Biopharmaceutical Sector

Weekly Update – Jan 22, 2024

STIFEL | Healthcare

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Mass Spectrometer used to discover Alzheimer's Biomarkers, Jan 2024

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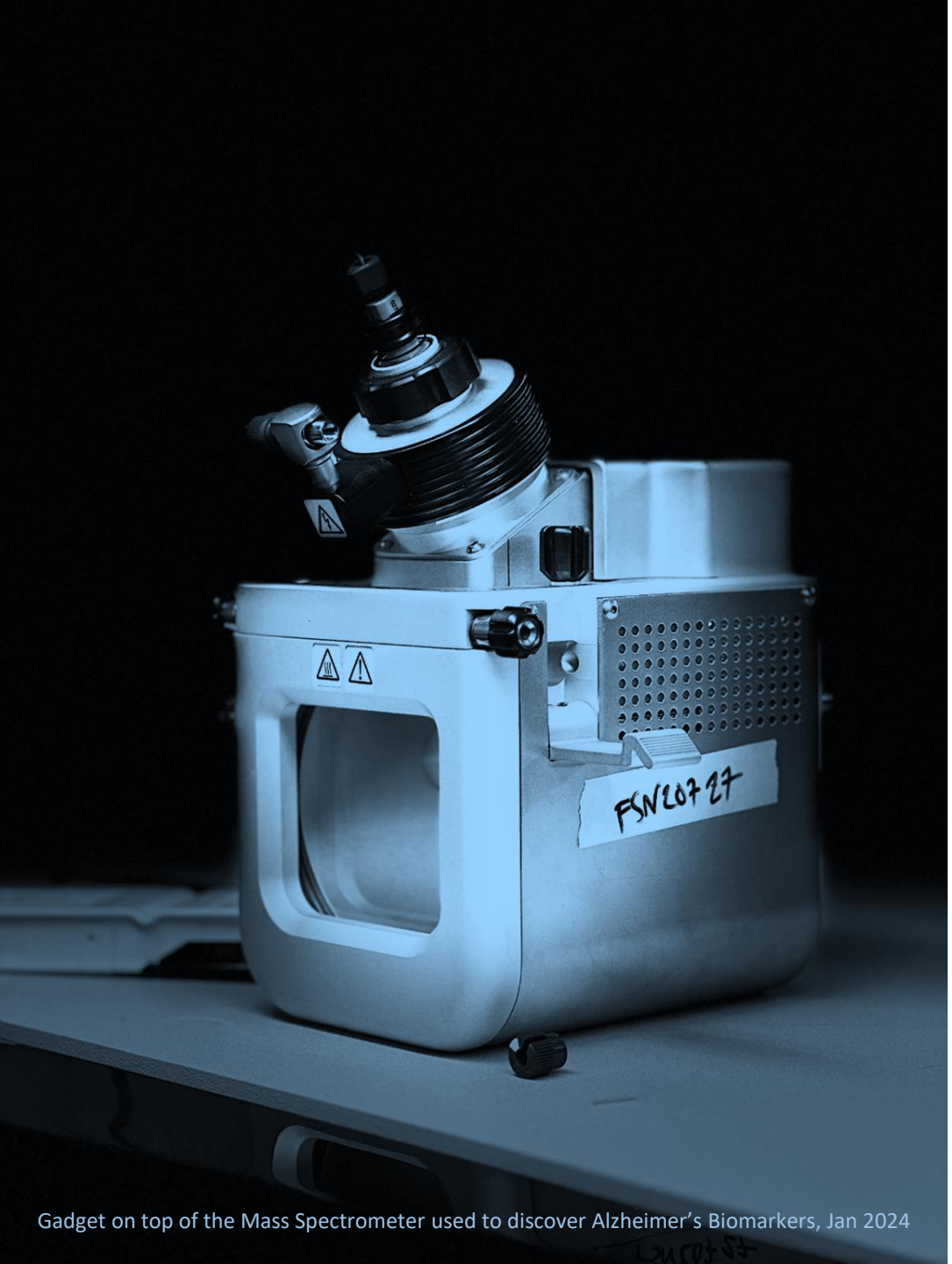


Gadget on top of the Mass Spectrometer used to discover Alzheimer's Biomarkers, Jan 2024

Accessing Past Issues

If you are not on the mailing list for this publication and wish to be added, please notify Natasha Yeung (yeungn@stifel.com). Recent issues in case you missed and want to read:

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)

Upcoming Events

Biotech Hangout held its latest event on Jan 19, 2024.

The next event will be on Jan 26, 2024.

January 19th Replay: https://twitter.com/i/spaces/1yoKMwmmwWDJQ

January 26th Session: https://twitter.com/i/spaces/1LyGBnZnebaGN

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

S&P 500 Hits New Record High Amid Signs of Easing US Economic Gloom

Dominic Rushe and Callan Jones, *The Guardian*, Jan 19, 2024 (excerpt)

The S&P 500 scaled a new all-time high on Friday amid signs that the economic despondency that has gripped US consumers may be easing.

The index climbed 1.2% to 4,838 on Friday afternoon, clearing a record last set two years ago. It has rallied more than 17% since late October.

Earlier in the day, an influential survey showed that consumer sentiment soared 13% in January to reach its highest level since July 2021.

The University of Michigan's monthly consumer sentiment index rose 9.1 points to 78.8, the biggest monthly advance since 2005 and far exceeding expectations.

The news came after a similarly sharp rise in December. Joanne Hsu, University of Michigan's director of surveys, said that over the last two months, sentiment has climbed a cumulative 29%, the largest two-month increase since 1991 as a recession ended.

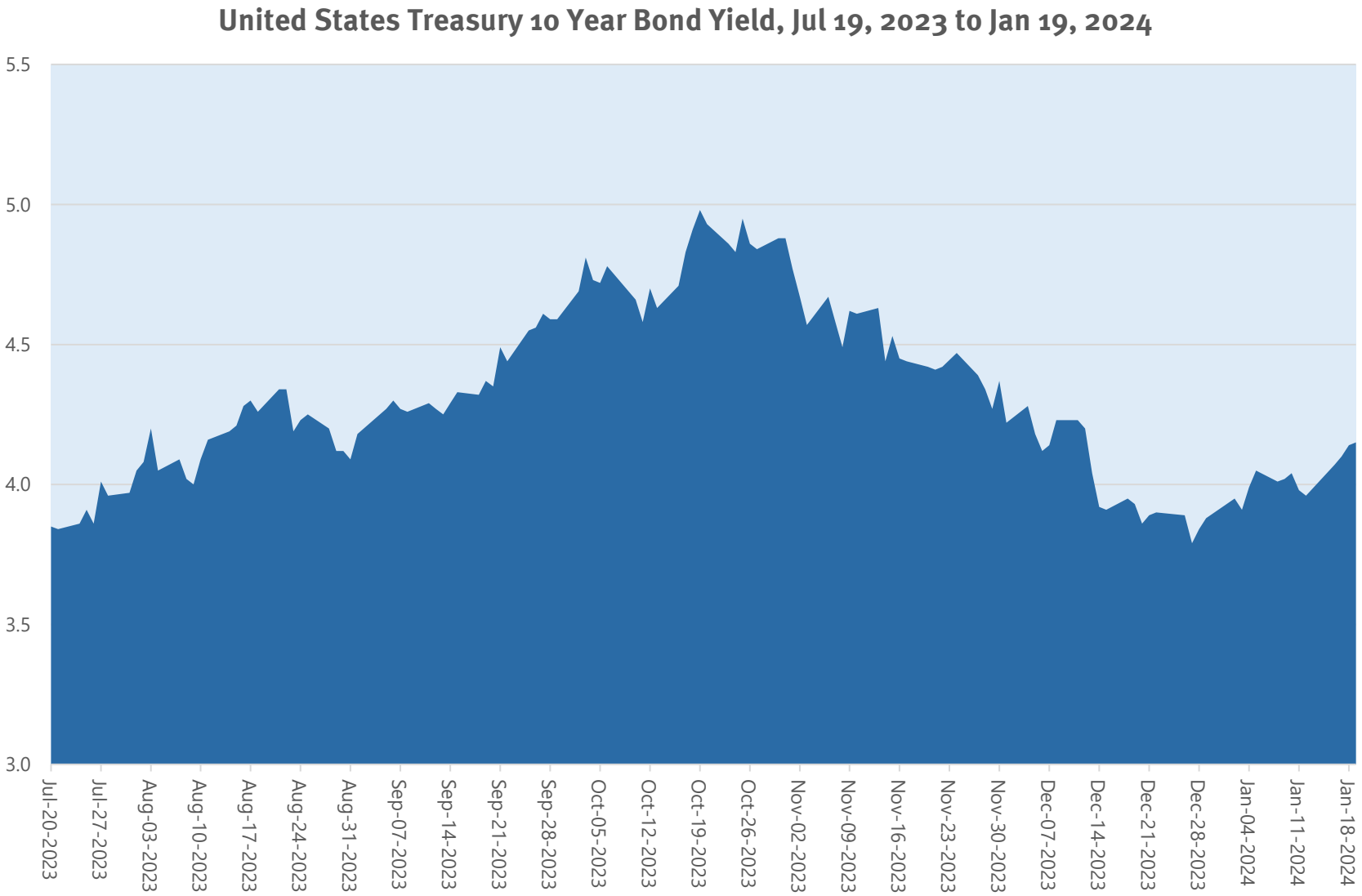
"Consumer views were supported by confidence that inflation has turned a corner and strengthening income expectations," said Hsu.

The rise was driven in large part by expectations that the rate of inflation will continue to decline. The survey found that consumers expect prices to climb at an annual rate of 2.9% over the next year, down from the 3.1% reported in December. Expectations about price rises over the next five to 10 years hit a four-month low of 2.8%.

The stock market did well last week on improving consumer sentiment and a boom in tech stocks tied to the generative AI opportunity.

Source: https://www.theguardian.com/business/2024/jan/19/us-economy-consumer-sentiment-rises

Ten-Year U.S. Treasury Yield Starting to Inch Up



Source: S&P CapitalIQ.

Ten-Year US Treasury Bond Yields have risen by 27 basis points since the start of the year.

The yield ended last week at 4.15%.

This is not great news for biotech.

We think last month's CPI number and the upcoming Treasury Quarterly Refunding Announcement (Jan 29th) are worrying bond investors.

Haley Makes Final Sprint in New Hampshire

Gram Slattery and James Oliphant, *Reuters*, Jan 20, 2024 (excerpt)

Former South Carolina Governor Nikki Haley was set to campaign across New Hampshire this weekend in a final push against Republican rival Donald Trump ahead of Tuesday's nominating contest, as the former U.S. president ramped up his verbal attacks and again targeted her Indian heritage.

Haley, who served as U.S. ambassador to the United Nations under Trump, has hit back at her former boss following his Iowa caucuses victory last Monday in a bid to thwart his momentum and pitch herself as the best alternative to face Democratic President Joe Biden in November's general election.

New Hampshire boasts a more moderate brand of Republicanism with a semi-open primary that can attract more centrist voters, who may be turned off by Trump's four criminal cases, authoritarian language and efforts to overturn his 2020 re-election loss.

One of two remaining candidates challenging Trump for the Republican nomination, Haley needs a strong showing after placing third narrowly behind Florida Governor Ron DeSantis as Trump handily won in Iowa, the first stop in the state-by-state battle to determine the party's choice to face Biden.

Nikki Haley is the most pharma friendly of the candidates running for President in 2024.

She is running well behind Trump in the polls for the New Hampshire primary which will be held next Tuesday.

Source: https://www.reuters.com/world/us/haley-makes-final-sprint-new-hampshire-trump-steps-up-attacks-2024-01-20/

Trump and Biden Both Hate Pharma—Investors Shouldn't

The drug sector had one of its worst years ever relative to the S&P 500 last year and now faces political attacks, but investors should focus on the value.

David Wainer, *Wall Street Journal*, Jan 19, 2024 (excerpt)

Donald Trump and President Biden have both taken a hard line on drug prices, while Florida Gov. Ron DeSantis has touted his state's effort to import drugs from Canada. During an election year that may see Republicans and Democrats seeking to outdo each other over who is tougher on insurance giants and big pharma, investors might want to tune the noise out.

That isn't to say that politics don't matter. During years where serious policy overhauls are on the table, election considerations tend to take over. That was the case for the insurance industry in both 1996 and 2008, as Bill Clinton, and later Barack Obama, took stabs at reforming the sector. During both those years, the insurance industry significantly underperformed the broader market.

But with the Biden administration already able to tout a law that will target drug prices paid by Medicare—and Republicans far from united on any serious changes to the healthcare system—valuations, earnings trajectories and macroeconomics might be more important signals in 2024.

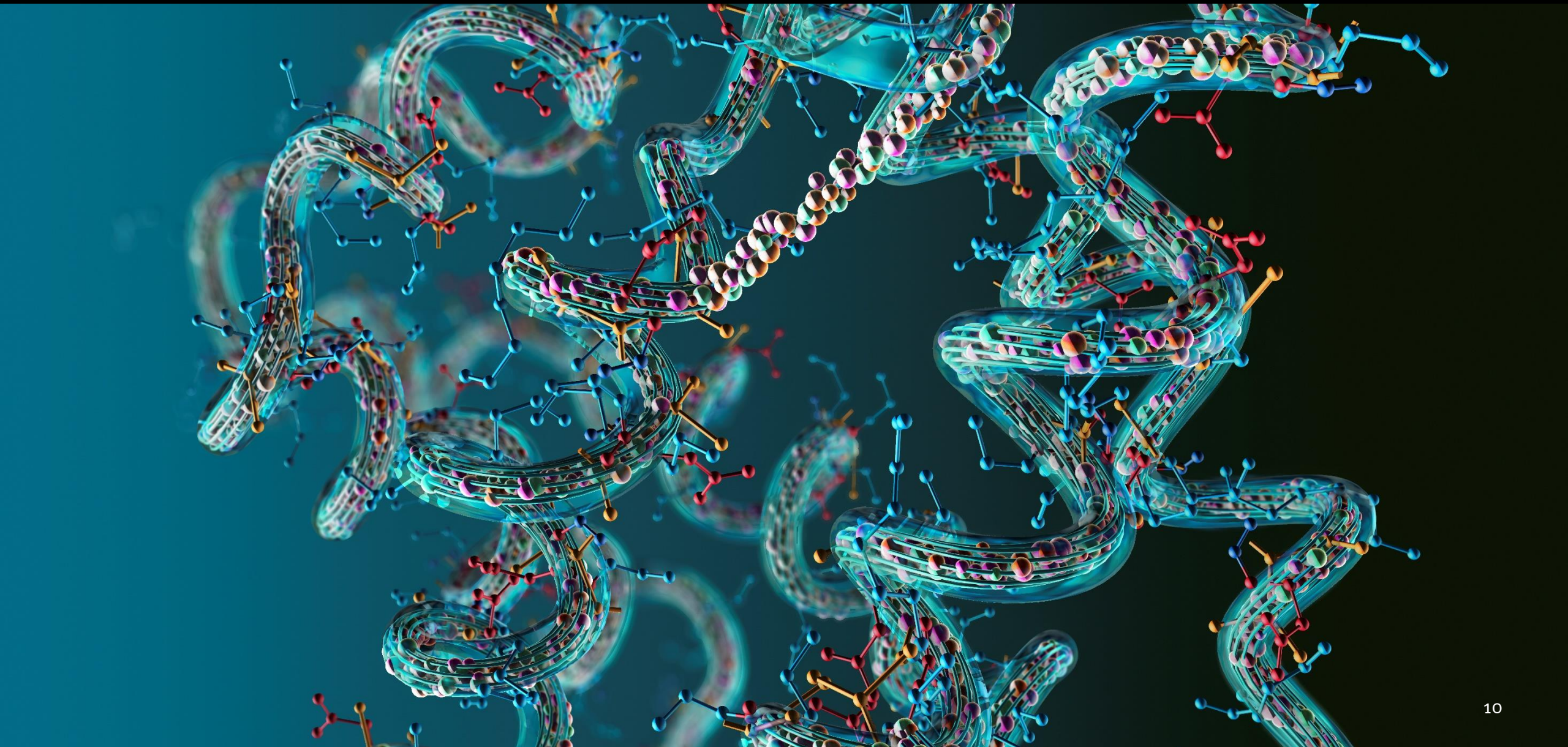
When it comes to valuations, healthcare looks attractive after posting one of its worst relative performances last year. The S&P 500 and the NYSE Arca Pharmaceutical Index were trading at roughly similar valuations at the start of last year, but drug companies are now cheaper thanks to the sector underperforming the S&P 500 by 21.4% in 2023.

So far, it seems investors are being tempted to rotate back into healthcare. The NYSE Arca Pharma Index is up 4% so far this year compared with a less than 1% gain for the S&P 500. While that sometimes is the case with losers catching a bid after tax-loss selling late in the previous year, there is evidence investors are adding to their positions in a serious way.

During elections held during downturns for the stock market, such as in 2000 and 2008, pharma outperformed the S&P 500 by an average of 27 percentage points. That makes sense, given that healthcare is viewed as a defensive sector. For investors looking to move toward more defensive postures, Johnson & Johnson, Amgen AMGN and Walgreens are three high-yielding stocks to make it on a list of the Dow's 10 highest dividend-yielding stocks—historical outperformers known as "Dogs of the Dow."

Source: https://www.wsj.com/health/pharma/trump-and-biden-both-hate-pharma-investors-shouldnt-04ac699b

Biopharma Market Update



Sentiment Flat Last Week

The Week of Jan 15th was not a great week for the biotech market by any measure.

After a week of great weather at JPM, we started that first “real week” of the year with a mixed market.

By Friday, the S&P 500, Nasdaq 100 and other tech heavy indices set all time records propelled by investor interest in tech semiconductor stocks tied to the generative AI boom.

This was despite the fact that the U.S. 10-year Treasury yield crept over 4% again on worries of inflation persistence. Worries about inflation were expressed in many quarters last week in the wake of the last CPI report.

In contrast, the XBI *dropped* for the week and is now down for the year.

Argggghh.

If you have a feeling of déjà vu, you aren’t alone.

Q1 2023 was marked by investor excitement in AI and a tech stock runup – accompanied by a very soft biotech market.

AI sizzle is a short-term thing and biotech remains long duration – hence the divergence between the sector values.

Rates crept up last week as investors fretted about inflation.

Soft Sentiment (continued)

There are two deeper factors at play: (1) weakness in the China stock market and (2) the absence of retail and generalist investor entry into biotech.

Lacking a broad theme to attract interest (e.g., mRNA vaccines), generalists are staying away and appear to be in an AI gold rush. Apparently, low biotech stock prices alone don't really get it done.

We also saw a notable lack of M&A activity last week. Sun finished out the buyout of Taro for $348 million but this deal had been announced many months ago.

Within the specialist driven biotech market, there were strong flows at work. We saw a billion in equity follow-ons again last week as seven biotechs tapped the secondaries market for deals of $50 million or more.

An interesting factoid is that there are 43 specialist funds that have picked up nearly $20 billion in gains from M&A announced since the Immunogen deal last November 30th. This money isn't going to be on the sidelines for long. As capital gets returned from the recent wave of dealmaking it should work to sustain existing and new stories in the biopharma market. One can't help but think the strength thus far in 2024 in names like Arrowhead or Zealand involves fund positioning for future M&A following recent deal takeouts.

We remain optimistic about the biotech market in 2024. It's innovation against macro right now. And the macro picture has improved, is improving and is going to improve. Inflation is being held up by rental prices, but these are imputed and far from real prices. Oil prices matter too and are being inflated by issues in the MidEast that are unlikely to persist throughout the year. While consumer sentiment is strong, pricing pressures are rapidly falling as the economy normalizes.

Conversations with a variety of market participants confirm what most of us intuitively know: there is an unusually large amount of money on the sidelines –waiting for the market to turn. This wave of cash is headed for biotech shores and shouldn't be too long in coming.

Forty-Three Specialist Investors Have Made $19.6 Billion in Proceeds from Pharma M&A Deals Since November 30, 2023

Much of these proceeds are expected to return to the market in the form of follow-ons, IPOs and open market purchases.

Dollars shown are in millions

Target	Aiolos Bio	Ambrx	Harpoon	Gracell	RayzeBio	Karuna	Icosavax	Cerevel	ImmunoGen	Total	Count
Buyer	GSK	J&J	Merck	AZ	BMS	BMS	AZ	AbbVie	AbbVie		
Announced	1/9/2024	1/8/2024	1/8/2024	12/26/2023	12/26/2023	12/22/2023	12/12/2023	12/6/2023	11/30/2023		
Upfront Cash $mm	$1,000	$2,000	$680	$1,000	$4,100	$14,000	$800	$8,700	$10,100		
Bain Life	$500*	$0	$0	$0	$0	$0	$0	$3,149	$0	$3,649	2
T. Rowe	$0	$26	$0	$0	$69	$2,023	$76	$351	$147	$2,693	6
Fidelity	$0	$42	$0	$0	$76	$1,059	$35	$465	$218	$1,895	6
Capital Research	$0	$0	$0	$0	$84	$1,497	$0	$41	$0	$1,622	3
Wellington	$0	$0	$0	$0	$260	$475	$0	$0	$500	$1,235	3
Viking	$0	$0	$0	$0	$444	$413	$0	$0	$0	$857	2
Redmile	$0	$0	$0	$0	$125	$0	$0	$0	$661	$785	2
RA Capital	$0	$0	$60	$86	$0	$0	$94	$0	$503	$743	4
Janus	$0	$0	$0	$0	$0	$0	$0	$0	$668	$668	1
Perceptive	$0	$0	$0	$0	$52	$0	$0	$526	$0	$578	2
Darwin	$0	$528	$0	$0	$0	$0	$0	$0	$0	$528	1
Cormorant	$0	$314	$63	$0	$79	$0	$0	$0	$0	$456	3
Avoro	$0	$66	$0	$0	$270	$0	$0	$46	$0	$381	3
Rock Springs	$0	$0	$0	$0	$0	$186	$14	$121	$0	$321	3
Fairmount	$0	$0	$0	$0	$82	$0	$0	$0	$224	$306	2
Orbimed	$0	$0	$0	$96	$176	$0	$0	$0	$0	$273	2
Sofinnova	$0	$0	$0	$0	$162	$0	$0	$0	$77	$239	2
Paradigm	$0	$111	$0	$0	$0	$0	$0	$122	$0	$233	2
Eventide	$0	$0	$0	$0	$0	$126	$0	$23	$0	$149	2
TCG X	$0	$0	$0	$31	$58	$0	$58	$0	$0	$148	3
Vivo Capital	$0	$0	$0	$113	$0	$0	$27	$0	$0	$139	2
Avidity	$0	$0	$0	$0	$0	$101	$0	$31	$0	$132	2
Point72	$0	$0	$0	$0	$0	$127	$0	$0	$0	$127	1
Samsara	$0	$0	$0	$0	$124	$0	$0	$0	$0	$124	1
Deep Track	$0	$117	$0	$0	$0	$0	$0	$0	$0	$117	1
Tavistock	$0	$0	$0	$0	$0	$0	$0	$0	$117	$117	1
Commodore	$0	$111	$5	$0	$0	$0	$0	$0	$0	$117	2
Logos	$0	$0	$0	$26	$0	$0	$44	$34	$0	$103	3
Millennium	$0	$0	$0	$0	$0	$0	$0	$102	$0	$102	1
Nextech	$0	$99	$0	$0	$0	$0	$0	$0	$0	$99	1
Woodline	$0	$0	$0	$0	$0	$0	$0	$0	$91	$91	1
Citadel	$0	$24	$41	$0	$0	$0	$25	$0	$0	$90	3
Adage	$0	$0	$0	$9	$0	$0	$0	$72	$0	$81	2
Invus	$0	$0	$0	$0	$0	$0	$0	$78	$0	$78	1
Laurion	$0	$0	$0	$0	$65	$0	$12	$0	$0	$77	2
Federated	$0	$76	$0	$0	$0	$0	$0	$0	$0	$76	1
Franklin	$0	$0	$0	$0	$55	$0	$0	$0	$0	$55	1
Total	$500	$1,532	$201	$428	$2,182	$6,006	$384	$5,162	$3,206	$19,602	

Source: Stifel analysis of CapIQ reports on holdings in last reporting period before deal announcement. Investors shown with at least one Ph.D. on staff. Investors with less than $50 million of proceeds not included in table but are included in the total at bottom of table.

* Bain's percentage holding of Aiolos not disclosed. We assume it is 50%.

The XBI Closed at 87.1 Last Friday (Jan 19). Down 3.7% for the Week

The XBI is down 2.5% for the year to date. The Nasdaq Biotech Index is flat for the year. Not the start we would have wished for in biotech in 2024.

Biotech Stocks Down Last Week

Return: Jan 12 to Jan 19, 2024

Nasdaq Biotech Index: -1.7%
Arca XBI ETF: -3.7%
Stifel Global Biotech EV (adjusted): -2.9%*
S&P 500: 1.1%

Return: Jan 1 to Jan 19, 2024

Nasdaq Biotech Index: +0.1%
Arca XBI ETF: -2.5%
Stifel Global Biotech EV (adjusted): -0.8%*
S&P 500: +1.2%

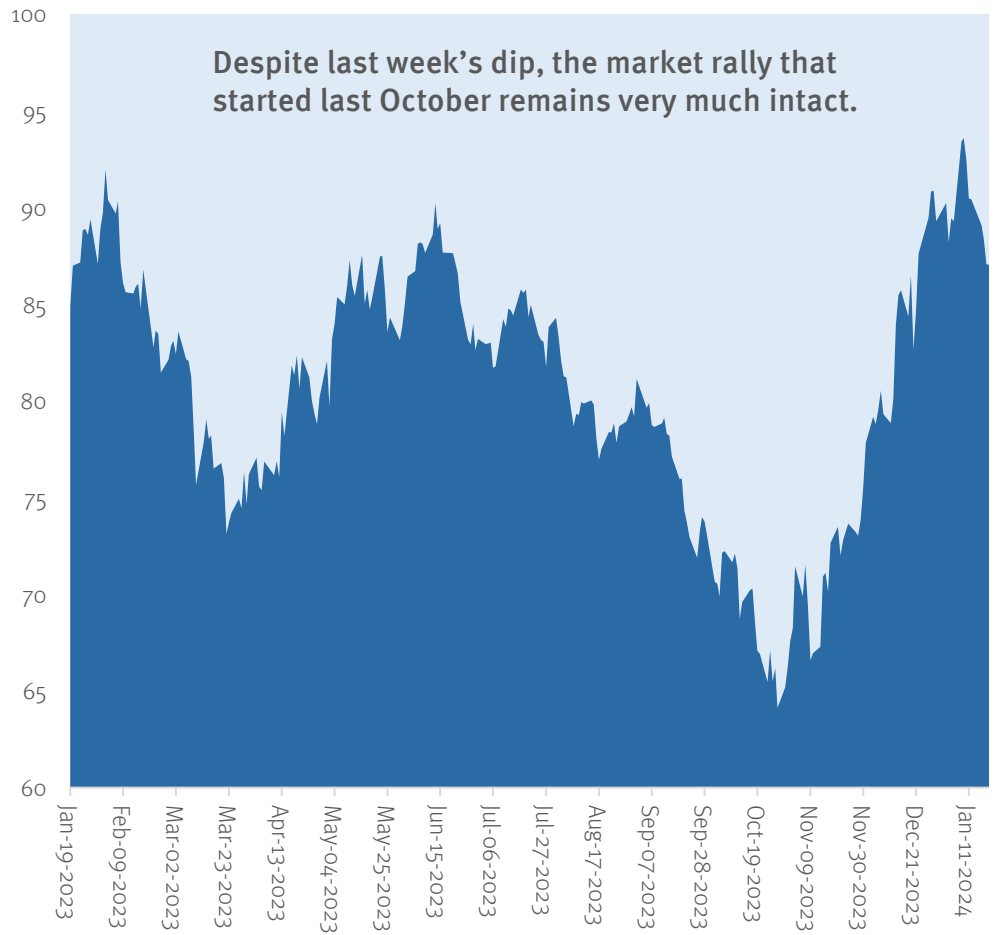
VIX Up a Bit

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 12, 2024: 12.7%
Jan 19, 2024: 13.3%

10-Year Treasury Above 4%

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 3, 2024: 3.95%
Jan 12, 2024: 3.96%
Jan 19, 2024: 4.15%

XBI, Jan 19, 2023 to Jan 19, 2024



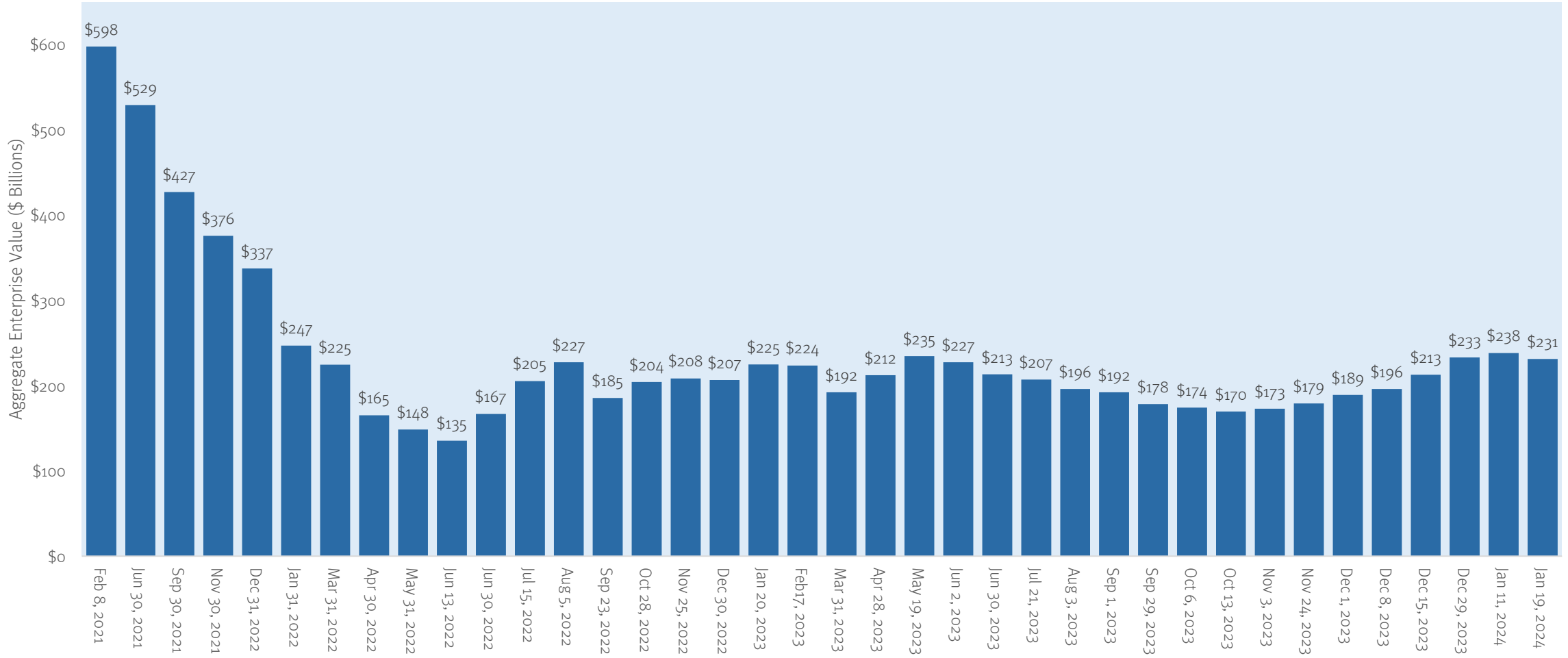
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Dropped 2.9% Last Week

The total enterprise value of the global biotech sector is down 0.8% for the year to date. The rally that started 13 weeks ago has started went into slight reversal last week as interest rates began to inch up again.

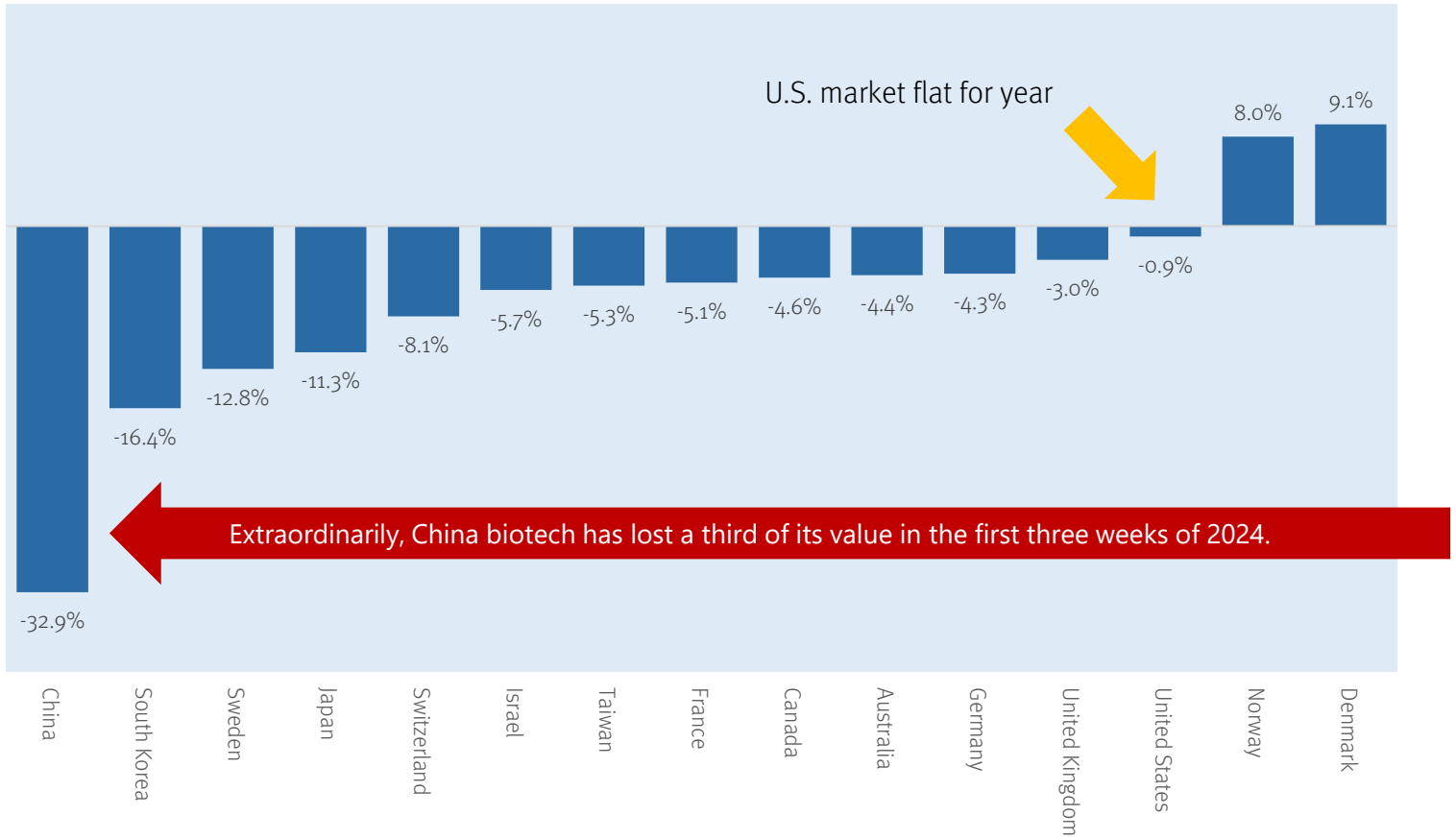
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Jan 19, 2024 ($ Billions)

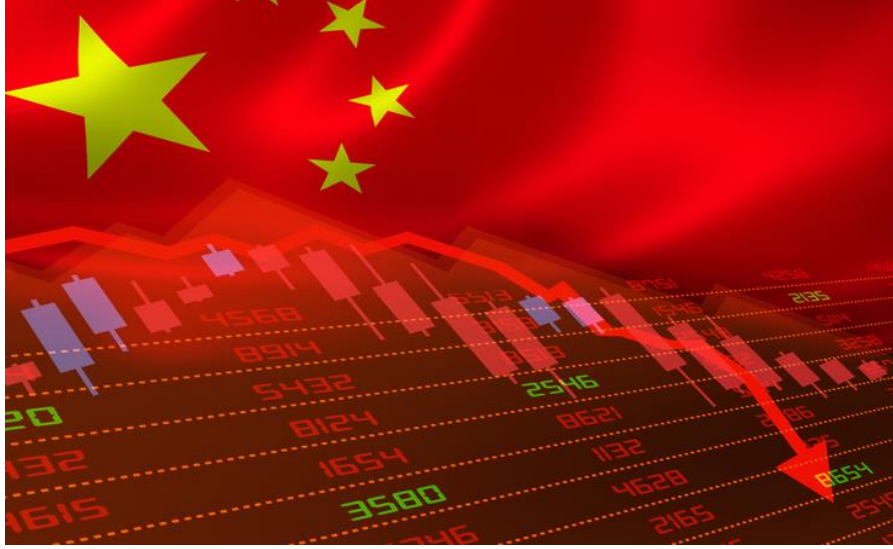


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

China Biotechs Have Been Hit Hard Thus Far in 2024. U.S. Biotech is Flat

Aggregate Value Change of Biotech by Country, Dec 30, 2023 to Jan 19, 2024





Chinese stock rout accelerates as foreign investors sell out

Hudson Locket and Joe Leahy, *FT*, Jan 18, 2024 (excerpt)

A punishing sell-off for Chinese equities has worsened in recent days, as international investors who bet on a rebound lose faith that economic stimulus from Beijing is on the way. The Hang Seng China Enterprises index, a closely followed gauge of large Chinese listings in Hong Kong, has dropped about 11 per cent so far this month after losing 14 per cent last year. The benchmark CSI 300 index for domestically traded stocks has shed more than 5 per cent, after taking into account the renminbi's depreciation against the dollar. International investors "just threw in the towel" after a speech by Premier Li Qiang at Davos on Tuesday lacked any hint of new government measures to boost the economy or financial markets, said the head of trading at one investment bank in Hong Kong.

Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange. China story: https://www.ft.com/content/35fba64d-3720-4eb9-ae19-82a173409c68

Global Biotech 2024 Top Decliner List Heavy With China Names

Top Ten Decliners by Drop in Enterprise Value from Dec 30, 2023 to Jan 19, 2024 ($ millions)

Company	HQ Country	Value Drop YTD ($ Millions)	Percent Drop YTD	Enterprise Value (Jan 19, 2024, $ Millions)	Comment
RemeGen	China	-$1,164	-29.22%	$2,821	False online rumors. China stocks weak.
ImmunityBio	US	-$939	-24.18%	$2,943	Transaction with Oberland ahead of FDA news.
Keymed Biosciences	China	-$614	-44.69%	$759	Big selloff of China stocks.
Denali Therapeutics	US	-$604	-31.74%	$1,299	No specific news.
Akeso	China	-$537	-11.51%	$4,129	Big selloff of China stocks. No other news.
Gyre Therapeutics	US / China	-$536	-27.53%	$1,410	Big selloff of China stocks.
Intellia Therapeutics	US	-$442	-23.83%	$1,414	Cutting staff. Narrowing pipeline.
Neumora	US	-$428	-20.46%	$1,663	No specific news.
Moonlake	Switzerland	-$411	-12.90%	$2,778	No specific news.
BioArctic	Sweden	-$397	-17.38%	$1,886	EMA going to convene adcomm for lecanemab

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

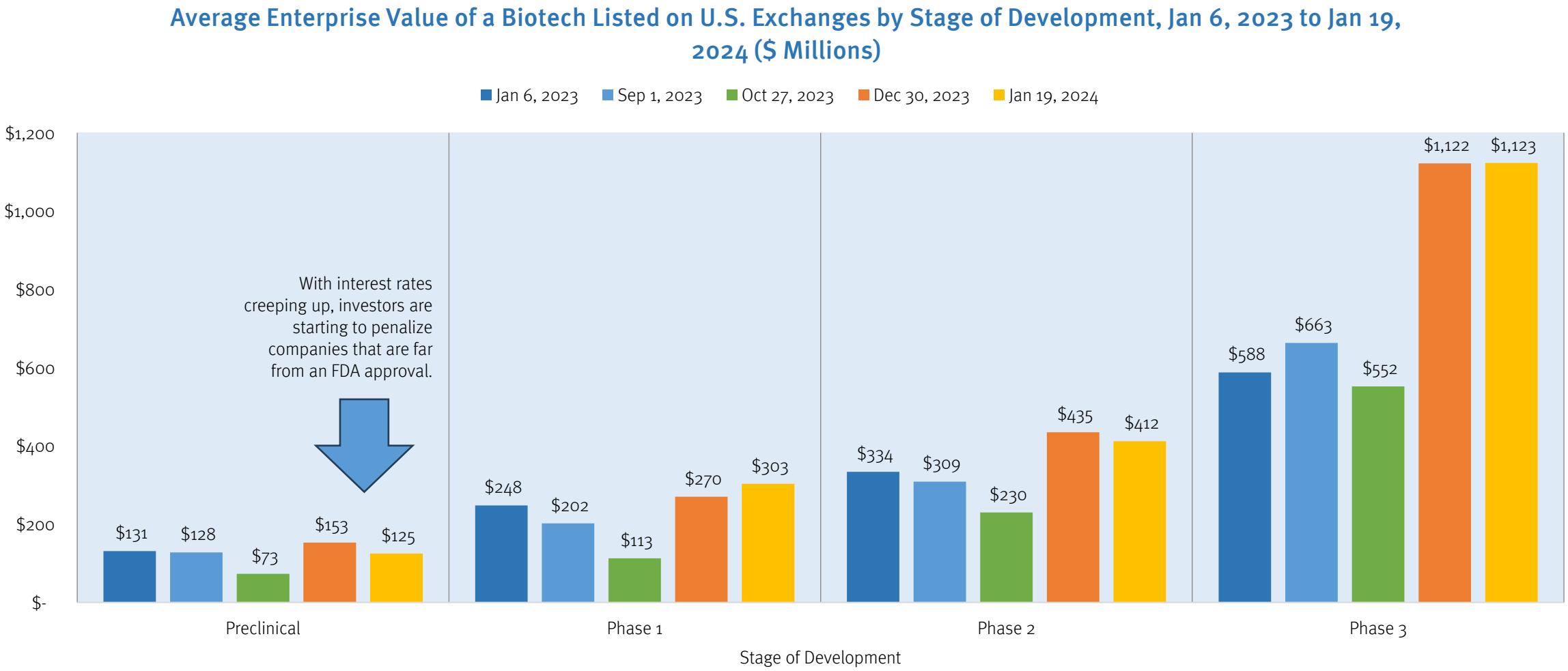
Global Biotech 2024 Top Ten Gainer List

Top Ten Gainers by Increase in Enterprise Value from Dec 30, 2023 to Jan 19, 2024 ($ millions)

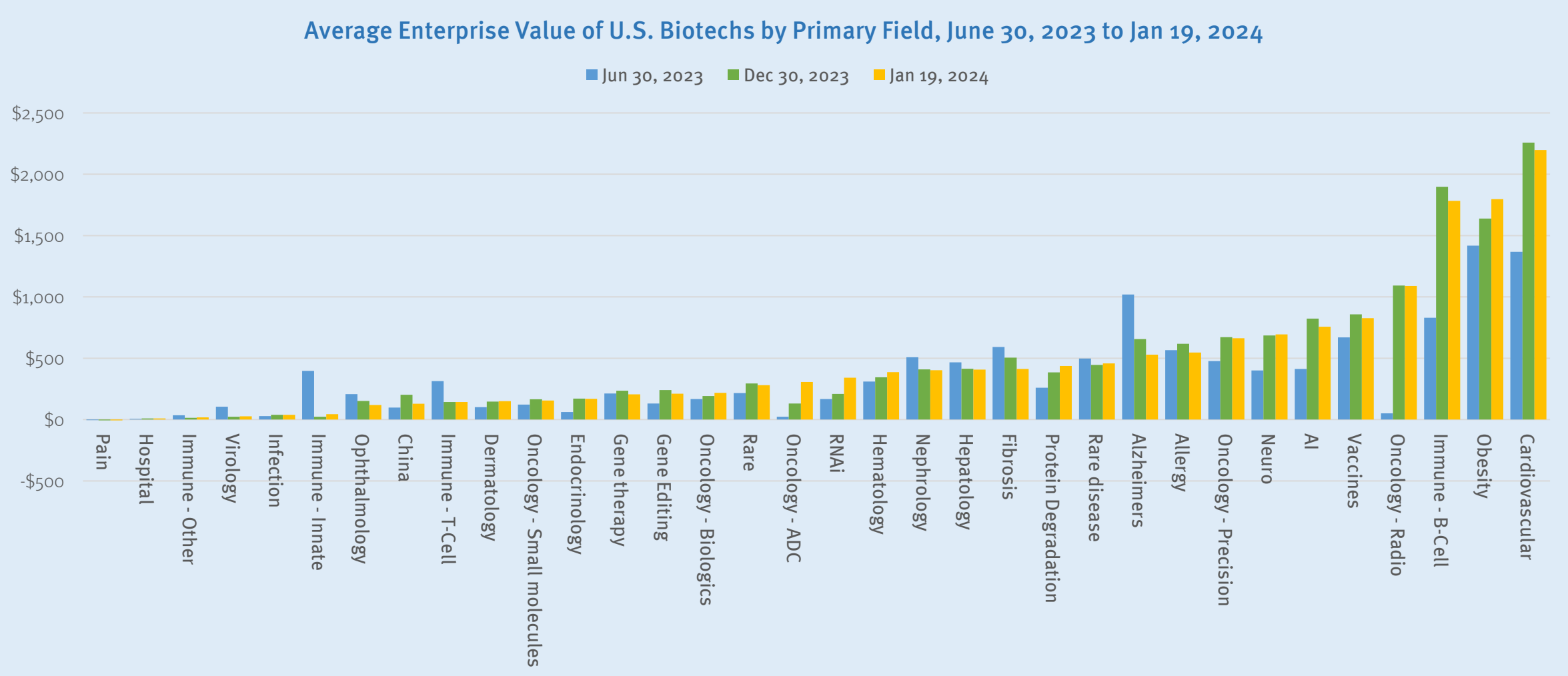
Company	HQ Country	Value Gain YTD ($ Millions)	Percent Gain YTD	Enterprise Value (Jan 19, 2024, $ Millions)	Comment
Arrowhead Pharma	United States	$871	26.48%	$4,162	Strong analyst support
Ambrx Biopharma	United States	$848	123.87%	$1,532	Acquisition by J&J
Zealand Pharma	Denmark	$810	26.87%	$3,823	Buyout rumors. Hedge funds registering
Longboard Pharma	United States	$742	840.07%	$831	Positive epilepsy data
Summit Therapeutics	United States	$701	40.35%	$2,438	Positive Phase 2 data
NewAmsterdam Pharma	Netherlands	$686	136.88%	$1,187	Released timing of data readouts
Keros Therapeutics	United States	$608	66.29%	$1,526	New drug for treating obesity revealed
IDEAYA Biosciences	United States	$602	33.75%	$2,387	Analyst upgrades
Dyne Therapeutics	United States	$451	65.62%	$1,137	Positive DM1 data
Merus	Netherlands	$432	37.47%	$1,586	New HNSCC Data

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

Valuations for Preclinical Companies Dropping Most In First Three Weeks of 2024



Obesity Biotechs Gaining Value in First Weeks of 2024 While Alzheimer's, B-Cell, Vaccines and AI Dropping A Bit of Value

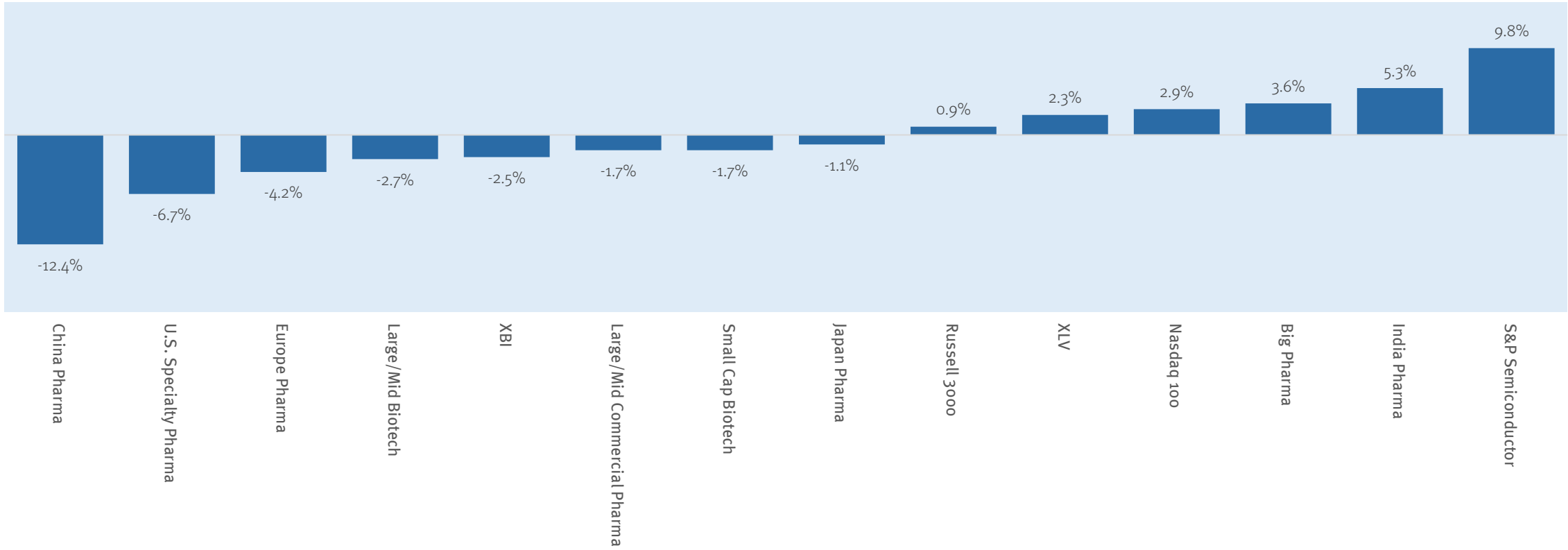


Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Where Has the Pharma Market Done Best So Far in 2024?

India pharma and big pharma are having a good year and are even ahead of the tech heavy Nasdaq 100 Index (although behind the smoking hot semiconductor market). In contrast China pharma, U.S. specialty pharma and Europe pharma are performing relatively poorly.

Group Equal-Weighted Share Price Return, Dec 30, 2023 to Jan 19, 2024

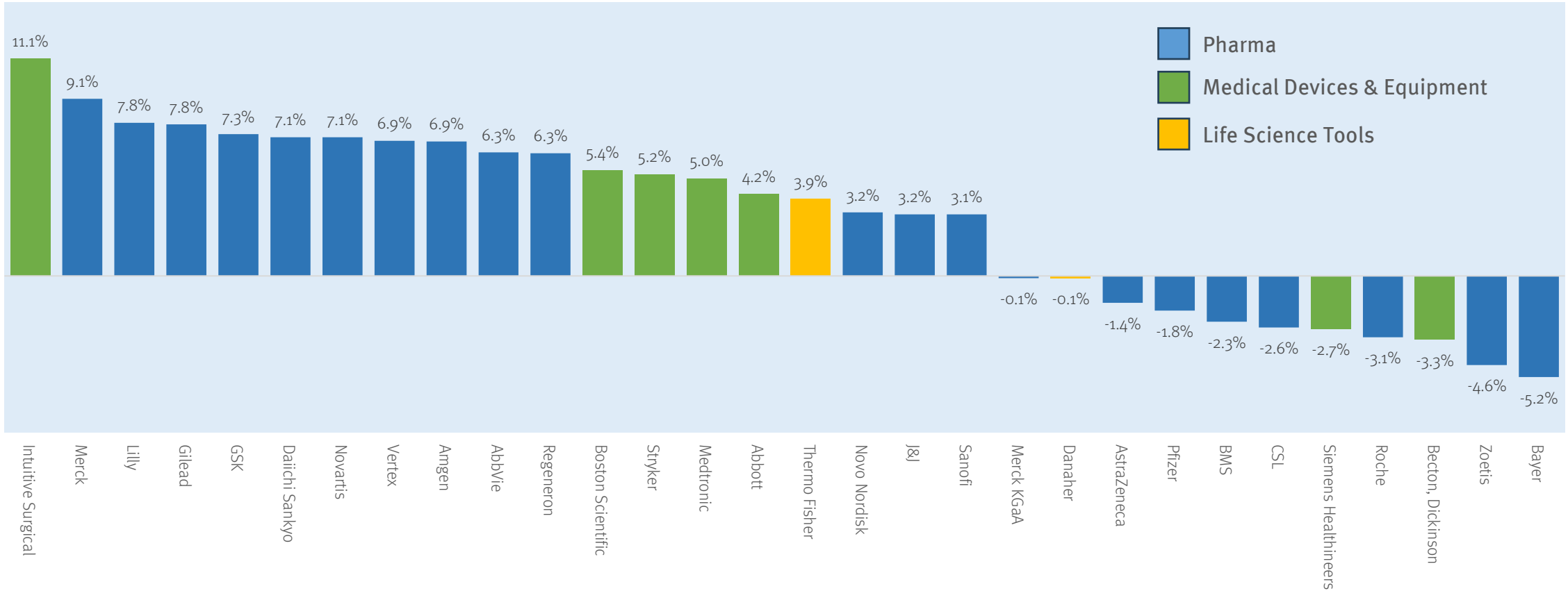


Notes: These data are from S&P CapitalIQ and are compiled into equal-weighted indices. Big pharma includes PFE, LLY, MRK, ABBV, NOVO B, ROG, JNJ, AMGN, AZN, NOVN and SAN. China Pharma includes 600276, 1093, 2186, BGNE, 000963, 600196, 000538, 600518, 002422, 000597, 3692 and ZLAB. India Pharma includes 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. Large / midcap commercial pharma includes VRTX, ARGX, ALNY, BMRN, INCY, NBIX, OGN, IONS, EXEL, ALKS, ITCI, HRMY, INDV, BPMC, MRTX, SAGE, IDIA, APLS. US specialty pharma includes SUPN, EGRX, CPRX, PCRX, IRWD, JAZZ, COLL, BHC, BLCO, ARQT, HLS, ASRT, OPTN, GTHX, ANIK, HROW, PHAT, ESPR, CALTX, AMARIN, OPK, LQDA, RIGL, EYPT, MRNS, ALIM, TRVN. Large / MidCap biotech includes KRTX, MDGL, CERE, CYTK, ARWR, PCVX, DNLI, VIR, CRSP, PRTA, BEAM, AKRO, IMVT, VRNA, VTYX, SWTX, SNDX and Small Cap biotech includes LCTX, GLSI, GRPH, CYDY, OMER, SVRA, THRD, EVLO, TCRT, CMRX, TSHA, DTIL, OVID, TNYA, VXRT, CUE, XFOR, ATHA, TRVI, CTXR, SELB, CRMD, MTNB, AKBA.

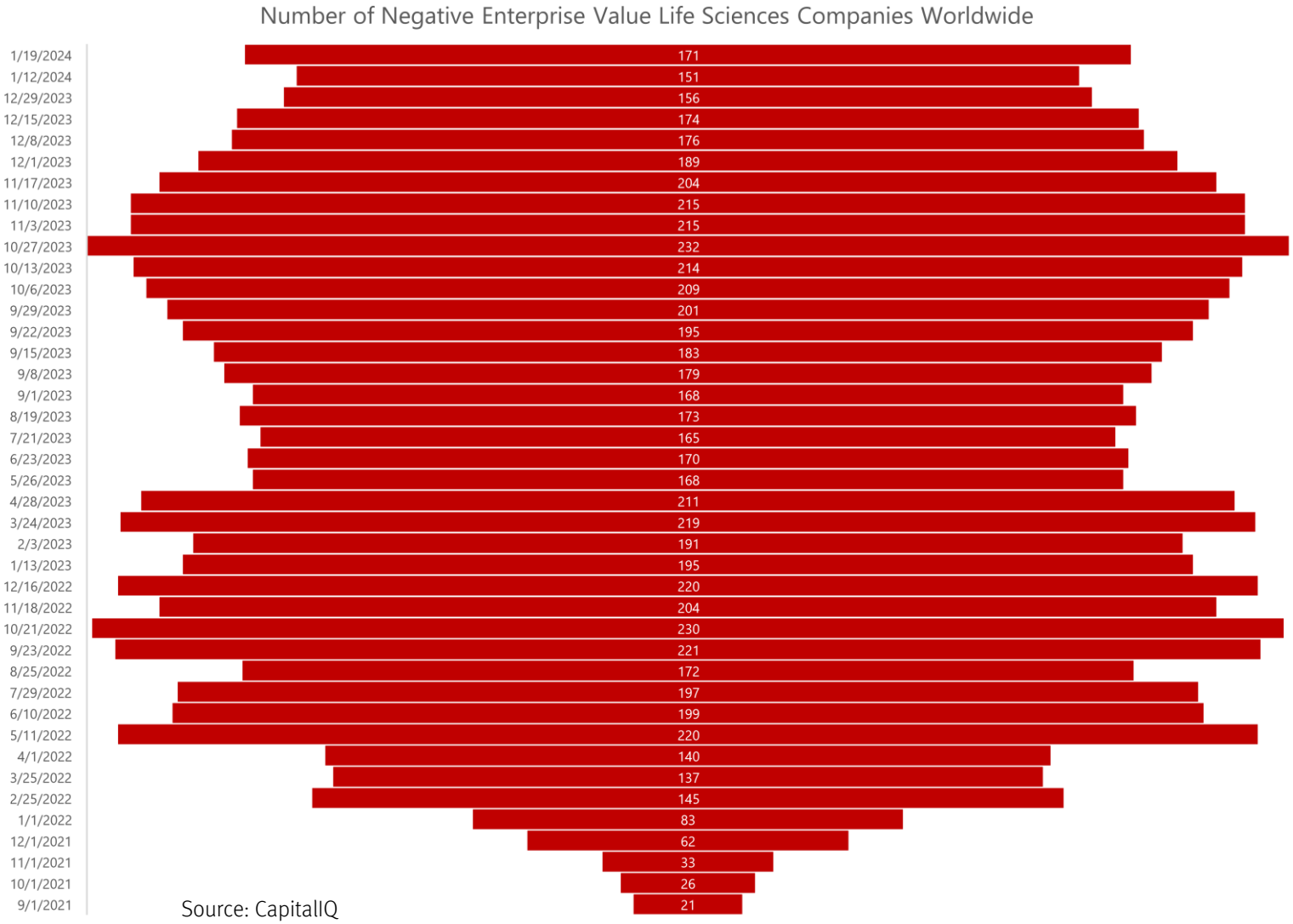
Large Cap Life Sciences Performance Year to Date

Ten of the top eleven large cap performers so far in 2024 are large pharma. While there are some laggards, big pharma as a group has attracted buyers and is performing nicely relative to 2023.

YTD Share Return for Top 30 Life Sciences Companies by Value



Number of Negative Enterprise Value Life Sciences Companies Rose to 171 in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide rose from 151 a week ago to 171 last Friday.

This is quite a sharp rebound and is consistent with investor concerns about the value of early-stage companies in a rising rate environment.

Life Sciences Sector Value Dropped 1.4% Last Week

Last week saw a 1.4% decrease in life sciences stocks worldwide. The sector lost $133 billion in value.

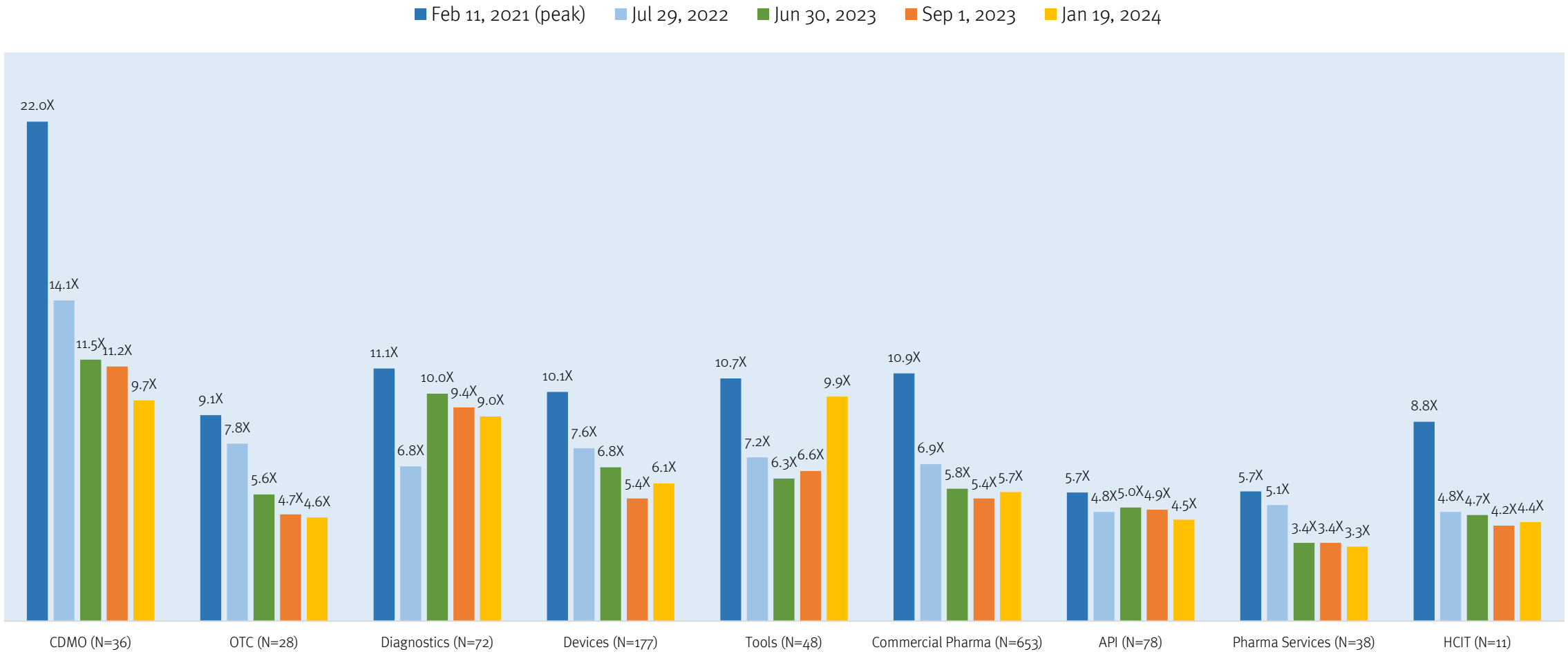
Sector	Firm Count	Enterprise Value (Jan 19, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$81,808	-3.7%	-3.1%	-4.6%
Biotech	804	$231,263	-2.9%	6.4%	-5.1%
CDMO	40	$142,227	-2.0%	2.0%	-27.8%
Diagnostics	82	$269,582	-2.0%	-2.7%	1.1%
OTC	30	$27,684	-3.0%	-0.7%	-8.2%
Pharma	723	$5,984,700	-1.6%	3.2%	2.7%
Services	39	$193,698	-0.5%	-5.4%	-13.4%
Tools	51	$677,666	0.5%	-0.5%	-14.0%
Devices	181	$1,655,139	-0.7%	2.4%	2.1%
HCIT	11	$21,498	-0.2%	-3.5%	-28.7%
Total	2042	$9,281,767	-1.4%	2.4%	0.1%

Source: CapitalIQ

Life Sciences Revenue Multiples Increasing

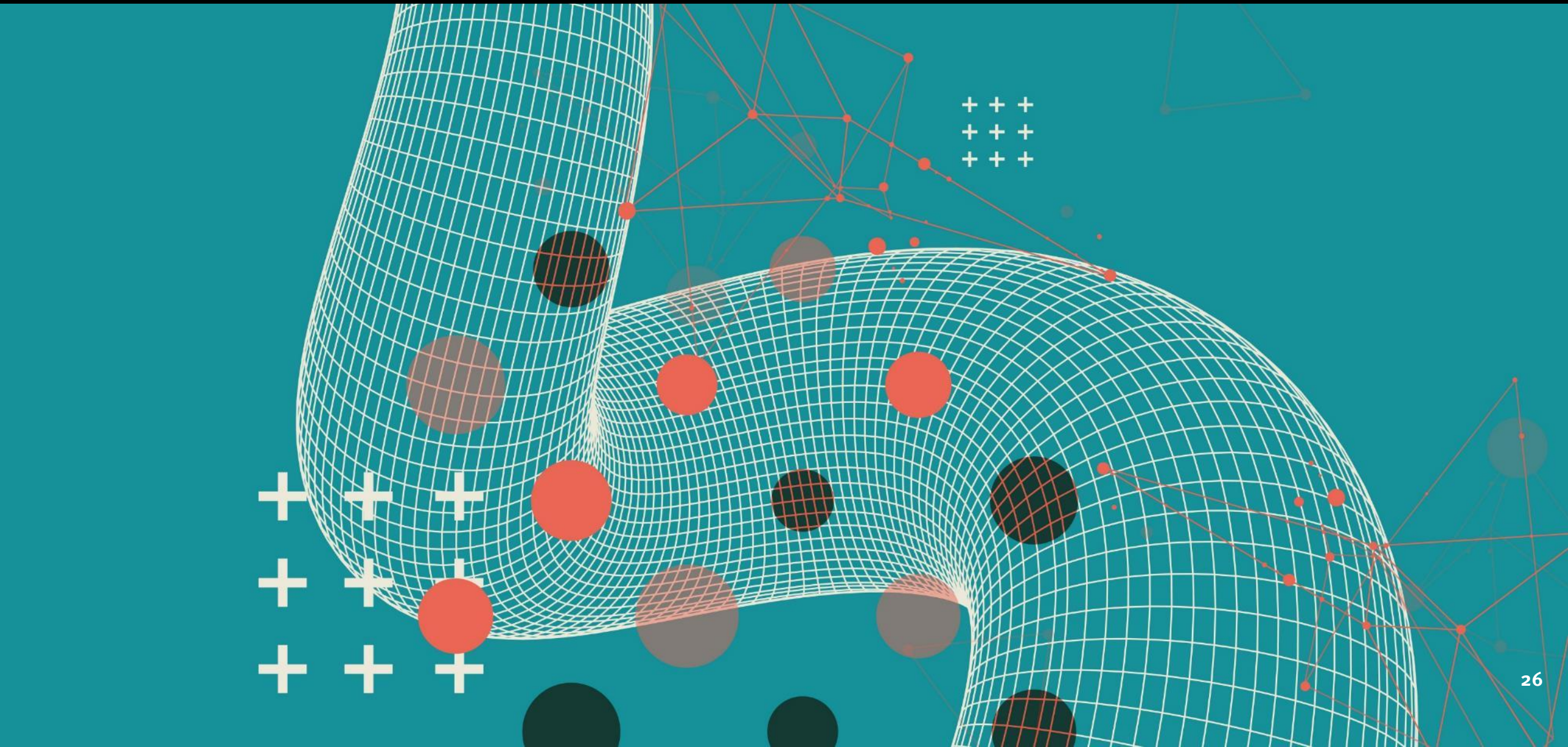
The largest sectors are commercial pharma and medical devices. Revenue multiples are up in both over the last four months. Tools multiples are up substantially. In contrast, CDMO and diagnostics multiples have continued to drop.

Average Revenue Multiples by Subsector of the Global Life Sciences Sector, Feb 2021 to Jan 2024



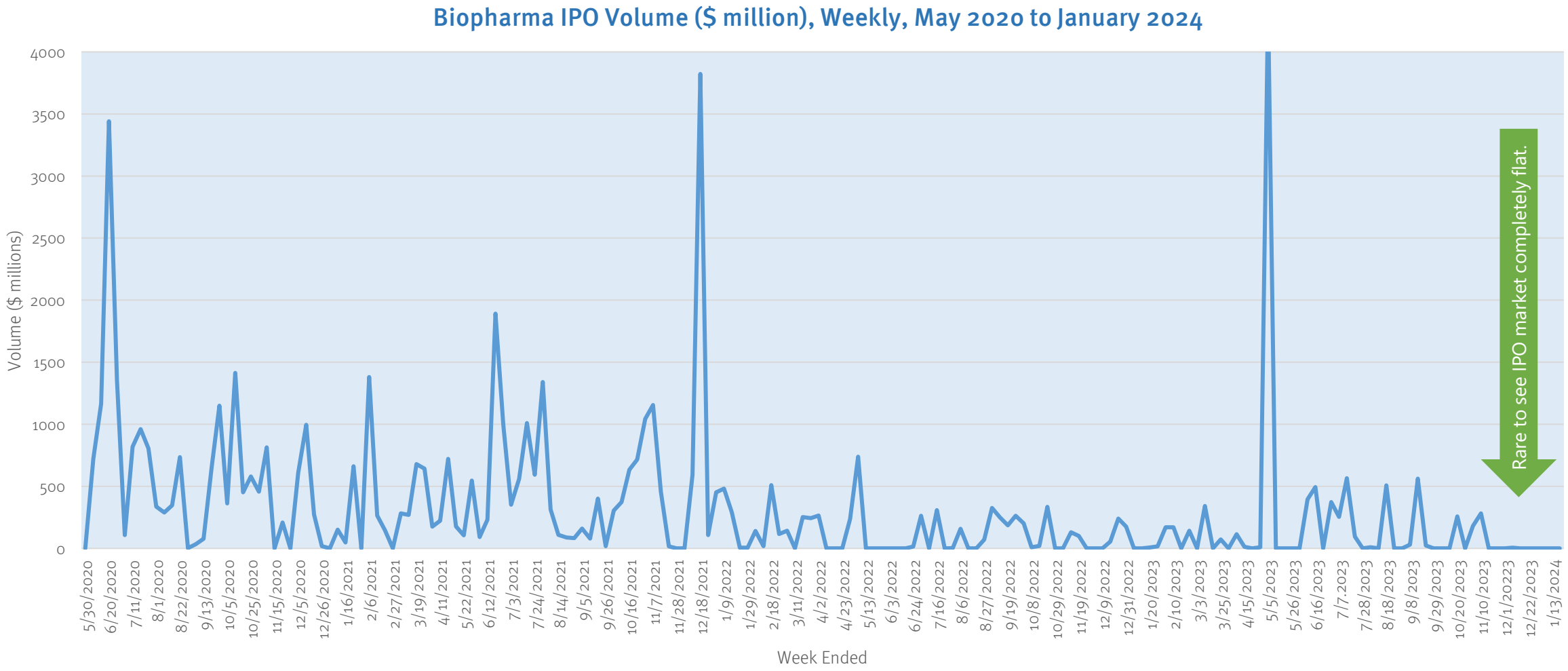
Source: CapitalIQ

Capital Markets Update



No Biopharma Initial Public Offerings in Last Nine Weeks

While the IPO backlog has been filling up, we have not seen a biopharma go public anywhere in the world since early November of 2023.



Source: Data from CapitalIQ and Stifel research.

Dual Track Processes Popular in 2024

Annalee Armstrong, Gabrielle Masson, *FierceBiotech*, Jan 17, 2024 (excerpt)

Biotech executives are reaching into a deep bag of tricks to come up with the best possible ways to live up to their ultimate potential. The dual-track option, where a company pursues both an IPO and an acquisition, is becoming not just the norm, but a necessity.

Some are taking it a step further, many industry experts told Fierce Biotech on the sidelines of the J.P. Morgan Healthcare Conference last week. “There are three tracks. We have clients that are pursuing IPO funding, or licensing or M&A. And it's really which will come together first,” said Randy Sunberg, chair of the North America Healthcare & Life Sciences Group, and partner in the transactions group for Baker & Mckenzie.

It’s all part of a frenzied biotech market coming down from a prolonged bear market. Executives are keeping their options open and are more prepared to change plans at a moment’s notice.

Carmot Therapeutics used a dual-track process this fall, ultimately selling off to Roche for $2.7 billion in December. CEO Heather Turner confirmed that the biotech had been considering an IPO at the same time.

A company can’t just turn up on Wall Street and start an initial public offering, so this dual-track process means a lot of time, energy and money spent for an option that ultimately might never happen.

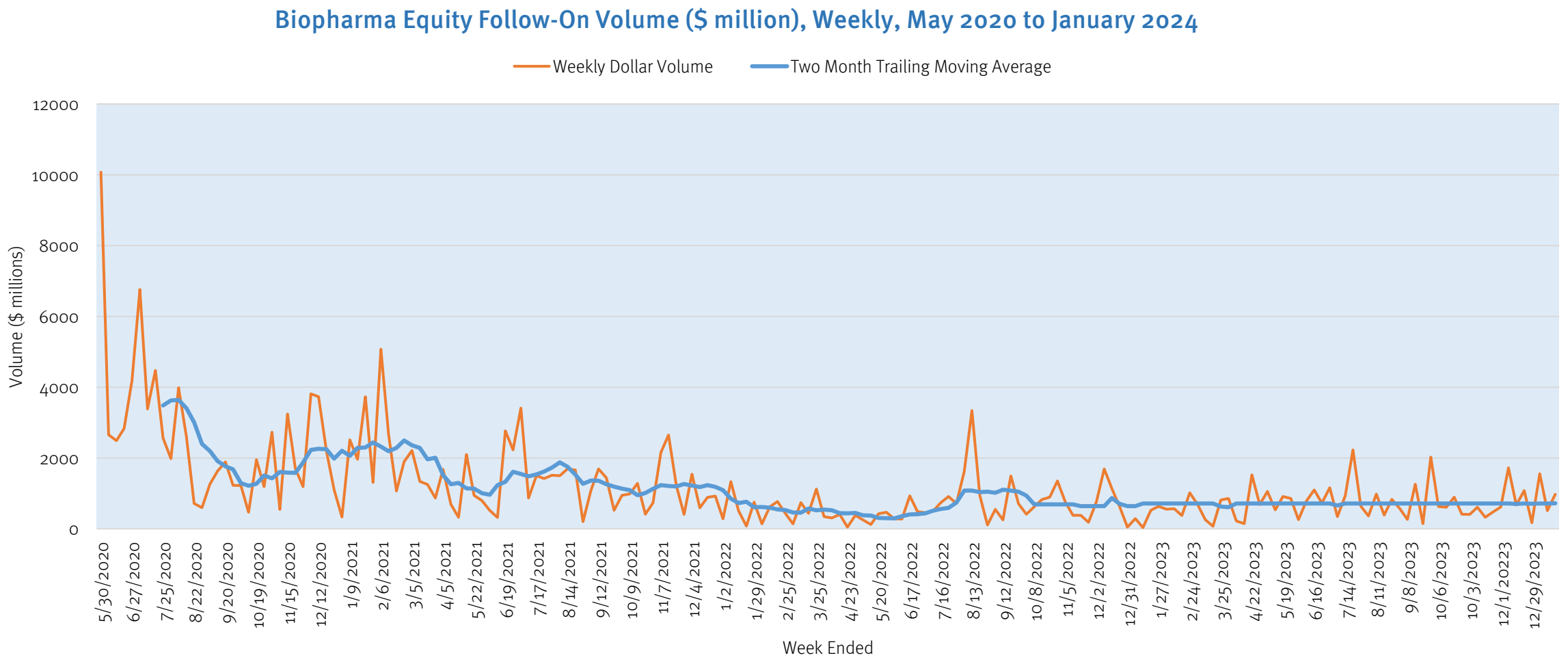
“It is resource intensive, obviously. And you also don't want to bet on two tracks and not be able to deliver on either,” said Mubadala Capital investor Ayman AlAbdallah.

Sharon Flanagan, San Francisco managing partner for Sidley, said that companies have to hire lawyers, and auditors and bankers to work on the listing.

Source: https://www.fiercebiotech.com/biotech/biotech-dealmakers-its-everything-everywhere-all-once

Close to $1 Billion in Follow-On Volume Last Week

We continue to have a very active follow-on market this January with nearly $1 billion in issuance getting done last week. The pace of issuance activity this month has not been seen since Q3 of 2022.

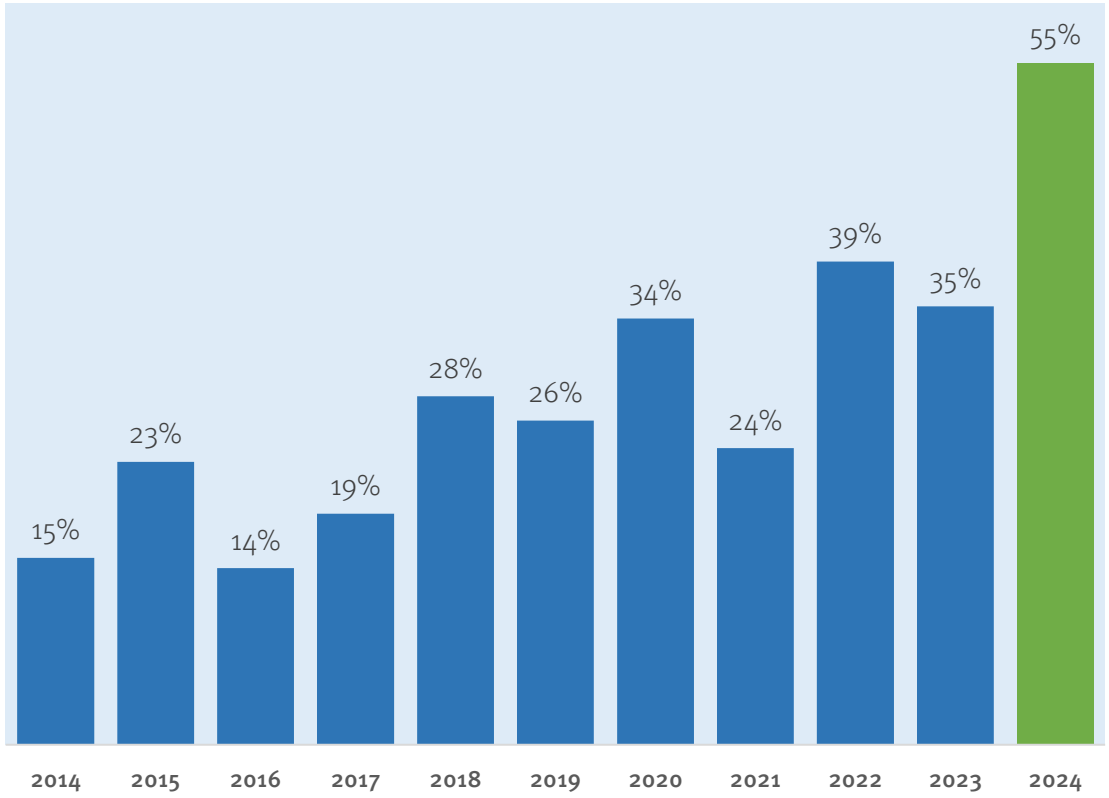


Source: Data from CapitalIQ and Stifel research.

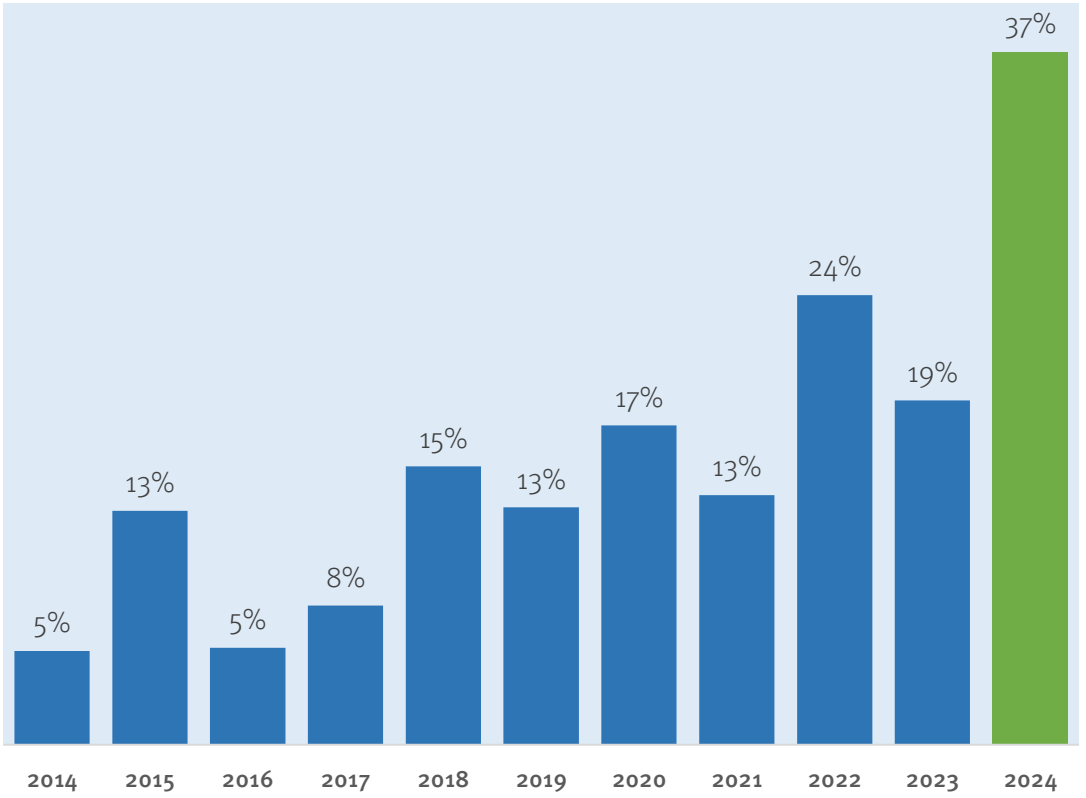
Biopharma Offerings Over Half of All U.S. Equity Issuance So Far in 2024

If one looks at the total U.S. equity IPO and follow-on market (excluding PIPEs), 2024 has been an exceptional year for biopharma. The biopharma sector has accounted for 55% of total issuance by deal count and 37% of issuance by dollar volume. This is unprecedented.

Percent of All IPOs and Follow-Ons on U.S. Exchanges that are Biopharma, 2014 to 2024



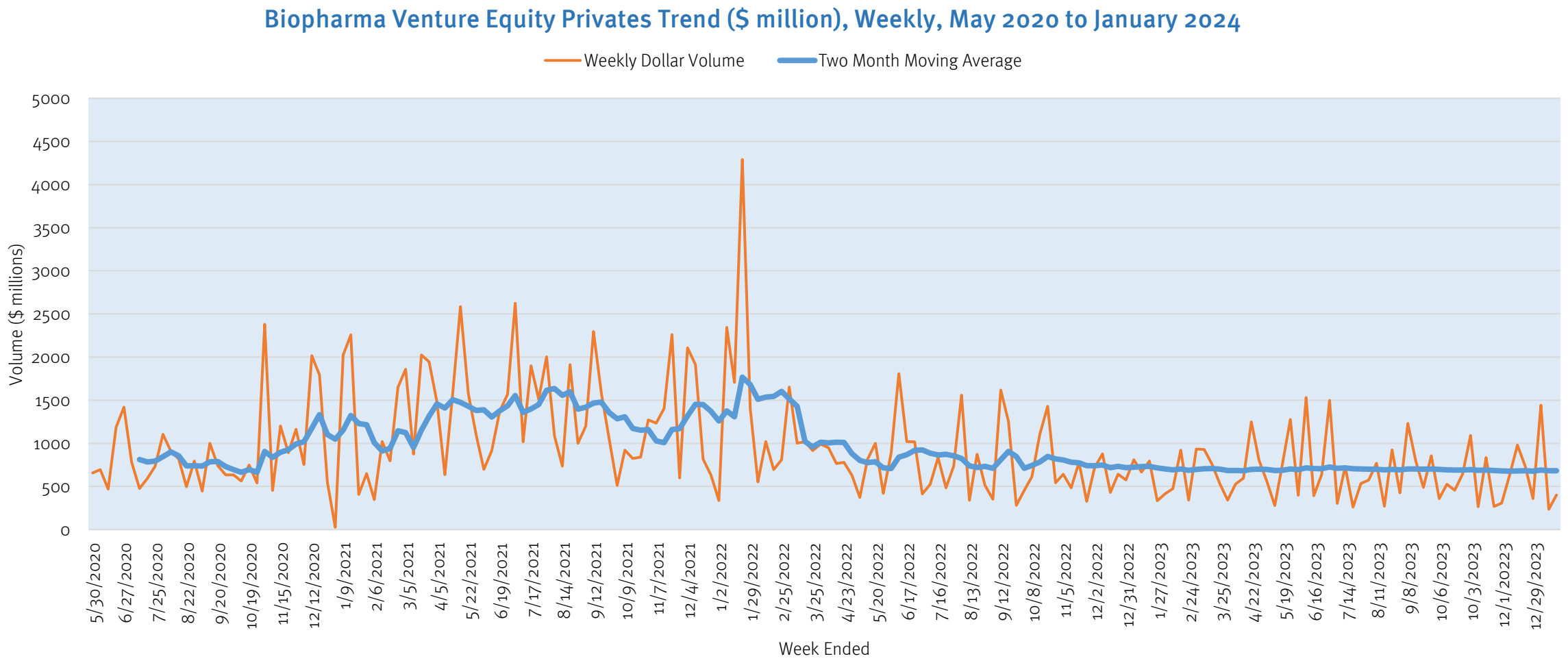
Percent of All IPOs and Follow-On Dollar Volume on U.S. Exchanges that is from Biopharma Offerings, 2014 to 2024



Source: Data from CapitalIQ and Stifel research. PIPEs excluded. Only offerings of $50 or more are considered in this analysis.

Last Week Slow for Venture Privates

We saw $401 million of venture privates last week. The last two weeks have been much slower than the first week of the year which was a barnburner for deal volume.



Source: Data from CapitalIQ, Crunchbase.

Tr1X, Inc. Announces $75 Million Series A Financing to Develop Best-in-Class Universal Allogeneic Regulatory T (Treg) and CAR-Treg Cell Therapies

SAN DIEGO, Jan. 17, 2024 /PRNewswire/ -- Tr1X, Inc. today announced its emergence from stealth with a $75 million Series A financing to bring universal allogeneic regulatory T (Treg) and CAR-Treg cell therapies to the clinic to treat and potentially cure autoimmune and inflammatory diseases. The financing was led by Bay Area-based The Column Group, with participation from NEVA SGR and Alexandria Ventures. The Company appointed William Lis Chief Executive Officer, strengthened its leadership team with other biopharma industry veterans, and announced members of the Board of Directors and Scientific Advisory Board.

"We are thrilled to partner with Bill Lis, Maria Grazia Roncarolo and Tr1X's world-class team to revolutionize the field through its innovative, breakthrough science," said Leon Chen, Ph.D., MBA, Partner at The Column Group and Tr1X Board Member. "With its experienced management team at the helm, we are confident in Tr1X's ability to bring curative cell therapies to patients who currently require life-long treatment and management."

Science and Pipeline

The Company's science is primarily based on the work of Tr1X's Scientific Founder Maria Grazia Roncarolo, M.D., the discoverer of Type 1 regulatory T (Tr1) cells, which have features that can benefit patients with autoimmune and inflammatory diseases. Tr1 cells, a differentiated subpopulation of regulatory T cells, are crucial for maintaining homeostasis and tolerance in healthy individuals and have several important functions. These include dampening of local inflammation and downregulation of the inflammasome, suppression of pathogenic effector T cell responses, and induction of long-term tolerance as observed in preclinical models and patients.

Tr1X's proprietary technology enables the conversion of $CD4^+$ T cells isolated from healthy donors into Treg-like cells that have a similar function and profile to naturally occurring Tr1 cells. These cells can be further engineered to target specific tissues or organs to enable local, targeted immunomodulation. With a proprietary, GMP-grade, closed-loop system that provides consistency, quality and reliability at scale, Tr1X can enable production of its products at commercial volume.

Source: https://www.prnewswire.com/news-releases/tr1x-inc-announces-75-million-series-a-financing-to-develop-best-in-class-universal-allogeneic-regulatory-t-treg-and-car-treg-cell-therapies-to-treat-and-potentially-cure-autoimmune-and-inflammatory-diseases-302036679.html

"The ability to develop a pipeline of medicines based on our work on regulatory T cells represents the culmination of decades of discovery and research into the underpinnings of immunological tolerance and autoimmunity, Tr1 cells have unique properties and represent the ideal therapeutic platform from which to develop 'immune reset' products. Our two platforms have the required attributes to address a broad set of indications, including dual targeting of pathogenic T and B cells. These engineered cells have the potential to induce tolerance, which could transform the lives of people living with chronic autoimmune diseases by providing them with a cure instead of ongoing treatment."

Maria Grazia Roncarolo, MD
Co-Founder and Head of R&D
Tr1X Bio

Ratio Therapeutics Announces $50M Series B Financing to Advance Targeted Radiotherapies for Cancer Treatment

BOSTON, Jan. 17, 2024 /PRNewswire/ -- Ratio Therapeutics Inc. (Ratio), a pharmaceutical company that employs a suite of innovative technologies to develop best-in-class radiopharmaceuticals for the treatment and monitoring of cancers, today announces the close of its $50M Series B financing, bringing the total raised to date to over $90 million. The latest round witnessed continued participation from Series A leads Schusterman and Duquesne and welcomed among others PagsGroup, Bristol Myers Squibb and the Center for Technology Licensing at Cornell University.

This financing will expand the applications of the company's proprietary technology platforms, Trillium™ and Macropa™, to develop novel best in class fit-for-purpose radiopharmaceuticals. Additionally, the funding will drive the clinical development of the company's fibroblast activation protein-alpha (FAP) targeted radiopharmaceutical therapeutic.

"The FAP-targeted therapeutic program has the potential to provide much needed treatment to patients with multiple types of cancer," said Dr. Mey Boukenna of PagsGroup, the Boston-based family office of Stephen Pagliuca. "With Ratio's unique assets and technology, and Drs. Babich and Hoppin standing as pioneers in the radiopharmaceutical field, we believe they are very well positioned to advance novel radiopharmaceutical cancer treatments and diagnostics into the clinic."

Ratio THERAPEUTICS

"This funding advances Ratio's technology platforms and will help launch clinical trials for our FAP-targeted radiotherapeutic which aims to treat a broad array of solid-tumor cancers. We are grateful to our investors for their confidence in our technology. We have filed two INDs and completed enrollment in both radiation dosimetry studies in support of two of our corporate partnerships. Now we have the backing to move our first therapeutic candidate into clinical trials by the end of this year."

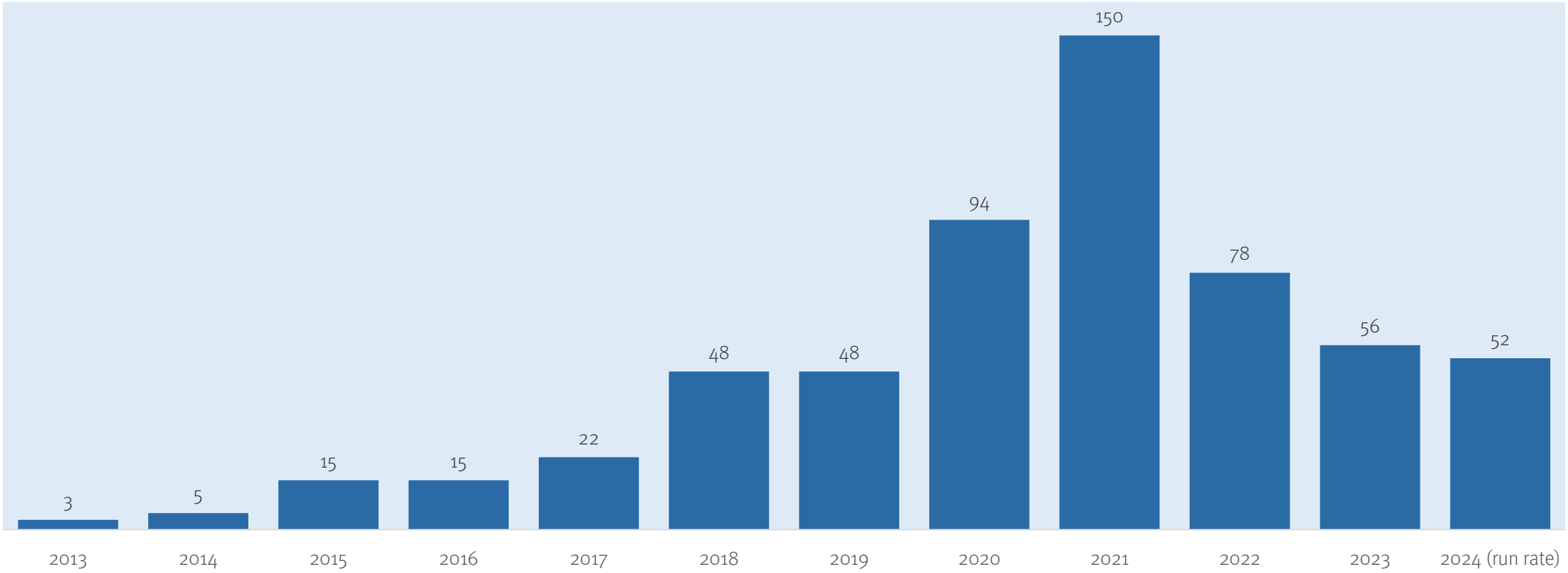
Jack Hoppin
Chief Executive Officer
Ratio Therapeutics

Source: https://www.prnewswire.com/news-releases/ratio-therapeutics-announces-50m-series-b-financing-to-advance-targeted-radiotherapies-for-cancer-treatment-302036375.html

Run Rate of $100MM+ Venture Privates Continues to Drop in 2024

It's early days but it looks like the count of large venture deals is going to drop again in 2024. There hasn't been a deal for $100mm or more since January 6th.

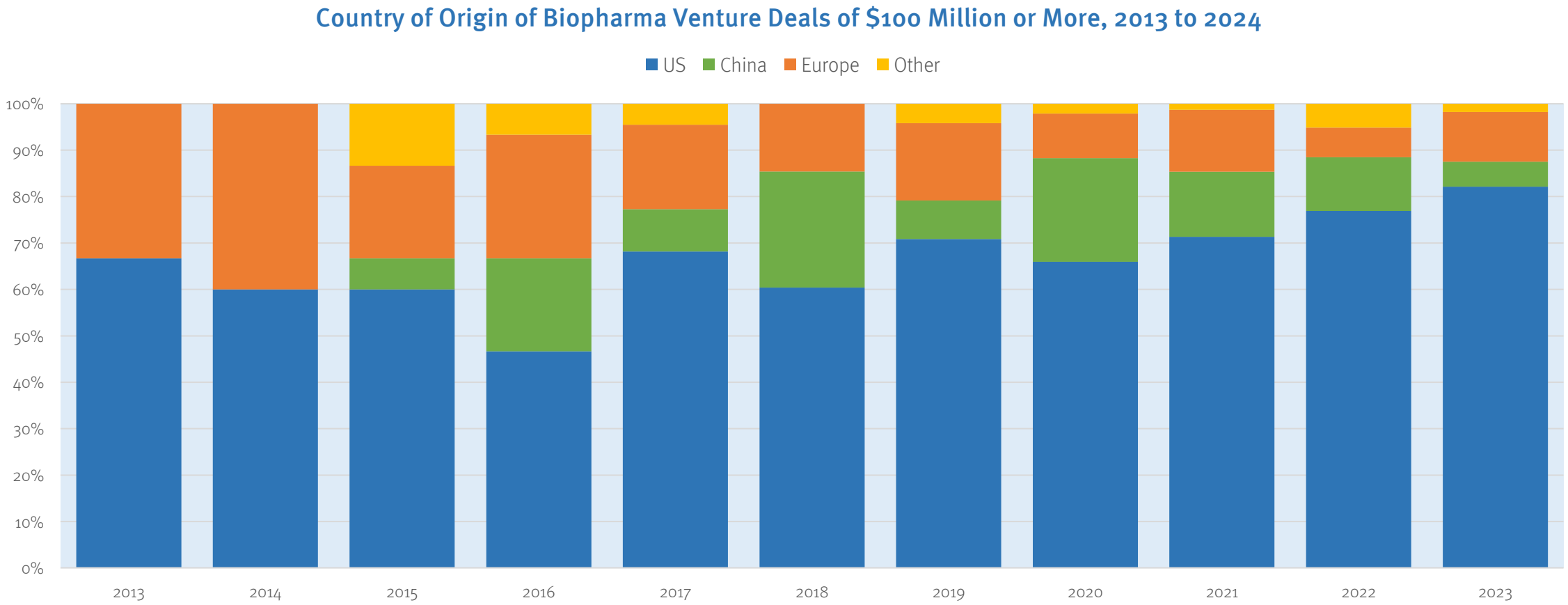
Count of Biopharma Venture Deals of $100 Million or More, 2013 to 2024



Source: DealForma and Stifel analysis.

17% of $100mm+ Venture Deals Done by ex-U.S. Issuers in 2023. Down from 52% in 2016

Larger venture privates are more likely to be done in the U.S. than ever before. Both Europe and China saw a significant drop-off in large venture financings in 2023. The U.S. venture ecosystem appears to be getting more powerful on a relative basis over time.



Source: DealForma and Stifel analysis.

Mirae Launches U.S. Biotech Venture Fund

Brian Gormley, *Wall Street Journal*, Jan 18, 2024 (excerpt)

A South Korean financial giant has launched a U.S.-based biotechnology venture fund in an effort to participate in more of the top deals in the industry.

Mirae Asset Financial Group, which has $535 billion in assets under management, has launched its first U.S.-based biotech venture-capital fund, a $50 million pool the firm expects will be the first of a series of venture funds targeting U.S. life sciences startups, said Dr. Naveen Krishnan, a managing director who heads the new investment group, Mirae Asset Capital Life Science.

Biotech venture financing has slipped from heights reached during the pandemic, as a slowdown in initial public offerings has forced venture firms to make additional investments in existing portfolio companies.

Mirae Asset Financial, founded in 1997, has businesses spanning sectors including investment banking, insurance, venture capital and public-market funds. As a result, startups initially backed through the new biotech venture pool could have a source of funding over the long term by also raising capital from other Mirae funds, Krishnan said.

Mirae is a giant and highly successful Korean asset manager.

Source: https://www.wsj.com/articles/korean-asset-manager-mirae-launches-u-s-biotech-venture-fund-2043287e

Novo Holdings Plans to Ramp up Dealmaking

novo holdings
Investors in life science

Nick Paul Taylor, *FierceBiotech*, Jan 19, 2024 (excerpt)

Novo Holdings is fattening up as patients slim down. Boosted by the Wegovy windfall, the fund manager's CEO Kasim Kutay expects to do “a fair amount” more deals in 2024 and to open a second office in Asia.

Speaking to Bloomberg TV in Davos, Kutay outlined how the success of Novo Nordisk, one of two Novo Holdings operating companies, will affect his activities in 2024 and beyond. The operating companies are providing “significant dividends” that Novo Holdings will use to execute a strategy that calls for half of its money to go into life sciences.

A buyout team will use some of the money. The unit, called the principal investment team, does “a fair amount of buyout activity in the life sciences and healthcare sector,” Kutay said, and there will be more to come as the GLP-1 money flows into Novo Holdings.

“We did a couple of them last year. We anticipate doing a fair amount more in 2024, and indeed going forward because the cash flows that are coming our way are going to be obviously quite significant, if you look at the forecasts in terms of how the GLP-1 class is going to be doing in the coming years,” Kutay said.

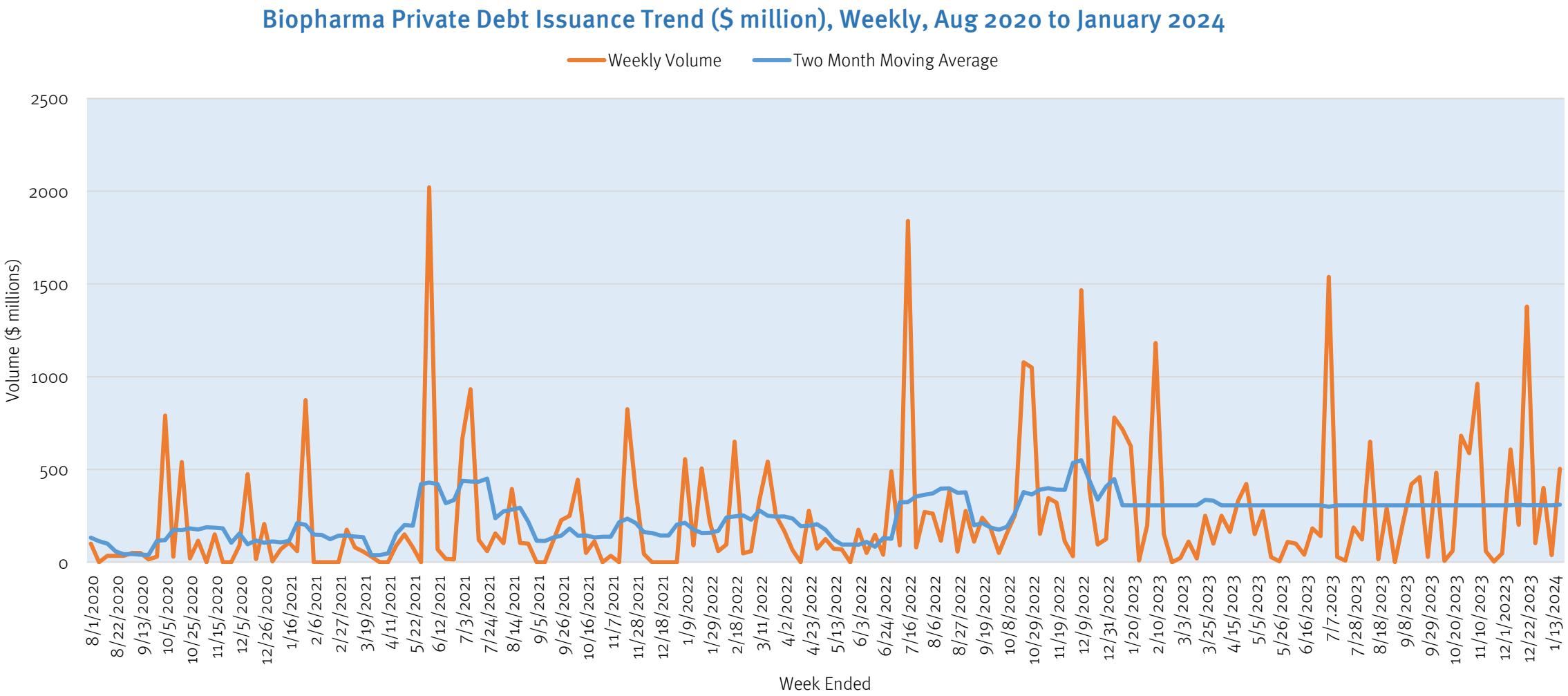
Kutay sees “a lot of activity” in the biotech venture space, although the reasons for the hubbub over the past 12 months is more positive for the investors providing the money than the drug developers seeking it out.

“We actually had a very active year, because we found valuations very attractive. The biotech sector took a bit of a hammering starting in about late ‘21, so we found ‘23 an interesting, very interesting, time to take advantage of that,” Kutay told Bloomberg TV.

Source: https://www.fiercebiotech.com/biotech/novo-holdings-plans-ramp-dealmaking-amid-wegovy-windfall

Weekly Global Biopharma Private Debt Placement Market Open in December

Last week saw several large debt and royalty deals get done led by BridgeBio's $500 million synthetic royalty monetization transaction.



Source: Data from CapitalIQ, Crunchbase.

BridgeBio Secures Up to $1.25B in Financing, Prepares for Potential Product Launch

Tyler Patchen, *Biospace*, Jan 19, 2024 (excerpt)

BridgeBio is getting a major financial shot in the arm as it prepares to potentially take one of its products to market. On Thursday, the biotech announced that it secured funding from Blue Owl Capital and the Canada Pension Plan Investment Board via its subsidiary CPPIB Credit Investment, bringing BridgeBio's capital to a total of $1.25 billion.

The financing comes as the company anticipates the launch of its drug acoramidis to treat transthyretin amyloid cardiomyopathy (ATTR-CM). If the drug is approved by the FDA, it will compete with Pfizer's Vynamax and Vyndaquel—the only ATTR-CM drugs currently available.

"Our newly strengthened balance sheet will enable us to serve ATTR-CM patients with a well-resourced launch of acoramidis, as well as patients with genetic diseases more broadly with multiple Phase II readouts for blockbuster indications anticipated over the next few years," BridgeBio CFO Brian Stephenson saidin a statement.

The deal with Blue Owl and CPPIB Credit includes a $500 million cash payment—$300 million from Blue Owl and $200 million from CPPIB—to BridgeBio should the FDA approve acoramidis, in exchange for royalties of 5% on net sales globally for the drug. The royalty payments are capped at 1.9 times the invested capital.

Additional funds of up to $300 million can be provided at BridgeBio and Blue Owl's mutual consent to "support strategic corporate development activities."

Sandip Agarwala, managing director at Blue Owl Capital, said in a statement that acoramidis "has demonstrated an impressive and differentiated clinical profile, and we believe it will be an important advancement in treating ATTR-CM."

This seems like a mutually beneficial deal. BridgeBio sold a capped 5% synthetic royalty on a single product for $500 million.

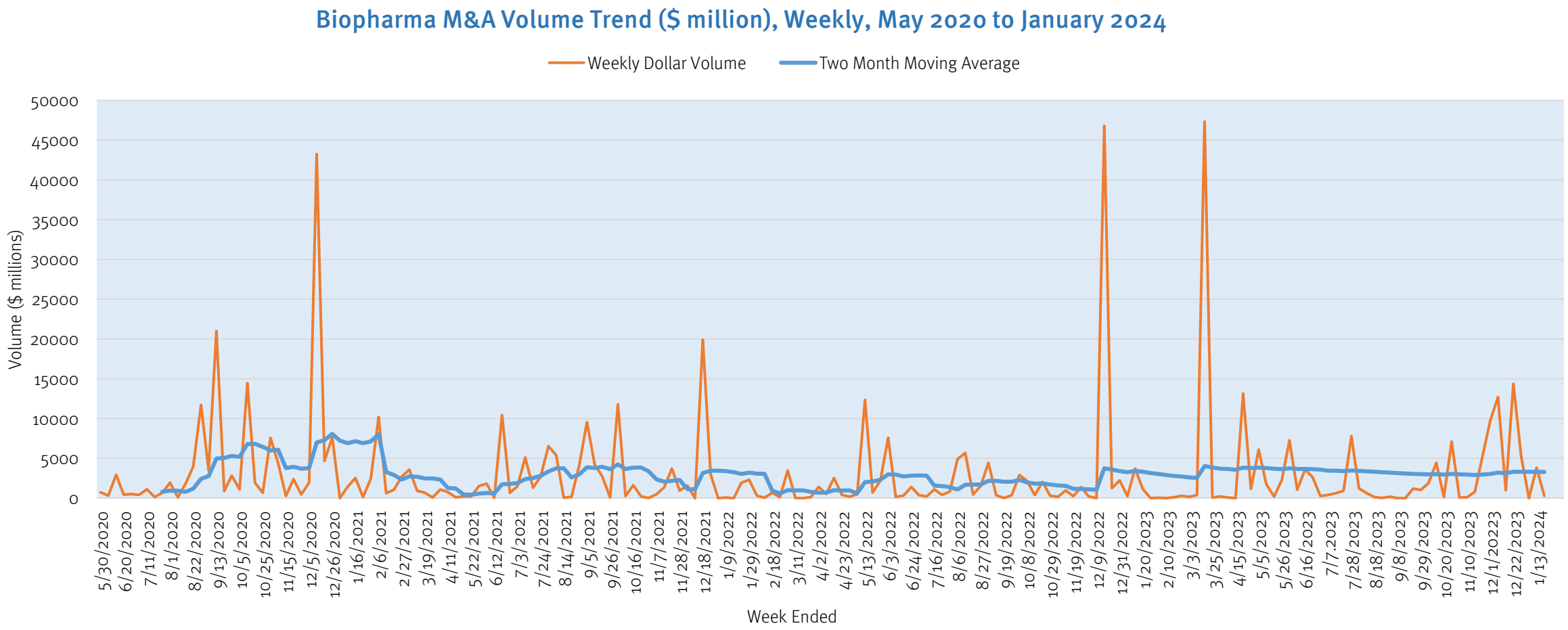
Blue Owl and CPPIB are able to put a significant amount of money to work in a relatively low risk deal with a double digit return profile.

Source: https://www.biospace.com/article/bridgebio-secures-1-25b-in-financing-prepares-for-potential-product-launch/

Deals Update

M&A Market Slowed Down Last Week

After a strong week for M&A at #JPM24, the market slowed down last week. In China, Xi'an Beilin Pharmaceutical Co., Ltd. agreed to acquire a 63% stake in Chongqing Duoputai Pharmaceutical Technology Co for $62 million. The Taiwanese firm Bora Pharma acquired Upsher-Smith.



Source: S&P, CapitalIQ

Private Equity Predicts Deal Rebound as Sellers Capitulate on Prices

Arash Massoudi, Anne-Sylvaine Chassany and Antoine Gara, *Financial Times*, Jan 19, 2024 (excerpt)

Private equity executives are predicting a sharp increase in takeover activity as buyout firms that have held on to investments in the hope of higher prices finally begin to capitulate.

There has been a marked drop in private equity groups selling portfolio companies since a peak in 2021, as rising interest rates have made financing more difficult and hurt valuations.

Investors in buyout funds have begun to increase pressure on groups to sell long-held investments and start returning cash, however, forcing them to reckon with lower prices and lock in returns."

Sellers have conceded to lower valuations and the pressure to meet a certain return on investment is ticking," Pete Stavros, co-head of global private equity at KKR, told the Financial Times at the World Economic Forum in Davos.

Firms entered the new year sitting on a record $2.8tn in investments, creating what consultancy Bain & Co last year called "a towering backlog" of potential sales. Many private equity investors have begun to demand cash returns before they commit to new funds, increasing the urgency of asset sales.

"For the last 24 months, there has been a disconnect on valuation expectation between buyers and sellers. There is now a real sense of pragmatism setting in," said Anna Skoglund, who leads the European financial and strategic investors group at Goldman Sachs.

Last year, Veritas Capital, the private equity owner of healthcare software company Cotiviti, agreed to sell a 50 per cent stake to Carlyle in a deal that valued the business at up to $13bn before the transaction collapsed. In December, the FT reported KKR was now in talks at an $11bn valuation.

Source: https://www.ft.com/content/abea759d-3556-43f1-905f-26aeb30c18dc

Advanced Medicine Partners Launches to Set New Standard for Manufacturing and Testing Advanced Medicines

Press Release, Durham NC, Jan 17, 2024 (excerpt)

Advanced Medicine Partners, an organization that delivers process development, manufacturing, analytical development and testing for advanced therapy products, today announced its launch from Jaguar Gene Therapy with funding led by Deerfield Management Company, with additional investors including ARCH Venture Partners, Nolan Capital and others. The newly independent company is helmed by a team of experts who were directly responsible for the CMC efforts for numerous commercially available therapeutics including three globally approved gene therapies. The organization will continue to lead CMC efforts for Jaguar Gene Therapy's pipeline programs, will support CMC work for Deerfield academic projects and private portfolio companies, and has initiated work for several biotech and pharmaceutical clients.

Advanced Medicine Partners has a proprietary and proven development platform and has established a robust and reproducible adeno-associated virus (AAV) manufacturing process, which is among the most productive in the industry and consistently generates industry-leading functional full capsid ratios. Advanced Medicine Partners' process has been used with multiple genes of interest as well as multiple wild-type AAV serotypes and engineered capsids. This manufacturing process prioritizes patient safety while reducing cost of goods and will strive to set the standard for what regulatory agencies expect and patients deserve. The company has also developed a suite of platform analytical methods that can be licensed and offers assay development services.

Advanced Medicine Partners brings extensive operational experience from Jaguar Gene Therapy and other biotechnology companies, including AveXis, Novartis and Amgen. The Advanced Medicine Partners team has manufactured upwards of 350 total non-GMP batches and supplied over 20 preclinical studies, including IND-enabling efficacy and good laboratory practice (GLP) toxicology studies, as part of Jaguar. In addition to Advanced Medicine Partners' manufacturing and analytical testing capabilities, the company offers GMP tech transfer capabilities and virtual CMC support.

Advanced Medicine Partners currently operates with more than 33,000 square feet of lab, office and warehouse space in Cary and Durham, North Carolina. The company is in the process of building out a 174,000-square-foot GMP manufacturing facility in Durham. Advanced Medicine Partners has the ability to build dedicated capacity for partnered companies in this new facility.

This is the latest in a series of pharma services spinouts from gene therapy and cell therapy companies.

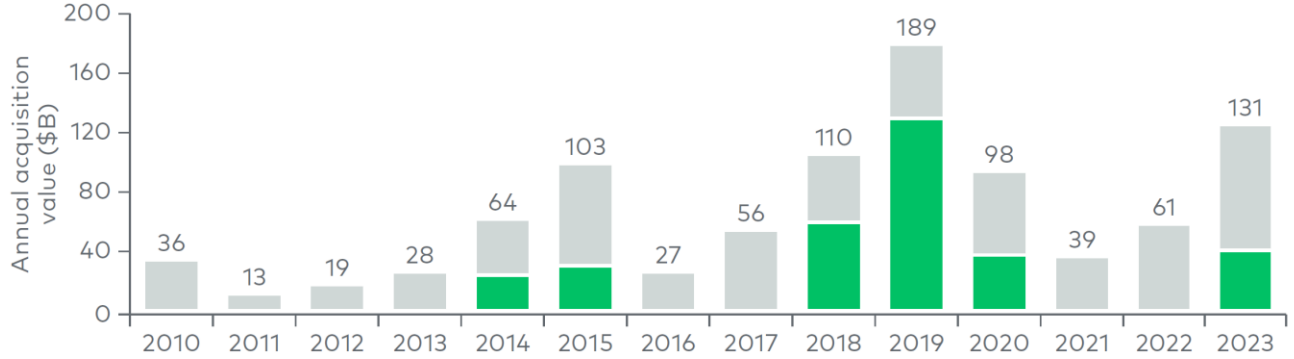
Source: https://www.businesswire.com/news/home/20240117676350/en/Advanced-Medicine-Partners-Launches-to-Set-New-Standard-for-Manufacturing-and-Testing-Advanced-Medicines

LEK Analysis: Last Year Saw a Record Number of large Pharma M&A Deals by Dollar Volume (if Transformational Deals Left Out)

LEK, "Optimizing Pharmaceutical Portfolios Through M&A," Jan 16, 2024

Analyzing these figures when excluding transformational M&A, defined as transactions exceeding $25 billion in equity value and surpassing 20% of the acquirer's market capitalization, the past year stands out as one of the most active in the past decade. This surge in recent M&A activity is likely attributable to an improvement in the macroeconomic environment and the pressures resulting from imminent drug pricing negotiations impacting pharma revenue covered by CMS Part D.

Biopharma M&A transactions (2010-2023)

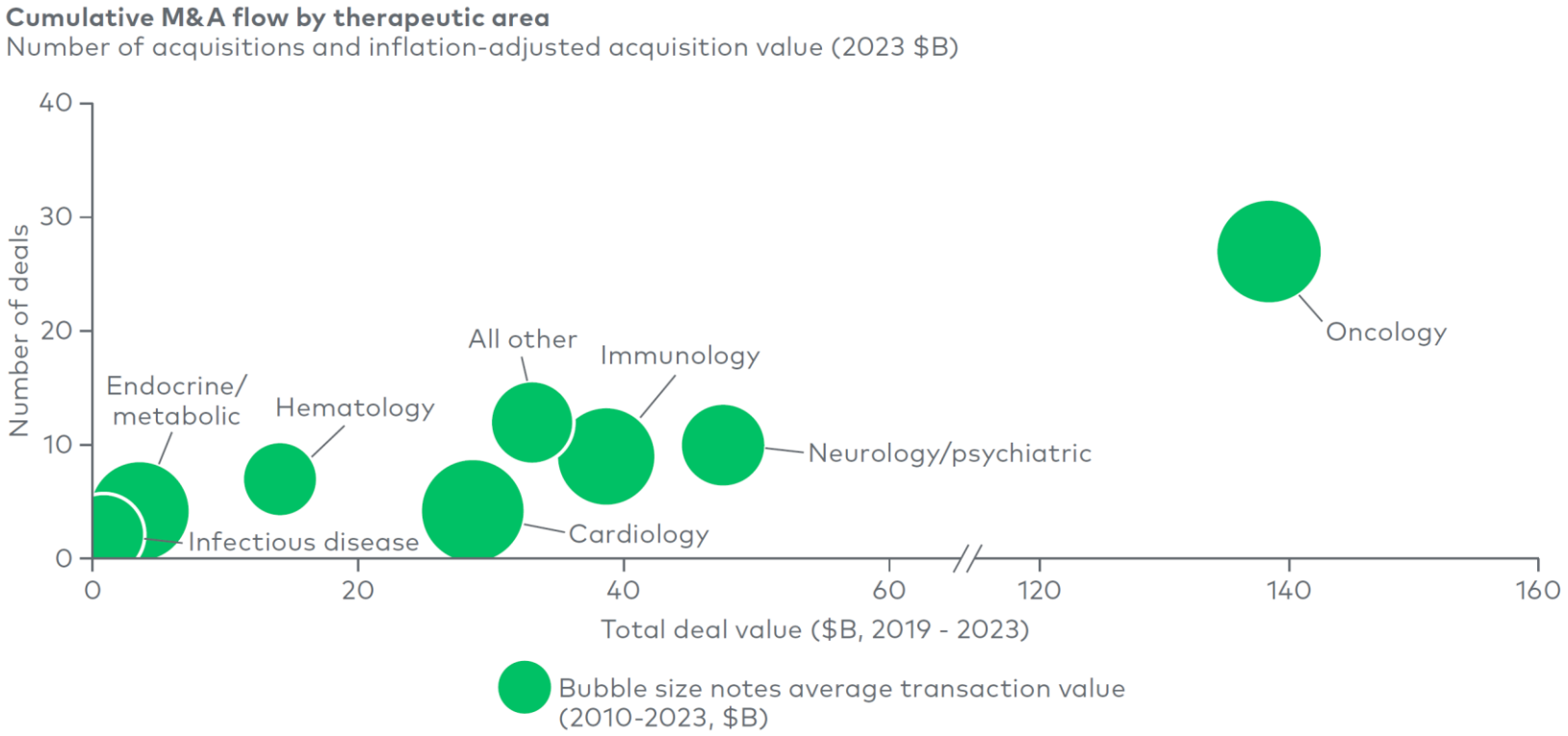


	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Number of transactions	10	7	10	16	14	11	11	12	15	16	17	13	15	28
Average transaction ($B)	3.6	1.8	1.9	1.7	4.6	9.4	2.5	4.7	7.3	11.8	5.8	3.0	4.1	4.7
Average transaction excl. transf. M&A ($B)	3.6	1.8	1.9	1.7	3.0	7.1	2.5	4.7	3.4	3.7	3.7	3.0	4.1	3.3

A detailed analysis of the acquirer ecosystem reveals that the top 15 acquirers have been particularly active, responsible for approximately 80% of the total roughly $1 trillion transaction value since 2010. These top acquirers have completed on average five acquisitions since 2010. Impressively, their M&A activities have significantly ramped up in the past five years, with an average annual M&A investment of $6 billion since 2019. This marks a substantial increase, doubling from the previous annual average of $3 billion.

Source: https://www.lek.com/insights/hea/global/ei/optimizing-pharmaceutical-portfolios-through-ma

LEK Analysis: After Oncology, Neuroscience Has Been the Second Most Active Area for Big Pharma M&A

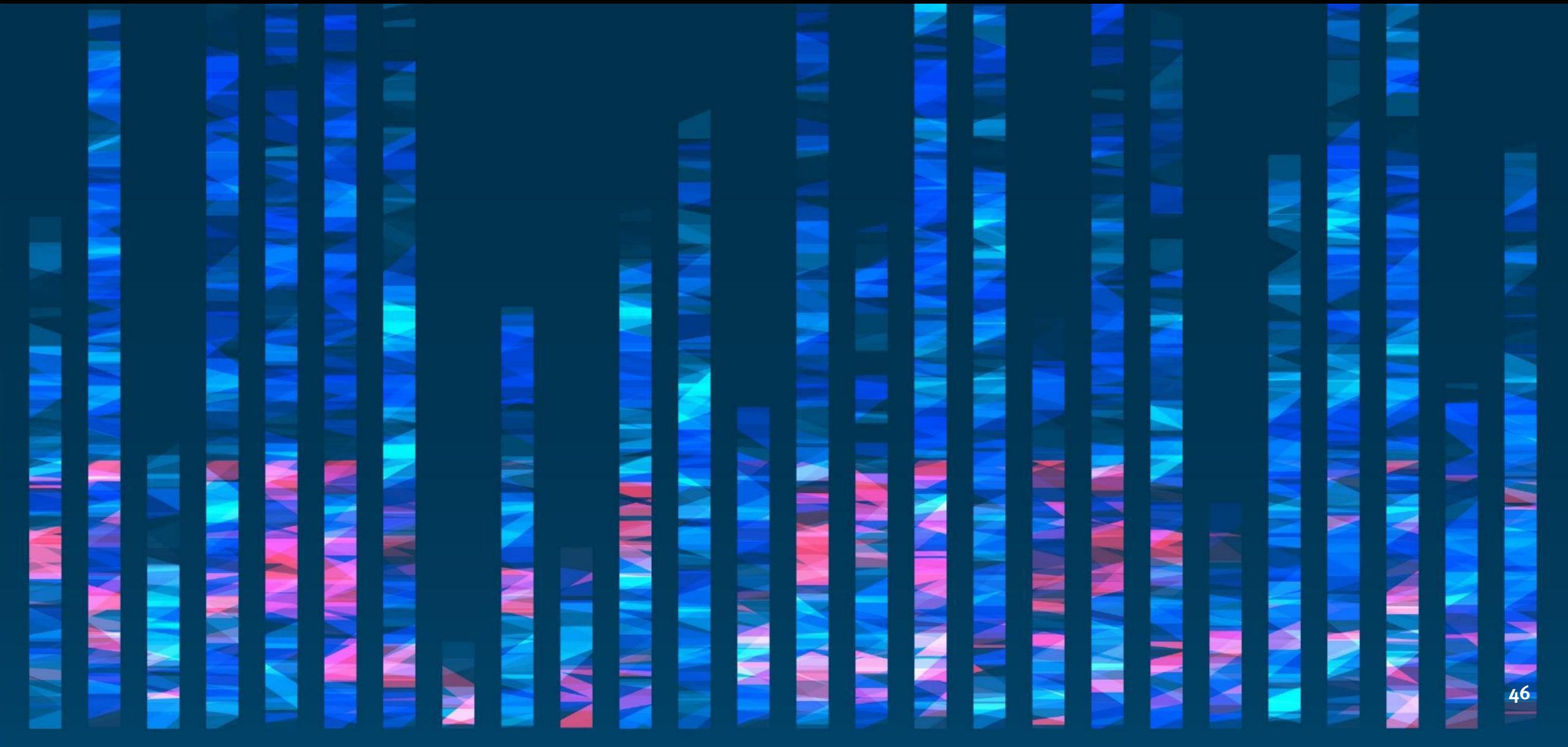


In examining the breakdown of deals by therapeutic area, oncology continues to dominate biopharmaceutical M&A activity (see Figure 4). Since 2010, the total transaction value in oncology has surpassed the combined value of the next three therapeutic areas. More recent trends, since 2019, further underscore this dominance, with oncology constituting approximately 25% of the overall deal value and 30% of the deal volume in the sector.

While the focus on oncology is likely to remain steady, the fields of neuroscience and psychiatry saw a significant surge in late 2023, particularly with recent deals like AbbVie's acquisition of Cerevel and BMS' purchase of Karuna. This makes it the second-most-valuable area in cumulative acquisition value since 2019, with a staggering $30 billion in M&A in 2023 alone.

Source: https://www.lek.com/insights/hea/global/ei/optimizing-pharmaceutical-portfolios-through-ma

Industry News



Obesity Drug Firms Choose Golden Goose Pricing

Robert Cryan, *Reuters*, Jan 18, 2024 (excerpt)

NEW YORK, Jan 18 (Reuters Breakingviews) - Pharmaceutical companies have started 2024 off with their usual bang, raising the list prices for diabetes drugs such as Novo Nordisk's Ozempic and Eli Lilly's, Mounjaro, according to the Wall Street Journal. In the complicated U.S. healthcare system, these prices don't have much to do with reality for most people, as about two-thirds of the population is covered by commercial health insurance, and those institutions negotiate to receive big discounts. But list prices matter when the similar drugs are prescribed for weight loss, where more people pay out-of-pocket. As drug pushers know, reaching the masses is ultimately more lucrative than reaching the classes.

Both Wegovy and Zepbound, the two drugs that are sold for weight loss, are listed at over $1,000 a month. Only about a fifth of employers covered prescription weight loss therapies as of last March, according to the International Foundation of Employee Benefit Plans. As a result, many patients must pay full boat for the drugs if they want to use them to get skinny.

Even with the cost, demand seems nearly insatiable. Lilly's Zepbound grew by about 25,000 new prescriptions weekly in December, and CEO David Ricks said the company may not be able to make enough of the drug this year. For now, the producers are somewhat constrained. And Lilly and rival Novo Nordisk should be able to reap huge margins from patients who are willing to pay full boat.

Yet the two companies are offering a discount – half off to patients with commercial insurance that doesn't help pay, roughly similar to the discount insurers typically negotiate – to pique interest while clinical results seem miraculous.

While that means fewer golden eggs today, the goal is harvesting more over time. Obesity is a risk factor in nearly every major cause of death in developed nations. The companies are gambling that as the beneficial evidence of weight loss accumulates, insurance coverage will become standard. Since weight is gained once patients stop taking obesity drugs, the lower price can get people hooked.

Source: https://www.reuters.com/breakingviews/obesity-drug-firms-choose-golden-goose-pricing-2024-01-18/

Senator Sanders Warns J&J, Merck CEOs Could Be Subpoenaed on Drug Pricing

Tristan Manalac, *Biospace*, Jan 19, 2024 (excerpt)

Sen. Bernie Sanders (I-VT), chairman of the Senate Health, Education, Labor, and Pensions Committee, on Thursday proposed serving subpoenas to the CEOs of Johnson & Johnson and Merck. The committee is set to vote on the subpoenas on Jan. 31, 2024.

The subpoenas would force both executives to provide testimony as to why their companies "charge substantially higher prices for medicine in the U.S. compared to other countries," according to Thursday's announcement. Bristol Myers Squibb CEO Chris Boerner, along with at least one other pharma executive, has previously agreed to testify on drug pricing before the Senate health committee.

If approved, these would be the first subpoenas issued by the Senate Health, Education, Labor, and Pensions (HELP) Committee in more than four decades. The last time the committee issued subpoenas was in 1981.

"It is time to hold these pharmaceutical companies accountable for charging the American people the highest prices in the world for the medicine they need," Sanders said in a statement. "As the HELP Committee considers legislation to lower prescription drug prices, it is critical that these CEOs explain how they determine the price of medicine in the United States."

In November 2023, Sanders—along with all Democratic members of the HELP Committee—invited the CEOs of Merck, J&J and BMS to testify in a hearing about the "outrageously high cost of prescription drugs." The hearing was set for Jan. 25, 2024.

Four pharma CEOs have previously volunteered to testify before the HELP Committee, including the heads of Sanofi, Novo Nordisk, Eli Lilly and Moderna. J&J and Merck have yet to commit.

Sanders called it "absolutely unacceptable" that the CEOs of J&J and Merck have so far "refused an invitation by a majority of the members of the HELP Committee."

It's not too hard to pick up on two basic facts: (1) this is a big election year and (2) the Democrats aren't doing so well in the polls.

They are pulling out the tried and true "pharma beating" tactic in the middle of primary season.

Interestingly, a bunch of pharma CEO's have so far refused to show up.

It will be interesting to see how this all plays out in political "silly season".

Source: https://www.biospace.com/article/senator-sanders-warns-that-j-and-j-merck-ceos-could-be-subpoenaed/

Five Years After Closing the Shire deal, Takeda is Ready to Harvest From its Latest Reinvention

Meagan Parrish, *Pharmavoice*, Jan 19, 2024 (excerpt)

Five years ago this month, Takeda Pharmaceuticals completed a $62 billion acquisition of Shire — one of the largest deals in pharma history. The anniversary has triggered a fresh wave of scrutiny over its value and mixed bag of results.

The deal grew the global footprint of Japan's largest pharma, helping it expand into lucrative European and U.S. markets. It also bolstered Takeda's pipeline and funneled more R&D funds toward vaccines and plasma-derived therapies (PDT). And although the company took on about $60 billion in debt to complete the acquisition, Takeda leveraged divestitures to lower its debt burden and exceeded its predicted cost savings a year ahead of schedule. Yet, for all those benefits, Reuters reported in December that the megadeal hasn't delivered value to Takeda's shareholders and represents a case-in-point for the risky and complex gamble of high-profile megamergers.

And when PharmaVoice met with Chris Arendt, the company's chief scientific officer and head of research, at the J.P. Morgan Healthcare Conference this month, Takeda was emerging from a fresh round of topsy-turvy news.

"Takeda is in a really good place," he said. "We are where we want to be this far out from the Shire deal in terms of capabilities and R&D strategies."

With a recent hot streak in partnerships, increased R&D in new modalities and an ongoing commitment to unmet needs, Takeda rolled into the new year with plenty of positive momentum.

"We're looking at where pioneering science is emerging," he said. "You can look at what other companies are doing and follow the latest press releases into the latest biological space, but we look at the next step changes, and try to advance what's cutting edge."

"Our transformation was about planting the seeds," Arendt said. "A lot of our R&D was seeding and now it's maturing — 2024 is about bearing fruit in terms of clinical readouts."

This year will also mark an overall shift in Takeda's pipeline from being "historically weighted toward earlier stage programs to having more in later stage development," Arendt said.

With the launch of newly approved drugs underway, TAK-279 moving into phase 3 trials, a drug development engine that's churning hard — the company recorded $4.8 billion in R&D investments in 2022 — and an eye out for new partnership opportunities, Takeda isn't done with its latest reinvention.

"We'll surprise you with more deals you may not have seen coming," Arendt said.

Source: https://www.pharmavoice.com/news/takeda-shire-chris-arendt-nimbus/704972/

Bayer Rolls Out New Operating Model, Eliminates Managerial Staff

Tristan Manalac, *Biospace*, Jan 18, 2024 (excerpt)

Bayer on Wednesday revealed a new operating model meant to cut back on bureaucracy and hierarchies, as well as streamline the company's structures, in an effort to boost its operational efficiency.

The model, dubbed Dynamic Shared Ownership (DSO), is designed to "make the company much more agile," according to Bayer's announcement. The restructuring initiative will include job cuts over the next couple of months to be completed by the end of 2025, at the latest.

"In line with the principles of DSO, the implementation will be largely decentralized, meaning that its scope cannot be quantified for the time being," according to the company. Bayer employs some 22,200 staff in Germany and, as of the end of 2023, had a global headcount of more than 101,000.

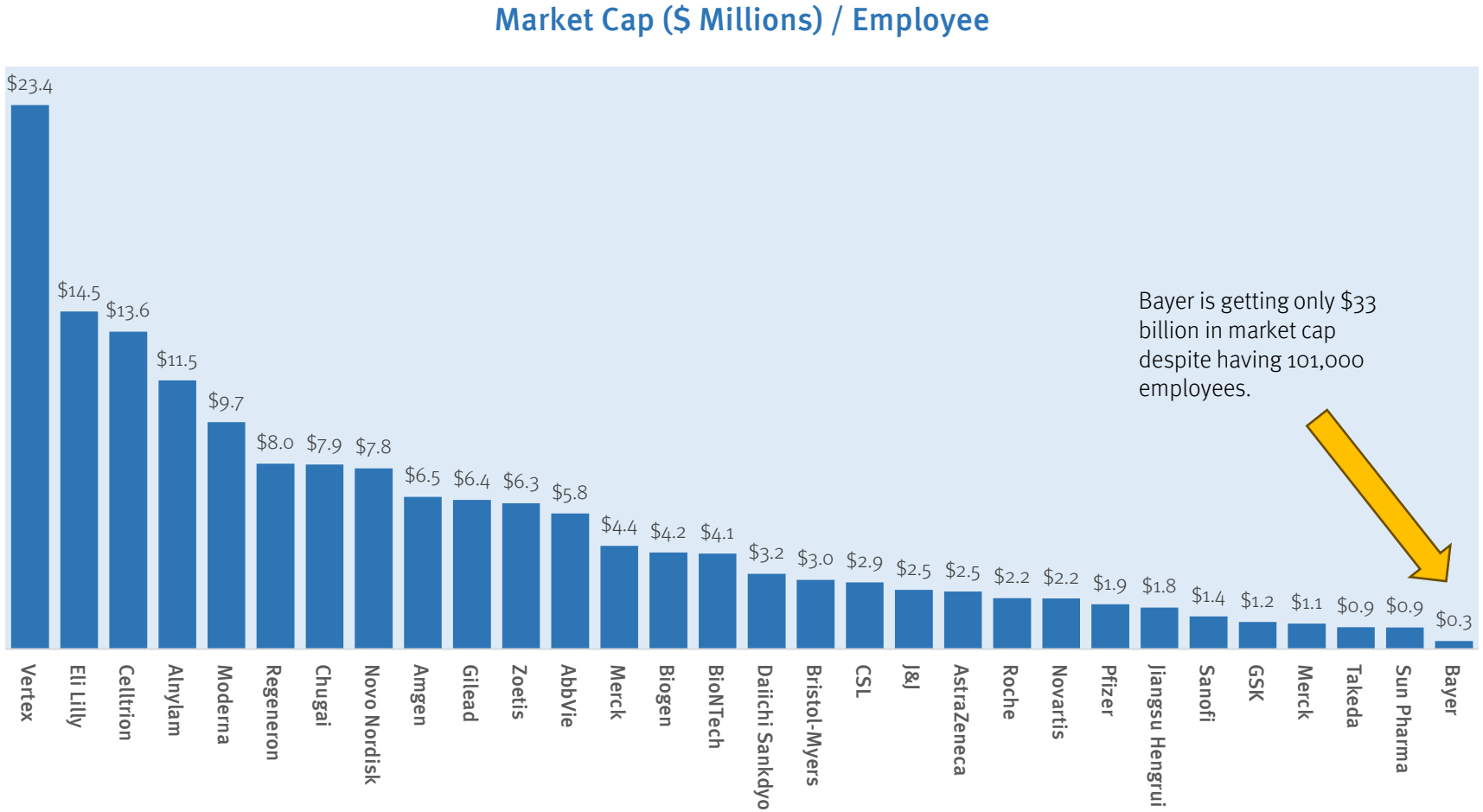
Though Bayer has not specified how many posts the layoffs will affect, Barbara Gansewendt, chairwoman of the Group Executives' Committee at the company, said in a statement that it "will come at the expense of many managerial employees." The committee represents the interests of manager-level staff at Bayer.

Gansewendt called these layoffs an "extremely bitter development" for Bayer, adding that there is "no viable alternative" for the company. Affected staff will receive an "attractive" severance pay and will be given adequate support to help them find "new employment as quickly as possible," she said.

Anderson inherits from the previous CEO—Werner Baumann, who had served Bayer for 35 years—a company reeling from the disastrous acquisition of the agricultural giant Monsanto. The buyout, signed in September 2016 for $66 billion, was at the time touted by Baumann as a "major step forward" for the company's crop science business.

Source: https://www.biospace.com/article/bayer-rolls-out-new-operating-model-eliminates-managerial-staff-in-restructuring/

The Median Pharma Sustains $3.7 Million in Market Cap for Every Employee. In Contrast Bayer Sustains $300k in Market Cap Per Employee.



Bayer is in dead last in terms of its ratio of market value per employee (among the top 30 pharmas by market cap).

The only company that is anywhere close is Sun Pharma which has most of its employees in India. And these are engaged in generics manufacture.

Even then, Sun's MC/Emp ratio is three times higher than that of Bayer.

LEK White Paper on Pharma Product Launches

LEK, January 16, 2024

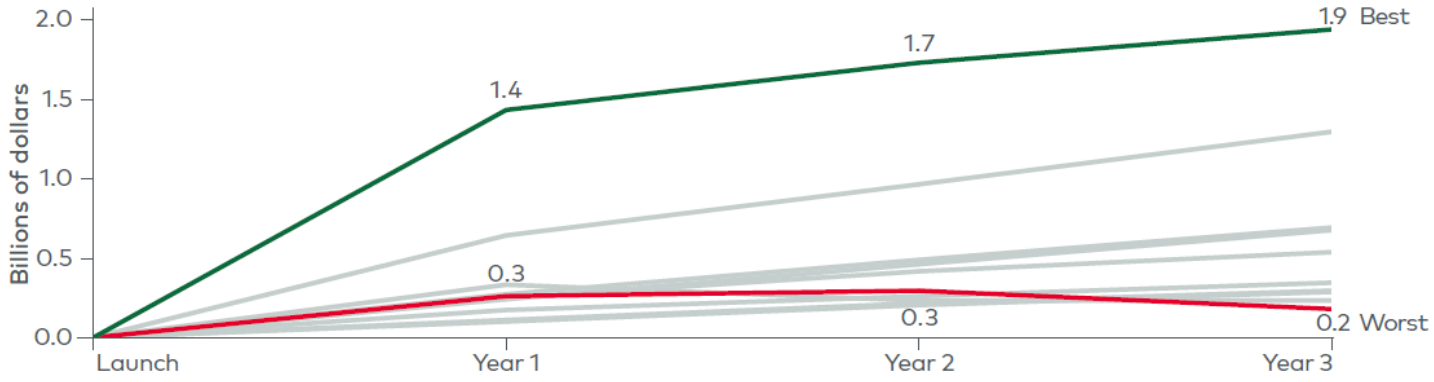
Collectively, the top 10 pharmaceutical companies achieved approval for 78 innovative products between 2015 and 2019, with revenue data accessible for 62 of these products. These 62 products averaged about $600 million in U.S. revenue in the third year after approval.

Upon examining the average revenues in the third year post-launch, substantial variability was observed among the 62 products. The revenue disparity was striking, with the highest performing launch generating $6.3 billion, in stark contrast to the lowest-performing one, which earned less than $10 million. The median revenue per product stood at $260 million, highlighting the wide range of outcomes in these launches.

More importantly, there is also considerable variation in launch performance at the company level among large pharmas (see Figure 1). This variation is evident in their average revenue, ranging from $1.9 billion to $0.2 billion, and in their median revenue from $1 billion to $110 million, three years post-launch. This represents a notable ninefold difference between the highest- and lowest-performing companies.

Figure 1

Mean US company net revenue per product launched across top 10 pharma companies, by year post-launch (products launched 2015-19)



Source: Evaluate Pharma; Company 10-Ks (2015-19); L.E.K. research and analysis

Source: https://www.lek.com/insights/hea/us/ei/variability-large-pharma-launch-performance

LEK White Paper (continued)

The benefit of repeated launches in core therapeutic areas

In our analysis of top pharmaceutical companies, we observed a higher proportion of launches in core therapeutic areas, defined as areas where the company already had established revenue streams before the launch of a new product. Notably, 80% of the launches were in these core areas. These launches, encompassing 50 products, showed significantly higher average revenues per product compared to launches in noncore therapeutic areas — $670 million versus $280 million, representing a 2.4-fold difference. At the company level, this pattern persisted. The three highest-performing companies launched over 90% of their products into existing therapeutic areas. In contrast, the bottom three performers introduced 30% of their new products into areas outside their established core, highlighting a clear strategic divergence.

The benefits of introducing new products into existing therapeutic areas, where companies have established capabilities and stakeholder relationships, are clear. In these areas, companies can utilize their top talent, draw upon existing commercial infrastructure, leverage key relationships with stakeholders and apply insights from previous launches. Particularly important is the presence of an established commercial infrastructure that is scaled and customized to provider and patient needs, enabling accelerated launch uptake. Both the infrastructure and the experience also enable companies to foresee and navigate commercialization challenges, realign launch resources with anticipated commercial potential and capitalize on synergies.

The need for early life cycle expansion

The strategic role of indication expansions in product strategy is essential. Companies that effectively invested in indication expansions, such as adding new lines of therapy, targeting different patient segments or addressing new diseases, consistently demonstrated higher average revenues. This trend is highlighted in the performance gap between the top and bottom companies: the top three performers averaged 1.4 extensions per product within three years of launch, while the bottom three managed only 0.4 extensions.

This significant difference emphasizes the critical impact of an early and well-planned product life cycle strategy, often entailing some level of preemptive investment to achieve outstanding revenue outcomes. Given equal circumstances, companies should give precedence to assets with the versatility to address multiple diseases. Investing early and accepting the associated risks in these programs can be more advantageous if the potential for incremental revenue justifies it, rather than adopting a cautious, phased approach.

These observations may need to be reevaluated considering the changes brought about by the Inflation Reduction Act passed in August 2022. The act's introduction of Medicare price negotiation is perceived by many in the industry as akin to a loss of exclusivity event, mainly because there's no minimum limit set for the prices Medicare can negotiate.

Source: https://www.lek.com/insights/hea/us/ei/variability-large-pharma-launch-performance

General Catalyst Buys a Healthcare System Last Week

Scott Kirsner, *Boston Globe*, Jan 18, 2024 (excerpt)

The health care system seems persistently resistant to upgrades. So is the solution buying a hospital, and giving it an infusion of technology and new ideas?

That's the approach proposed by General Catalyst, a Cambridge venture capital firm, which announced Wednesday that it would buy Summa Health, a nonprofit health care system in Akron, Ohio.

With 7,000 employees, Summa is the largest employer in its county, operating hospitals, community health centers, medical practices, and a small health insurance arm, SummaCare. But Summa has been losing money in recent years. In the announcement of the deal, General Catalyst managing director Hemant Taneja and longtime hospital executive Marc Harrison said "the focus isn't on taking costs out. It's on putting innovation in."

How could this deal become a model of health care reinvention? Both Taneja and Harrison, former chief executive of Intermountain Health in Utah who joined General Catalyst in October, have penned books laying out lofty visions. And how might it go off the rails? Remember Haven, the Boston-based venture that was going to rethink health insurance from the ground up — but closed up shop after three years and had negligible impact? In that first category, it's tempting to think of using Summa as a "closed loop system" where General Catalyst, and the tech companies in which it invests, could get administrators, physicians, and nurses all using new tools that could make delivering care more efficient, from finding a doctor to scheduling an appointment to getting treatment. Inside this closed loop — where Summa provides insurance coverage to a portion of the patients it treats — you could also gather data about what worked best, and ideally stop doing what wasn't working.

Harrison and Taneja like to use the phrase "health assurance" when they talk about their aims with the deal. What does that mean, exactly? It's "the transformation of health care from a 'sick care' system to a resilient, proactive system designed to help people stay well," Harrison said in an email. The goal, he said, isn't to turn Summa into a playground for entrepreneurs with half-baked prototypes that they believe could help doctors and nurses do their jobs better.

"A key point is that we do not see this as a place where very young early startups will be brought into play to 'test,'" Harrison writes. "We'll be looking for much more mature companies that actually have a proof of concept. In particular, we're focused on technology that reduces friction for patients and providers."

Source: https://www.bostonglobe.com/2024/01/18/business/general-catalyst-summa-health/

General Catalyst "Health Assurance" Idea

Hemant Taneja, Partner, General Catalyst, *Medium*, July 15, 2020

Today, I am excited to announce the release of my new book, UnHealthcare: A Manifesto for Health Assurance. It is a reflection of several years deeply engaging with the healthcare community and understanding how technology can have a transformative impact. It is the beginning, I hope, of a new era in health innovation — one that sees technologists partner with healthcare stakeholders to put the patient-provider relationship back at the center of health experiences.

Though we are early on in the rearchitecting of healthcare, we've seen the magic of pairing a consumer mindset with responsible data use to create highly individualized healthcare experiences. Seeing the impact our portfolio companies — Color, Livongo, Mindstrong, Oscar, and Ro amongst others — have had as they build from first principles and the way in which doing so allows them to create fast-growing businesses is great proof of what's to come. We believe that the next decade will see some of the most meaningful venture capital returns come from the healthcare sector.

The Health Assurance System

We believe that creating a system of "health assurance" is integral to this transformation — this is the central thesis of UnHealthcare. Health assurance is a new category of innovation that is committed to bringing modern consumer experiences and accelerating rational economic behavior through innovative business models. Beyond the economic opportunity we see for health assurance, we have a moral imperative to create this system as costs skyrocket while outcomes plummet. In a health assurance world, care moves out of the reactive, scales, one-sized paradigm it currently operates in. Instead, health assurance companies, built on open tech standards with empathetic user design and the responsible use of AI, allow for fewer, more tailored interactions with care providers. Digital and physical care will start to blend as existing and new providers alike have more ways of engaging with individuals.

Health assurance companies will begin the important job of closing the gap in access to and quality of care. Technologies like telehealth consultations, connected devices, and AI-driven chat interactions, will help extend the reach of medical professionals, especially in underserved areas and in high-demand specializations. Ultimately, the health assurance model should deliver a healthcare experience that is more affordable and price transparent and drives better outcomes.

We also know that reimagining healthcare is not something technologists can or should do on their own. I'm incredibly grateful to be working with Dr. Steve Klasko, my co-author, and health systems like Thomas Jefferson that are embracing innovation and thinking about it from an integrative perspective. Steve and I have spent the last year working together not only on our book but also on creating a framework for how healthcare systems and startups can partner to move healthcare into the 21st century.

Source: https://medium.com/health-assurance/announcing-unhealthcare-8d6fb147d774

We read Taneja and Klasko's book *UnHealthcare* two years ago. It provides a highly practical, reasonable and thoughtful approach to combining a consumerist, humanist, creative and efficient approach to better healthcare. We are very excited to see what this team and their colleagues will be able to do with Summa Health. We like the fact that it's not a giant system so there should be room to maneuver and improve outcomes and costs for patients. A key positive is that Trasko already restructured Thomas Jefferson Health before with excellent results.

Is General Catalyst's ‘Bold Bet' the Future of Healthcare? Hospital Execs are Watching

Giles Bruce, *Becker’s Hospital Review*, July 15, 2029

Hospital C-suite leaders told Becker's that time will tell whether General Catalyst's acquisition of an Ohio health system is the future of healthcare — but they are paying close attention.

The venture capital firm said Jan. 17 it agreed to purchase Summa Health, a three-hospital system based in Akron, and turn it into a for-profit entity. The arrangement is part of General Catalyst's Health Assurance Transformation Corp., or HATCo, run by Marc Harrison, MD, the former president and CEO of Salt Lake City-based Intermountain Health.

"Hats off to HATCo!" said Aaron Miri, chief digital and information officer of Jacksonville, Fla.-based Baptist Health. "I commend General Catalyst and Summa Health for taking a giant leap of faith into uncharted waters. I do think you will see more of these kinds of relationships once HATCo successfully navigates the regulatory, medical staff, patient experience, payer relations and other dynamics that every health system has to navigate. There's a tremendous amount of unknown that I do applaud the courage to go forward and learn from."

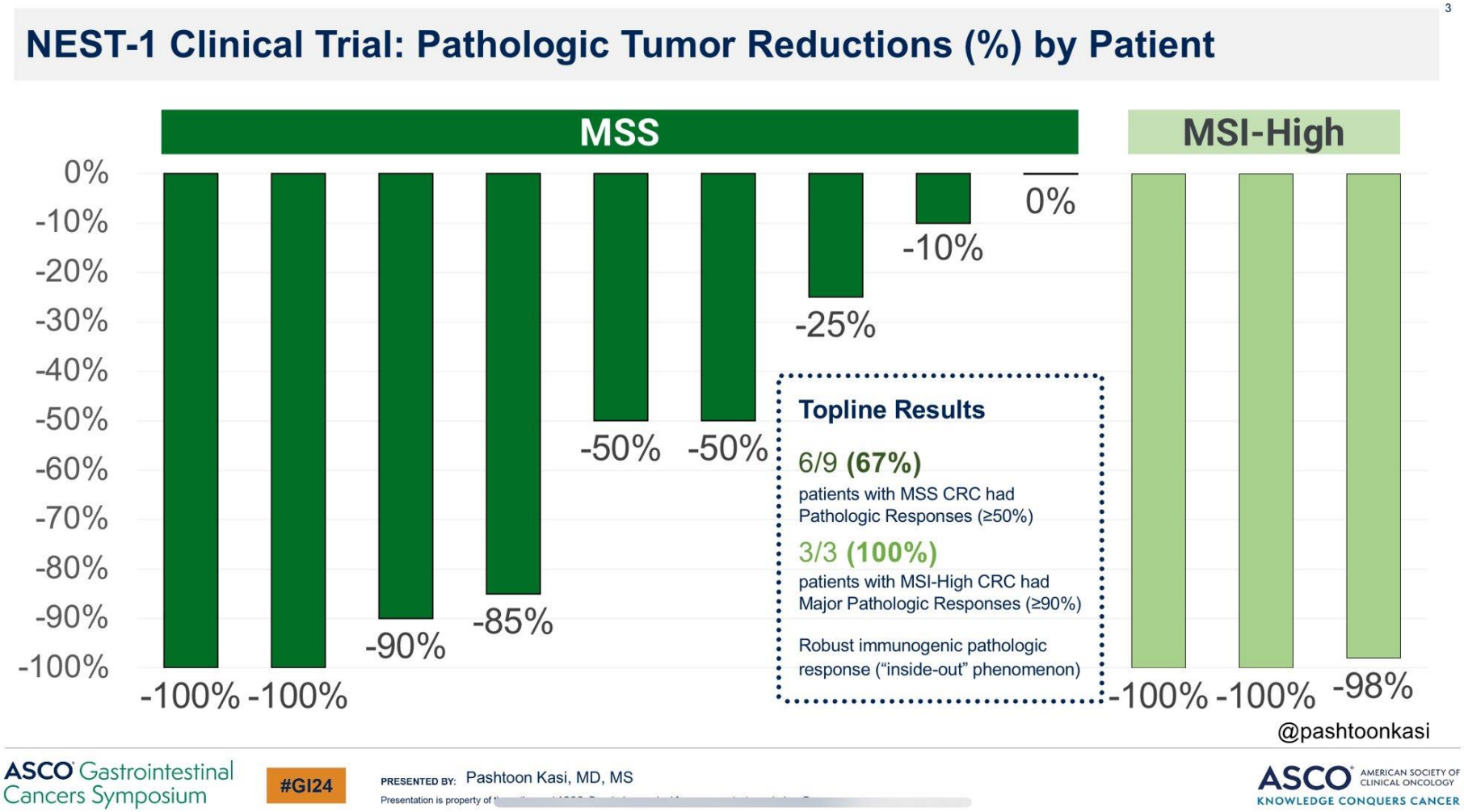
Richard Zane, MD, chief innovation officer of Aurora, Colo.-based UCHealth, called the deal a "bold move" that essentially turns an entire health system into a "digital laboratory for not only tech development but also to better understand the levers on value and risk.“ "By making it for-profit and perhaps tolerating financial losses on the health system side to realize larger potential gains on the venture side is most assuredly creative. Perhaps not too dissimilar from other health systems who leverage margin across providers, hospitals and a health plan by tolerating losses in one for gains in another," he said. "Hoping that patient care remains the true north, this could be a remarkable story."

"If there is one thing in healthcare you can predict, it is that organizational integration will continue in novel and innovative ways to drive disruption," said Jennifer Stephens, DO, chief value and ambulatory care officer for Allentown, Pa.-based Lehigh Valley Health Network. "This acquisition, in particular, will be interesting to follow given the nuances of a for-profit transition, tech-startup portfolio, and value-based care vision. My take is that those niche elements are not likely to occur as part of a larger trend, causing this deal to fall into a category of its own."

General Catalyst's stated goals of shifting American healthcare from a system of "sick care" and making it more accessible are enviable ones, said Michael Hasselberg, PhD, RN, chief digital health officer of University of Rochester (N.Y.) Medical Center. He called the firm's tech-focused, "health assurance" strategy "fascinating."

Source: https://www.beckershospitalreview.com/innovation/is-general-catalysts-bold-bet-the-future-of-healthcare-hospital-execs-are-watching.html

Impressive Data at ASCO GI from Agenus Over Weekend



Treatment with neoadjuvant botensilimab (AGEN1181) plus balstilimab (AGEN2034) led to robust responses and prolonged circulating tumor DNA (ctDNA)/minimal residual disease (MRD) negativity in patients with resectable mismatch repair–proficient (pMMR) and mismatch repair–deficient (dMMR) colorectal cancer (CRC), meeting the primary end point of the phase 2 NEST-1 trial (NCT05571293), findings from which were presented at the 2024 Gastrointestinal Cancers Symposium.1

A total of 67% of patients with microsatellite stable (MSS) CRC (n = 9) experienced pathologic responses, defined as tumor reduction of at least 50%, and 100% of patients with microsatellite instability–high (MSI-H) CRC (n = 3) experienced major pathologic responses, defined as tumor reduction of at least 90%. In the MSS population, tumor reductions of 100% (complete response [CR]; n = 2), 90% (n = 1), 85% (n = 1), 50% (n = 2), 25% (n = 1), and 10% (n = 1) were observed. In the MSI-H population, tumor reductions of 100% (CR; n = 2) and 98% (n = 1) were observed.

Source: https://www.onclive.com/view/neoadjuvant-botensilimab-balstilimab-combo-induces-early-efficacy-in-pmmr-dmmr-crc

Neoadjuvant botensilimab plus balstilimab (BOT/BAL) in resectable mismatch repair proficient and deficient colorectal cancer: NEST-1 clinical trial.

Pashtoon Murtaza Kasi, Mehraneh D. Jafari, Heather Yeo, Lea Lowenfeld, Uqba Khan, Alana Nguyen, Despina Siolas, Brandon Swed, Sahrish Khan, Madeleine Wood, Allyson J. Ocean, Elizabeta C. Popa, Kelly A. Garrett, Encouse Golden, Preethi Guniganti, Xi K. Zhou, Alessio Pigazzi, Manish A. Shah, Erika Hissong#, Manuel Hidalgo#

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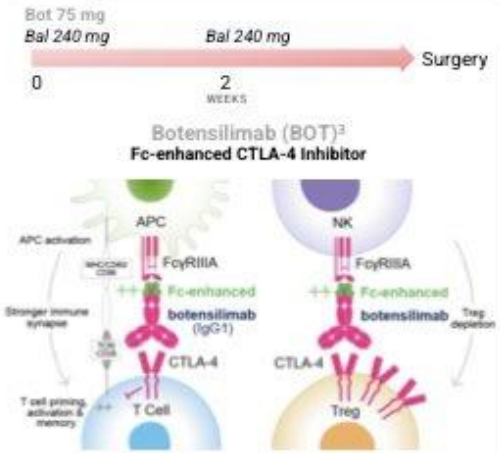
Abstract#117

Poster Board#: H2

BACKGROUND/METHODS

- Effective therapies for colorectal cancer (CRC), particularly in those ~85-95% with **proficient mismatch repair/microsatellite stable (pMMR/MSS)** cancer, are a critical unmet need.[1]
- **Botensilimab (BOT),** a multifunctional next-generation **anti-CTLA-4 antibody**, with balstilimab (BAL), an anti-PD-1 antibody, has a response rate of > 20 % in patients with heavily pretreated pMMR/MSS metastatic CRC.[2]
- NEST-1 (NCT05571293) is the first study to evaluate **neoadjuvant** BOT and BAL in CRC patients eligible for surgery.
- **Investigator-initiated trial supported by Agenus Inc.**

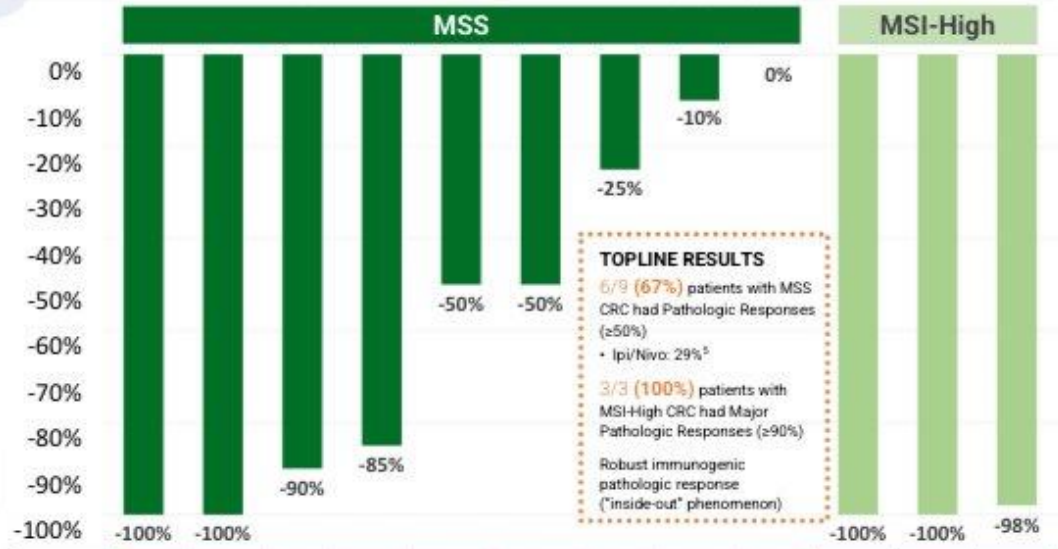
Study schema[1]



- ↑T cell priming, expansion, memory
- ↑Frequency of activated APCs
- ↑Treg depletion
- ↓Complement mediated toxicity

References: 1. Kasi PM et al. Oncogene. 2023 Oct; 42 (44): 3252-3259. | 2. El-Khoueiry AB. Journal of Clinical Oncology 2023 41:4_suppl, LBA8. | Adapted from Wilky B, et al. Oral Presentation at CTOS 2023, Dublin, Ireland. Paper 31. | 4. Acknowledgements: DrawImpacts for the illustration. | 5. Chalabi et al. Nat Med. 2020 Apr;26(4):566-576; Verschoor et al. J Clin Oncol 40, 2022 (suppl 16; abstr 3012).

Pathologic tumor reductions (%) by patient



TOPLINE RESULTS

6/9 (67%) patients with MSS CRC had Pathologic Responses (≥50%)
- Ipi/Nivo: 29%[5]

3/3 (100%) patients with MSI-High CRC had Major Pathologic Responses (≥90%)

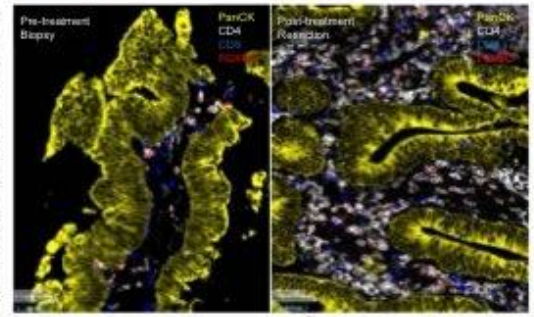
Robust immunogenic pathologic response ("inside-out" phenomenon)

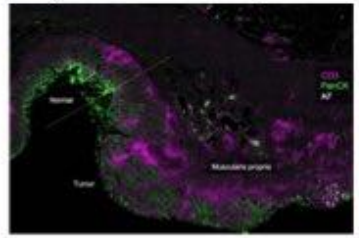
Patient ID (Sex)	11(M)	7*(M)	1(M)	2*(F)	8(F)	10(F)	4(M)	3*(F)	12(F)	5(M)	9*(M)	6(F)
Race/Origin	Caucasian	Southeast Asia	Southeast Asia	African American	Arab/Middle Eastern	Hispanic/ Mexican	African American	Caucasian	African American	Arab/Middle Eastern	Caucasian	Caucasian
Path Response	100%	100%	90%	85%	50%	50%	25%	10%	0%	100%	100%	98%
Stage Pre-treatment	T3N1a IIIB	T2N0 I	T2N1a IIIA	T3bN2a IIIB	T3bN2b IIIC	T3dN2b IIIC	T3N2a IIIB	T3aN1b IIIB	TXN0	T3N2b IIIC	T3dN2b IIIC	T3N2a IIIB
Stage Post-treatment	T0N0 No tumor	T0NX No tumor	T1N0 I	T1N0 I	T3N0 IIA	T3N0 IIA	T3N1b IIIB	T4aN2b IIIC	T2N1a IIIA	T0N0 No tumor	T0N0 No tumor	T2N0 I
Days until surgery(from C1D1)	38	64	30	24	36	27	21	29	29	34	57	42
ctDNA (baseline)	+	Negative	N/A	N/A	+	+	N/A	N/A	+	+	+	+
ctDNA (MRD)	Negative X 2	Negative X 3	Negative X 1	Negative X 2	Negative X 2	Negative X 1	Negative X 4	N/A	Negative X 3	Negative X 4	Negative X 2	Negative X 4
Mutations	*KRAS*^{A146}/ *HER2+*	*TP53/APC*	*TP53/ CTNNB1*	*KRAS*^{G12V}/ *APC*	*TP53/APC*	*TP53/ATM/ CTNNB1*	*APC*	*KRAS*^{A146}/ *TP53/ BRAF*^{K483T}	*KRAS*^{G12D}/ *APC/TP53*	*MSH2/ BRCA2/ KRAS*^{G12S}	*MSH2/ TP53/ KRAS*^{G12D}	*N/A*
TMB (Mut/Mb)	9.4	8.6	6.4	4.7	4.7	7.1	4.7	5.5	3.1	105	N/A	N/A
Adverse Events	Grade-3 Diarrhea#	Grade 1: Chills/ Fever	No AEs	Grade 1: Chills/Headache Grade 2: Fever	Grade 1: Chills, Headache, Dizziness Grade 2: Fatigue	No AEs	No AEs	Grade 1: Flu-like symptoms, Fever	No AEs	No AEs	No AEs	Grade 1: Fatigue, Rash, Headache

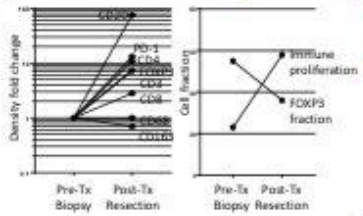
*rectal cancer. # only 1 patient (ID-11) had grade-3 diarrhea that resolved the same day of infliximab 10 mg/kg administration 1-time dose. Surgery was performed six days later without any complications. Five patients (4 females) had fever/fatigue/flu-like symptoms within 7-10 days of BOT/BAL ("Early Immune Activation Syndrome"). Resolved with NSAIDs/symptom management.

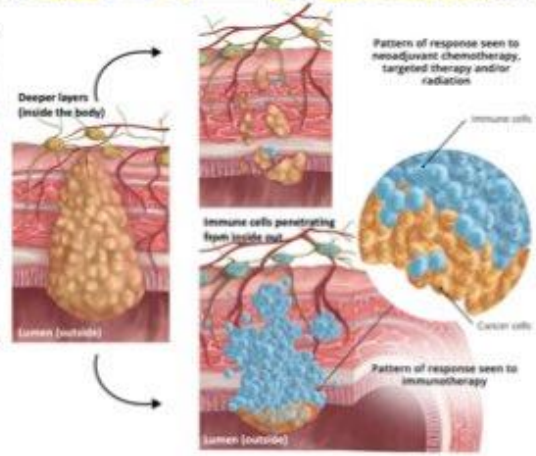
RESULTS

Tissue immune-microenvironment correlates assessed pre- and post-treatment with immunotherapy by RareCyte Inc. (Seattle, WA) using their 13-marker immune-oncology panel on colon and rectal cancer samples on a single paraffin-embedded slide simultaneously at 20X using the Orion instrument. Analyses show a significant increase and a diverse array of immune cells in more than one instance, shedding novel insights into the mechanism and pattern of immune responses.





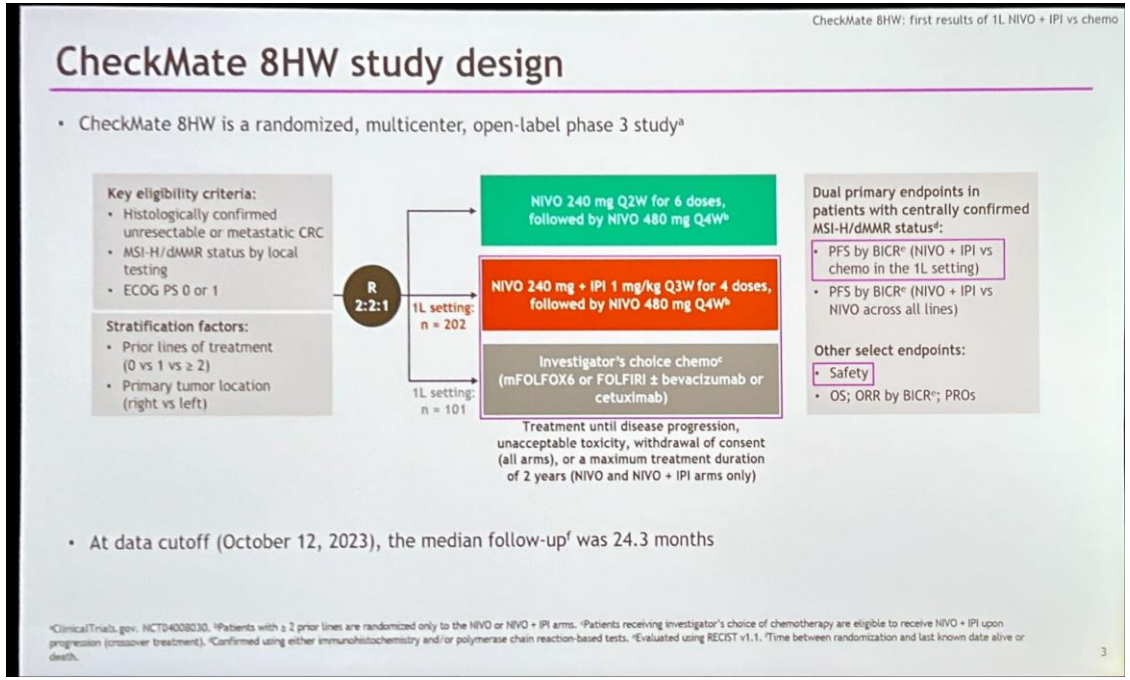


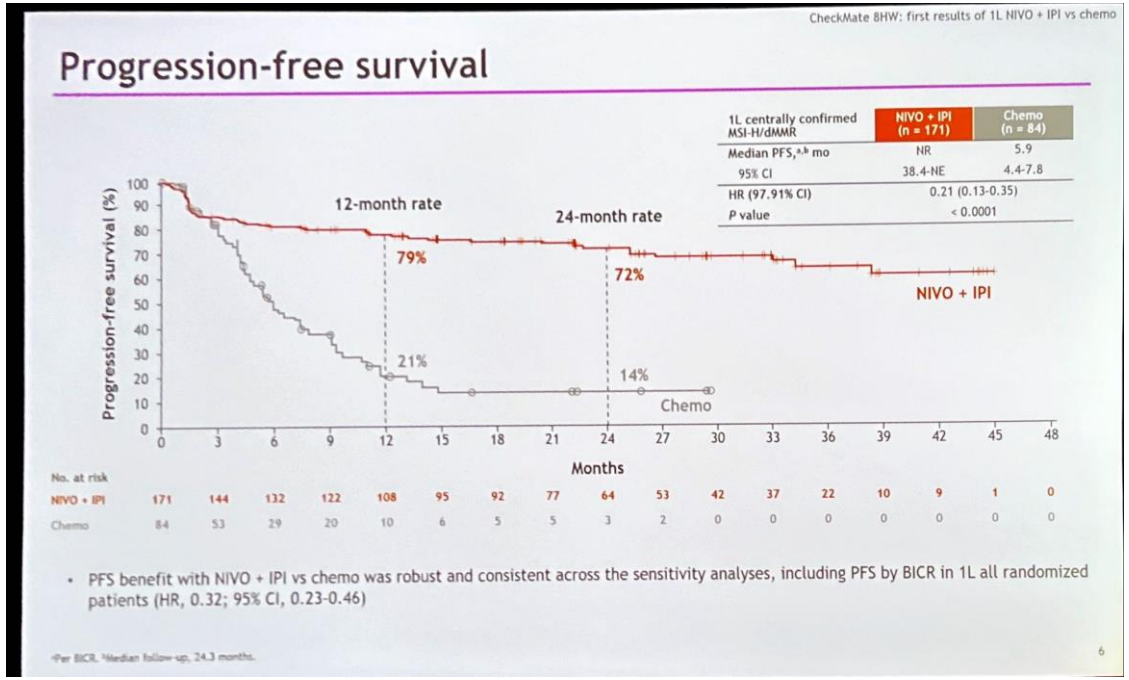


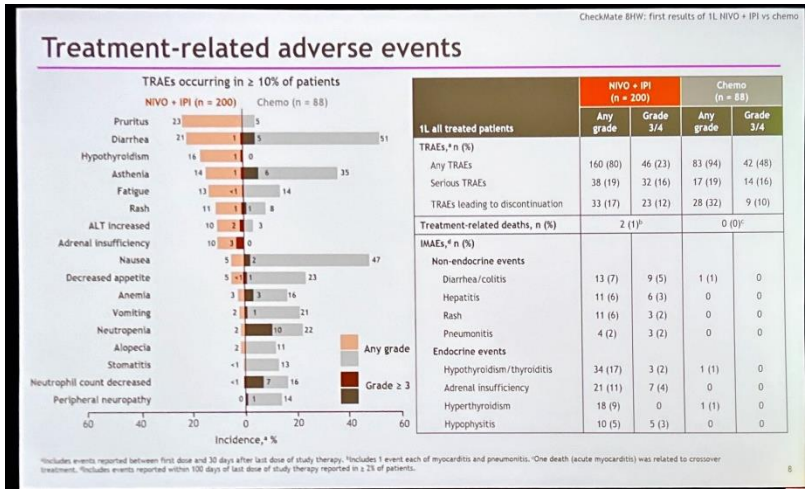
CONCLUSIONS

- **The study met its primary endpoints**.
- Neoadjuvant BOT/BAL is a **safe** and **active** regimen both in pMMR/MSS and dMMR/MSI-H CRC.
  - 6/9 (67%) pMMR/MSS patients with ≥50% reduction, 2/9 with CR
  - 3/3 (100%) dMMR/MSI-H with deep response (≥98% reduction), 2/3 with CR
- **No surgery was delayed** due to any treatment-related adverse events (TRAEs).
- All patients positive for ctDNA at screening **cleared ctDNA** (7/7 – 100%). 11/11 (100%) tested have **remained ctDNA/MRD negative** on more than 30 times cumulatively.
- Post-treatment tumor IHC demonstrates **robust T cell infiltration**, T reg depletion, and dendritic cells/myeloid repolarization.
- **Clinical downstaging** and deep pathological responses provide a framework for reduced reliance on surgery and/or adjuvant chemotherapy in future studies.
- **NEST-1 trial (NCT05571293) has expanded enrollment** to evaluate an 8-week course over the current minimum 3-week course for MSS, and the necessity for surgery for MSI-High.

Very Strong Nivo/Ipi at ASCO GI in Metastatic CRC

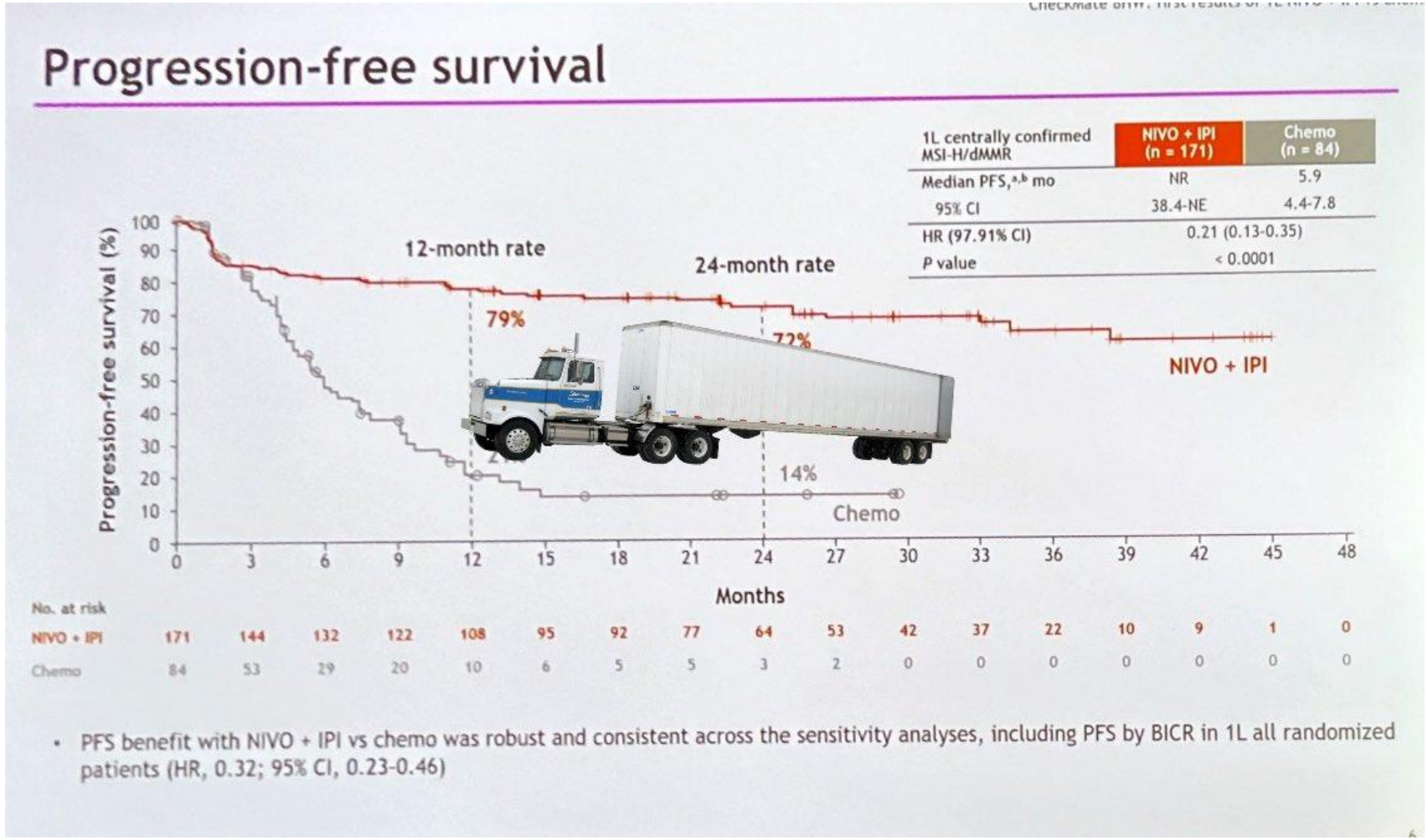






Source: https://twitter.com/MyriamChalabi/status/1748764208328814920

One Observer of BMS Data Suggests New Statistical Test: The “Truck Test”



“These data are so good you could drive a truck between the Kaplan-Meier curves.”

Source: https://twitter.com/PTarantinoMD

Epigenetic Editing – the Power of CRISPR Without Cutting DNA

Jim Cornall, *Labiotech*, January 19, 2024 (excerpt)

Epic Bio is an epigenetic editing company, leveraging the power of CRISPR without cutting DNA.

The company's proprietary Gene Expression Modulation System (GEMS) includes the smallest Cas protein known to work in human cells. This enables in vivo or ex vivo delivery via a single viral vector.

Epic's lead program, EPI-321, is in IND-enabling studies for the treatment of facioscapulohumeral muscular dystrophy (FSHD). Aadditional programs seek to address alpha-1 antitrypsin deficiency (A1AD), heterozygous familial hypercholesterolemia (HeFH), and other indications.

This week, we discuss epigenetic editing, why it's reversible, and how it can treat FSHD and other conditions. Our guest is Epic Bio founder, Dr Stanley Qi, one of the original inventors of CRISPR.

Source: https://www.labiotech.eu/podcast/epigenetic-editing-crispr-without-cutting-dna/

What is epigenetic editing?

"We've been working on this very different spectrum of the CRISPR, which is we do not focus on gene editing. CRISPR allows us to cut the DNA and modify the sequence on that particular site of the DNA. However, since day one, our inspiration is less about this cutting ability."

Qi said that CRISPR acts like precise scissors, but Epic Bio is more inspired by the precision than the scissors. He added that this has led to two inventions. Beyond the gene editing applications enabled by the nuclease CRISPR–Cas9 and CRISPR–Cas12a, the invention of the nuclease-dead Cas molecules (dCas9 and dCas12a) offers a platform for the precise control of genome function without gene editing.

As an RNA-guided DNA binding platform, dCas9 was first repurposed to regulate transcription. Cas9 is a large, multi-domain protein. However, early work showed silencing the two endonuclease domains (the HNH domain that cleaves the target DNA strand, and the RuvC domain that cleaves the non-target DNA strand) in Cas9 via point mutations resulted in a nuclease-dead dCas9 that could bind to DNA.

Typhoid Mary Revisited: Study Reveals How Some Bacterial Infections Become Chronic

Leah Eisenstadt, *Broad Institute*, January 19, 2024 (excerpt)

In the early 1900s, a cook named Mary Mallon, better known as "Typhoid Mary", spread Salmonella Typhi, the causative agent of typhoid fever, to dozens of her patrons even though she showed no symptoms. Many people today harbor pathogenic Salmonella bacteria for years without feeling sick, making them potential sources of new infections.

A new study by scientists at the Broad Institute of MIT and Harvard, along with colleagues at Tel Aviv University and the Sheba Medical Center in Israel, sheds light on the biological mechanisms that enable another kind of Salmonella to evade the immune system and cause long-term infections. The team focused on the "nontyphoidal" forms of Salmonella, which cause food-borne illness and, like the typhoidal form, can linger in the body long after the initial infection. By examining the genomes of bacteria collected from hundreds of people with persistent Salmonella infections, they discovered genetic mutations that both reduce the bacteria's "virulence," or ability to infect, and dampen the host's immune responses, creating a kind of molecular camouflage that shields the bacteria from the immune system's gaze. This insight could one day lead to new diagnostic approaches or treatments that prevent these infections from becoming chronic. The work appears in Cell Host & Microbe.

To begin answering that question, the Earl group and the Broad's Microbial Omics Core team led by co-senior author and institute scientist Jonathan Livny connected with the lab of Ohad Gal-Mor, an assistant professor at Tel Aviv University who is co-senior author on the new study.

In the new study, the researchers examined samples from 256 patients in the collection whose infections lasted at least 30 days. They confirmed that most of the cases were due to chronic infection by the same strain, rather than reinfection by different strains of the same bacteria. After analyzing the genomes of Salmonella in patient samples at various time points, the team highlighted mutations in two genes, barA and sirA, that arose in the bacteria repeatedly during chronic infection.

Source: https://www.broadinstitute.org/news/study-reveals-how-some-bacterial-infections-become-chronic

Star Wars: Inside a Bacterial Defense System — and Its Defeat

Beth Dougherty, Harvard Medical School, January 11, 2024 (excerpt)

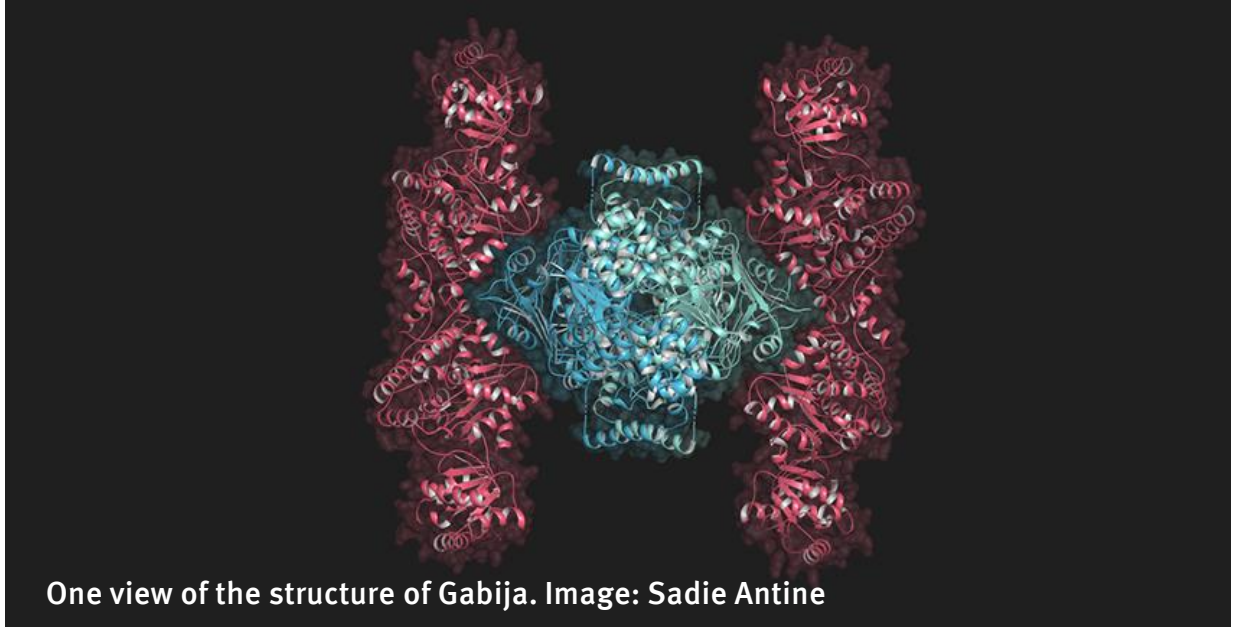
If you've seen the original Star Wars movie, you might wonder whether the iconic Tie fighter was modeled after the Gabija protein complex, a bacterial defense system.

From a certain angle, they appear to share the same distinctive shape: a deadly center protected by two wings. They also share a purpose: defend the realm.

But the structure of Gabija was revealed only recently. It was solved for the first time by virology doctoral candidate Sadie Antine in the lab of Philip Kranzusch, professor of microbiology at Harvard Medical School and Dana-Farber Cancer Institute.

Understanding how Gabija and other elements of bacterial defense systems look and work — along with the mechanisms that viruses known as phages use to overcome these defenses and infect bacteria — promises to illuminate broader aspects of immunity, including human immunity and immune responses to cancer.

Already, the team has revealed an unexpected strategy that phages might use to neutralize Gabija in the evolutionary arms race between bacteria and phages.



One view of the structure of Gabija. Image: Sadie Antine

"This is the importance of basic science," said Kranzusch, senior author of the paper. "We're learning how cells defend against infection."

Gabija is one of hundreds of defense systems found in bacteria. It is present in about 15 percent of all bacteria whose genes have been sequenced.

To learn what Gabija looks like when it is a fully formed molecular machine, also known as a protein complex, Antine used a technique called X-ray crystallography. The process involves coaxing the bacteria to make the protein complex, crystallizing the complex so that it is immobile, and then scattering X-rays off it to get a precise, atomic-level 3D snapshot of the structure.

Source: https://hms.harvard.edu/news/inside-bacterial-defense-system-its-defeat

AI Jobs to be Done in Life Sciences

Becky Pferdehirt, Bryan Faust, Zak Doric, and Vijay Pande, Andreesen Horowitz, Jan 10, 2024 (excerpt)

We have long believed that AI will fundamentally reshape biotech and healthcare, positioning us at the brink of an AI-driven Industrial Revolution. But when will we see this payoff? Put more boldly, when will the majority of new drugs be designed with AI? The first wave of therapeutic candidates designed and optimized by AI/ML tools are making their way through clinical trials now, and new NDA/BLA applications referencing AI are accelerating rapidly. However, it's crucial to recognize that solely counting the number of approved AI-enabled medicines is a lagging indicator of success, overlooking the expanse of treatments still in development (and the long time lag due to clinical trials).

To contextualize this point, consider the evolution of the natural language processing (NLP) field. Initially, GPT-2 marked a significant step forward but had notable limitations in areas like fact-checking and contextual understanding. In contrast, GPT-4 and other large language models (LLMs) have now catalyzed a generative AI renaissance, anticipated to contribute trillions to the global economy. In biotech and health, we are in the early innings (the equivalent of the GPT-2 era) of a significant shift in life sciences R&D driven by AI, and view the continued acceleration of AI research, the increasing number of AI-driven pharma partnerships, and the tangible time- and cost-savings in drug development realized by AI-enabled discovery platforms to be material leading indicators flagging an imminent and substantial transformation in the life sciences ecosystem.

Source: https://a16z.com/ai-jobs-to-be-done-in-life-sciences/

How does this future get realized? We recently wrote about the "Jobs to be Done" (JTBD) for AI in enterprise healthcare. In life sciences, the combined existence of large amounts of complex, multimodal data paired with labor-intensive, high cost tasks creates an optimal opportunity for AI to fundamentally change the future of an entire field. Here, we describe our view of the JTBD in life sciences where we believe AI will have the largest impact.

AI jobs to be done in life sciences

Human pathway biology

Hypothesis generation and prioritization lies at the heart of scientific discovery in life sciences. It's a labor-intensive process that demands sifting through extensive research literature to identify promising avenues for investigation. Here, the AI Scientist emerges as a game-changer, automating literature reviews, analysis of experimental data, and hypothesis generation, with potential to achieve superhuman capabilities. State-of-the-art LLMs can assimilate learnings from the entire corpus of scientific work produced throughout human history, a scale unattainable by any single human.

While we're only starting to see early signs of the immense promise of such an approach (e.g. insitro, Future House, SciSpace, BioAge), it's easy to envision a near future where researchers frequently consult an AI Scientist for pressure-testing new ideas and helping prepare research proposals.

AI Jobs to be Done in Life Sciences (continued)

Becky Pferdehirt, Bryan Faust, Zak Doric, and Vijay Pande, Andreesen Horowitz, Jan 10, 2024 (excerpt)

This efficiency extends to experimental design and data analysis, where AI can unveil hidden insights from complex datasets, which can in turn inform new hypotheses. Moreover, digital twin technology, spanning from whole-cell to whole-human simulations, foretells a future of in-silico testing and systemic understanding of diseases. Coupled with AI-driven lab automation, there's potential to minimize human intervention, thereby establishing a continuous learning loop that accelerates the cycle of discovery.

AI for TA selection/pipeline prioritization

One of the most important decisions a therapeutic platform company must make (and continually re-make) is what overall therapeutic areas and specific therapeutic targets to point their technology towards. This is such a crucial task that an entire sector of consulting companies has been built around it, servicing both small biotech and large biopharma. Successful therapeutic area selection and pipeline prioritization requires the synthesis of large amounts of both historical data and the ability to accurately predict future competitive landscapes in order to inform strategic decisions for a company's pipeline. We view this area as a compelling job for AI, where large amounts of complex data must be synthesized and the ultimate result is relatively forgiving to mistakes.

AI for preclinical development

AI is set to disrupt virtually every aspect of the preclinical drug development lifecycle, from target discovery to final formulation. In fact, across both biotech and pharma, we're already witnessing tangible reductions in therapeutic discovery & development timelines in the informed design of efficacious small molecules, proteins, or cell and gene therapies.

Saving time and dollars on the clinical side

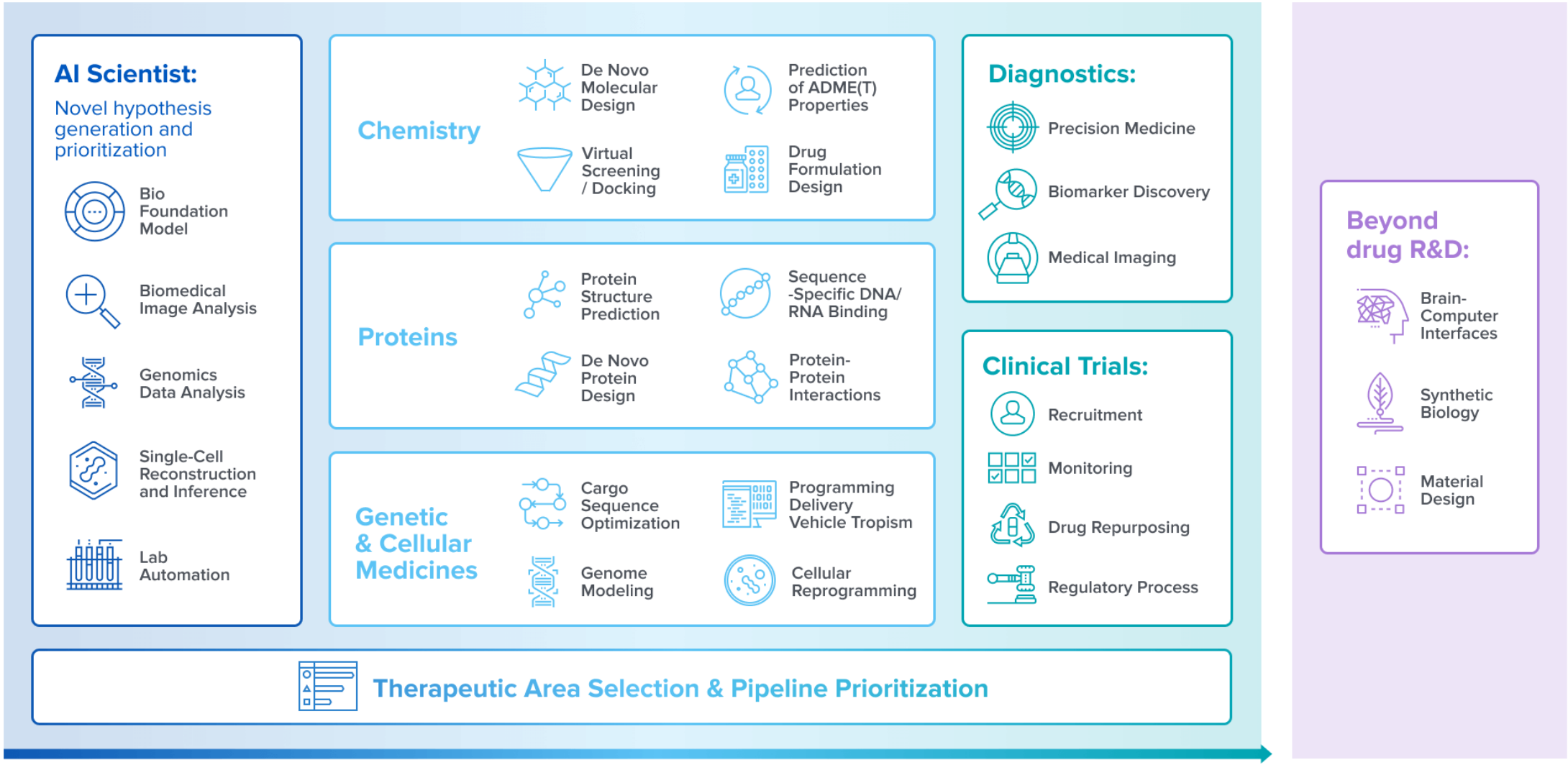
Over half of the total investment in the drug development process is spent during the clinical development phase. We view the seamless integration of AI into jobs across clinical development as one of the clearest paths to reducing the cost and timelines for drug development, and ultimately improving patient care. Clinical development yields a vast amount of varied data, offering ample opportunities for AI-driven solutions to refine multiple aspects of clinical development. Even modest improvements could significantly reduce both the high costs and extended timelines of drug development, a compelling value proposition to pharma. For example, LLM guided clinical trial design and protocol drafting could level the playing field between small biotechs and large pharma. Additionally, AI-driven patient selection for clinical trials could enroll patients more effectively and precisely, improving recruitment across sites and overall trial success rates.

Source: https://a16z.com/ai-jobs-to-be-done-in-life-sciences/

AI Jobs to be Done in Life Sciences

AI is transforming the drug development process from basic science to drug approval

a16z Bio + Health



Medical AI Could be 'Dangerous' for Poorer Nations, WHO Warns

David Adam, *Nature*, Jan 18, 2024 (excerpt)

The introduction of health-care technologies based on artificial intelligence (AI) could be "dangerous" for people in lower-income countries, the World Health Organization (WHO) has warned.

The organization, which today issued a report describing new guidelines on large multi-modal models (LMMs), says it is essential that uses of the developing technology are not shaped only by technology companies and those in wealthy countries. If models aren't trained on data from people in under-resourced places, those populations might be poorly served by the algorithms, the agency says.

"The very last thing that we want to see happen as part of this leap forward with technology is the propagation or amplification of inequities and biases in the social fabric of countries around the world," Alain Labrique, the WHO's director for digital health and innovation, said at a media briefing today.

Overtaken by events

The WHO issued its first guidelines on AI in health care in 2021. But the organization was prompted to update them less than three years later by the rise in the power and availability of LMMs. Also called generative AI, these models, including the one that powers the popular ChatGPT chatbot, process and produce text, videos and images.

LMMs have been "adopted faster than any consumer application in history", the WHO says. Health care is a popular target. Models can produce clinical notes, fill in forms and help doctors to diagnose and treat patients. Several companies and health-care providers are developing specific AI tools.

Source: https://www.nature.com/articles/d41586-024-00161-1

In many quarters, there is a quite conservative reaction to generative AI.

To take a counterpoint to this recent WHO guidance, LMM's would seem to be particularly helpful in nations where existing medical infrastructure is sparse.

Further, it is not difficult to design LMM's that are regionally / spatially aware, thereby addressing the potential concern voiced by the WHO last week.

IQVIA Institute: Global Use of Medicines Report

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2024-outlook-to-2028

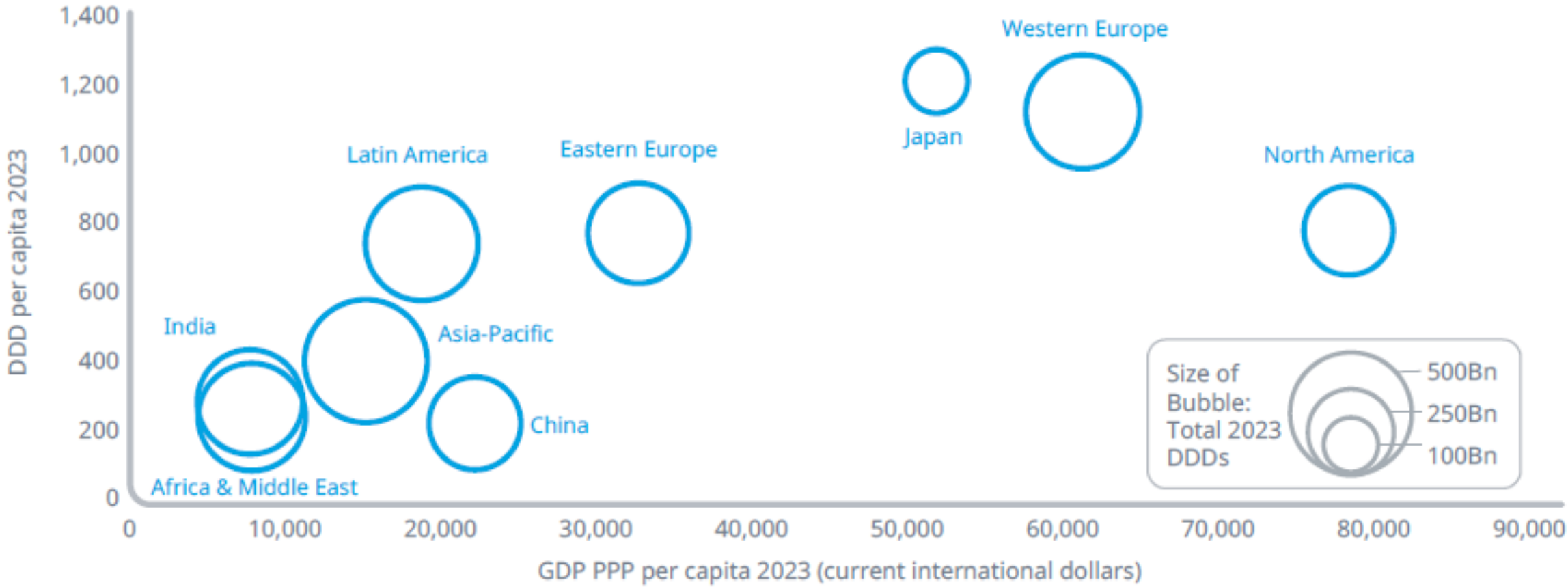
Key Conclusions

1. Growth outlook for use of pharmaceuticals is raised by 2 percentage points despite lower expectations for COVID-19 vaccines and therapeutics
2. This increase in growth outlook is driven by more patients getting treated with better medicines, especially in immunology, endocrinology, and oncology
3. Medicine use in Latin America and Asia will grow faster than other regions over the next five years
4. Global use of medicines grew by 14% over the past five years and a further 12% increase is expected through 2028, bringing annual use to 3.8 trillion defined daily doses
5. Global spending on medicine using list prices grew by 35% over the past five years and is forecast to increase by 38% through 2028
6. The updated outlook for the U.S. market, using estimated net prices, is being raised by 3 percentage points to 2-5% CAGR through 2028, reflecting higher recent growth and expected further increased patient use of higher value therapies

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2024-outlook-to-2028

Per capita use of medicines varies by GDP with use in higher income countries typically higher than in lower income ones

Exhibit 3: Defined Daily Doses (DDD) per capita by region compared to per capita gross domestic product PPP, current international dollars



Source: IQVIA Institute, Dec 2023; The World Bank, Jul 2023; International Monetary Fund, Oct 2023.

Historical and projected use of medicines by region, 2018–2028, Defined Daily Doses (DDD) in billions

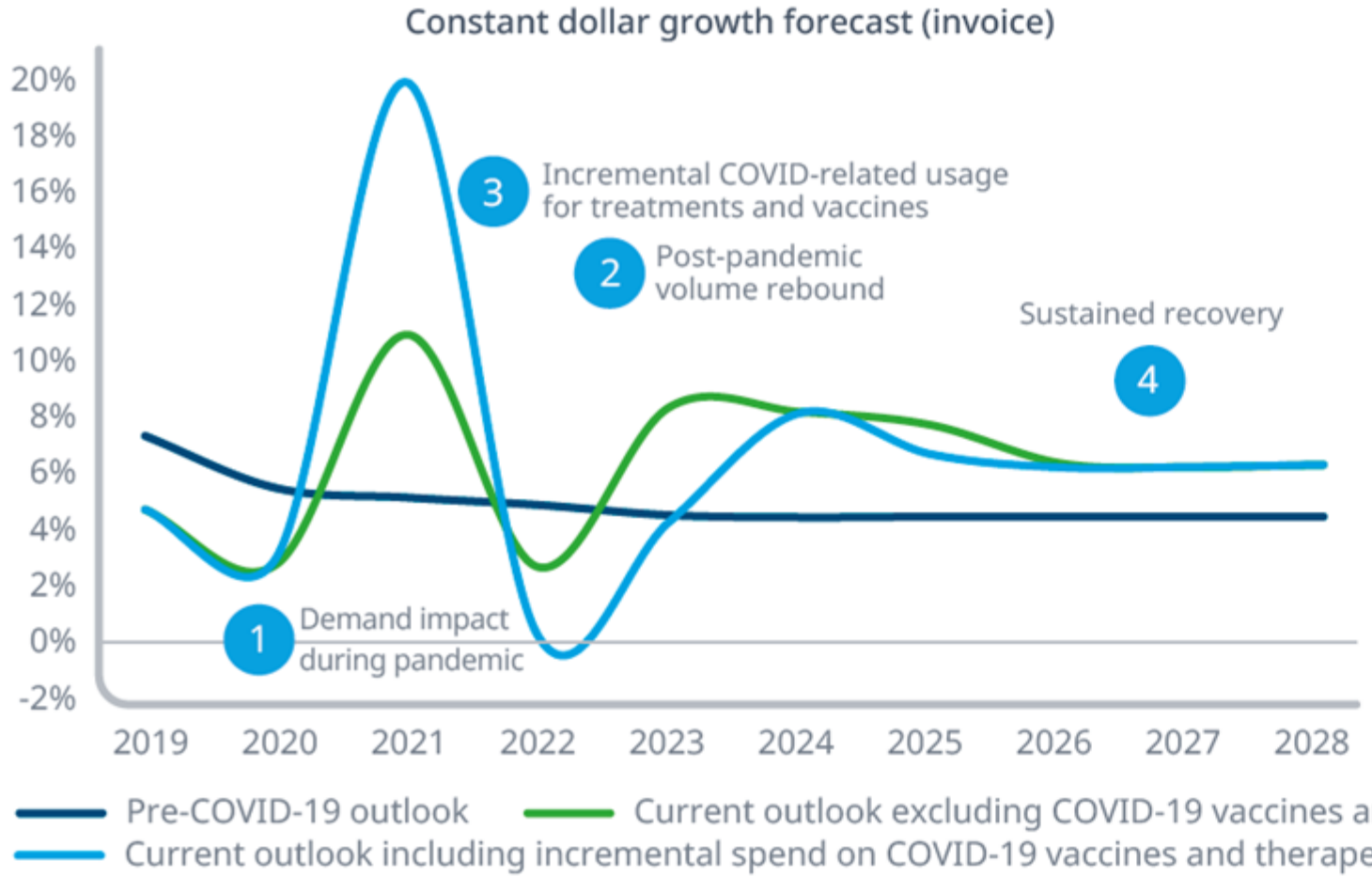
Source: IQVIA Institute, Dec 2023.

Notes: Chart represents IQVIA Institute estimates of global defined daily doses (DDD). These estimates are based on IQVIA audited data and application of WHO-DDD factors in IQVIA MIDAS as well as additional DDD calculation assumptions developed by the IQVIA Institute (see Methodology). Asia-Pacific does not include China, India, and Japan which are reported separately. 2023 volume is based on actual data as of June 2023 and projected for the remainder of the year.

Report: Global Use of Medicines 2024: Outlook to 2028. IQVIA Institute for Human Data Science, January 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2024-outlook-to-2028

Comparison of current outlook to pre-COVID-19 outlook



Key events in the outlook

1 **2020:** Growth -3.0% slower than pre-pandemic projection (~$39Bn)

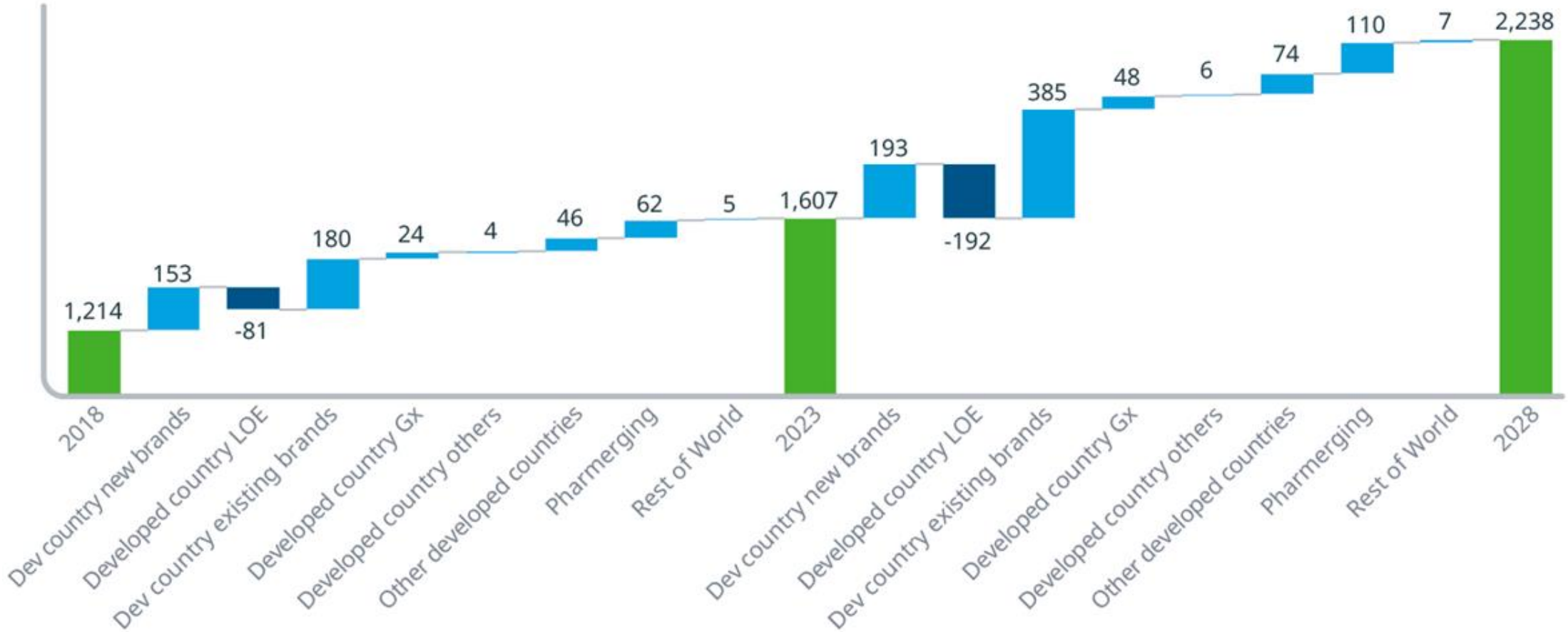
2 **2021:** +14.2% higher growth including vaccines and therapeutics compared to spending without them

3 **2022/3:** COVID vaccine and therapeutic use has slowed, resulting in lower growth

4 Sustained recovery of market will drive long-term growth 1–2% higher than the pre-pandemic outlook

Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Dec 2023.
Notes: Pre-COVID outlook based on IQVIA Market Prognosis, Sept. 2019 edition which included projections to 2024 and which has been extended to include the periods to 2027 with a linear projection. Current outlook based on IQVIA Market Prognosis Sept. 2023 edition. Incremental COVID vaccine and therapeutic scenario based on current outlook combined with incremental spending for vaccines and novel COVID-19 therapeutics.
Report: Global Use of Medicines 2024: Outlook to 2028. IQVIA Institute for Human Data Science, January 2024.

Global spending and growth, US$Bn 2018–2028, excluding COVID-19 vaccines and therapeutics

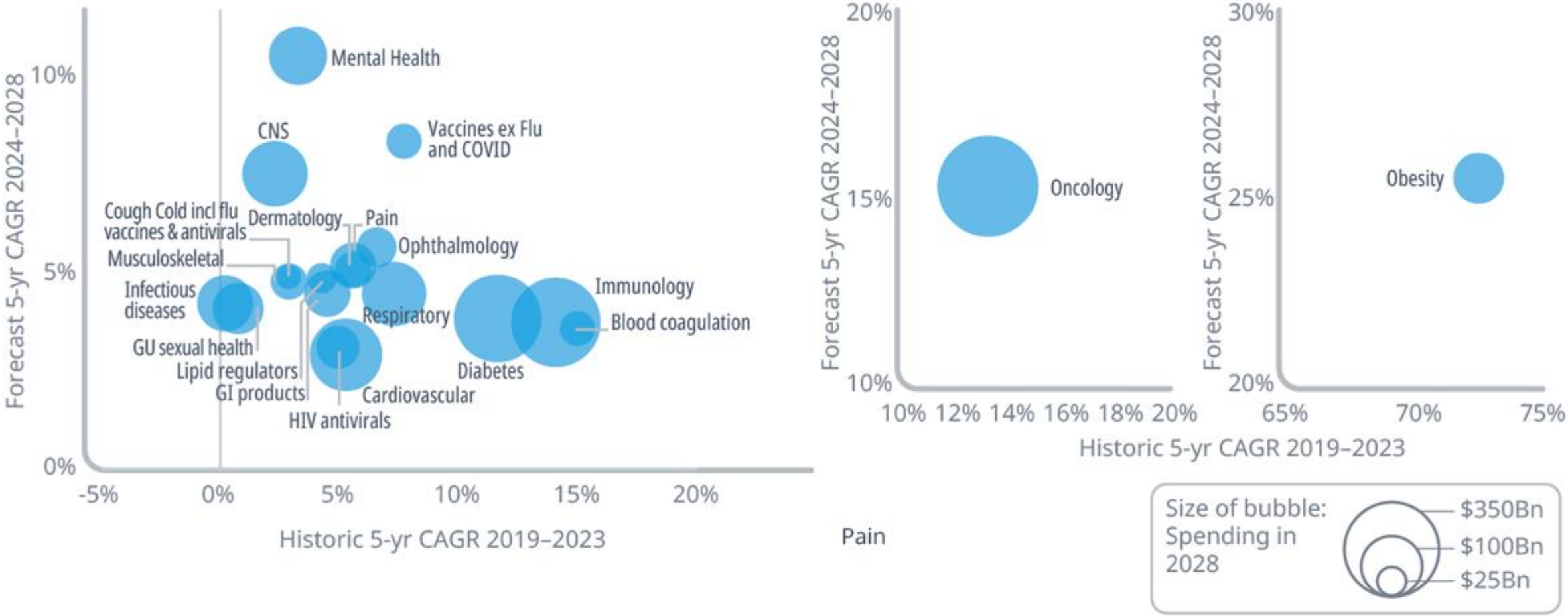


Source: IQVIA Market Prognosis, Sep 2023; IQVIA Institute, Nov 2023.

Notes: Developed countries refer to the top 10 developed markets (U.S., Japan, Germany, France, Italy, Spain, UK, Canada, South Korea, Australia. Other developed include countries from the World Bank's income segmentation, and include high and upper-middle income countries, with the exception of pharmerging markets. Pharmerging markets are those with per capita GDP by purchasing power parity (PPP) <$30,000/year and forecasted 5-year aggregate pharma sales growth >$1bn (absolute or rounded) in at least two forecasts. Note that Pharmerging and Other Developed segments have been revised with this edition, with several countries now being included in Other developed which were previously Pharmerging. See definitions for details of these regional definitions. Spending and growth do not include COVID-19 vaccines and therapeutics.

Report: Global Use of Medicines 2024: Outlook to 2028. IQVIA Institute for Human Data Science, January 2024.

Global historic and forecast growth for top 20 therapy areas



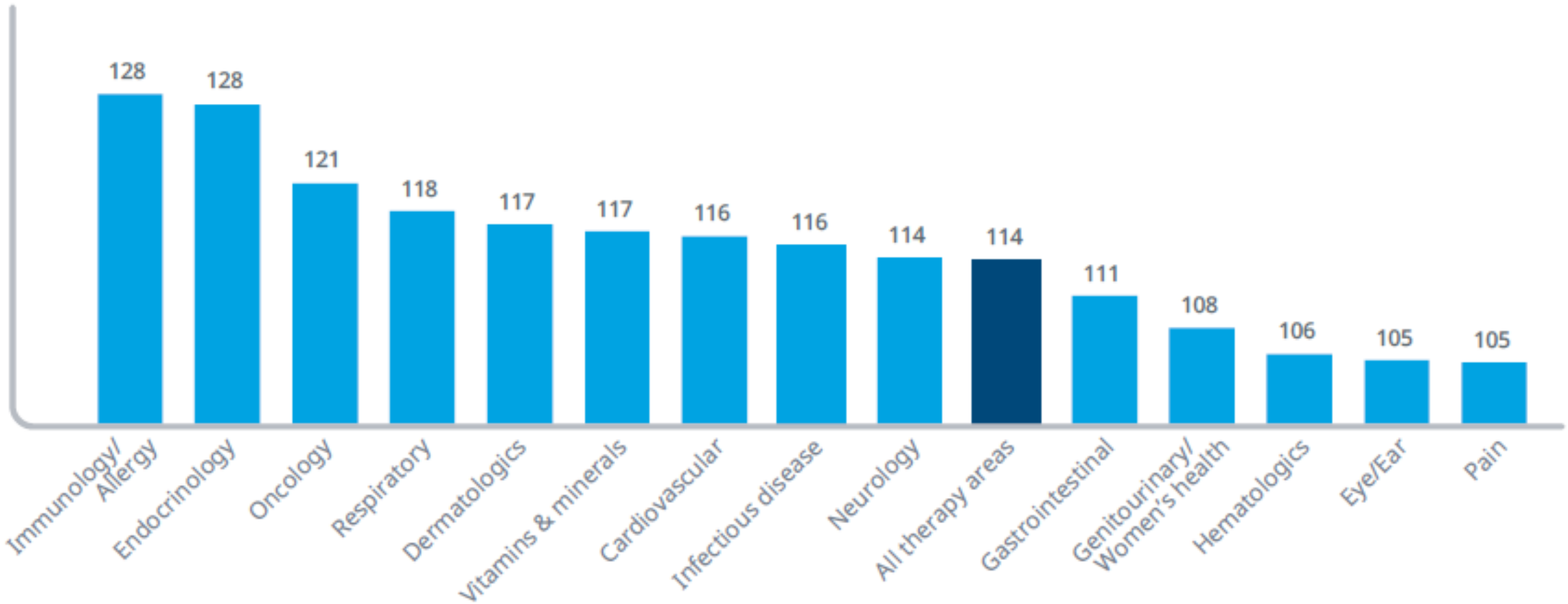
Source: Source: IQVIA Forecast Link, Dec 2023.

Notes: Bubble Size represents forecast in 2028; COVID Vaccine and therapeutics are not included. Oncology includes therapeutic oncology only and not supportive care. Immunology includes small molecule and biologic treatments for a range of diseases as noted. Neurology includes central nervous system disorder treatments and mental health treatments but does not include pain management or anesthesia. Pain includes narcotic and non-narcotic analgesics, muscle relaxants and migraine treatments. Cardiovascular includes hypertension and other cardiovascular treatments with the exception of lipid regulators, which are shown separately.

Report: Global Use of Medicines 2024: Outlook to 2028. IQVIA Institute for Human Data Science, January 2024.

Medicine use has been growing across therapy areas since 2019, with highest growth in immunology, endocrinology, and oncology

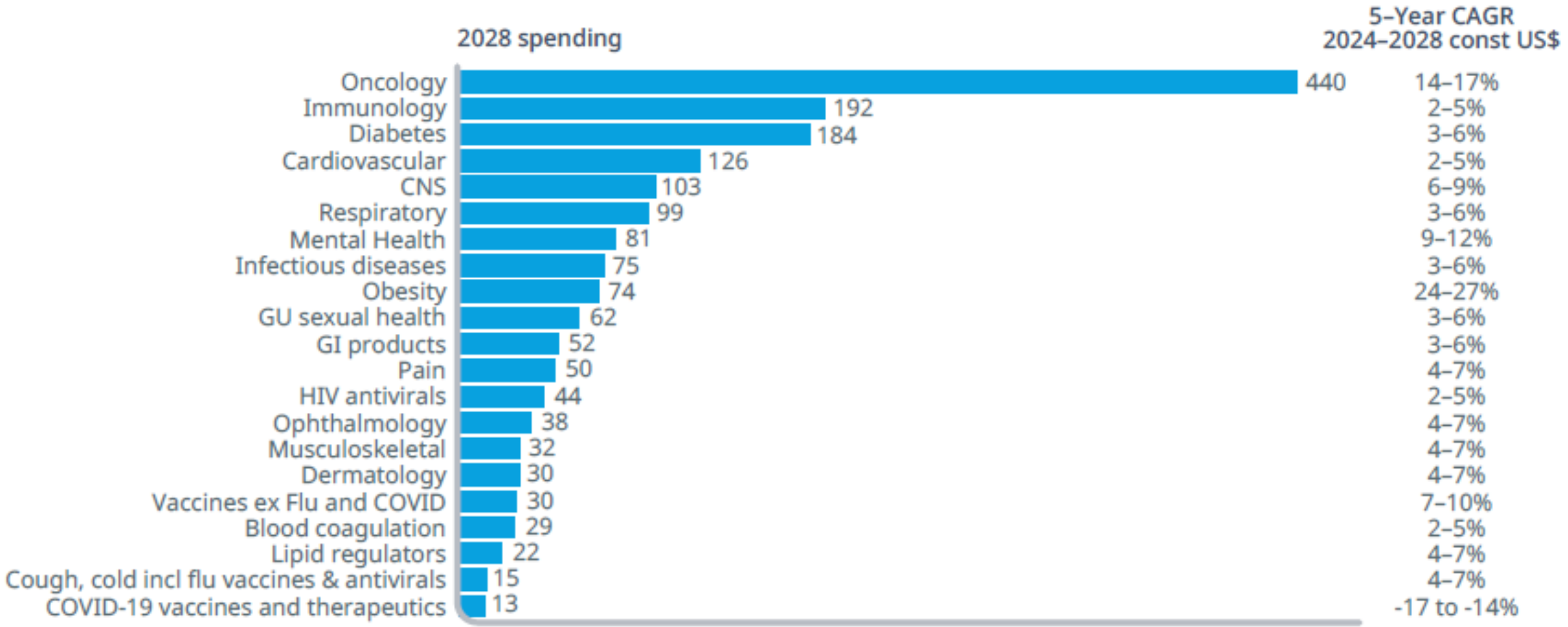
Exhibit 6: Defined daily doses (DDD) in 2023 across select therapy areas indexed to 2018 values (2018 value = 100)



Source: IQVIA MIDAS, Jun 2022; IQVIA Institute, Dec 2023.

Oncology and obesity lead growth while immunology slows due to biosimilars; many other classes are growing in mid-single digits

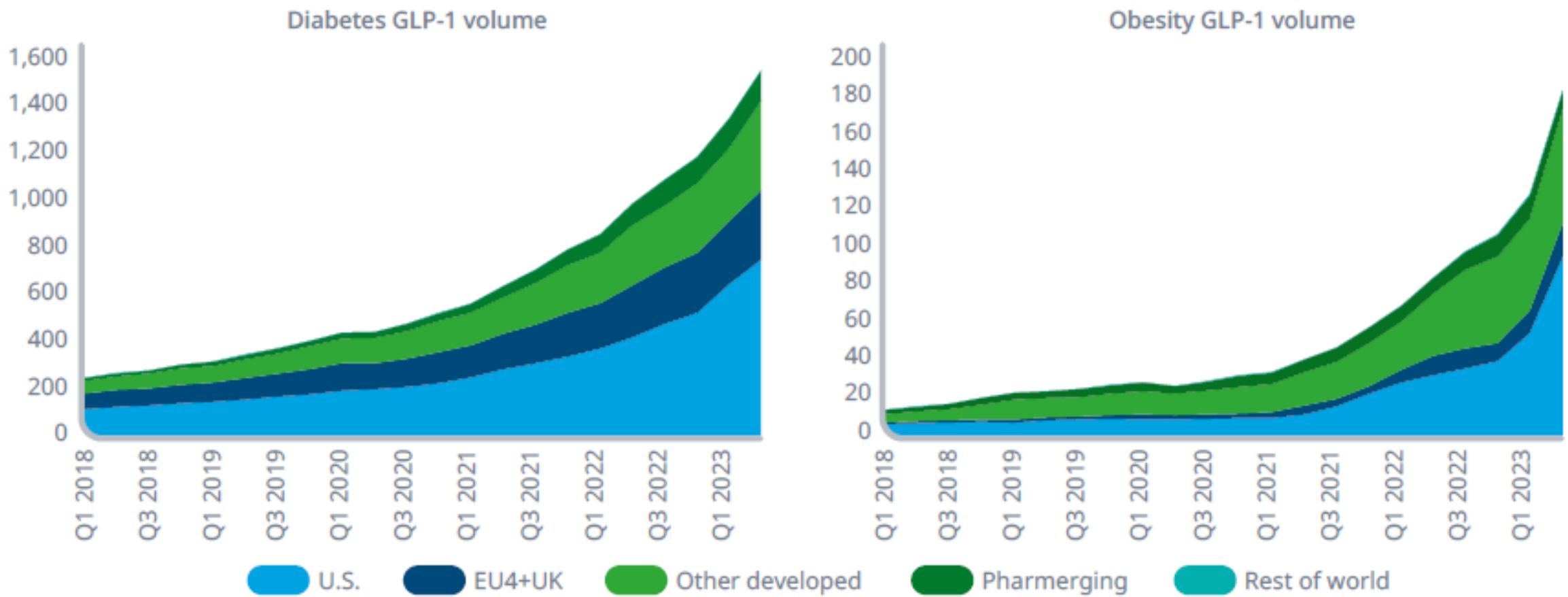
Exhibit 37: Top 20 therapy areas in 2028 in terms of global spending with forecast 5-year CAGRs, const US$Bn



Source: IQVIA Forecast Link, IQVIA Institute, Dec 2023.

GLP-1 agonists have seen rapid uptake in both diabetes and obesity, predominantly in the U.S. and other developed markets

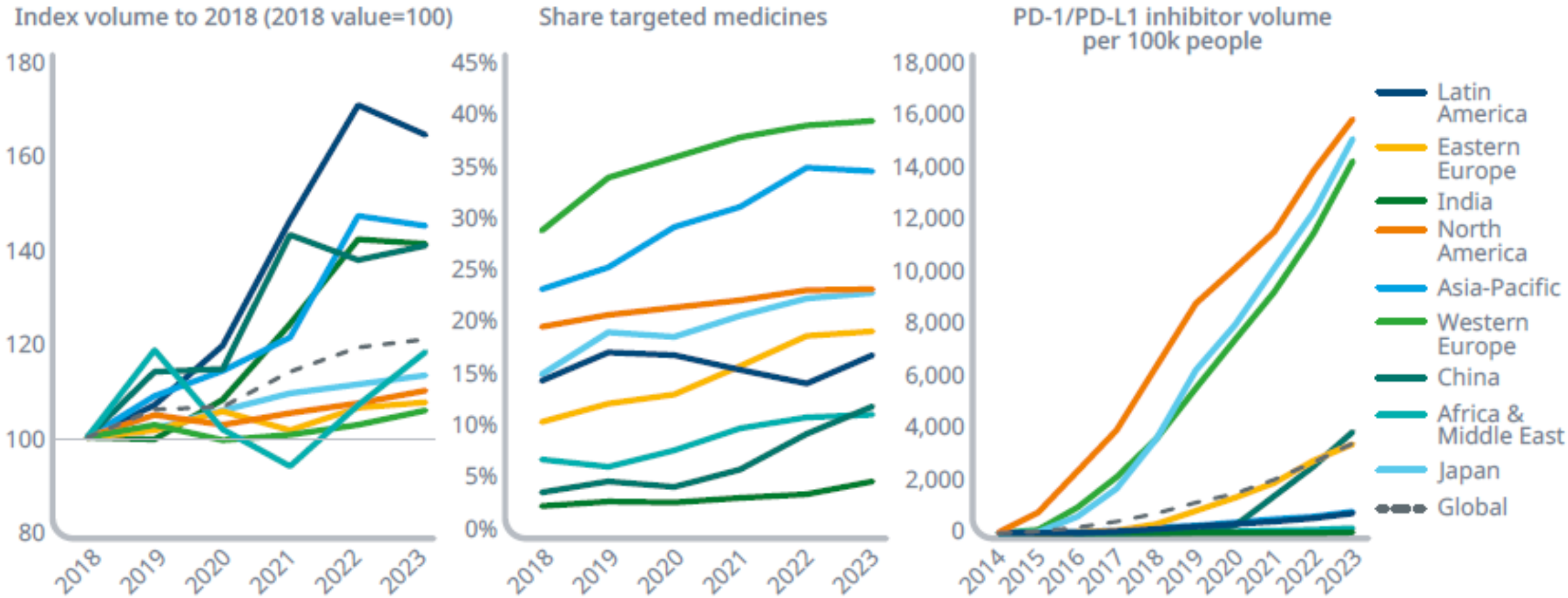
Exhibit 9: Quarterly GLP-1 agonist volume in defined daily doses (DDD) in millions, Q1 2018–Q2 2023



Source: IQVIA MIDAS, Jun 2023; IQVIA Institute, Dec 2023.

Developing regions have seen higher oncology growth since 2018 driven by expanded access to traditional chemotherapy

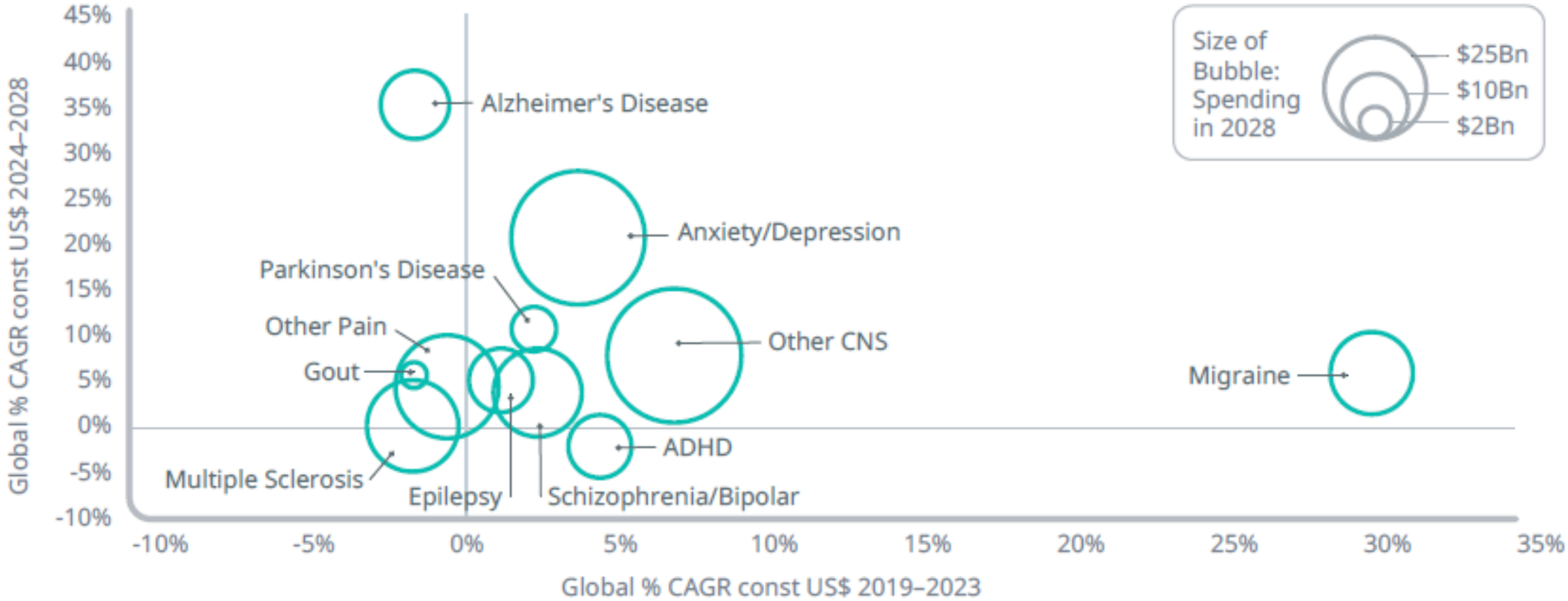
Exhibit 10: Oncology Defined Daily Dose (DDD) volume growth, targeted medicines share of volume, and PD-1/PD-L1 uptake by region



Source: IQVIA MIDAS, Jun 2023; IQVIA Institute, Dec 2023.

New therapies in Alzheimer's and anxiety/depression are expected to drive spending growth in neurology

Exhibit 43: Leading CNS disorders global market growth dynamics



Source: IQVIA Forecast Link, IQVIA Institute, Dec 2023.

Disclosure

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