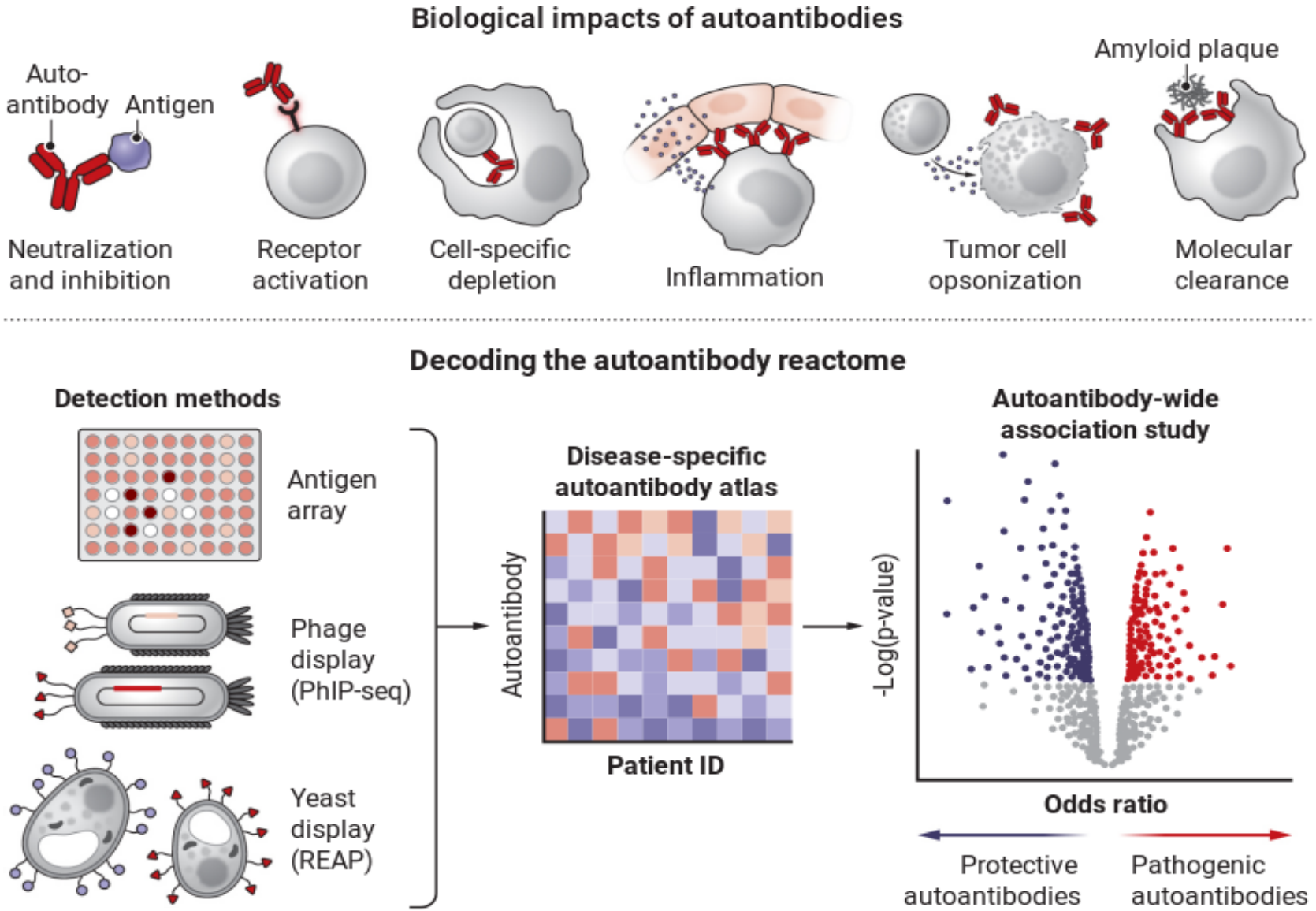
The protective effects of autoantibodies are apparent across numerous diseases. For example, the presence of autoantibodies against tumor-associated antigens (TAAs) has long been appreciated to represent a positive prognostic factor for patients with a variety of cancers. Multiple studies have linked TAA-reactive autoantibodies—such as anti–mucin 1 (MUC1) in various epithelial cancers and anti–human epidermal growth factor receptor 2 (HER2) in breast cancer—with better survival and recurrence outcomes in patients. These autoantibodies have been hypothesized to elicit immune-directed tumor cell killing, contributing to improved tumor control. In other cases, determining the specific molecular targets of tumor-reactive autoantibodies led to the identification of new TAAs, including NY-ESO, MAGE, BAGE, GAGE, and HOM-MEL-40. Cancer autoantibodies have thus provided a key line of evidence to support a role for the immune system in tumor surveillance and revealed previously unidentified targets for cancer therapy. Autoantibodies may have other effects on tumors, such as modulating therapeutic responses, but this requires further research.

Pharmacologic strategies that knock out autoantibodies indiscriminately may not be ideal because some antibodies against self may serve a beneficial purpose.

Source: https://www.science.org/doi/10.1126/science.abn1034

Figure: The Influence of Autoantibodies on Health and Disease

Autoantibodies elicit a diverse array of biological effects that result in disparate health outcomes, with both pathogenic and protective clinical effects. Emerging autoantibody discovery technologies such as antigen microarrays, phage immunoprecipitation sequencing (PhIP-seq), and rapid extracellular antigen profiling (REAP) now enable “autoantibody-wide association studies” to identify putatively causal autoantibodies present within the autoantibody reactome, analogous to genome-wide association studies. Disease-modifying autoantibodies identified in this way can elucidate new drug targets and provide a template for therapeutic development.



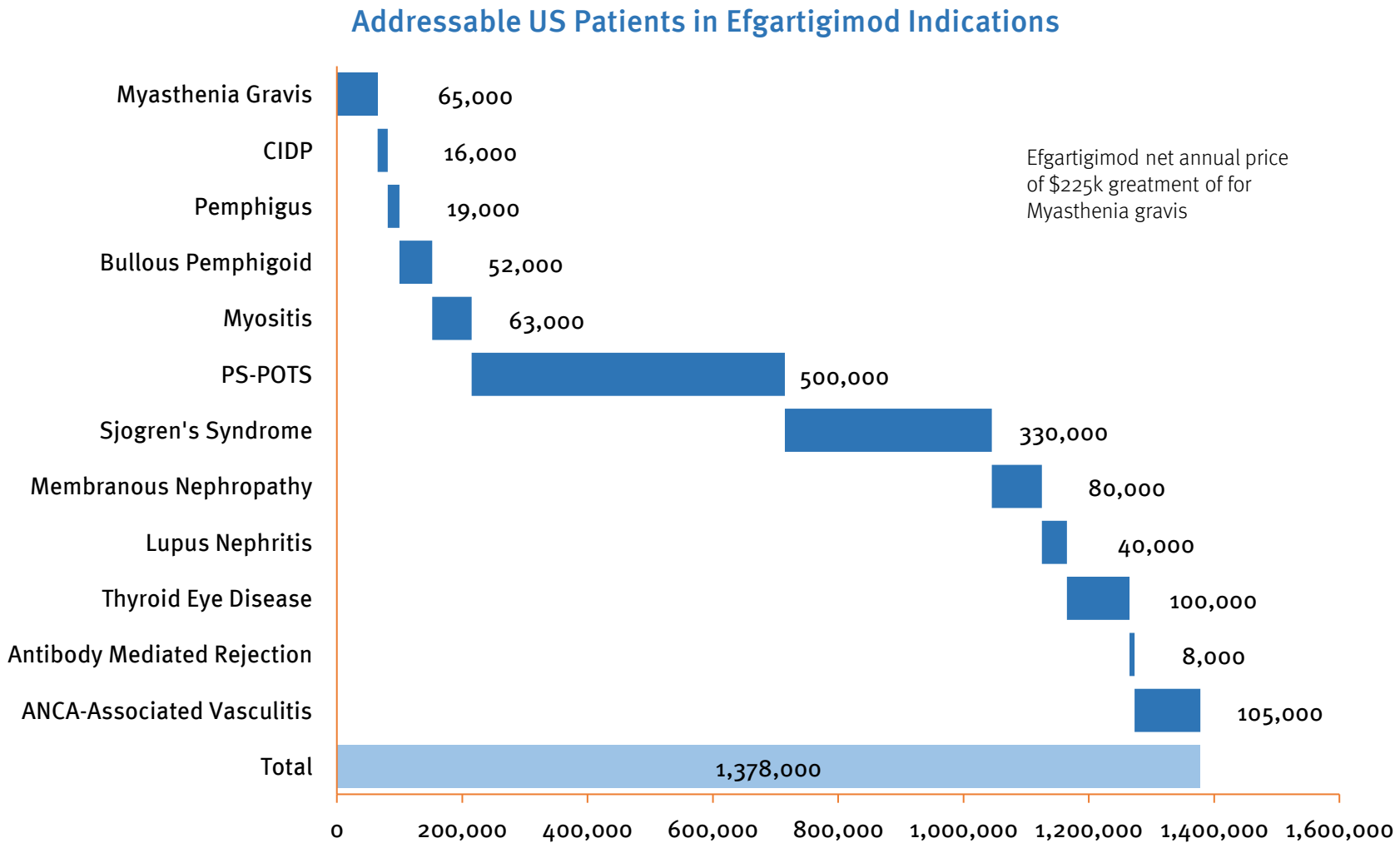
Source: *Science*, “Decoding the autoantibody reactome,, Volume: 383, Issue: 6684, Feb 2024, Pages: 705-707, https://www.science.org/doi/10.1126/science.abn1034

Current Pharmacologic Approaches to Autoantibodies

Blockers of FcRn IgG Binding Site	There are numerous companies that are focused on B-cell biology in one way or another. These include the FcRn companies such as Argenx which has achieved approval of efgartigimod for myasthenia gravis, ITP etc and Immunovant which is mid-stage. FcRn companies (including J&J, Alexion and UCB) focus on preventing the recycling of IgG thereby reducing the amount of all IgG by roughly 75%. While clinically attractive, these therapies may be risky for patients insofar as they also reduce levels of protective / beneficial antibodies.
Fc Gamma mAbs & Bispecifics	There is increasing recognition that the B and T-cell immune response is a coordinated one and that there is an opportunity to both downregulate B-cells and T-cells. Several companies are exploring this idea with both IgG regulators and Fcγ regulating drugs. Some of the most exciting companies in the field of autoimmunity (e.g., ImUnity, Nuvig, Seismic) are to be found in this area.
B-Cell Ablation (Car-T)	Another class of companies such as AstraZeneca/Gracell, Cabaletta, Immix, Kyverna and Novartis are pursing the direct ablation of pathogenic B-cells with Car-T drugs. Cabaletta, for example, has reported remarkable reduction of advanced lupus using a CD-19 CAR-T therapy.
B-Cell Ablation (Antibodies)	Another class of companies such as TG Therapeutics develop therapeutics that ablate B-cells. Specifically, the therapies in development focus on cell surface markers that are heavily expressed on B-cells including CD19, CD20 and BCMA. The results from anti-CD20 antibodies (e.g., Rituxan®) are well understand and have pointed to important treatments for several autoimmune diseases and liquid tumors (caused by abnormal growth of B-cells).
IgG Degraders / IgG Traps	Yet another approach highlighted by Biohaven is to pursue extracellular degraders that remove pathogenic IgG. These therapies can be generalized IgG degraders or, instead, specific to a particular species of IgG. This type of therapy, therefore, has the potential to specifically target an autoimmune disease without impacting the overall antibody repertoire.

Source: Stifel Research

Argenx Just Scratching the Surface with Efgartigimod



Autoantibody-driven disease is far from being penetrated by Argenx's efgartigimod.

There are over **80 autoantibody driven diseases affecting ~240mm people globally.**

Source: Stifel research and brokerage reports

Relatively Common Diseases Caused by Autoantibodies

Disease	G8 Prevalence	Impact	Unmet Medical Need / Opportunity
Grave's Disease	10,800,000	Moderately debilitating	20% of patients not responsive
Grave's Orbitopathy (sequellae of GD)	10,800,000	Moderately debilitating	20% of patients not responsive
Celiac Disease (subset)	8,800,000	Moderately debilitating	High need
Autoimmune thyroiditis (Hashimoto's)	5,900,000	Moderately debilitating	Little need
Fibromyalgia (subset)	5,300,000	Moderately debilitating	High need
Vitiligo	3,630,000	Moderately debilitating	High need
Inflammatory Bowel Disease	3,220,000	Moderately to highly debilitating	Some need
Autoimmune urticaria	2,500,000	Moderately debilitating	Some need
Autism (subset with FRAA)	2,440,000	Severely debilitating	High need
Deep Vein Thrombosis (subset)	2,362,500	Severely debilitating	Some need
Sjogren's Syndrome	1,680,000	Not debilitating for vast majority patients	Little need
Systemic Lupus Erythematosus	827,000	Severely Debilitating for many patients	High need
Lupus Neuropsychiatric	415,000	Debilitating	High need
ANCA Associated Vasculitis	366,240	Debilitating	Moderate need
IgA Nephropathy (subset)	360,000	Severely debilitating	High need
Sclerosis - CREST syndrome	197500	Moderately debilitating	High need
Antiphospholipid syndrome	197,000	Debilitating	High need
Myasthenia Gravis	185,000	Severely Debilitating	Moderate need
Immune Thrombocytopenic Purpura	128,000	Sometimes debilitating in adults	Moderate need
Autoimmune hepatitis	126,000	Can be debilitating	High need
Henoch-Schonlein purpura (HSP)	123,000	Not debilitating	Little need
CIDP	120,000	Debilitating	Moderate need
Diabetes Type I	115,000	Debilitating	High need
Warm Autoimmune Hemolytic Anemia	114,250	Severely Debilitating	High need
Lupus Nephritis	105,000	Moderately to highly debilitating	High need

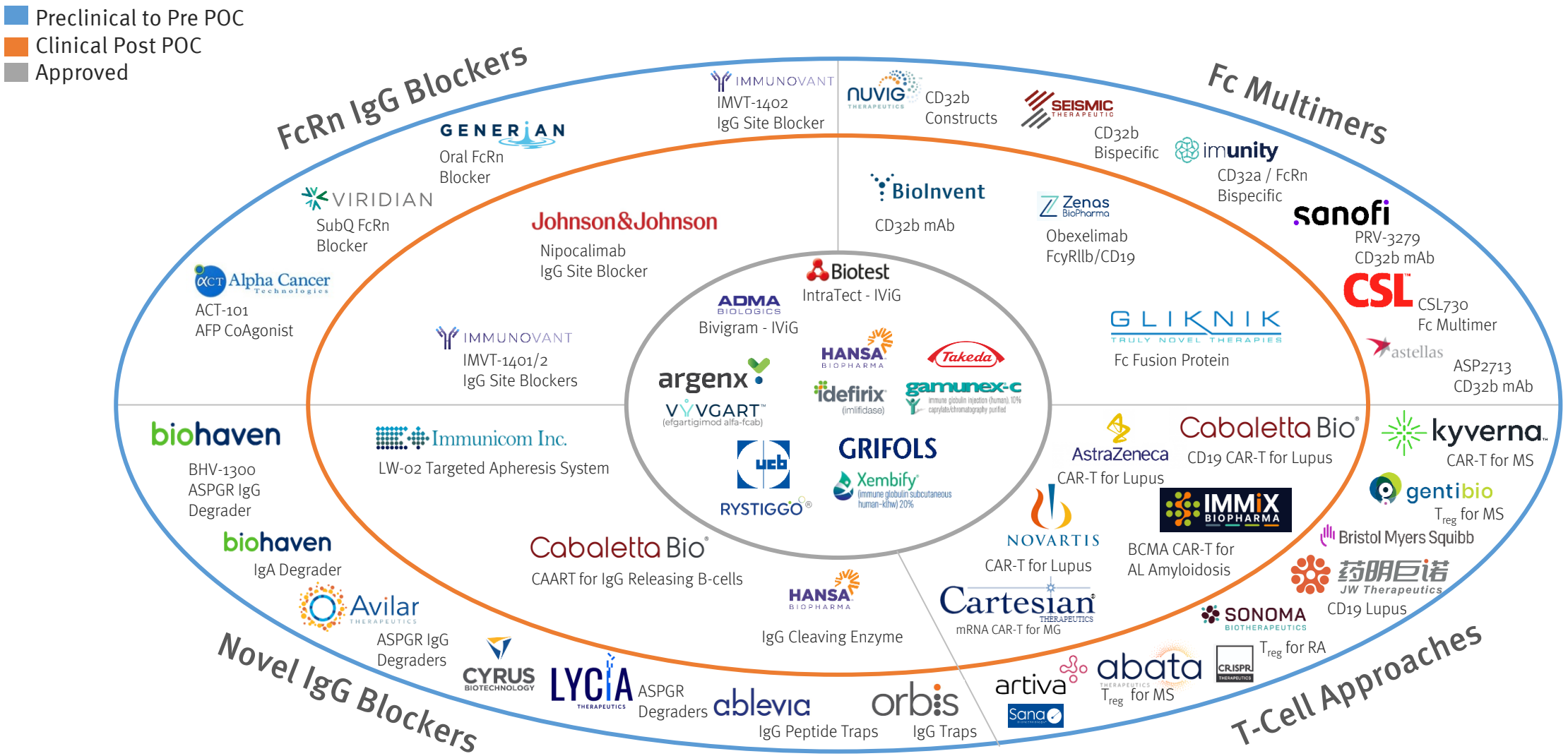
Source: Stifel Research

Less Common Diseases Caused by Autoantibodies

Disease	G8 Prevalence	Impact	Unmet Medical Need / Opportunity
Pemphigus vulgaris	90,000	Debilitating	Moderate need
Herpes gestationis	85,000	Moderately debilitating	Moderate need
ALS	75,000	Severely Debilitating	High need
Fibrosing alveolitis	70,500	Severely debilitating	High need
Membranous Nephropathy	66,000	Debilitating	High need
Polymyositis (PM)	56,130	Debilitating	High need
Rheumatic fever	43,600	Not debilitating for vast majority patients	Little need
Erythema nodosum	25,200	Moderately debilitating	High need
Pemphigus Foliaceus	19,000	Moderately debilitating	Moderate need
Discoid lupus	18,000	Moderately debilitating	High need
Bullous Pemphigoid	14,000	Sometimes debilitating in adults	Moderate need
Neuromyelitis Optica (NMOSD)	13,000	Severely Debilitating	Moderate need
Autoimmune neutropenia	12,000	Sometimes debilitating in adults	High need
Guillain-Barré Syndrome	11,000	Debilitating	Moderate need
Dermatomyositis (DM)	9,400	Moderately debilitating	High need
Autoimmune pancreatitis	9,200	Not debilitating for vast majority patients	High need
Essential mixed cryoglobulinemia	9,000	Moderately debilitating	High need
Cold agglutinin disease	4,800	Severely debilitating	High need
Autoimmune orchitis	3,100	Moderately debilitating	High need
Anti-MAG Peripheral Neuropathy	2000	Moderately debilitating	High need
Cicatricial pemphigoid	1,700	Moderately debilitating	High need
Autoimmune retinopathy	1,550	Severely debilitating	High need
Lambert-Eaton Myasthenic Syndrome	1,300	Severely debilitating	High need
Goodpasture's syndrome	1,120	Debilitating	High need
Linear IgA disease (LAD)	950	Moderately debilitating	High need

Source: Stifel Research

Pipeline of Drugs that Ablate Autoantibodies



Source: Stifel Research

Disclosure

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